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ANNEXURES

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Annexure 28

RESEARCH ON TOBACCO IN INDIA
(INCLUDING BETEL QUID AND ARECA NUT)

An annotated bibliography of research on
use, health effects, economics, and control efforts

Cecily Stewart Ray

with Prakash Gupta and Joy de Beyer

August 2003

Health, Nutrition and Population (HNP) Discussion Paper

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Health, Nutrition and Population (HNP) Discussion Paper

ECONOMICS OF TOBACCO CONTROL PAPER NO. 9

RESEARCH ON TOBACCO IN INDIA (INCLUDING BETEL QUID AND ARECA NUT)

An annotated bibliography of research on use, health effects, economics, and control efforts

Cecily Stewart Ray[a] with Prakash Gupta[b] and Joy de Beyer[c]

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Paper prepared for the World Bank for the meeting on Tobacco Control Research in India, held in New Delhi, India on April 10-11, 2002.

The on-line version of this annotated bibliography will be updated periodically. Readers are encouraged to send additional references and abstracts to the authors.

Abstract: This report is a compilation of references and abstracts of all research on tobacco in India from 1985 to 2003. Studies are organised by subject matter, and within each sub-topic, are arranged by year of publication with most recent studies listed first, and for studies published in the same year, alphabetically by author's last name. The studies include tobacco use surveys, studies on tobacco-related mortality, tobacco-related diseases both cancerous and non-cancerous, according to body system and site, and other health problems associated with tobacco use and environmental tobacco smoke. Other topics include the toxicity of tobacco products, educational interventions and the psychology of tobacco use, tobacco control measures and policies, reports on tobacco advertising and sponsorship and research into the tobacco health hazards faced by tobacco workers. It also includes studies on tobacco employment, tobacco growing and technology, and the economics of tobacco. The following databases were searched: Pub Med, Medline, and J-Gate (a new Indian database). The keywords used for the searches were '(Tobacco OR smoking) AND India', as well as names of diseases known from international research findings to be associated with tobacco, 'AND India'. In some cases, reports were excluded if they were duplicative, or the methodology or findings were unclear.

The report is also available on-line, at to http://www.actindia.org/databases.html or www.actindia.org -- click on "databases", or through www.worldbank.org/tobacco. In future, all the abstracts will be available also on the WHO 'Health Internetwork' (HIN) website, that is under development. The electronic file is available upon request, from the authors.

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Keywords: tobacco, nicotine, bidi, tendu, gutkha, paan masala, smoking, areca nut, betel-quid, chewing tobacco, smokeless tobacco, reverse smoking, chutta, environmental smoke, passive smoking, second-hand smoke, sidestream smoke, India, cancer, tuberculosis, pulmonary disease, CVD, coronary vascular disease, respiratory disease, stroke, peripheral vascular disease, adverse pregnancy outcomes, nutritional status, tobacco control, tobacco policy, economics of tobaeco

Disclaimer: The findings, interpretations and conclusions expressed in the paper are entirely those of the authors, and do not represent the views of the World Bank or the World Health Organization, their Executive Directors, or the countries they represent.

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The electronic file for this document (word.doc file) is available upon request from Cecily Ray or Joy de Beyer, for readers who wish to be able to search or sort the file for personal use. The file can be sent by email, or on CD or diskette.

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PREFACE

In 1999, the World Bank published "Curbing the Epidemic: governments and the economics of tobacco control", which summarizes trends in global tobacco use and the resulting immense and growing burden of disease and premature death. In 2000, there were nearly 5 million deaths from tobacco each year, and this huge number is projected to grow to 10 million per year by 2030, given present consumption trends. Already about half of these deaths are in high-income countries, but recent and continued increases in tobacco use in the developing world is causing the tobacco-related burden to shift increasingly to low- and middle-income countries. By 2030, seven of every ten tobacco-attributable deaths will be in developing countries.

"Curbing the Epidemic" also summarizes the evidence on the set of policies and interventions that have proved to be effective and cost-effective in reducing tobacco use, in countries around the world. Tax increases that raise the price of tobacco products are the most powerful policy tool to reduce tobacco use, and the single most cost-effective intervention. They are also the most effective intervention to persuade young people to quit or not to start smoking. This is because young people, like others with low incomes, tend to be highly sensitive to price increases.

Why are these proven cost effective tobacco control measures –especially tax increases– not adopted or implemented more strongly by governments? Many governments hesitate to act decisively to reduce tobacco use, because they fear that tax increases and other tobacco control measures might harm the economy, by reducing the economic benefits their country gains from growing, processing, manufacturing, exporting and taxing tobacco. The argument that "tobacco contributes revenues, jobs and incomes" is a formidable barrier to tobacco control in many countries. Are these fears supported by the facts?

In fact, these fears turn out to be largely unfounded, when the data and evidence on the economics of tobacco and tobacco control are examined. The team of about 30 internationally recognized experts in economics, epidemiology and other relevant disciplines who contributed to the analysis presented in "Curbing the Epidemic" reviewed a large body of existing evidence, and concluded strongly that in most countries, tobacco control would not lead to a net loss of jobs and could, in many circumstances actually generate new jobs. Tax increases would increase (not decrease) total tax revenues, even if cigarette smuggling increased to some extent. Furthermore, the evidence shows that cigarette smuggling is caused at least as much by general corruption as by high tobacco product tax and price differentials, and the team recommended strongly that governments not forego the benefits of tobacco tax increases because they feared the possible impact on smuggling, but rather act to deter, detect and punish smuggling.

Much of the evidence presented and summarized in "Curbing the Epidemic" was from high income countries. But the main battleground against tobacco use is now in low- and middle-incomes countries. If needless disease and millions of premature deaths are to be prevented, then it is crucial that developing counties raise tobacco taxes, introduce comprehensive bans on all advertising and promotion of tobacco products, ban smoking in public places, inform their citizens well about the harm that tobacco causes and the benefits of quitting, and provide advice and support to help people who smoke and chew tobacco, to quit.

In talking to policy-makers in developing countries, it became clear that there was a great need for country-specific analytic work, to provide a basis for policy making, within a sound economic framework. So the World Bank and the Tobacco Free Initiative of the World Health Organization (as well as some of the WHO regional offices and several other organizations, acting in partnership or

independently) began to commission and support analysis of the economics of tobacco and tobacco control in many countries around the world.

Most of the other papers in this Discussion Paper series report results of new, previously unpublished analyses of tobacco economics and tobacco control issues. Clearly, this annotated bibliography is different, being a compilation of references and abstracts of research which has been published elsewhere, often in refereed journals.

Our hope is that the information compiled in this report will be a useful reference for researchers and others who are looking for information on tobacco use and its impact in India, or on tobacco control in India.

Joy de Beyer

Tobacco Control Coordinator
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The internet version was designed and created by Vishal Bal. It is available at www.actindia.org -- click on "databases", or go directly to http://www.actindia.org/databases.html.

This analysis was carried out with the aid of grants provided by the World Bank and the Office on Smoking and Health at the US Centers for Disease Control.

The authors are also grateful to the World Bank for publishing the report as an HNP Discussion Paper.

INTRODUCTORY NOTE

This bibliography is an attempt to compile a list of 'all' tobacco and areca nut related research conducted in India since 1985, providing references and abstracts. Most of the abstracts were originally prepared by the authors. The purpose of creating this database is to form a pool of information, which can be drawn upon by tobacco control researchers, advocates for tobacco control and those specializing in public health policy.

This compilation contains abstracts on reports of tobacco use surveys, tobacco related mortality, tobacco related diseases both cancerous and non-cancerous, according to body system and site, and other health problems associated with tobacco use and environmental tobacco smoke. Other topics include the toxicity of tobacco products, educational interventions and the psychology of tobacco use, tobacco control measures and policies, reports on tobacco advertising and sponsorship and research into the tobacco health hazards faced by tobacco workers. Also included are tobacco employment studies, tobacco agriculture and technology, and the economics of tobacco. There are many more studies on the health problems caused by tobacco use than on other topics, reflecting the seriousness of the health impact of tobacco use.

The following **databases were searched**: Pub Med, Medline, and J-Gate (a new Indian database). The keywords used for the searches were 'Tobacco AND India', Smoking AND India, as well as names of diseases known from international research findings to be associated with tobacco, 'AND India'. Proceedings of other meetings on research related to tobacco provided additional sources. We are grateful to the librarians who helped with the literature searches, and to those who contributed articles and other publications from their own collections.

Some judgment was used in **selecting material** for this database, both according to its quality and to the usefulness of the information for framing tobacco control policies or interventions. We decided to include only publications from 1985 onwards. Some papers were excluded because they duplicated another paper by the same author/s, or because the methodology or statistics were unclear. In addition to research studies, some editorials, letters and news articles containing fresh viewpoints, interesting ideas, useful summaries or information were also included. The compilers of this bibliography are not responsible for any errors made by the authors of articles whose abstracts appear in the document. Readers should read the original papers carefully before using information contained in the abstracts.

A **table of contents** is included for quick location of abstracts and references, in which articles are categorised by topic area. Within each topic, articles are listed in reverse chronological order, but ascending alphabetical order of authors last names within the same year. Codes have been given for each article, designating the topic category, the year of publication (or of preparation), and the first three letters of the first author's last name. The table of contents shows the topic codes. Some articles are listed more than once, if they fall into more than one of the categories. Both codes are given with each listing. At the end of this document, there is a **full alphabetical listing** by last name of the first author, to make it easy to search for particular articles, and then locate them in the bibliography according to

the classification code used. The electronic word file is available from the authors upon request (by email, or we can send a CD ROM or diskette), so that users can search and sort the articles electronically. The files are also available on-line at the ACT-India website www.actindia.org and through the World Bank website: www.worldbank.org/tobacco.

The following **types of reports** are included: analytical reports, case series studies and case reports, case-control studies, cohort studies, comparative studies, cross-sectional studies and cross-sectional follow-up studies, detection camp reports, descriptive reports, incidence studies, intervention studies, histological studies, news reports, overviews of research results, predictive reports, proceedings, reviews of studies, recommendations, and tobacco use surveys. There are also a few clinical, biophysical and biochemical studies.

Abstracts and most references to biological research have not been included in this compilation due to the highly technical and specialized nature of this area of research. Tobacco or areca nut research involving animal subjects was omitted also.

A tremendous amount of biological research on the effects of tobacco on the cells of the oral mucosa has been done in India. Researchers in cancer cytogenetics have mostly studied changes in the oral mucosa leading to cancer and the related abnormalities in the DNA structure of oral mucosal cells. Broadly, the main findings are that tobacco acts on cells as a mutagen, disrupting the inherited regulation mechanisms for repair and reproduction, putting them on the road to cancer. Individuals who have inherited defective DNA repair genes are more likely than people with normal DNA to develop cancer within their lifetime, but even persons with normal cell DNA from birth can develop cancer. The main message from cytogenetic research is that tobacco in all forms is carcinogenic and poses health risks to everyone exposed to it. Similarly, experiments with extracts of areca nut (sometimes erroneously referred to as betel nut), have demonstrated that substances it contains interact with and damage DNA, eventually making cells unhealthy and potentially cancerous.

Several health problems, which have been found through various studies conducted in the West to occur more frequently in smokers, have either not been studied in India, or not after 1985. These topics include periodontal disease (studied prior to 1985 in India), peptic ulcer and oesophageal reflux, impotence, osteoporosis, and cervical and breast cancers. Tobacco as a risk factor for these conditions might be worth investigating in India. It should be noted that results on the association of diabetes with tobacco use are also found with the studies on circulatory diseases, since diabetes is a risk factor for circulatory diseases.

This annotated bibliography on tobacco is perhaps the first attempt of its kind. There may be shortcomings and unintended omissions. We shall be most grateful to readers for pointing those out and contributing new as well as missed papers. We urge those working in any fields under-represented here to contribute further articles. This would improve this database and make future versions more useful and comprehensive. The database will be expanded and updated periodically.

Cecily Stewart Ray, Prakash C. Gupta and Joy de Beyer

1. Tobacco Use Surveys and Reports

Tobacco use surveys have been conducted in different areas of India to gather data on the use of tobacco by the population, awareness of the health effects of tobacco and attitudes toward tobacco use and efforts to discourage its use (usually called "tobacco control"). The purpose of these surveys is usually for planning awareness programmes. Other articles summarized here are reports of distilled knowledge on tobacco use patterns or of events that changed tobacco use in an area. This section is divided into subsections, by the type of population reported on.

1.1 Youth in general

Two articles are summarized here: the first on tobacco use in youth in the Southeast Asian Region, pointing out similarities among youth of the different countries in the region and particularities of tobacco use by Indian youth, and the second on reasons why Indian youth use tobacco and the forms it takes. With the second article, we are making an exception to the cut-off point of 1985.

TUS India (2002) Gup: Review
Gupta, PC and Ray, C. **Tobacco and youth in the south east Asian region.** *Ind J Cancer*, 39 (1), 2002, 5-35.

Tobacco use among youth in South-East Asian countries was reviewed using available literature. Youth who are out-of-school, earning, less educated and live in rural areas are more likely to use tobacco and start during the preteen years. Better educated youth may know the health effects of smoking but the dangers of passive smoking are generally unknown. Youth are fairly unconcerned about the present or future effects of tobacco use on health but do favour tobacco control measures. Children and youth are more responsive than adults to tobacco education. In India, a manufactured smokeless tobacco product, gutkha, has been targeted toward youth and has become extremely popular. An evolving epidemic of oral submucous fibrosis attributed to gutkha use has been documented among youth, with a resultant increase in oral cancer in lower age groups. Children in India are often illegally employed in bidi manufacturing. This review points out the need for specific actions.

TUS India (1982) Agh: Descriptive report
Aghi, M. B. **Patterns of smoking among children in India.** Contribution to UICC Manual on Smoking and Children, Geneva, 1982.

While peer pressure and parental example are important all over India in determining the use of tobacco by children, the dynamics of smoking behaviour are different in urban and rural areas. In **urban areas** the young often smoke because their peers smoke. However

peer pressure is not to the same degree among all the economic classes. Traditional values do not favour smoking among the young and never among females. The real problem in urban areas is located among urban poor. Boys under the age of 10 years and sometimes even 5 to 6 years smoke. Their most common reason is not peer pressure but their film hero who smokes. In the **rural areas** many people believe in multi-magical properties of tobacco and are unaware of the hazards of smoking. Tobacco is believed to be able to cure toothache. Advertisements for cigarettes are not to be found in villages, nor are health warnings against tobacco use. A bundle of bidis does not have any warning. Illiteracy, however would be an impediment to a warning's effectiveness. Gujarati village boys start smoking from the ages of 9 and 10 onwards, seeing their parents smoke. Young rural men often take to smoking to appear modern, open minded, tough and smart and often to show that they are educated. Many villagers in Gujarat believe smoking facilitates bowel movement in the morning. People generally believe that tobacco gives relief from gas, stomach acidity, headache and indigestion, hence when their sons complain of such problems, they give them bidi or hookli to smoke. Young boys who work in agriculture begin smoking because others are smoking and local employers in shops give bidis to young boys to attract them to work in their shops. Gossip groups, commonly seen in rural areas, are conducive to smoking. In rural Andhra Pradesh the following observations have been made: A young boy who is not smoking gets coaxed into it by his friends. Many young boys believe that smoking while watching a play or movie adds to the fun of watching it. Young boys going to work are told by their counterparts that to relax one must smoke. The majority of young girls smoke on advice of elder folks for things like fulfilment of a wish or longing during pregnancy, as a cure for anaemia, asthma and for getting relief from toothaches. A few young boys and girls take up smoking to show that they are grown up. A belief exists that one should not see a non-smoker's face in the morning as this could bring ill luck. Conclusion: It should be brought to the attention of policy makers that no awareness exists in rural India on the ill effects of tobacco. There is room for improvement in awareness in urban areas also. The responsibility for generating such awareness rests on the policy makers, whose policies and budgets impact the country.

1.2 School children

This section on tobacco use in school children is divided into two subsections. The first subsection summarizes results of surveys conducted at different times by different researchers using their own methodologies, while the second one contains surveys in various states in India conducted within a short time span (2001-2002) using identical methodology, as part of the Global Youth Tobacco Survey.

1.2.1 Independent surveys of school children

The articles in this section report on surveys of tobacco use and awareness among school children in areas of Punjab, Gujarat, Goa (2), Tamil Nadu, Karnataka, Haryana, and Maharashtra. The definition of a tobacco user is not clearly spelled out and may not be comparable across all the studies, but it is clear from each of them that tobacco use is

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practiced among Indian school children. In areas of low adult use, like Goa and Punjab, tobacco is making inroads among the youth.

TUS India (2002) Kau: Tobacco use survey
Kaur S and Singh S. **Cause for concern in Punjab villages. High levels of Gutkha intake among students**. *Lifeline,* Volume 7 January 2002, 3-4.
(Department of Agricultural journalism, Punjab Agricultural University – Ludhiana)

A random survey among rural school children in five villages around Mullanpur, Punjab State, covering 100 students from 5 schools, was conducted with the objective of finding out the extent of gutkha use (a form of chewing tobacco) among village students, their level of awareness about hazards of tobacco and to suggest remedial measures. The results showed that 66 of the students regularly used gutkha, a matter of concern for parents, teachers and administrators. Of the 66 students found using gutkha, it was seen that 19 consumed it every day while 31 took it almost every day, and 16 said they took gutkha 2 to 3 times a week. Most of the users began in 7th or 8th standard. As many as 97 % of the students were aware of gutkha. Nearly 60% came to know of tobacco from school, and one third through advertisements on TV, magazines and ads painted on public buses. The authors observed that gutkha was available at roadside stands, tea stalls, cigarette shops and grocery stores and even bookshops. Above all it is conveniently priced at Re. 1, within easy reach of school children. In conclusion, the concern is that if gutkha consumption is so high among students in Punjab, the situation could be much worse in other states where religion does not play a deterrent role against tobacco use.

TUS India (1998) Pat: Tobacco use survey
Patel S, Shah R, Pati H, Gandhi P, Bhatt S, Venkur GK. **Awareness and use of substances among high school students.** Abstracts of scientific papers presented at the Golden Jubilee Annual National conference of the Indian Psychiatric Society, 1998. *The Indian Journal of Psychiatry* Vol. 40 Supplement, April, 1998.

Immediately after a 45 minute drug awareness programme, knowledge about tobacco and alcohol was assessed in 964 students studying in grades 9 to 12 in high secondary school of Baroda. It was assessed using a 20 item questionnaire administered in a classroom. A majority of the students had adequate knowledge. Incorrect responses were common regarding the following items: alcohol dependence is a disease, alcohol ensures good sleep and quitting smoking is impossible. Substance use was reported by 38 out of 964 students (3.9%) and it was limited to smoking, smokeless tobacco, alcohol and cannabis.

TUS India (1997) Kri: Tobacco use survey
Krishnamurthy S, Ramaswamy R, Trivedi U, Zachariah V. **Tobacco use in Rural Indian Children.** *Indian Pediatrics,* Vol. 34-october 1997.

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(Department of Preventive Oncology, S.S.B. Cancer Hospital And Research Center, Kasturba Medical College and Hospital)

Background: Tobacco-related disease kills an estimated half million people a year in India and most adult users start young. Objective: To assess the degree, nature and pattern of tobacco use by children in rural areas. Subjects and Methods: A Tamil, Gujarati or Kannada translation of an internationally developed English questionnaire was administered to 335 children, both school going and non students, in rural southern Tamil Nadu, rural Gujarat, and slum semiurban areas in Bangalore, Karnataka. The Chi square test for linear trend in proportions was used to test the relationship between 1) The child's awareness of the health hazards of his or her tobacco habits, and 2) the significant persons who use tobacco in the child's environment. Odds ratios of each form of tobacco use were calculated for each score of awareness.
Results: The harmfulness of smoking was better known to children (68% boys, 94% girls) than that of chewing/applying (44% boys, 63% girls) or using snuff (51% boys, 64% girls). Ignorance of harmful effects was significantly associated with smoking and snuff use. Ever smoking was associated with an increased number of adult users in the child's world. Regarding the possibility of future use of tobacco, 83% of 94 girls and 49% of 241 boys said "No" while 11% girls and 47% boys were ambivalent. Only 1 boy said "yes". Conclusion: (i) Nearly 50% of rural children, boys more than girls, experiment with tobacco, mostly as snuff (nashyna, chhinkni) even by 10 years of age; (ii) Snuff use decreases, while smoking and chewing increase with age; (iii) Smoking is better known as a health hazard than chewing or snuff use; (iv) Tobacco use by elders influences children; (v) A larger study with objectively validated answers from 6 to 20 years olds, in and out of school is needed.

TUS India (1995) Kap: Tobacco use survey

Kapoor SK, Anand K and Kumar G. **Prevalence of Tobacco Use Among School and College going Adolescents of Haryana.** *The Indian Journal of Paediatry* 1995, 62: pp 461-466.

The study is about the prevalence of tobacco use among the school- and college-going adolescents of Haryana State in northern India. 1130 male and 256 female students were given a self administered questionnaire regarding tobacco use. Ballabgarh town of Haryana and the village around Ballabgarh were studied. Children from Class VIII to XII and college students in the Arts and Commerce discipline were the subjects of this study. A total of 166 (12%) students had ever smoked. About 6% of the children in the age group 13-14 years had ever smoked which increased to around 15% among those of age 18 years or more. The prevalence in males was 14.2% compared to 2.3% in females. The prevalence of current smokers was 7.1% Smokeless tobacco use was nonexistent. Similarly there were no rural-urban differences. Majority of smokers had started the habit at 10-15 years of age, though 36% had smoked at least once before the age of 10 years. Almost 80% said that their family members disapproved of smoking. Both the smokers and nonsmokers were well aware of the adverse effects of smoking.

TUS India (1992) Vai: Tobacco use survey

Vaidya SG, Vaidya NS, and Naik UD. **Epidemiology of tobacco habits in Goa, India.** In: Gupta PC, Hamner JE III, Murti PR, eds. *Control of Tobacco-related Cancers and Other Diseases.* Proceedings of an International Symposium, TIFR, Bombay, January 15-19, 1990. Oxford University Press, Bombay, 1992, pp 315-320.
(Goa Cancer Society, Dona Paula, Goa, India)
Note: this article is cited in Traquet-Chollat C. Evaluating Tobacco Control Activities-Experiences and guiding principles, WHO, Geneva, 1996, pp 151-152, as an example of an evaluation of school interventions.

Children have been a particular target of tobacco advertising in Goa, India. Use of tobacco in different forms is very common and starts at a young age. Sweets and candies that look like cigarettes are sold in packages similar to cigarette packets. A tobacco product in paste form has been sold in toothpaste-like tubes. Called a "creamy snuff", this product is initially used as toothpaste. Because of this problem, the Goa Cancer Society conducted several epidemiological studies to determine the prevalence of tobacco habits among school-children and adults, to educate school children through a specially designed curriculum on tobacco habits and interventions, and to assess the feasibility of using schoolchildren to encourage their parents and the community in general to stop using tobacco.

Surveys The first survey was carried out from 1986 to 1987. Thirty-one schools were randomly selected from 73 villages, and self-administered questionnaires distributed to 6271 children. Information was elicited on socio demographic data, the nature of tobacco habits, the age of starting to use tobacco, and the possible influence of parents and family members. About 13.4% of boys and 9.5% of girls used tobacco, mostly of the smokeless variety. They began use as early as five years of age and most were introduced to tobacco use by family members and friends. The second survey was carried out the following year on persons aged 15 and over. A house-to- house survey was carried out on a 40% systematic sample from the 73 villages in the first survey. Information on age, sex and tobacco use was collected on 29,713 individuals. The results showed that 33% of men and 20% of women used tobacco.

Interventions Following these two surveys, education about tobacco habits and interventions was given to students in 46 selected villages. Class teachers were given a three-hour training course. A sample of 448 boys and 338 girls from the intervention areas were interviewed again and were compared with a sample of a similar number of boys and girls from the non-intervention areas. At the same time as the school-based intervention, information on tobacco was also distributed to the community by multipurpose health workers and Anganwadi (child welfare) workers. The main measures used were assessment of cognitive and attitudinal changes towards tobacco use following the school health intervention, and the cessation rate among adults who were influenced by the children in the community. (The study did not, however, make clear which were the results of the school health education and which were attributable to the community-based intervention of the Anganwadi). Children who received health education on tobacco and intervention methods were instrumental in achieving a stoppage rate of 9.7% among adults. Moreover, there was a significant difference in

attitude among children who had been given the programme, compared with the control group. The former group developed a negative attitude towards tobacco. The investigation focused on the importance of including health education material on tobacco in school curricula. It highlights the findings that such material is useful in shaping children's attitudes towards tobacco and in conveying the intervention messages to their parents.

TUS India (1991) Jay: Tobacco use survey
Jayant K, Notani PN, Gulati SS, Gadre VV. **Tobacco usage in school children in Bombay, India. A study of knowledge, attitude and practise.** *Indian J Cancer* 1991 Sep;28(3):139-47.
(Cancer Research Institute, Parel, Bombay, India)

A study of knowledge, attitudes and practice with regard to tobacco usage was conducted among 1278 boys and 353 girls studying in the final year in various schools in Bombay. The proportion of boys using some form of tobacco (including experimenters/triers) was significantly higher in private English medium schools (22.5%) than in private Indian language schools (6.9%) or municipal Indian language schools (13.8%). There was also a significant difference between the two types of Indian schools. The only girls in the study were from Indian language schools and the proportion of tobacco users was very low (1.1%). Most (86%) boys who used tobacco were smokers. Hence the detailed analysis is restricted to smokers. Several probable factors influencing smoking behaviour were studied. It was found that a significantly higher proportion of boys smoked if their father or best friend smoked. Generally boys were more sensitive to best friend's or elder brother's disapproval than to parental. They were well informed about harmfulness of smoking but knowledge about specific health hazards was limited. Most of them had a positive attitude towards nonsmoking and smoking control programmes. Tobacco use has been proven to be a major health hazard. Although its use in adults in India is common, prevalence in adolescents in urban schools is not yet high. Before the situation changes we need to mount anti-tobacco educational programmes and work towards a non-tobacco generation to contain the harmful consequences of tobacco usage.

TUS India (1989) Vai: Tobacco use survey
Vaidya SG and Naik UD. **Study of Tobacco Habits in School Children in Goa.** In: Sanghvi LD and Notani PP, eds. *Tobacco and Health: The Indian Scene*. Proceedings of the UICC workshop, 'Tobacco or Health', April 15-16, 1987. Tata Memorial Centre, Bombay, 1989, pp 169-173.

Children notice everything that happens around them, very often without knowing the significance, but which has profound influence on their behaviour later, when they group up. There is hardly a child who does not know the smoking and chewing habits of their parents and teachers and there is hardly any parent or teacher who knows the tobacco or for that matter probably any other habits of their children or wards. A survey conducted in nine schools in villages of Goa, India covering 1668 children by self-administered

structured questionnaire revealed that 18% were tobacco habitués. The prevalence of tobacco habits was higher in boys (22%) than in girls (13%). The common habits were the use of "mishri" or "masheri" (i.e. roasted and powdered tobacco rubbed over the gums with the index finger) and "creamy snuff" toothpaste. While 84% (256) of the habitués had a single habit, 12% and 4% had double and triple habits respectively. The mean age of acquiring the habit was 11.9 years. Almost 75% of the habitués stated family influence as the most common influencing factor.

TUS India (1987) Moh: Tobacco and other drug use survey
Mohan D et. al. **A multicentred study of drug abuse among students** (sponsored by the Ministry of Welfare, Government of India). Preliminary Report, AIIMS, New Delhi 1987.

This study found that among males, the most commonly abused psychoactive drug was alcohol (58.5%), followed by tobacco (19.3%) and opium (6.3%). Tobacco and alcohol are two major sources of revenue for the government and are actively promoted by companies that process or produce them.

1.2.2 Global Youth Tobacco Surveys in India

WHO and CDC developed the Global Youth Tobacco Survey (GYTS) to track tobacco use among youth across countries using a common methodology and core questionnaire, allowing comparability across surveys. The GYTS surveillance system is intended to enhance the capacity of countries to design, implement, and evaluate tobacco control and prevention programs. Funding for the GYTS has been provided by the Centers for Disease Control and Prevention, Canadian Public Health Agency, National Cancer Institute, UNICEF, and the World Health Organization-Tobacco Free Initiative. The Tobacco Free Initiative (TFI) of the WHO and the CDC also provide technical assistance to the GYTS.

"Fact sheets" are available for India, summarising major findings of the surveys completed so far in 19 states/cities. Prevalence of tobacco use ranges from 4 percent to 63 percent among the full student samples; from 6 percent to 69 percent among boys, and from 2 percent to 56 percent among girls. Prevalence rates, and the percent of students who smoke but said they wanted to stop, are summarized below. The website for the factsheets: http://www.cdc.gov/tobacco/global/GYTS.htm

State/city	% students who use tobacco (all forms)	% girls	% boys	% smokers who would like to stop
Arunachal Pradesh	50	54	44	60
Assam	36	45	25	67
Bihar	59	61	51	67
Central Bihar	11	10	3	67
Culcutta	18	19	15	48
Delhi	5	6	3	No data
Goa	5	6	3	No data
Maharashtra	13	13	11	No date
Manipur	62	74	47	22
Meghalay	44	58	32	59
Mizoram	54	58	49	85
Mumbai	4	6	2	81
Nagaland	63	69	56	81
Navoday	11	13	8	92
Rajastan	18	22	10	71
Sikkim	55	68	38	27
Tamil Nadu	7	8	5	73
Tripuna	44	50	37	33
West Bengal	15	17	8	76

Source: GYTS surveys, accessed on-line http://www.cdc.gov/tobacco/global/GYTS.htm

About the GYTS Survey:

Methodology

- School-based survey of students aged 13-15 years
- Can include public and private schools
- Multistage sample design with schools selected proportional to enrolment size
- Classrooms chosen randomly within selected schools
- All students in selected classes eligible for participation
- Anonymous and confidential self-administered questionnaire
- Computer-scannable answer sheets
- Requires only 30 - 40 minutes to administer
- Fieldwork conducted in 6 - 8 weeks
- Country-level data with regional level stratification possible
- Core questionnaire
- Country may add questions to the questionnaire

The GYTS Questionnaire is composed of "core" country-approved questions designed to gather data on seven topics:

Prevalence of cigarette smoking and other tobacco use among young people

- How many young people have experimented with smoking cigarettes or use other forms of tobacco products

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- The age at which young people begin cigarette smoking
- What brand of cigarettes young people smoke
- Where young people usually smoke

Knowledge and attitudes of young people towards cigarette smoking

- The strength of intention to remain nonsmokers among young people who never smoked (index of susceptibility)
- What young people perceive to be the social benefits and the health risks of smoking cigarettes
- The extent of peer pressure on young people to begin cigarette smoking

Role of the media and advertising on young people's use of cigarettes

- How receptive young people are to cigarette advertising and other activities that promote cigarette use
- Awareness and exposure of young people to antismoking messages

Access to cigarettes

- Where young people usually get their cigarettes
- Whether sellers refuse to sell young people cigarettes because of their age
- How much money young people spend on cigarettes

Tobacco-related school curriculum

- What young people were taught in school about tobacco
- Young people's perceptions of their school's programs to prevent cigarette use

Environmental tobacco smoke (ETS)

- The extent of young people's exposure to smoking at home and in other places
- Young people's perceptions about the harmful effects of ETS

Cessation of cigarette smoking

- The short- and long-term likelihood that young cigarette smokers will quit.
- For surveys in India, the core questionnaire was expanded to include bidi smoking and smokeless tobacco use.

TUS India (2003) Sin: GYTS surveys

Sinha DN[1], Gupta PC[2], Pednekar MS.[2] **Tobacco use among students in Eight North-eastern states of India.** *Indian Journal of Cancer* 2002; 3:1-45.

([1] School of Preventive Oncology, Patna, India; [2] Tata Institute of Fundamental Research, Mumbai, India)

Objectives: To obtain baseline information about prevalence of tobacco use among school children in eight states in North-eastern part of India. Methods: A two-stage probability sample of students in grade 8-10 corresponding to 13-15 years of age was selected in each of the states and surveyed through anonymous, self-administered questionnaire. Results: Among the sampled schools, the school response rate was 100% in all states except Tripura (92%) and Meghalaya (96%). Over 80% of the eligible students participated in the survey. Among the respondents, the proportion of boys ranged between 50%-55%. The range of ever tobacco use was from 75.3% (Mizoram) to 40.1% (Assam). Over 65% users reporting initiation at 10 years of age or earlier in all states except Mizoram (23.1%). The range of current tobacco use (any product) ranged

from 63% in Nagaland to 36.1% in Assam. Current smokeless tobacco use ranged from 49.9% in Nagaland to 25.3% in Assam. Among the North-eastern states, Mizoram reported the highest smoking (mainly cigarette) prevalence (34.5%) and Assam reported the lowest smoking (mainly cigarette) prevalence (19.7%). Smoking among girls (8.3%-28.2%) was found to be high in North-eastern India. Cigarette smoking (8.6%-23.1%) was the most preferred form of smoking among students in all North-eastern India. Over half of cigarette smokers (53.2%-96.3%) and a high proportion of smokeless tobacco users (38.5%-80.8%) reported feeling like having tobacco first thing in the morning. Conclusions: Tobacco use including smoking was very high, even among girls, in all eight states in the North-eastern part of India. Signs of tobacco dependency were already visible in these students, more among those who smoked.

TUS India (2001) Ose: Review
Osei MR and Karki YB. **The Tobacco Smokescreen Victims: Women and Children.** *Lifeline,* October 2001: 6: 1-5. WHO SEARO, New Delhi, India.

This short report summarizes prevalence data for India and other countries in the region, and summarizes the results of Global Youth Tobacco Survey from 7 states in India and compares the data with the GYTS from Sri Lanka and Indonesia.

1.3 College students

Four studies are summarized here, one is an unpublished thesis on college students' tobacco use in Karnataka, the next two were done to form the basis for a tobacco control programme in colleges of Maharashtra and Andhra Pradesh respectively, with the former mainly looking at smokeless tobacco and the latter looking only at smoking.

TUS India (2003) Ano: News articles report on tobacco use survey
Anon. All smoke and no hope in sight. Times of India, May 29, 2003
http://timesofindia.indiatimes.com/cms.dll/html/uncomp/articleshow?xml=0&artid=47806294

The articles refers to a study of trends of tobacco consumption by 800 young collegians, conducted by the Consumer Education and Research Center (CERC). It cites the S Yellore, Director, Torch division of CERC as saying that the study finds two main reasons for students becoming addicted to tobacco – peer pressure and the influence of movies and television, and that "most believe "it wont happen to me".

TUS India (1999) Nic: Tobacco use survey
Nichter SM, Nichter M, Sickle DV. **Tobacco use among male college students in Karnataka.** (unpublished) Submitted to Social Science and Medicine as: Prevalence and Patterns of tobacco use among college students in South India.
(University of Arizona, Department of Anthropology, Tucson, Arizona)

The objective of this research was to study the use of tobacco, smoking and gutkha among college students in Karnataka. A sample of 1,606 male students whose mean age was 20 years was interviewed. Various aspects of tobacco use like prevalence of smoking and gutkha usage, age of initiation, use across religious groups, types of tobacco products, reasons for tobacco use, perceived benefits of smoking cigarettes, social and family influences and perceptions of addiction and advertising were studied.
Some of the major findings of this research were that 36% had ever tried smoking and 18% had ever tried chewing gutkha. A quarter of those who had ever tried cigarettes were daily smokers and another quarter were occasional smokers. The rest had either quit or only experimented a few times. Among youth who smoked 5-6 cigarettes per day, about half of these cigarettes were smoked alone. The mean age of initiation for smoking cigarettes and chewing gutkha among college students was about 17 years. Over 80% believed that cigarette smoking was increasing among boys. Students thought that smoking could relieve tension and boredom and give a kick.

TUS India (1998) Han: Tobacco/pan masala use survey

Hans G. **Prevention of Cancer in Youth with Particular Reference to Intake of Paan Masala and Gutkha.** NSS Unit, TISS, Mumbai, India, 1998.

This is a report of inputs provided by the Tata Institute of Social Sciences to sensitize National Service Scheme (NSS) officials and peer educators about the hazards of paan masala and gutkha addiction, as to motivate and enable them to initiate prevention campaigns through NSS. It also has a section to help readers understand the problem. The document includes a report of the study conducted by the author, on paan masala and gutkha addiction amongst students in Maharashtra state. The study is exploratory in nature covering 20 Principals and 1200 students from junior and degree colleges. Colleges communicate clear disapproval of smoking, but not of paan masala or gutkha use. The study identifies misinformation about the effects of these products amongst the Principals, and notes the need to inform them better about these threats to young people's health. Amongst students, addiction to the following forms of tobacco intake was: Cigarettes (smoking): 10.6%, Tobacco Chewing- 6.7 %, paan masala- 9.9 %, and gutkha- 9.6%. Of those who took these products, very few were addicted to a single product - 15 % of those who smoked, 2 % of those who ate paan masala, 13 % of those who ate gutkha and 14 % of those who chewed tobacco in other forms, were addicted to a single product, while the remaining used other forms of tobacco, alcohol and beer. While paan masala/gutkha addiction is found in both rural and urban areas, it appeared to be greatest in small towns followed by villages. Male students spent more on these products than females. The study also confirmed that male students got more pocket money, thus giving them more opportunity to buy these products if they wanted to. The study recommends a peer approach to counter peer pressure. Eighty per cent of students were not addicted to any substance, and three fourth of students who did use various substances said that they did so for fun or enjoyment. These finding hold much potential for a peer-based strategy.

TUS India (1991) Gav: Tobacco use survey
Gavarasana S, Doddi VP, Prasad GV, Allam A, Murthy BS. **A smoking survey of college students in India: implications for designing an antismoking policy.** *Jpn J Cancer Res* 1991 Feb;82(2):142-5.
(Lions Cancer Treatment & Research Centre, Visakhapatnam, India)

A survey of 599 college students was conducted in Andhra Pradesh, India, to help formulate an anti-smoking policy for youth. There were 64.6% boys and 35.4% girls between 15 and 22 years, and 8.2% of students (n = 49, 48M + 1F) who were smokers. It is taboo for girls to smoke. There is no current anti-smoking policy and one is proposed based on the smoking survey results. The policy includes parental pressure to curb smoking, and a ban on (1) advertising of tobacco products, (2) smoking in public places and (3) teachers smoking in school. A majority of the students expressed approval for an increase in the price of cigarettes. The survey revealed a gap in the knowledge of students about the ill effects of smoking, which can be rectified by health education programs.

1.4 Health professionals (including medical and dental students)

Of these seven studies, four examined medical students and one, dental students, one surveyed medical school students, faculty and practitioners, and one focused on physicians at a conference. Three of the studies were conducted in Patna; and one each in Surat, Kanpur and Chandigarh, and the other had a national sample. Tobacco use in Patna students was particularly high (around half) and was reported to have increased over the years. Smoking was mainly confined to males. Two studies linked tobacco smoking to emotional problems. The different definitions of tobacco use – occasional and regular – make comparisons difficult.

TUS / Circ India (2001) Gup: Survey
Gupta A, Gupta R, Lal B, Singh AK, Kothari K. **Prevalence of coronary risk factors among Indian physicians**. *J Assoc Physicians India*. 2001 Dec;49:1148-52.
(Government ESI Hospital, Jaipur.)

Of 1,000 physicians attending a national conference, 256 agreed to participate in a survey to determine risk factors. Smoking or tobacco use was seen in only 5 participants, all males (2.3%).
(For full abstract, see Circ / TUS India (2001) Gup: Survey)

TUS India (2001) Sin: Tobacco use survey
Sinha DN, Gupta PC. **Tobacco and areca nut use in male medical students of Patna.** *Natl Med J India* 2001 May-Jun;14(3):176-8.

Assessment of the use of tobacco and areca nut products among medical students is important because of the impact of the example they will set for their patients as future

care givers. A tobacco use survey was conducted during July to October 1998 among male medical students of the Patna Medical College and Hospital. Of the 509 male students, 400 (93.2% - Editor's comment: must be a typo in either number or %) responded to the questionnaire (mean age: 20.4 years). Questions on tobacco use included the age and school class level at initiation, the type of products used, frequency of use and knowledge of their harmful effects. Questionnaires were distributed in the classrooms and absent students were interviewed in their hostels. Responses on habits were confirmed by third persons. Only 18.8% were non-users, 43% were regular users and 0.7 % were regular areca nut users. In addition, 9.2% were occasional tobacco users and 27.5% were occasional areca nut users. Awareness of product-specific ill effects of use were known to less than 13% of first, second and third year students. In the fifth year this rose to 67 %. Awareness of the ill effects of smokeless tobacco and areca nut products was much lower than knowledge about smoking. Year of initiation peaked at class ten. No student reported initiation during the fifth year of medical school, but some had started during the fourth year. Compared to an earlier survey conducted in 1970, the proportion of regular tobacco users had remained constant around 43%, but chewing habits had increased while smoking had decreased. There was also an additional 36% of occasional users (mostly of areca nut containing products). The increase in regular and occasional use of chewing products was due to a high use of manufactured smokeless tobacco (gutkha, which contains both tobacco and areca nut) and areca nut products (pan masala). Interventions at school and college level designed to prevent medical students from using tobacco and areca nut will impact the future of the health system and the nation's health.

TUS India (2001) Sin: Tobacco use survey

Sinha DN, Gupta PC, Pednekar MS, Singh JP. **Tobacco use among students of Patna Dental College – Bihar.** *Lifeline*. Vol. 6 – October 2001,11-12.
(School of Preventive Oncology, Patna, India, & Patna Dental College, Patna, India)

A study was conducted to ascertain the extent of tobacco use among students of the Dental College in Patna. During the academic year 2000-01, amongst the total of 88 students, 67 responded to a self-administered, structured questionnaire anonymously. Among the 41 male respondents, 65.9% reported current tobacco use and 26.8% past use. Among the 26 females, 38.5% reported current use and 11.5% past use. Current use was higher amongst senior students and higher age groups compared to junior students. Smokeless tobacco is almost as popular among girl students as among boys, while the higher level of tobacco use among boys is mainly due to cigarette smoking. Dentists from Patna Dental College, with its high prevalence of tobacco use, would be unlikely to counsel their patients against using tobacco, a major determinant of oral health status. There is a need for an in-depth study of tobacco use among students, and a review of the content and quality of the dental curriculum to highlight the hazards of tobacco and enhance the knowledge of the teachers and students on this topic. Also, specific interventions that will help prevent tobacco use among dental students are urgently required.

TUS India (1998) Sin: Tobacco use survey with psychological analysis

Singh RK. **To study the relation between tobacco smoking and adjustment among MBBS male students**, in *The Asian Journal of Psychology and Education*, 1998 June;31(3-4): pp 30-32.

The aim of the study was to explore psychological factors related to adjustment of M.B.B.S. male students of Patna and Gaya medical colleges. One hundred fifty students were selected randomly, of whom seventy-five were tobacco smokers and seventy-five were non -smokers. The results showed that smokers had poor adjustment in the area of home, physical health, social and emotional health and they also differed from nonsmokers in personal life.

TUS India (1994) Zul: Tobacco use survey

Zulfikar AR, Vankar GK. **Psychoactive substance use among medical students**, in *The Indian Journal of Psychiatry* 1994;36(3):pp 138-140.

Using a standard epidemiological survey instrument for psychoactive drug use, 215 medical students in three classes from Medical College, Surat were studied. One third of all students reported non-medical drug use. The substances ever used were: betel nut 13%, smokeless tobacco 3%, cigarettes 12%, alcohol 13.5%, cannabis 0.9% and benzodiazepines 3.7%. Use during the last month was reported for four substances and daily use was reported for cigarettes only (3.2%). Cigarette and benzodiazepine use mostly began after entry to medical college. Men and final year students had higher prevalence of drug use.

TUS India (1990) Sar: Tobacco use, knowledge and attitude survey

Sarkar D, Dhand R, Malhotra A, Malhotra S, Sharma BK. **Perceptions and attitude towards tobacco smoking among doctors in Chandigarh.** *Indian J Chest Dis Allied Sci* 1990 Jan-Mar;32(1):1-9.

(Department of Internal Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh)

Two hundred and eighteen randomly selected doctors drawn from among the faculty and students of Postgraduate Institute of Medical Education and Research; Interns and staff at the General Hospital; and General practitioners of the Chandigarh city, were administered a structured questionnaire. Among them 31.6% were current smokers whereas 23.3% had stopped smoking (ex-smokers). All but one of the smokers were men who smoked cigarettes. Spirit of experimentation and peer influence were important initiating factors whereas the habit was continued mainly to concentrate on work/study. Doctors were uniformly aware of the detrimental effects of smoking, particularly its association with lung cancer, chronic bronchitis and coronary artery disease, and this was the major reason for their abstaining or wanting to quit the habit. The relation of smoking with oral cancer, laryngeal cancer, emphysema and peripheral vascular disease was not well appreciated. Counselling patients about hazards of smoking was practised significantly

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less often by smoking doctors and surgeons. The options favoured by doctors for preventing smoking included a ban on tobacco advertising, specific health warning on cigarette/bidi packs, and restriction of smoking in public places, particularly hospitals and clinics.

TUS India (1990) Tan: Tobacco use survey
Tandon AK, Singh SK, Chandra S. **Psychosocial study of Cigarette Smoking.** *Indian Journal of Psychiatry* 1990;32(2):pp 159-161.

The study was carried out to assess the smoking habit among medical students and its relationship to demographic, social and psychological characteristics. The study was carried out on the students of G.S.V.M. Medical College, Kanpur. A questionnaire was given to all 1293 students; 854 (733 male and 121 females) responded adequately. There were 263 (30.79%) smokers (6 females), and 591 non-smokers (115 females). Socio economic factors did not differentiate the two groups. The two groups were similar except that the married group had more male smokers (44.3%) than the unmarried group (29.1%). Thirty-nine students (16.15%) of 1st year, 63 students (26.59%) of 2nd year and 69 students (43.1%) of final year were smokers, as well as 12 interns (46.1%) and 80 post-graduates (42.8%). Among smokers 116 (77.3%) had a family history of smoking whereas in 147 (20.9%) there was no family history of smoking. The percentage of mild smokers (using fewer than 5 sticks per day) was 63.5% whereas heavy smokers (more than 10 sticks per day) was 16.3% and the rest were moderate smokers (6-10 sticks per day). The highest mean duration of smoking was found among the P.G. students, followed by interns. As many as 34.3% said they smoked because of failed relationships with a friend and only 8.5% associated it with failure in examination. Alertness was felt after smoking by 33.2% of smokers and increase in concentration power was felt in 28.3% of cases. The percentage of mild smokers was highest in first year students and minimum in senior students. The highest percentage ascribed smoking to being unhappy without any justified cause (30.89%) in moderate smokers, and (13.17%) in the mild smokers. No consistent pattern of psychological state could be obtained in smokers.

1.5 Education personnel and other professional groups

These articles include one on personnel in schools and two on university personnel, and one on media professionals. Tobacco use is high among adults who have daily contact with students, and among people who influence public opinion.

TUS India (2002) Sin: Tobacco use survey
Sinha DN, Gupta PC, Pednekar MS, Jones JT, Warren CV. **Tobacco use among school personnel in Bihar, India.** *Tobacco Control* 2002;11:82-85
(School of Preventive Oncology, Patna)

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The article (published as a letter) describes the Global School Personnel Survey (GSPS) conducted in Sept-Oct 2000 in Bihar. The objectives of this cross sectional survey were 1) to obtain baseline information on tobacco use, 2) to evaluate the existence, implementation and enforcement of tobacco control policies in schools, 3) to understand knowledge and attitudes towards tobacco control policies, 4) to assess training and material requirements for implementing tobacco prevention and control interventions and 5) to verify some information obtained from the Global Youth Tobacco Survey. Out of 697 eligible school personnel, 637 participated. Prevalence of smoking among women was 31% and 47.4% among men. Almost all school personnel (91%) agreed that tobacco was addictive and 83% said that it had serious health consequences. Everyone replied, except two, that there was no policy on tobacco use either for students or personnel. Also a large proportion (90.4%) wanted a policy prohibiting tobacco use by students and surprisingly even more wanted a policy prohibiting tobacco use among school personnel (93.9%). Another striking finding was that 80% wanted tobacco companies not to sponsor sports events and 95% wanted a complete ban on tobacco advertisements. Surprising, even though a majority were tobacco users, 78.4% agreed with the need to increase prices of tobacco products, with no difference between users and non users. The findings dispel the myth that Indian women do not smoke. They show encouraging support for measures to reduce tobacco use, even among smokers.

TUS India (2000) Sin: Prevalence survey
Sinha DN, Gupta PC. **Tobacco Use Among Media Personnel In Patna.** *Lifeline*, May 2000, 8: 5-6. WHO SEARO, New Delhi, India.

This pilot study looks at tobacco use among media personnel, hypothesizing that it may influence their coverage of tobacco and its control. The study site is the largest of the 6 or 7 major printing establishments in Patna, the Aryavarta Press. Employees were trained to help conduct a survey, using a self-administered survey questionnaire. The response rate was 81% (300/370 employees; most non-respondents were on leave). Information was checked with a pan and tobacco shopkeeper at the entrance to the organization, and by asing staff about tobacco use by their colleagues. 89% of respondents used tobacco: 30 smokers (10%), 156 (52%) chewers and 81 (27%) smoked and chewed. Nearly 58% of respondents knew that tobacco was not good for health; 35% knew it caused cancer. But 7% were completely unaware of the health consequences of tobacco use. Most (56%) spent less than Rs. 1,000 per year on tobacco products, 21% spent more than Rs. 5,000. Work continues to examine the relationship between use and reporting on tobacco.

TUS India (1997) Kum: Tobacco use survey with sociodemographic analysis
Kumar A, Mohan U, Jain VC. **Influence of some socio-demographic factors on smoking status of academicians.** *Indian J Chest Dis Allied Sci* 1997 Jan-Mar;39(1):5-12.
(Upgraded Dept of Social and Preventive Medicine, KG Medical College, Lucknow.)

Among many habits of life style, smoking is one which is acquired by children during their years at school, and teachers may exert an influence on their students' attitudes and behaviour. To monitor smoking habits of teachers, 573 teachers of Lucknow University were surveyed with the help of a questionnaire based on WHO guidelines. Overall, 21.4% and 12.3% of male teachers reported themselves as current and ex-smokers respectively. None of the female teachers admitted to being a smoker. Significantly higher prevalence of smoking was observed among teachers of sixth decade, Muslims and unmarried. Engineering faculty had the highest proportion (30.2%) of current smokers followed by medicine (25.2%). The study also found a significant association between smoking in teachers and the smoking status of their parents, siblings, children and best friends. There is a need to create smoking cessation opportunities for teachers so as to establish a non-smoking environment in the schools and colleges.

TUS India (1997) Yun: Tobacco use survey
Yunus M, Khan Z. **A baseline study of tobacco use among the staff of Aligarh Muslim University, Aligarh, India.** *J R Soc Health* 1997 Dec;117(6):359-65.
(Dept. of Community Medicine, J N Medical College, Aligarh Muslim University, India)

A cross-sectional survey of 2,439 university employees and research scholars was carried out using a questionnaire. The objective was to assess the prevalence and type of tobacco use and to collect background data for planning health education programmes. The overall prevalence of tobacco use was 51.5% among males and 30.3% among females. There were no female smokers, the preferred habit of tobacco use among women being chewing. Prevalence of smoking was significantly higher among non-teaching staff. Among females, the prevalence of tobacco chewing was higher in non-teaching staff members. Tobacco use (smoking and other forms) rose with age. However, even at 20-30 years of age 25.4% of males were addicted to smoking. Most--60.6%--had smoked for more than 10 years. Among staff members (both teaching and non-teaching) the reason for smoking was either to relax or because of addiction, whereas the research scholars smoked to improve their image or for enjoyment/pleasure. The reasons given by users of other forms of tobacco were boredom, to pass the time or for no reason at all. Among non-users, the majority were aware of the harmful effects of smoking. Family pressure and traditions were also important reasons for not smoking.

1.6 Non-student youth

Two articles find higher tobacco use among non-student youth than among students, a third finds high prevalence of smoking and other risky behaviors among working youth, and very low knowledge of the risks.

TUS India (1993) Ban: Tobacco use survey with psycho-social analysis
Bansal Raj K, Banerjee S. **Substance use by child laborers.** *The Indian Journal of Psychiatry* 1993;35(3):pp 159-161.

The study highlights substance use patterns in 300 randomly selected child laborers aged 5-15 years, from 6 slums in Surat city. It identifies the micro-social and macro-social stressors, which initiate and perpetuate their substance use. It observed that 135 (45%) of the child laborers had used some substance, with a mean of 1.5 substances used per child. Tobacco smoking was the most common form of substance abuse followed by tobacco chewing, snuff, cannabis and opium. The author notes that most studies carried out so far in India have focused on substance abuse by young adults and college students. Scant attention has been paid to the various psychosocial aspects of children and adolescents who are increasingly using substances earlier, due to the changes caused by industrialization, urbanization and resultant adverse effects in the environment (WHO 1979 and 1986). This study found that the commonest reason for substance use was curiosity or experimentation. Substance abuse is known to be a psycho-social problem of multi-factorial nature, and this study found that unfavorable psychosocial environmental factors like urbanization, low socio-economic living conditions, educational and recreation deprivation, work load, low pay etc. played a significant role in substance abuse.

TUS India (1992) Ban: Random survey

Bansal RK. **Sexual behaviour and substance use patterns amongst adolescent truck cleaners and risk of HIV / AIDS.** *Indian J Matern Child Health.* 1992 Oct-Dec;3(4):108-10.

This study was conducted at transport nagar in Indore, a major industrial and commercial center of Madhya Pradesh. Usually each truck has a staff of 3, comprising 1 senior driver, 1 junior driver, and a cleaner, usually a child or an adolescent. 210 such adolescent truck cleaners were surveyed by random sampling of the parked trucks present in the transport nagar. A semi-structured questionnaire was administered to these adolescents using the oral interview technique. The age distribution of the adolescents indicated that 17 were 15-16 years old, 63 were 16-17, 61 were 17-18, and 69 were 18-19. When the income was low, the owners or the senior drivers provided meals and minor expenses. 80% of the adolescents were illiterate, 10.5% were literate, 6.2% had primary education, and 3.3% had middle school education. 88.1% of the cleaners were away from home for 24-28 days a month, 7.1% for less than 24 days, and 4.8% for over 28 days. 25.2% of the cleaners had a history of sexual activity, commonly with prostitutes. 88.6% of the senior drivers regularly visited prostitutes, and in many cases the adolescents' payment to the prostitute was financed by the senior driver. 94.3% of these adolescents had engaged in unprotected sexual intercourse, and the remaining 5.7% had used condoms infrequently. 98.5% of them had not heard of HIV and AIDS. 4.3% had a history of sexually transmitted diseases and had been treated by general practitioners. Substance abuse was fairly common among these young people (140 smoked, 9 chewed tobacco, 2 used opium, and 2 used alcohol more than twice per week), and the cost for those substances was primarily met by the senior truck driver or the owner. The trend was similar for sexual activity, as 25.2% had engaged in sex (12.9% once, 7.1% twice, and 5.2% several times).

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Special programs are required for these adolescents to educate them about the risks of unprotected sex and drugs in order to prevent them from contracting HIV/AIDS.

TUS India (1989) Gup: Tobacco use survey
Gupta R, Narang RL, Verma S, Panda JK, Garg D, Munjal A, Gupta KR, Gupta A, Kumar A, and Singh S. **Drug abuse among non student youth labour,** in *The Indian Journal of Psychiatry*, Oct 1989, 29 (4), pp 559-362.

This is a study of 257 non-student youth from Ludhiana district, aged 15 to 24 years. It looks at socio-demographic variables, and extent and frequency of drug abuse. By vocation they were: factory workers (121), rickshaw pullers (102) and railway coolies (34). Details of drug use show that tobacco (60.31%) was most frequently used, followed by alcohol (51.36%). Common reasons for use were curiosity, to keep awake or alert, to overcome boredom and to celebrate social occasions. This finding of this study of non student youth corroborate the study of students by Mohan et al. (1978) which reported that tobacco was the most commonly reported substance used followed by alcohol, for a student population. Varma et al. (1979) reported that next to alcohol, tobacco was the drug most used by students.

1.7 General population

Articles in this section report on tobacco habits in the general population.

TUS India (2002) Ban: Exploratory study
Bansode NN. **An exploratory study on gutkha and smokeless tobacco consumption.** *Nurs J India.* 2002 Jun; 93(6):127-8.

(no abstract available)

TUS / ECON India (2002) Gup: Analytic report
Gupta I, Sankar D. **Tobacco Consumption in India: A fresh look using the National Sample Survey.** Discussion paper no. 47/2002, *Institute of Economic Growth,* Delhi. (Institute of Economic Growth, University Enclave, Delhi-110 007, India)

Reports prevalence for rural and urban households, men and women, and by age group, socio-economic category and State. For abstract, see ECON / TUS India (2002) Gup: Analytic report.

TUS India (2002) Sen: Prevalence survey
Sen U. **Tobacco Use in Kolkata.** *Lifeline*, May 2002, vol 8:7-9. WHO SEARO, New Delhi, India.

(Dept of Epidemiology and Biostatistics, Chittaranjan National Cancer Institute, Kolkata, India.)

A multi-stage cluster sample survey of 100 respondents from each of 60 clusters (total sample of 12,000) of adults (over 18 years) was carried out in Kolkata. Data were collected on demographic and socio-economic characteristics and tobacco use, using standard WHO definitions. Among men, 28% smoked and 36% chewed tobacco, amond women there were 0.5% smokers and 19% chewers. One third of men said they began tobacco use before age 20, 8% between 20 and 30, and a surprising 60% after the age of 30. Initiation age was much younger among smokers: 60% began before the age of 20, and only 8% after the age of 30 years. Tobacco use prevalence (all forms) was highest in the 30-50 age group. Smoking was strongly correlated with socio-economic group: prevalence was 50% among the lowest groups, 36% among the middle groups and 14% among the highest groups. An education gradient was also found, with 47% of respondents who were illiterate or had only informal or primary level education being smokers, and 27-26% smoking prevalence among those with middle-level or more income, but no difference between those with a middle-level education and graduates. Chewing was found much more among lower income people.

TUS India (2000) Ann: Opportunistic consumer survey

Annigeri, VB. **Tobacco Related Diseases: So Far So Bad.** Dharward, Karnataka, 2000. Working Paper No. 5. Part of the research project on "*Economics of Shifting from Tobacco Cultivation, An Action research Project*". Centre for Multi-Disciplinary Development Research, Dharward, Karnataka, 2000.

This 25 page working paper reports on a survey of 500 consumers of tobacco, half from rural areas in the Nippani belt of Belgaum district in Karnataka state, and the other half from taluka headquarters, to represent urban areas. An opportunistic sampling method was used, in which investigators approached people who were leaving places where they had just bought tobacco products, and went home with them to collect data on the person and they family members. The following data were collected:

Social category	cigarettes	Bidi	Gutka	Raw tobacco	snuff	Total
Scheduled castes	14	22	24	39	1	100
Scheduled tribes	8	26	23	42	1	100
Others	10	20	26	43	1	100

The data are also presented by age and gender, education. Tobacco was found to account for just over 7% of all household expenditures in the survey. The most common reasons given for using tobacco was the influence of friends (54%) and that parents and other family members used tobacco (26%). A regression was run to try and explain the number of years of tobacco use, as a function of sex, age, caste, education, occupational

status, expenditures on tobacco as a percent of total consumption expenditures, frequency of consumption and self-rated health. In all cases, age dominates (as would be expected, since the dependent variable is expressed in years of use); this is not the standard way of specifying a regression equation to explain consumption.

The introduction describes the varieties of tobacco, the steps involved in cultivation and curing, and key economic facts on tobacco production, export and taxation in India, as well as the patterns of consumption. It lists the diseases associated with tobacco use, and summarizes some of the epidemiological literature from India and elsewhere.

TUS India (1998) NSS: Population survey data

National Sample Survey Organization (NSSO): **A Note on Consumption of Tobacco in India: NSS 50 Round (1993-94).** *Sarvekshana,* January-March 1998, pp. 76-89. Journal of NSSO, Department of Statistics, Ministry of Planning. Government of India.

This report releases data on tobacco consumption habits of the Indian population as distinct from data on the quantity and value of tobacco consumption, which was released in an earlier issue of the journal (see: ECON India (1996) NSS: Analytical Report). The NSS asked members of each of 115,354 households about four types of tobacco use: smoking, chewing, snuff, and use of burnt tobacco powder or paste. They were asked whether they consumed tobacco in any of the four forms, and if so, whether their use was regular or casual (occasional). The answers were used to generate estimates of prevalence of each type of tobacco use, in rural/urban areas, and in each state and union territory of India, and compared to similar data from the 43rd round survey done in 1987/88.

TUS India (1997): Descriptive report

Types of tobacco used in India and its origin. *Anubhav*: Monthly on Social Issues, Dec. 1997, vol.1, issue 9, pp 9-11, Yuva, Pune.

Observing that the Portuguese traders introduced tobacco in India in the late 16th & 17th Century, this article describes briefly the varied forms of its use, reasons and the present scenario. In smoked form-cigarettes, *bidis, cigar, cheroot, chuttas, dhumti, hookli, chilum* and *hookah* are in use. Smokeless tobacco is being used in the form of *paan* with tobacco, *paan masala, gutkha, mainpuri* tobacco, *Mawa,* tobacco-lime preparation, application- *Mishri, bajjar, Gadhaku,* red tooth powder and creamy stuff. In India, there are various reasons for the use of tobacco. Many women say that they use tobacco to relieve teeth-related complaints. Among men the most important reason is peer group influence. Paan masala and gutka are very convenient to carry and are easily available at low cost even in remote villages; important reasons for their popularity. A sample of 25 women by SEWA, Ahmedabad (reference not cited in detail) has shown that at least 11 of them consume gutkha for relaxation while the rest said that it worked as a panacea for stomach ache, headache and dental pain. Many are attracted to gutkha by television advertisements. It is estimated that out of 400 million people above 15 years of age, 47

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per cent use tobacco in one form or another; 72 per cent of tobacco users smoke bidi, 12 per cent smoke cigarettes and 16 per cent use tobacco in the smokeless form (specific reference not cited). The following three references were given at the end: Times Of India, 'Tobacco-related diseases on the rise in India', warns WHO, 31 May 1997. Asian Age- 'Attention Gutkha Addicts. It can clamp your mouth shut' by N.Ganesh. Nation Needs Cancer Prevention' by Narayan Seva Sanstha, Udaipur.

TUS (1997) WHO: Descriptive report
WHO. **Tobacco or Health: A Global Status Report,** WHO, Geneva, 1997.

This global report gives a global overview on the issue of tobacco or health, followed by 2-page profiles for each member country of WHO. It estimates there are 1100 million smokers in the world, of whom 300 million are in developed countries and 800 million are in developing countries. However fewer cigarettes are smoked daily per smoker in developing countries (14) compared to developed countries (22). In South East Asia, the average number of cigarettes smoked per day is 14. Estimated smoking prevalence for men and women 15 years and older in the early 90s in South East Asia Region was 44% for men and 4 % for women. The world's 25 leading tobacco growing countries in 1994 contributed 90% of the world's tobacco. The list includes 6 countries from South East Asia: India, Indonesia, Pakistan, Bangladesh, Thailand and Korea. They contributed almost 15 % of global tobacco leaf production. Five of these 6 countries (excluding Pakistan) were also among the world's top 25 countries manufacturing cigarettes. Korea was the only South East Asian country in the world's top 25 importers of cigarettes, and only Indonesia rank amongst the world's leading 25 exporters of manufactured cigarettes. Thailand stands out in the region for its comprehensive tobacco control programme.

TUS India (1992) Bho: Descriptive report
Bhonsle RB, Murti PR and Gupta PC. **Tobacco Habits in India.** In: Gupta PC, Hamner JE III, Murti PR, eds. *Control of Tobacco-related Cancers and Other Diseases.* Proceedings of an International Symposium, TIFR, Bombay, January 15-19, 1990. Oxford University Press, Bombay, 1992, pp 25-46.
(Basic Dental Research Unit and WHO Collaborating Center for Oral Cancer Prevention, Tata Institute of Fundamental Research, Bombay, India)

Following the introduction of tobacco into India by the Portuguese in about 1600, its use spread rapidly to all parts of the country, percolating into all sections of society. Tobacco is smoked, chewed, sucked or applied to teeth and gums in diverse ways. Many of these methods are specific to particular geographic regions. Bidi and cigarette smoking are practiced widely in all regions. Other smoking habits include chutta and dhumti, which are also smoked in reverse (i.e., with the lighted end inside the mouth), hookli (clay pipe), chilum and hookah. Chewing tobacco in betel quid is the most popular form of smokeless tobacco use. Others comprise tobacco-lime mixture (khaini), tobacco-areca nut preparations like mawa, mainpuri tobacco and pan masalas. Mishri, gudhaku and creamy snuff are initially used as teeth cleaning material, but quickly become addictive.

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1.8 Rural communities

This subsection contains eight abstracts on tobacco use in rural communities, mainly among adults. One study found that illiterate tobacco users expressed willingness to give up tobacco after the harmfulness of the habit was explained to them, which was also the case in an intervention in a village in Kerala (see Int India (1988) Bha in section 8).

TUS India (2002) Cha: Population survey
Chandra V, Ganguli M. **Smoking Among The Elderly in Rural Haryana: (India):** *Lifeline*: May 2002, 8:4. WHO SEARO, New Delhi, India.

Data were collected between 1991 and 1999, drawn from 28 villages in Haryana, India, with a total population of 63,237. The report is for 4,811 people aged 55 and older. Tobacco use prevalence was reported to be 71% (males 88%, females 53%). Men reported much earlier initiation ages (typically 15-24) that women, who typically began aged 25 or older. Cigarette smoking was uncommon (6.2%), most smokers used bidi (58.3%) or hookah (73.3%).

TUS India (1998) Cha: Tobacco use survey with socio-demographic analysis
Chaturvedi HK, Phukan RK, Zoramthanga K, Hazarika NC, Mahanta J. **Tobacco use in Mizoram, India: sociodemographic differences in pattern.** *Southeast Asian J Trop Med Public Health* 1998 Mar;29(1):66-70.
(Regional Medical Research Centre, NE Region (ICMR) Dibrugarh, Assam, India)

A study on tobacco use was carried out in Aizawl district of Mizoram, India, to assess the prevalence and pattern of tobacco use. An area served by two Sub-health centers representing town and village populations was selected for a household survey in which 375 people (age 10 years and above) were interviewed about their tobacco habits. Use of tobacco was high among males (56.6%) and females (45.7%), but the high prevalence of smoking among males (42.3%) and chewing among females (27.9%) indicates sex differences in tobacco use patterns. Age and occupation had significant association with tobacco use but influence of education was very low and its association was not significant. The mean age for starting tobacco chewing and smoking for males and females varied significantly. However, the mean age at which use started for adolescent and young (10-29 years) tobacco users was 17.2 years (SD +/- 2.3). Though there are some limitations to this study, it revealed differential patterns of tobacco use, which is valuable information for prevention efforts.

TUS/Nut India (1994) Cho: Tobacco use survey with analysis of health effects
Choudhary S, Choudhary SK, Mishra S. **Effect of Tobacco chewing on Physical Health of Tribal Population,** in the *Maharashtra Journal of Extension Education*, Vol. 13, 1994,pp 237-240.

The study was conducted in Nov-Dec 1991. Cases were selected from the rural tribal population of Rewa District, a village near Kankar. The main objectives of the study were (1) to estimate different diseases caused by tobacco chewing and (2) assess the nutritional status of tobacco chewers as compared to non tobacco chewers. The sample consisted of 200 individuals, of whom 128 were tobacco chewers and 72 were non-tobacco chewers. Tobacco chewers showed higher intensity of disease symptoms compared to non-tobacco chewers. The symptoms for mouth ulcers (35.16%), hypertension (7.03%), anemia (46.09%) and skin diseases (3.13 %) prevailed only in tobacco chewers and not in non-tobacco chewers. A higher incidence of headache (52.34%), night blindness (50.78%), burning abdomen (38.28%) and chest pain (34.38%) was observed in tobacco chewers as against 40.28 %, 6.94%. 25% and 11.11% in non tobacco chewers respectively. Persons with low nutritional status suffered more than those with high and medium nutritional status.

TUS India (1994) Geo: Tobacco use survey with socio-demographic analysis
George A, Varghese C, Sankaranarayanan R, Nair MK. **Use of tobacco and alcoholic beverages by children and teenagers in a low-income coastal community in south India.** *J Cancer Educ* 1994 Summer;9(2):111-3.
(Regional Cancer Centre, Trivandrum, Southern India)

To plan and implement cancer control measures, information about the baseline habit patterns of the community is needed. A coastal village near Trivandrum, Kerala, Southern India, supported mainly by the fishing industry, was identified for this study with regard to establishing measures to control oral cancer there. Adults in coastal Kerala have been found to have very high levels of tobacco and alcohol use, and oral cancer is prevalent in Kerala. Smoking and chewing tobacco and drinking alcoholic beverages are the major risk factors for this cancer. The socioeconomic status and literacy of the fishermen of Kerala are low. A survey was conducted to study the tobacco and alcohol use habits of 146 children and teenagers in this village. The percentages of study subjects with pan-tobacco-chewing, smoking, and drinking habits were 29%, 2%, and 3%, respectively. Use correlated negatively with education and positively with number of children per family. This survey provides information that can be used to plan cancer education efforts, including redesigning the school curriculum and focusing on high-risk groups.

TUS India (1992) Gav: Tobacco use survey with sociological analysis
Gavarasana S, Gorty PV, Allam A. **Illiteracy, ignorance, and willingness to quit smoking among villagers in India.** *Jpn J Cancer Res* 1992 Apr;83(4):340-3.
(Lions Cancer Treatment Research Center, Visakhapatnam, India)

During field work to control oral cancer, difficulties in communication with illiterates were encountered. A study to define the role of illiteracy, ignorance and willingness to quit smoking among the villagers was undertaken in a rural area surrounding Doddipatla Village, Andhra Pradesh, India. Out of a total population of 3,550, 272 (7.7%) persons,

mostly in the age range of 21-50 years, attended a cancer detection camp. There were 173 (63.6%) women and 99 (36.4%) men, among whom 66 (53 men and 13 women) were smokers; 36.4% of men and 63% of women were illiterate. Among the illiterates, it was observed that the smoking rate was high (56%) and 47.7% were ignorant of the health effects of smoking. However, after being imparted health education on the harmfulness of tobacco, the attitude of illiterate smokers was encouraging, as 83.6% were willing to quit smoking. Further research is necessary to design health education material for 413.5 million illiterates living in India (1991 Indian Census). A community health worker, trained in the use of mass media, using a person-to-person approach, may help smokers, including illiterates, to quit smoking.

TUS India (1991) Gav: Tobacco use survey with sociological analysis
Gavarasana S, Gorty P, Allam A. **Is Illiteracy an Impediment to the control of smoking habit?** *Oncology oral* Vol. 2. Ed. Verma AK. Proceedings of the international cancer congress on Oral Cancer, 1991; Bangalore, Macmillan India, pp 43-46.

The objective of the study was to find out the role of illiteracy in the control of cancer and in curbing tobacco usage. A survey was carried out among persons attending a camp conducted in 10 villages around village Doddipatla in West Godavari District of Andhra Pradesh, south India. A doctor examined all the tobacco users (smokers) and informed them on a one-to-one basis that tobacco causes cancer, chronic lung disease and heart disease; then he asked them whether they were willing to quit smoking. Out of 272 attending the camp, 36.4% were males and 63.6% were females. Of males, 63.6% and of females, 37% were literate. The rate of smoking was similar among both literates and illiterates (23% and 25.5% respectively), but a greater proportion of illiterates were unaware of the ill effects of tobacco use (20% among literates and 41% among illiterates were unaware). However, over eighty percent of illiterate smokers were willing to quit smoking after receiving health education. A similar proportion of those willing to quit was found among literate smokers. It was concluded that illiteracy was not an impediment to motivating smokers to quit if the information gap is bridged. A community health worker trained in use of mass media methods of health education for illiterates may help curb smoking habit in rural India.

TUS India (1989) Vai: Tobacco use survey with economic analysis
Vaidya SG, Naik V. **Tobacco habits in Goan Village,** in *Social Welfare,* 35 (12), March 1989, pp 40-41.

The paper reports a study conducted in rural areas of four talukas of the central zone. The study covered 54,809 tobacco habitues, of whom 34,031 were male and 20,858 were female. Estimates were done of the amount spent per year by a male habitue and a female habitue. Total spending on tobacco by village was estimated from the average amount spent by a male/female habitue in the selected villages, multiplied by the estimated number of habitues in the village. The process of calculating personal

expenses, for those who unthinkingly spend any amount from Rs. 1 to Rs. 10 per day on tobacco, does seem to set a thinking process in the individual.

TUS India (1986) Moh: Tobacco and other drug use survey
Mohan D, Sundaram KR, Sharma HK. **A study of drug abuse in rural areas of Punjab (India).** *Drug Alcohol Depend* 1986 May;17(1):57-66.

In 1976 an epidemiological survey of drug abuse was conducted in 24 rural villages of four Community Development Blocks (CDB) in three districts of Punjab State bordering Pakistan covering 1,276 households. The majority of households had one user. Both men and women reported the use of traditional drugs, i.e. alcohol, tobacco, opium and cannabis. In males, the commonest drug used was alcohol (58.3%), followed by tobacco (19.3%), opium (6.3%) and cannabis (1.2%). The majority of the female respondents were non-users, but a very small number reported use of tobacco, alcohol and opium. The observations are compared with other studies and implications discussed.

1.9 Urban communities

Articles on tobacco use by urban dwellers, mainly adults, are summarized in this subsection. One report on attitudes and behaviours of north Indian smokers, found that they continued smoking despite aversion to the habit and disapproval of their family members. In a Bombay study, over 60% of both male and female residents of lower class neighbourhoods interviewed were tobacco users; smokeless forms were the most popular. A Delhi study on smoking habits found two subpopulations: the white-collar cigarette smokers and the lower income beedi or chutta smokers. Another study conducted in Delhi on smoking examined only highly educated men and found that 32% smoked and three fourths of the smokers were worried about the ill effects of smoking on themselves and on others.

TUS India (2002) Moh: Cross-sectional survey
Mohan D, Chopra A, Sethi H. **The co-occurrence of tobacco and alcohol in general population of metropolis Delhi.** *Indian J Med Res.* 2002 Oct;116:150-4.
(Drug Dependence Treatment Centre, All India Institute of Medical Sciences, New Delhi, India.)

Background and objectives: The association between tobacco and alcohol use behaviours has not been explored in India. This study reports on the co-occurrence of tobacco and alcohol use in a representative general population in metropolis Delhi at two points of time a year apart. Methods: Matched data on 10,312 individuals age 10 years or older from 2,937 households were available for survey I and survey II. They included 5,414 males and 4,898 females. The subjects were interviewed by non clinical staff using a structured proforma based on DSM III R criteria on the use of tobacco, alcohol, cannabis and opioids. Results: Among women, use of only tobacco was reported. Among males,

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the prevalence of use of 'only tobacco', 'only alcohol' and concurrent smoking and drinking was 18.1, 3.3 and 9.6 per cent respectively. Concurrent use was higher in the age group 31-40 yr and dependence higher in the 41-50 yr age group. Both at surveys I and II current smokers had higher percentage of alcohol drinkers compared to tobacco abstainers; dependent smokers had higher percentage of dependent drinkers. The use of alcohol at survey II was higher among tobacco smokers compared to tobacco abstainers identified at survey I (OR = 5.77, 95% CI 4.3-7.7). Interpretation and conclusion: Our results demonstrate a positive correlation between smoking and drinking. The findings lend support to existing evidence suggesting associations between tobacco and alcohol use. Smoking proved to be a powerful predictor of alcohol use. It is suggested that professionals who treat alcoholism should pursue the cessation of smoking among their patients.

TUS India (2002) Moh: Cross-sectional survey
Mohan D, Chopra A, Sethi H. **Incidence estimates of substance use disorders in a cohort from Delhi, India.** *Indian J Med Res.* 2002 Mar;115:128-35.
(Drug Dependence Treatment Centre, All India Institute of Medical Sciences, New Delhi, India.)

Background and objectives: There are no reports of incidence studies in the Indian setting on substance use disorders in the general population. This survey-resurvey carried out in metropolis Delhi estimated the incidence rates of substance use disorders. Methods: A cross-sectional survey was carried out at two points of time with an interval of one year in a representative sample from the general population of metropolis, Delhi. The instrument was precoded, structured and based on DSM III-R operationalised criteria for use of tobacco, alcohol, cannabis and opioids (past one month). Matched data for two points of time were available for 5414 males and 4898 females. Results: In the total cohort, the annual incidence rates (per 100 persons) among males for any drug use, alcohol, tobacco, cannabis and opioids were 5.9, 4.2, 4.9, 0.02 and 0.04 respectively. Among females, incidence of any drug use was 1.2/100 persons. Interpretation and conclusion: Results showed that males have higher incidence for both not-dependent and dependent use for all the drug categories. Females had a higher incidence of dependent tobacco use.

TUS / Circ / CResp India (2001) Kho: Cross-sectional survey
Khokhar A, Mehra M. **Life style and morbidity profile of geriatric population in an urban community of Delhi.** *Indian J Med Sci.* 2001 Nov;55(11):609-15.
(Department of Community Medicine, Maulana Azad Medical College, Delhi-110002.)

A cross-sectional study was carried to find out the lifestyle pattern and morbidity profile of geriatrics residing in urban community of Vikram Nagar, Delhi. Women constituted 56.25% and men 43.75% of a total of 128 study subjects. Hindus were 89.06% and Sikhs 10.93%. Age group of 60-75 years accounted for most of the study population. 85% of the subjects complained of one or more health problems. 90.62% of them suffered from

dental problems. A significantly higher proportion of women suffered from problems of locomotion/joints and anemia as compared to men whereas genitourinary problems were higher in men as compared to women. 42.55 of the women and 30.76% of the men were obese. Current smokers constituted 15.62% of the women and 30.76% of the men, whereas 30.35% of the men were current consumers of alcohol. As low as 10.15% of the population engaged in regular physical activity. 55.46% of the subjects were vegetarian. 22.65% suffered from disturbed sleep pattern. Smoking showed statistically significant association with hypertension and respiratory tract diseases. Physical activity showed association with obesity and disorder of locomotion. Behavior and lifestyle modification in the form of primordial prevention and counselling of the high risk groups should be carried out to improve the quality of life of the aged!

TUS India (1997) Sar: Tobacco use survey
Sarma PV, Dhand R, Malhotra A, Malhotra S, Sharma BK. **Pattern of tobacco smoking in north Indian adults.** *Indian J Chest Dis Allied Sci* 1990 Apr-Jun;32(2):83-93.
(Department of Internal Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh)

An exploratory study was conducted among 200 apparently healthy current smokers aged 15-45 years to determine their attitudes and behaviour regarding tobacco smoking, using a specifically designed precoded questionnaire. Females constituted 10% of the study group. The 73 participants who smoked cigarettes exclusively were from urban backgrounds and were noted to inhale the smoke more frequently than bidi or hukka smokers. Parental and peer group influence, as well as curiosity in late teenage years were the major reasons for starting smoking which was however continued mainly to obtain the stimulatory and or relaxing effects of nicotine. Health hazards of smoking, particularly lung cancer and heart disease, were widely known and fear of these was the most important reason for smokers wishing to quit the habit. Half of the subjects had attempted to stop but failed due to withdrawal symptoms and lack of a suitable substitute. The divergence between attitude and behaviour of smokers is highlighted by this study since smokers continued to smoke despite being averse to smoking and the disapproval of their habit by their family members. There were important differences in the pattern of smoking and perceptions of various groups of smokers regarding societal permissiveness, awareness of health hazards, and measures to control smoking.

TUS India (1996) Gup: Tobacco use survey with sociodemographic analysis
Gupta PC. **Survey of sociodemographic characteristics of tobacco use among 99,598 individuals in Bombay, India using handheld computers.** *Tobacco Control* 1996 Summer;5(2):114-20.
(Tata Institute of Fundamental Research, Bombay, India)

Objectives: To study the diversity and sociodemographic characteristics of tobacco use in Bombay, India. Design: Population-based, cross-sectional, house-to-house survey with face-to-face interviews in the city of Bombay during 1992-94. Data was input directly

into a programmed, handheld computer (electronic diary). Participants: Permanent residents of the city of Bombay aged 35 years and older. Main outcome measures: Tobacco use in various smoking and smokeless forms. Results: 99,598 individuals were interviewed (60% women, 40% men). Among women, prevalence of tobacco use was high (57.5%) but almost solely in the smokeless form. Among men, 69.3% reported current tobacco use and 23.6% were smokers. The most common smokeless tobacco practice among women was mishri use (44.5% of smokeless users) and among men betel quid with tobacco (27.1%). About half of smokers used bidi and half smoked cigarettes. Chewing areca nut without tobacco was rare (< 0.5% of smokeless users). Educational level was inversely associated with tobacco use of all kinds except cigarette smoking. Conclusions: The pattern of tobacco use varies across India and, in Bombay, is very different from other areas. Using handheld computers to collect data in the field was successful.

TUS India (1996) Nar: Tobacco use survey
Narayan KM, Chadha SL, Hanson RL, Tandon R, Shekhawat S, Fernandes RJ, Gopinath N. **Prevalence and patterns of smoking in Delhi: cross sectional study.** *BMJ* 1996 Jun 22;312(7046):1576-9.
(Diabetes and Arthritis Epidemiology Section, National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix, AZ 85014, USA)

Objective: To determine the prevalence and predictors of smoking in urban India. Design: Cross sectional. Setting: Delhi, urban India, 1985-6. Subjects: Random sample of 13,558 men and women aged 25-64 years. Main outcome measures: Smoking prevalence; subjects who were currently smoking and who had smoked > or = 100 cigarettes or beedis or chuttas in their lifetime were defined as smokers. Results: 45% (95% confidence interval 43.8 to 46.2) of men and 7% (6.4 to 7.6) of women were smokers. Education was the strongest predictor of smoking, and men with no education were 1.8 (1.5 to 2.0) times more likely to be smokers than those with college education, and women with no education were 3.7 (2.9 to 4.8) times more likely. Among smokers, 52.6% of men and 4.9% of women smoked only cigarettes while the others also smoked beedi or chutta. Compared with cigarette smokers, people smoking beedi or chutta were more likely to be older and married; have lower education, manual occupations, incomes, and body mass index; and not drink alcohol or take part in leisure exercise. Conclusion: There are two subpopulations of smokers in urban India, and the prevention strategy required for each may be different. The educated, white collar cigarette smoker in India might respond to measures that make non-smoking fashionable, while the less educated, low income people who smoke beedi or chutta may need strategies aimed at socioeconomic improvement.

TUS India (1994) Bha: Tobacco use survey
Bhattacharjee J, Sharma RS, Verghese T. **Tobacco smoking in a defined community of Delhi.** *Indian J Public Health* 1994 Jan-Mar;38(1):22-6.
(National Institute of Communicable Diseases, Delhi)

A Community based study in urban Delhi, Delhi Admin Flats, Timarpur found that about 32 percent of adult males smoked. Proportion of smokers was highest in 41-50 age group, 31 percent of school teachers smoked. Out of all who tried to give up smoking, 8 percent reverted back after abstinence of two years or more. About three fourths of the smokers were worried about the ill effects of smoking on themselves and others. Significantly higher number of non-smokers expressed support for total stopping of advertisement and complete ban of sale of smoking tobacco.

TUS India (1992) Bas: Opinion Survey
Basu A, Ganguly SK, Datta S. **Demographic survey of opinions towards smoking: a pilot study.** J Indian Med Assoc 1992 Nov;90(11):292-94.
(Department of Radiotherapy, RG Kar Medical College Hospital, Calcutta.)

A survey (using a questionnaire) of 865 smokers analysed their opinions on aspects of smoking. The subjects were mostly males (97.11%), aged 21 to 50 years (80%). Heavy smoking is injurious to health is the opinion of most of the smokers (90%) particularly when maintained with other addictions (80%); tobacco is harmful not only when smoked but also when used in other forms (63%) and moderate smoking was thought to be not very harmful (43%). However, smoking is not necessary to make or maintain relations with others (70%). Statutory warning has no marked effect on the habit (70%), participants were dubious about the role of legal restrictions but thought that advertisements encourage the habit definitely (63%). Three out of 4 persons know the problems of smoking and almost the same proportion think that smoking can be stopped or at least checked. There were differences of opinion about who to consult, if problems arise from smoking. Family physicians could play an important role in quitting decisions.

1.10 Women

A study of women in Mumbai found that one third used tobacco while pregnant, and their babies had double the incidence of low-birth weight, compared to women who did not use tobacco. Other articles provide general information on how tobacco affects women (including pregnant women), children and families in India. (See also Section 4.7.2 on adverse pregnancy outcomes).

TUS India (1999) Sud: Descriptive Report
Sudarshan. R., and Mishra, N. **Gender and Tobacco Consumption in India.** *Asian J of Women's Studies* 1999; 15,1:84-114.
(National Council of Applied Economic Research, New Delhi)

Debates around the production and consumption of tobacco have attempted to weigh the adverse ecological and health impact of tobacco cultivation against its potential to generate employment, income, and foreign exchange. Over the last decade, opinion in

favour of reducing consumption has gained strength. This paper briefly reviews the origins and spread of the habit from the Americas to Europe and Asia, and contemporary debates for and against tobacco use. The situation regarding tobacco use in India is described using gender disaggregated data from recent surveys conducted by the National Council of Applied Economic Research (NCAER) and the National Sample Survey (NSS). The data bring out regional disparities and differences between male and female consumption patterns. It is suggested that some conventional wisdom regarding tobacco consumption can be questioned. For example, the highest levels of prevalence are not among the urban and affluent, but among the very poor. Women and children are the new focus of tobacco companies. In India the most interesting emerging trend in consumption is the development of new smokeless tobacco products, such as gutka, which is widely consumed by women. The implications are that tobacco policy has to be multi-faceted; and that health research and tobacco control policy need to clearly evaluate the health effects of new products.

TUS / Preg-Outcome India (1990) Meh: Comparative study
Mehta AC and Shukla S. **Tobacco and pregnancy.** *Journal of Obstetrics and Gynecology of India* 1990;40(2):pp 156-160.

A preliminary survey on tobacco use during pregnancy was conducted at N. Wadia Maternity Hospital, Mumbai in April 1987, and 500 women were interviewed. The main objective of this study was to determine the incidence of Low Birth Weight (LBW) babies amongst tobacco users and nonusers. All the respondents were treated in free wards. Of the women interviewed, 322 (64.4%) were from the antenatal clinics and 178 (35.6%) were delivered cases. Out of the 500 women, 167 (33.4%) consumed tobacco during their pregnancy. Among users, 158 used it by applying to teeth and gums, 8 chewed tobacco and only one smoked. As many as 195 (39%) husbands of these 500 women consumed tobacco while their wives were pregnant: 41 applied it to teeth and gums, 86 chewed it, and 68 smoked tobacco, 98 men took more than one mode. The LBW incidence for the hospital was 46.63%. In women who used no tobacco, the proportion of LBW was 36.28%, and amongst those who consumed tobacco in pregnancy the incidence was 64.62%. Krishna (1978) had reported that his study had shown a 15.8% incidence of tobacco use in pregnancy and all were chewing it. His study was conducted in Pune region. Verma et al. (1983) studied a population in Jabalpur, and a large majority of pregnant women ingested tobacco, rather than applying on gums or keeping in mouth. Both authors reported significantly lower birth weights in offspring of tobacco users compared to babies of nonusers. References: Krishna Kewal; *British Journal of Obstetrics and Gynecology,* 85, 726, 1978; Verma, R.C., Chansoriya M, Kaul K.K. *Indian Pediatrics,* 20, 105, 1983.

TUS India (1993) Agh: Descriptive report
Aghi M. **Tobacco Issues and concerns of women, children and families**, paper presented at the Tobacco Forum, IDRC, Ottawa Canada, in 1993.

Unaware of the ill effects of tobacco, rural women of India use tobacco in many ways. Rural women of Andhra, who smoke cheroots in reverse, use tobacco to freshen their breath in the morning, get rid of morning sickness when pregnant and to ease labour pains during delivery. In India, women and girls work in exploitative conditions in the production of bidis. Seen in a social perspective, educating rural Indian women on the ill effects of tobacco is only a part of what is needed to solve their many problems: illiteracy, poverty, malnourishment, inequality, bias and prejudices.

1.11 Data collection instruments

TUS India (2002) WHO: Multicenter study to validate a screening instrument. WHO ASSIST Working Group. **The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): development, reliability and feasibility.** *Addiction.* 2002 Sep;97(9):1183-94.

Aims: The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) was developed for the World Health Organization (WHO) by an international group of substance abuse researchers to detect psychoactive substance use and related problems in primary care patients. This report describes the new instrument as well as a study of its reliability and feasibility. Setting: The study was conducted at participating sites in Australia, Brazil, Ireland, India, Israel, the Palestinian Territories, Puerto Rico, the United Kingdom and Zimbabwe. Sixty per cent of the sample was recruited from alcohol and drug abuse treatment facilities; the remainder was drawn from general medical settings and psychiatric facilities. Methods: The study was concerned primarily with test item reliability, using a simple test-retest procedure to determine whether subjects would respond consistently to the same items when presented in an interview format on two different occasions. Qualitative and quantitative data were also collected to evaluate the feasibility of the screening items and rating format. Participants: A total of 236 volunteer participants completed test and retest interviews at nine collaborating sites. Slightly over half of the sample (53.6%) was male. The mean age of the sample was 34 years and they had completed, on average, 10 years of education. Results: The average test-retest reliability coefficients (kappas) ranged from a high of 0.90 (consistency of reporting 'ever' use of substance) to a low of 0.58 (regretted what was done under influence of substance). The average kappas for substance classes ranged from 0.61 for sedatives to 0.78 for opioids. In general, the reliabilities were in the range of good to excellent, with the following items demonstrating the highest kappas across all drug classes: use in the last 3 months, preoccupied with drug use, concern expressed by others, troubled by problems related to drug use, intravenous drug use. Qualitative data collected at the end of the retest interview suggested that the questions were not difficult to answer and were consistent with patients' expectations for a health interview. The data were used to guide the selection of a smaller set of items that can serve as the basis for more extensive validation research. Conclusion: The ASSIST items are reliable and feasible to use as part of an international screening test. Further evaluation of the screening test should be conducted.

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TUS India (2003) Moh: Cross-sectional survey with comparative study

Mohan D, Neufeld K, Chopra A, Sethi H. **Agreement between head of household informant and self-report in a community survey of substance use in India.** *Drug Alcohol Depend.* 2003 Jan 24;69(1):87-94.

(Department of Psychiatry, Drug Dependence Treatment Centre, All India Institute of Medical Sciences, New Delhi, India. davindermohan@hotmail.com)

This survey of 500 households in a New Delhi urban slum compared reports of substance use by the head of the household informant with individual self-report. Information from the two sources was compared for 1,132 people above the age of 15 years. The paired agreement regarding the use of substances was high (kappa=0.92; S.E.=0.01, z=92.0). The agreement regarding the presence of symptoms and classification of dependence for the use of alcohol, tobacco and opiates ranged from good to excellent and head of household reports had a high positive predictive value for the use of these substances. This method provides useful estimates of drug use and dependence for substances associated with observable physiologic withdrawal syndromes, and is less costly and quicker to perform than traditional self-report methodologies.

2. All Cause Mortality and Morbidity Related to Tobacco

The first report in this section is a wide review of mortality and morbidity associated with tobacco use. The second report recommends the use of verbal autopsy through the Sample Registration System to obtain cause-specific mortality. Other reports elucidate the effects on overall mortality and/or morbidity of tobacco use in India and point toward the need to obtain cause-specific mortality rates and relative risks for the manifold forms of tobacco use in the country. It has been estimated that among men, 19-40% of all deaths and among women at least 4% of all deaths are caused by tobacco in India.

All Mor India (2003) Cri: Review

Critchley JA, Unal B. **Health effects associated with smokeless tobacco: a systematic review.** *Thorax.* 2003 May;58(5):435-43.

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Background: It is believed that health risks associated with smokeless tobacco (ST) use are lower than those with cigarette smoking. A systematic review was therefore carried out to summarise these risks. Methods: Several electronic databases were searched, supplemented by screening reference lists, smoking related websites, and contacting experts. Analytical observational studies of ST use (cohorts, case-control, cross sectional studies) with a sample size of >/=500 were included if they reported on one or more of

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Annexure 27

Process evaluation of a tobacco prevention program in Indian schools--methods, results and lessons learnt.

Goenka S, Tewari A, Arora M, Stigler MH, Perry CL, Arnold JP, Kulathinal S, Reddy KS.

Health Educ Res. 2010 Dec;25(6):917-35. Epub 2010 Sep 30.

Abstract

In India, 57% of men between 15 and 54 years and 10.8% of women between 15 and 49 years use tobacco. A wide variety of tobacco gets used and the poor and the underprivileged are the dominant victims of tobacco and its adverse consequences. Project MYTRI (Mobilizing Youth for Tobacco-Related Initiatives in India) was a tobacco prevention intervention program, a cluster-randomized trial in 32 Indian schools which aimed to decrease susceptibility to tobacco use among sixth- to ninth-grade students in urban settings in India. This culture-specific intervention, which addressed both smokeless and smoked forms of tobacco, was Indian in content and communication. We qualitatively developed indicators which would help accurately measure the dose of the intervention given, received and reached. A multi-staged process evaluation was done through both subjective and objective measures. Training the teachers critically contributed toward a rigorous implementation and also correlated with the outcomes, as did a higher proportion of students participating in the classroom discussions and better peer-leader-student communication. A sizeable proportion of subjective responses were 'socially desirable', making objective assessment a preferred methodology even for 'dose received'. The peer-led health activism was successful. Teachers' manuals need to be concise.

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Annexure 30

Prevalence and Correlates of Tobacco use Among 10-12 Year Old School Students in Patna District, Bihar, India

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In order to assess the prevalence and correlates of tobacco use among school students (10-12 years), information on tobacco use and socio-demographic variables was collected from 1626 students (male 1027) using a questionnaire. Bivariate and multiple regression analysis were done. Ever users in the sample were 16.6% (95% CI 14.8, 18.4) and current users were 5.1% (95% CI 4.1, 61). Current use was significantly associated with male sex (OR 2.3, CI 1.09-5.14), students not participating in sports (OR 2, CI 1.04-4.04), tobacco use among friends (OR 4, CI 2.02-8.25), unaware of harmful effects of tobacco (OR 2.6, CI 1.1-6.14) and students who were used by parents and teachers to buy tobacco for them (OR 2.1, CI 1.4-4.19). Tobacco control programs focusing on male students, those who do not participate in sports, those whose friends use tobacco and those who are used by parents and teachers to buy tobacco are warranted.

Key words : *Prevalence, Smokeless tobacco, Tobacco use.*

TOBACCO use in adolescents has been called a "pediatric epidemic" because of increasing level of its use and dire public health implications(1).

In Bihar, Global Youth Tobacco Survey reported 58.9% current use of any tobacco product (male 61.4%, female 51.2%); 13.7% current smoking and 45.8% current smokeless tobacco use among students aged 13-15 years. In the same report, over 60% of ever users reported initiation at the age of 10 years or earlier(2). This inspired us to probe into the study of a much younger age group (10-12 years) of students to determine, prevalence and correlates of tobacco use among them. This study would help finding the minimal age of initiation at which intervention might prevent children from starting tobacco use.

Subjects and Methods

A cross sectional study was done among middle school students of 10 to 12 years old in Patna district during January-March 2004. Sample size was calculated on the basis of tobacco use prevalence of 58.9% among 13-15 years students in the GYTS Bihar study. Thus sample size came to 1031 ($n = 1.96^2 - *0.589 * 0.411/0.03$). As in the present study, clusters were taken randomly and not the individual student, an additional 50% was added to compensate for design effect. Hence, approximately (n = 1031 + 516 = 1547) 1600 students were targeted for this study. Moreover, this assumed prevalence for calculating the sample size was for slightly older age group children. Therefore expected prevalence in the current study was likely to be smaller.

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Details of schools were collected from Directorate of Education, Government of Bihar and District Education Officer (DEO), Patna district. The total number of schools was 2348 including exclusive boys' schools and girls' schools. For uniformity we selected only those schools, which had all the three classes of 5, 6 and 7 (n = 539). Most of these schools were government (95%) and a few (5%) schools were private including both aided and unaided. Private schools were mostly located in urban area.

Two stage cluster sampling design was used to select a representative sample of all students studying in classes 5, 6 and 7. The average number of students in government school classes was 15- 20 whereas in private schools, there were 40 or above. Thus at the first stage, from the list of three sample frames of schools *i.e.*, rural government (364), urban government (155), and private (20), we selected 15, 10 and 5 schools respectively by simple random sampling procedure. In the second stage, class-divisions were selected by random sampling. All students in the selected class divisions were eligible to participate. Non-response was due to absence in the class. Among 30 selected schools, 28 participated in the study (response rate 93.3%) as the school personnel of two schools were busy in election work. Among 2137 sampled students, 1626 responded (response rate 76.1%). This study represents 63,593 students (in 539 schools) in the age group 10-12 years.

Data were collected by pre-tested anonymous self-administered questionnaires in the classroom by one of the investigators (GS). Since these were young children the investigator clarified all doubts during data collection. Tobacco users were classified as: Ever Tobacco Users were those who had used any tobacco products in his/her lifetime even once. Current Tobacco Users were those who used any tobacco products any time in the last 30 days. Never Tobacco users were those who have never used any form of tobacco.

Data collected were entered in Excel spreadsheet and then analyzed with SPSS for Windows version 11.0. Bivariate analysis was done using Chi-square test. For multivariate analysis, multiple logistic regression analyses were done following stepwise method. For all the statistical tests, a 'P' value of <= 0.05 was considered statistically significant.

A written permission from relevant school authorities was taken before initiating the study. A verbal consent of the Principals of the schools selected for the study was taken, prior to starting the study. Informed oral consent was taken from all the participants. All participants were reassured about their anonymity during the administration of the questionnaire.

Results

Socio-demographic characteristics of the students are given in *Table I*. Tobacco use in any form in the study population by age group is given in *Table II*. Among 269 ever users 29.2% have initiated from class 3 when they were approximately 8 years old; among them 49.4% used pan-zarda as the first product. Distribution of ever users and current users by type of tobacco is given in *Table III*.

Among ever users, almost half had received their first tobacco from friends. Among current tobacco users, nearly half spent part or all their pocket money on tobacco. Among those who responded to this question (n = 980) 72.1% fathers and 13.9% friends used some form of tobacco; almost 25% of students were aware of teacher's use of tobacco in school. One-in four (24.7%) students was asked to bring tobacco for parents, relatives and teachers from the shop.

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TABLE I–*Socio-demographic Characteristics of the Students.*

Variable	Number of Students	Percent
Age (in completed years) n = 1624		
Less than 10 yrs	111	6.8
10 yrs	307	18.9
11 yrs	474	29.2
12 yrs	489	30.1
More than 12 yrs	243	15.0
Sex (n = 1626)		
Male	1027	63.2
Female	599	36.8
Religion (n = 1626)		
Hindu	1396	85.9
Muslim	187	11.5
Others	43	2.6
Place of residence (n = 1623)		
Village	640	39.4
Town	983	60.6
Place of living (n = 1626)		
Parent's home	1520	93.5
Other places	106	6.5

Over three fourth of students saw actor's use of tobacco and 75% of students saw advertisement of tobacco in TV and print media sometimes or many times in the 30 days preceding the study. More than half of students saw anti-tobacco message, in the 30 days preceding the study, mostly in TV. The majority (80.3%) of students was aware about the harmful effect of tobacco on health.

Ever use of tobacco was associated with sex of students ($p = 0.004$), location of residence ($p < 0.001$), occupation of father/mother ($p < 0.001$), sport activity ($p = 0.007$), tobacco use in the family ($p = 0.013$), by friends ($p < 0.001$), exposure to tobacco advertisement in media ($p = 0.008$), exposure to antitobacco media message ($p = 0.002$), and knowledge of harmful effects of tobacco ($p = 0.026$).

Current use of tobacco exhibited association with sex of students ($p = 0.008$), place of living ($p = 0.032$), sport activity in school ($p = 0.038$), amount of pocket money per day ($p = 0.006$), tobacco use by friends ($p < 0.001$) and teachers ($p = 0.008$), request to bring tobacco for others ($p < 0.001$), exposure to actors' use of tobacco in cinema and TV ($p = 0.043$), media exposure to antitobacco message ($p = 0.006$) and knowledge of harmful effect of tobacco ($p = 0.021$).

Multiple logistic regression analysis included independent variables, which showed statistically significant association with dependent variables. Ever tobacco use

TABLE II–*Tobacco Use in Any Form in the Study Population.*

Age group	Ever use		Current use	
	n	%	n	%
< 10 years	111	21.6	110	5.5
10 years	307	15.3	305	3.6
11 years	473	15.0	471	4.0
12 years	488	17.4	484	6.2
> 12 years	243	17.3	241	6.6
Total	1622	16.6	1611	5.1

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TABLE III—*Distribution of Current Users and Ever Users by Type of Tobacco Use.*

Type of tobacco	Current users (n = 80)		Ever users (n = 250)	
	Number	Percent	Number	Percent
Smokeless tobacco	69	86.2	224	89.6
Smoking tobacco	7	8.8	8	3.2
Tobacco in multiple form	4	5.0	18	7.2
Tobacco use byproducts				
Pan-zarda	24	30.0	125	50.0
Gul	22	27.5	26	10.4
Gutkha	13	16.3	52	20.8
Khaini	10	2.5	21	8.4
Bidi & Cigarette	7	8.8	8	3.2
Multiple form	4	5.0	18	7.2

was significantly associated with male sex (OR 2.0; 95% CI 1.2 - 3.4), urban resident (OR 2.3, CI 1.2-4.4), and tobacco use among friends (OR 5.4, CI 3.3-8.8). Current tobacco use was significantly associated with male sex (OR 2.3, CI 1.1-5.1), students not participating in sports (OR 2, CI 1.0-4.0), tobacco use among friends (OR 4, CI 2.0-8.2), unaware of harmful effects of tobacco (OR 2.6 CI 1.1-6.1) and students who were used by parents and teachers to buy tobacco for them (OR 2.1, CI 1.4-4.2).

Discussion

No Indian data are available from a representative district level sample of tobacco use among students aged 10-12 years in Bihar or other parts of India. However, a school based study of tobacco use by older children (13-15 years) in a representative sample of Bihar state(2) and a community based study in rural area of Sitamarhi district of Bihar(3) showed a higher prevalence of tobacco use compared to our study.

Smokeless tobacco use in the present study was much higher than that of smoking, which is consistent with results of other studies(2). The prevalence of current tobacco use was more among boys (6%) than girls (3.2%). This finding is consistent with studies on adolescent's tobacco use in other parts of India(4,5) and abroad(6).

Nearly one third of ever users in the present study turned out to be current users. This is consistent with WHO estimates and international data that among those adolescents who experimented with tobacco, approximately one third to one half continued as regular users(7, 8).

Even though tobacco use by small children is thought to be not culturally acceptable in Indian society, this study shows over 29% participants reported initiation of tobacco use when they were studying in class 3 corresponding to the age of eight years. Initiation at this young age of 8 years and continuing tobacco use would have very

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Key Messages

- Nearly 17% of 1626 middle school students aged 10-12 years ever used some form of tobacco and 5.1% were currently using tobacco.
- Among 82 current users one quarter initiated tobacco use from third standard (around 8 years).
- Students who were used by parents and teachers to buy tobacco were twice as likely to be current users.

serious adverse health effects and half of these children will prematurely die in very early middle life(9).

Among ever users, almost half (49.6%) of the students reported that tobacco was introduced by friends. A skill building program to avoid peer pressure is required at very early age.

Students who participated in sports were less likely to use tobacco compared to those who did not take part in sports. Teacher's use of tobacco was also positively associated with current use of tobacco among students(8,10).

Therefore, any tobacco control program in children, to be successful, should involve friends peer groups, and teachers, and target children not participating in sports.

In Bihar, especially in rural areas the parents, relatives and teachers find it easy to use the children to buy tobacco for them. This brings children much closer to tobacco products and inspires them to use tobacco. One-fourth of students in this study were asked by their parents and teachers to buy tobacco for them. This behavior of adults is a strong predictor of tobacco use among children (OR 2.1,95% CI 1.1-4.2).

Lack of knowledge of the harmful effects of tobacco on health was negatively associated with tobacco use by adolescents. This compares with other data, which indicate that awareness of harmful effects does not effectively prevent tobacco use in children(2,7,8,11). Therefore, the current preventive message needs to be modified to make tobacco control and intervention more effective.

Since the study did not cover the students who were absent on the day of study the result could underestimate the magnitude of tobacco use. Absence from school is among the strongest predictors of tobacco use in adolescent. Since this study was done only in children aged 10-12 years who attended school, this may not be representative of all children in this age group. Since the ages of participant students were very small, they might not have understood the questionnaire completely.

The rate of tobacco use was high, considering the very young age group of our sample. Our findings suggest that tobacco use prevention and control measures are warranted and should be started very early preferably at primary education level. To be maximally effective this comprehensive policy on tobacco control, should involve schools, teachers and parents and make them commit to implement and sustain such a program.

Acknowledgement

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Contributors: GS, DNS, KRT conceptualized and designed the study. GS was also involved in data collection and data entry. PSS was involved in sampling design, data analysis and interpretation. All authors contributed in writing the manuscript.

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Competing interests: None.

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inotropic drugs are used as soon as intravascular volume is restored. Many of our patients did receive inotropes. It should however, be appreciated that after completion of initial resuscitation the fluid leak from intravascular compartment to interstitial space ('third-space loss') does not stop immediately. Moreover, a significant proportion of administered fluid continues to move out of intravascular space. It has been shown that only about 20% of administered saline stays in intravascular compartment by the end of two hours(4). The capillary leak may take several hours, sometime days, before it is reversed. In such patients, therefore, the continuing management of intravascular volume requires replacement of ongoing' 'third space loss'. Usually, this is achieved by administration of maintenance fluids at a higher infusion rate but some patients need fluid bolus because of continuing rapid 'third space loss'.

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Tobacco use Among Students in Orissa and Uttar Pradesh

Orissa

The Global Youth Tobacco Survey (GYTS) in Orissa(1) carried out during January- March 2002 that provides the first representative database on tobacco use prevalence among school children in the age group of 13-15 years in Orissa, India.

Among 50 sampled schools; all participated (100%). Among 3541 eligible students 2913 (82.3%) participated in the survey. Ever tobacco use was reported by 20.5%; of them about 30% used their first tobacco at the age of ten years or earlier.

Current tobacco use (any product) was reported by 14.2%; current smokeless tobacco 10.9%; current smoking by 8.6%. Among smoking, bidi smoking was most common.

Over 2/3rd students saw tobacco products advertisements in TV and outdoor print media and over half in newspaper and social events. About 10% students had some object with tobacco products brand names and were offered free sample of tobacco products. Watching a lot advertisement using tobacco by actors {actors smoking, 100 vs 59.3% ($P < 0.05$); actors chewing 62.6% vs 44.1% ($P < 0.05$)}, vendors offered free samples {Cigarettes 35.4% vs 8.3% ($P = < 0.05$) Bidi 26.3% vs 9.3% ($P < 0.05$), Gutka 21.3% vs 9.1% ($P < 0.05$)}, having objects with tobacco brand logo {Something with Cigarette brand logo 21.2% vs 9.0% ($P < 0.05$); something with

Gutka brand logo 22.9% vs 9.1% (P <0.05)} was associated with tobacco use. Nearly 60% students purchased tobacco products in a store; of them about nearly 1/3rd (28.9%) were refused because of their minor age.

Uttar Pradesh

There is increasing global concern regarding tobacco use, especially among young and adolescents people which is referred as "pediatric epidemic"(2). This study provides the first representative database on tobacco use prevalence among school children in the age group of 13-15 years in Uttar Pradesh, India.

A school-based survey was conducted in mid 2002 (June-September) through trained survey administrators. it was a two-stage cluster survey in schools using a standardized questionnaire based on the Global Youth Tobacco Survey (GYTS)(1,3) to assess the knowledge, attitudes and behaviour of adolescents (13-15 years of age) towards tobacco use, their exposure to environmental tobacco smoke and pro-tobacco advertisement. The GYTS questionnaire consisted of 85 multiple choices questions, each with a maximum of 8 response categories. Every question was to be answered by each student.

Current tobacco use was defined as "the percentage of students who used any tobacco product on one or more days during the past 30 days".

Among 51 sampled schools, all participated. A total of 4542 students participated (86.6%); 73% were boys. The non-response was due to absence on the day of the survey.

Current use of any tobacco product was 23.1%%; current smoking was 11.2%; and current use of smokeless tobacco was 21.6%. There was no significant difference in current tobacco use between boys and girls. Among chewers, gutka use was the most popular (9.9%). Nearly one third of non-smoker students were exposed to environmental tobacco smoke at their homes and more than that (38.9%) at outside homes. Over 82% boys and girls saw a tobacco (cigarette or gutka) advertisement on billboards. Exposure to second hand smoke and tobacco promotions were found associated with current tobacco use. Over 85% users wanted to quit.

The prevalence of tobacco use among adolescent especially among girls is alarming. Immediate action is required to create a supportive environment for the health of young people by implementing comprehensive tobacco control policy.

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leak(1) and for diagnostic purposes(5).

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Global Youth Tobacco Survey (GYTS) - Delhi

Globally everyday about 80,000-1,00,000 youth initiate smoking, most of them are from developing countries(1). About one-fifth of all worldwide deaths attributed to tobacco occur in India(2). Global Youth Tobacco Survey (GYTS) was a global study of tobacco use habits and related determinants among youth (13-15 years) around the world(3). A total of 1731 out of 2183 randomly sampled students participated in the Delhi GYTS survey, from 50 sampled schools. Major findings are summarized below:

One in 10 students (10%) had ever used tobacco in any form. Proportion of students currently using any tobacco product was 4.5% (boys: 5.5%; girls: 3.1%). Of these, the proportion of students who had chewed pan masala, gutkha or zarda in the past 30 days was 1.3%. Among them, boys had a higher prevalence than girls (boys: 2.3%; girls: 0.3%).

Less than 6 in 10 reported having learnt about the dangers of smoking and the effects of tobacco use.

Over 3 in 10 students and significantly more boys than girls were exposed to smoke from others (passive smoking) in their home in the past 7 days.

Over 2 out of 10 students believed that boys who use tobacco have more friends. About 3 in 10 students thought smoking or chewing make boys look more attractive and over 1 in 10 students felt this for girls. However a significantly higher proportion of boys than girls felt that girls look more attractive with tobacco use.

More than 8 in 10 students had seen an advertisement or media message about cigarettes, gutkha/ pan masala or bidis on television, roadside outside on hoardings, bus or railway facilities, and shops in the past 30 days.

Only 26% of students were certain that smoking is harmful to their health.

About 4 in 10 current tobacco users reported freely purchasing tobacco products in a store.

The prevalence of tobacco use in any form among both boys and girls in this age group is in agreement with earlier published findings(4). The results indicate a definite need for including tobacco related information in the school curriculum. High exposure rates to

passive smoking require immediate policy interventions and programs to generate awareness among the public. The findings, on free access and availability of tobacco products to youth, despite there being a law in Delhi banning sale of tobacco products to anyone below the age of 18, are alarming.

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Annexure 33

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SUBSTANCE ABUSE TREATMENT, PREVENTION, AND POLICY

RESEARCH Open Access

Self-reported tobacco smoking practices among medical students and their perceptions towards training about tobacco smoking in medical curricula: A cross-sectional, questionnaire survey in Malaysia, India, Pakistan, Nepal, and Bangladesh

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Abstract

Background: Tobacco smoking issues in developing countries are usually taught non-systematically as and when the topic arose. The World Health Organisation and Global Health Professional Student Survey (GHPSS) have suggested introducing a separate integrated tobacco module into medical school curricula. Our aim was to assess medical students' tobacco smoking habits, their practices towards patients' smoking habits and attitude towards teaching about smoking in medical schools.

Methods: A cross-sectional questionnaire survey was carried out among final year undergraduate medical students in Malaysia, India, Nepal, Pakistan, and Bangladesh. An anonymous, self-administered questionnaire included items on demographic information, students' current practices about patients' tobacco smoking habits, their perception towards tobacco education in medical schools on a five point Likert scale. Questions about tobacco smoking habits were adapted from GHPSS questionnaire. An *'ever smoker'* was defined as one who had smoked during lifetime, even if had tried a few puffs once or twice. 'Current smoker' was defined as those who had smoked tobacco product on one or more days in the preceding month of the survey. Descriptive statistics were calculated.

Results: Overall response rate was 81.6% (922/1130). Median age was 22 years while 50.7% were males and 48.2% were females. The overall prevalence of 'ever smokers' and 'current smokers' was 31.7% and 13.1% respectively. A majority (> 80%) of students asked the patients about their smoking habits during clinical postings/clerkships. Only a third of them did counselling, and assessed the patients' willingness to quit. Majority of the students agreed about doctors' role in tobacco control as being role models, competence in smoking cessation methods, counseling, and the need for training about tobacco cessation in medical schools. About 50% agreed that current curriculum teaches about tobacco smoking but not systematically and should be included as a separate module. Majority of the students indicated that topics about health effects, nicotine addiction and its treatment, counselling, prevention of relapse were important or very important in training about tobacco smoking.

Conclusion: Medical educators should consider revising medical curricula to improve training about tobacco smoking cessation in medical schools. Our results should be supported by surveys from other medical schools in developing countries of Asia.

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Background

Tobacco use is one of the leading preventable causes of premature death, disease and disability around the world [1]. Tobacco use is one of the risk factors for six out of eight leading causes of death worldwide [2]. An estimated 4.9 million deaths occurring annually can be attributed to tobacco use. This may increase to 10 million by the year 2020, if the current tobacco use epidemic continues and more than 70% of these deaths are expected to occur in developing countries [3]. Medical students who are future doctors have an important role to be played in tobacco cessation and prevention efforts. On the contrary, a vast body of evidence shows that prevalence of tobacco smoking is fairly high among medical students. Ironically medical students themselves lack adequate knowledge about smoking-related diseases and tobacco cessation techniques [4].

Expert reviews have suggested that undergraduate medical students should be equipped with knowledge and skills to promote smoking cessation skills among their future patients [4-7]. However, a worldwide medical school survey on teaching about tobacco has reported that tobacco smoking issues are usually taught non-systematically as and when the topic arose. The survey also reported that only a tenth of surveyed medical schools had a specific tobacco module. Another tenth of medical schools located mainly in Africa and Asia do not teach about tobacco issues [8]. Further, Global Health Professionals Student Survey (GHPSS) has suggested introducing a separate integrated tobacco module in medical schools to augment other strategies of tobacco control [9,10]. A few studies about medical students training in tobacco cessation and prevention methods have been reported from developed countries [11-13]. Such studies are seldom reported from South Asian countries [8]. A multi-country survey (1986-89) about habits, knowledge and attitudes of medical students regarding tobacco was carried out by the International Union against Tuberculosis and Lung Diseases (IUATLD) in Europe, Africa, Middle-East and Asia [14-16]. The survey has reported that medical students lack knowledge about smoking cessation and preventive measures. In a study from Bahrain, primary care physicians reported that training about smoking cessation techniques was not given in their medical schools [17].

Considering the pitfalls in training medical students about tobacco smoking in Asian countries and the recommendations made by GHPSS, we thought it was imperative to assess prevailing practices of medical students about tobacco smoking, prevention and cessation techniques, their perceptions and attitudes towards training in medical schools. Since country profiles, chronic disease burden and medical education systems are similar in the region of South Asia, we aimed to carry out an exploratory survey about training of medical students in tobacco-related issues in five South Asian countries. The objectives of our survey were as follows:

1. To assess the current practices of medical students towards tobacco smoking habits among their patients during clinical postings/clerkships.

2. To assess the perceptions and attitudes of medical students about their training in tobacco smoking.

3. To determine the current tobacco use among medical students.

Methods

Study design

A cross-sectional, self-administered anonymous questionnaire-based survey was carried out.

Setting and Participants

Final year undergraduate medical students were selected for this survey. The students studying in final year were expected to have completed nearly two years or more of clinical rotational postings in various medical specialties. The participants were selected from the following medical schools in Malaysia, India, Pakistan, Bangladesh, and Nepal: Melaka-Manipal Medical College (MMMC), Malaysia (a medical twinning program affiliated to Manipal University, India), Yenepoya Medical College (YMC) affiliated to Yenepoya University and AJ Institute of Medical Sciences (AJIMS), Mangalore, India (affiliated to Rajiv Gandhi University of Health Sciences, Karnataka, India), Manipal College of Medical Sciences, Pokhara (MCOMS), Nepal (affiliated to Kathmandu University), Combined Military Hospital, Lahore Medical College (CMH, LMC), (affiliated to the University of Health Sciences, Lahore) Pakistan and Faridpur Medical College (FMC), Faridpur, Bangladesh (affiliated to the University of Dhaka).

The undergraduate medical course in the medical schools we surveyed is of four to five years duration with compulsory rotational internships after completion of the final qualifying examination. Medical curricula were mostly traditional, lecture-based except at MCOMS (Nepal), where problem-based learning (PBL) was emphasised and at MMMC (Malaysia) emphasis was laid on PBL and tutorials rather than lectures alone. In all the medical schools, clinical rotations start from the third year onwards. Students undergo clinical training in major medical, surgical and allied specialties during each academic year. Duration of clinical rotations is usually four to eight weeks. At MMMC students undergo clerkships in major medical and surgical specialties during fifth year.

Sampling and sample size

Since our survey was exploratory in nature, a convenient sample of medical school/s was selected from in each country. All medical students studying in the final year of the undergraduate medical course were included for the survey.

Questionnaire

After a detailed review of literature and informal discussions with students about the topic, we developed a structured questionnaire in English (Annexure-1). The questionnaire was pretested among 20 medical students in each of the medical schools where the survey was planned. During pretesting, students also gave a written feedback about the questionnaire. We modified the questionnaire based on pretest results and students' written feedback. In the final questionnaire, the first section contained instructions, and a statement about confidentiality of information to be provided. Subsequent sections were about demographic information, students' current practices about tobacco smoking habits among their patients seen during clinical postings, their attitudes (in a five point Likert scale) towards teaching about tobacco smoking in their curriculum. Medical students' practices about their patients' smoking habits were assessed as 'never' to 'always', their perceptions towards training about smoking in their medical school as 'strongly disagree' to 'strongly agree' and the rating of contents in the tobacco module as 'unimportant' to 'very important'. We also included some questions about medical students' tobacco smoking habits. These questions were adapted and modified from the Global Health Professionals Student Survey (GHPSS) core questionnaire [18]. An *'ever smoker'* was defined as one who had smoked during lifetime, even if had tried a few puffs, once or twice. A *'current smoker'* was defined as one who had smoked during 30 days prior to the survey including the ones who smoked every day [19].

Data collection

Ethical approval and/or permission to carry out the survey were obtained from each medical school. Between November, 2009 and May, 2010 questionnaire was administered by the collaborators who were working as teaching faculty at each site. At each site, the students were briefed about the purpose of the research and were invited to participate in the survey. The students were informed that their participation in the survey was anonymous, voluntary and was not compulsory. Assurance was given about anonymity and confidentiality of the information to be provided. Informed consent was sought from all the students in the questionnaire. However, to maintain anonymity the students who participated in the survey signed a separate sheet containing their names and roll numbers. They were also instructed that they should not enter any identifiable personal information in the questionnaire. The questionnaire was distributed to the students during small group teaching sessions such as student seminars, tutorials, self-directed learning, problem-based learning etc. Completed questionnaires were collected.

Data management and statistical analysis

We used SPSS (Statistical Package for Social Sciences) version 14.0 for statistical analysis. We ran frequencies to check for any inconsistencies in data entry. If any the inconsistencies were found, we verified them with the completed questionnaires which had a unique code. We calculated rates of *'ever smoker'* and *'current smoker'* among male and female students in each country according to our defined criteria. We presented the responses to the questions about students' practices regarding smoking among their patients seen during clinical rotations/clerkships as percentages for *'often'* and *'always'*. For the questions about the importance of topics in tobacco education module, we presented the results as percentages for *'important'* and *'very important'*. For questions about students' perceptions towards teaching about tobacco smoking we presented responses for *'agree'* and *'strongly agree'*. We also cross-tabulated these responses according to smoking status (*ever smoker* versus *never smoker*), gender and country. We used chi square test for statistical significance for observed differences between categorical variables. A p-value of less than 0.05 was considered as significant.

Results

Response rates and demographic characteristics

Overall response rate was 81.6%. The response rates in each country/site varied from 76% (Nepal) % to 83.2% (India). Median age of the students was 22 years (interquartile range 21, 23 years). Table 1 shows demographic information of the participants. Overall, the proportion of male and female students was 50.7% and 48.2% respectively. In all these sites the proportion of male and female students was nearly 50% except Pakistan (65% were females) and Nepal (67% were males). Distribution of students according to religion varied across the countries. Majority of the students were Muslims in Pakistan (99.4%), and Bangladesh (80.1%) while in Nepal the majority (86.2%) were Hindus. In India, students were Hindus (46.1%), Muslims (40.8), and Christians (10.6) while in Malaysia students were Hindus (29.5%) Muslims (26.5%), Christian (15.5%) and of other religions (24.0%).

Self-reported smoking habits

Prevalence of smoking in all countries according to gender is presented in Table 2. Overall prevalence of *'ever*

Table 1 Response rates and demographic profile of the participants according to country (Number and percentage)

	Malaysia N = 200	India N = 208	Pakistan N = 161	Nepal N = 152	Bangladesh N = 201	Overall N = 922
Response rates	83% (200/240)	83.2% (208/250)	80.5% (161/200)	76% (152/200)	83% (201/240)	81.6% (922/1130)
Median age (years) inter quartile range	21 (20, 22)	24 (23, 25)	21 (20, 21)	22 (21, 23)	22 (21, 23)	22 (21,23)
Gender						
Male	95 (47.5)	96 (46.2)	56 (34.8)	102 (67.1)	118 (58.7)	467 (50.7)
Female	97 (48.5)	109 (52.4)	105 (65.2)	50 (32.9)	83 (41.3)	444 (48.2)
Religion						
Hindu	59 (29.5)	96 (46.1)	1 (0.6)	131 (86.2)	36 (17.9)	323 (35.0)
Muslim	53 (26.5)	85 (40.8)	160 (99.4)	1 (1.7)	161 (80.1)	460 (49.9)
Christian	31 (15.5)	22 (10.6)	0	2 (1.4)	0	55 (5.9)
Others	48 (24.0)	4 (2%)	0	18 (11.3)	3 (1.5)	73 (7.9)
Residence						
Hostel resident	69 (34.5)	45 (21.6)	77 (47.8)	64 (42.1)	178 (88.6)	274 (29.7)
Day scholar	93 (46.5)	158 (76.0)	84 (52.2)	86 (56.6)	19 (9.5)	598 (64.9)
Selection criteria						
Merit scholarship	63 (31.5)	48 (23.1)	11 (6.8)	36 (23.7)	26 (12.9)	184 (20.0)
Self-financed	108 (54.5)	147 (70.7)	150 (93.2)	113 (74.3)	169 (84.1)	676 (73.3)

Some of the percentages may not add up to 100% due to some missing entries in the demographic section of the questionnaire

smokers' and *'current smokers'* was 31.7% and 13.1% respectively. Prevalence of 'ever smoker' was highest in Bangladesh (38.8%), followed by Malaysia (34.5%) and it was lowest in India (10.1%). Prevalence of smoking among males was higher than females in all countries which was statistically significant. Males students were more likely to be *'ever smokers'* (Unadjusted OR = 3.51; 95% CI 2.59 - 4.75) as well as *'current smokers'* (Unadjusted OR = 6.89; 95% CI 3.98 - 11.93). The difference in prevalence of smoking between countries was statistically significant for both *'ever smokers'* ($p < 0.05$) and *'current smokers'* ($p < 0.01$). Median age at initiation of smoking was 18 years which did not vary according to countries. Majority of current smokers smoked less than 10 cigarettes per day.

Medical students' practices regarding smoking habits among their patients seen during most recent clinical rotations or clerkships are shown in Table 3. In all the countries, majority (> 80%) of the students asked the patients about their smoking habits, (duration and number smoked per day). About 40% of the students informed their patients about health effects of smoking. Only a third or less of the students either counseled or assessed willingness to quit smoking or assisted them in making a quit plan for their patients who were smokers. These practices varied significantly across the countries, but not according to smoking habits of the students. Female students were more likely to ask about smoking habits of patients and also inform them about health effects of smoking.

Table 4 presents medical students' perceptions regarding medical professionals' role in tobacco control and teaching about tobacco smoking in the medical curriculum. The results are shown as number and percentage of students who responded as either *'agree'* or *'strongly agree'*. Majority (> 80%) of the students had agreed

Table 2 Smoking habits among medical students according to gender and country

Country	Ever smoker			Current smoker		
	Male	Female	Total	Male	Female	Total
Malaysia(N = 200)	47 (49.5)	22 (22.7)	69 (34.5) *	18 (18.9)	4 (4.1)	22 (11.0)
India(N = 208)	19 (19.8)	2 (1.8)	21 (10.1) **	14 (14.6)	0	14 (6.7) **
Pakistan (N = 161)	24 (42.9)	22 (21.0)	46 (28.6) *	11 (19.6)	6 (5.7)	17 (10.6) **
Nepal (N = 152)	39 (38.2)	10 (20.4)	49 (32.2) *	23 (22.8)	4 (8.2)	27 (17.8) *
Bangladesh (N = 201)	60 (50.8)	18 (21.7)	78 (38.8) **	33 (28.8)	2 (2.4)	35(17.4) **
Overall (N = 922)	206 (44.3)	81 (18.5)	292 (31.7) **	99 (22.5)	16 (3.9)	121 (13.1) **

*$p < 0.05$, **$p < 0.001$

Table 3 Final year medical students' clinical practices towards tobacco smoking habits among their patients during their clinical rotations or clerkships according to their smoking status

		Ever smoker		Current smoker	
		Often (%)	Always (%)	Often (%)	Always (%)
1	Ask about history of smoking? ¶	67 (22.9)	179 (61.3)	19 (16.8%)	71 (62.85)
2	Ask about duration of smoking?	80 (27.4)	158 (54.1)*	25 (221.1)	62 (54.9)*
3	Ask about number of cigarettes/beedies smoked per day? ¶	61 (21.0)	165 (56.9)	19 (17.0)	69 (61.6)
4	Informed or advised patients about health effects of smoking? ¶	59 (20.3)	58 (20.0)	21 (18.8)	26 (23.2)
5	Counseled my patients who are smokers during clinical postings?	54 (18.6)	33 (11.4)	27 (23.9)	15 (13.3)
6	Assessed the willingness of the patient to quit smoking?	48 (16.5)	26 (8.9)	20 (17.7)	14 (12.4)
7	Assisted the patient to make a plan to quit smoking?	32 (11.0)	25 (8.6)	17 (15.0)	14 (12.4)
8	Informed patients about effects of passive smoking?	69 (23.7)	33 (11.3)**	27 (23.9)	20 (17.7)

*p < 0.05, **p < 0.001, ¶ these were statistically significant according to gender
Differences between the countries were significant for all the items p < 0.001

about the following items: medical professionals have an important role in patients' smoking cessation, every patient should be asked about tobacco smoking, and all doctors should be competent about counseling and treatment for smoking cessation. Nearly 80% of the students agreed about the following items: medical professionals should be role models by being non-smokers to advice/counsel their patients, smoking among medical professionals is an obstacle for effective implementation of tobacco education and all medical schools should have facilities for smoking cessation. The perceptions of medical students about medical professionals' role in tobacco cessation were statistically significant according to smoking status and gender. Never smokers and female students were likely to respond as *'agree'* or *'strongly agree'*.

For questions about tobacco education in their medical school curricula, only a third felt that they are being taught adequately about health effects of smoking, and tobacco cessation methods. Nearly half of the students

Table 4 "Mark your level of agreement with following statements about teaching on tobacco smoking in medical schools"? Number and percentage of students responding as 'agree' or 'strongly agree'.

		Agree	Strongly agree
1	Medical professionals play an important role on advising public/patients about smoking cessation? *	382 (41.4)	433 (47.0)
2	In clinical practice, tobacco smoking history should be routinely taken for every patient? *	319 (34.6)	533 (57.8)
3	All doctors should be competent to advise patients about, counseling & treatment of smoking cessation. ¶*	351 (38.1)	487 (52.8)
4	Medical professionals should be role models by being non-smokers to advice their patients smoking cessation. ¶*	231 (25.1)	490 (53.1)
5	All medical schools should have smoking cessation clinics with facilities for counseling, treatment & follow-up. ¶	362 (39.3)	375 (40.7)
6	Smoking amongst medical teachers and students is a main obstacle in effectively implementing tobacco education.	281 (30.5)	362 (39.3)
7	The current curriculum teaches adequately about health effects of active and passive smoking.	298 (32.3)	122 (13.2)
8	The current curriculum teaches about clinical guidelines, tobacco cessation methods and its contraindications.	258 (28.0)	94 (10.2)
9	All medical colleges should teach the students about cessation, treatment & counseling for smoking. ¶*	244 (26.5)	306 (33.2)
10	Current curriculum teaches about tobacco smoking but not systematic integrated with other disciplines departments.	326 (35.4)	92 (10)
11	All medical colleges should include tobacco education as a separate module in their curriculum.	295 (32.0)	166 (18.0)

¶these items were statistically significant according to ever smoker versus never smoker
* these items were statistically significant according to gender

felt that they should be trained about tobacco cessation methods including counseling; current training about tobacco smoking is not systematic and integrated with other disciplines. About half of the students agreed that medical school curricula should include a separate module about tobacco education. Three quarters of the students from Bangladesh agreed about teaching tobacco cessation, and counseling, in a separate module of the medical curriculum.

Students' perceived importance of contents (topics) in the tobacco education module is shown in table 5. Majority (> 80%) of the students indicated following topics as either *'important'* or *'very important'*: health effects of tobacco smoking (active and passive), symptoms of nicotine addiction, benefits of cessation, clinical guidelines for cessation, types of treatment and counseling techniques. About half of the students indicated epidemiology of smoking, clinical rotations and tobacco control policies and regulations as *'important'* or *'very important'*. About three fourth of the students indicated contents of cigarette smoke, indication and contraindications of cessation treatment, prevention of relapse as *'important'* or *'very important'*. There was very little variation across the countries, according to gender and smoking habits of the students.

Discussion

Our exploratory survey from six medical schools in five South Asian countries has identified some gaps in medical students' practices about tobacco cessation and counseling. Self-reported use of cigarette smoking among medical students, students' perception about lack of adequate and systematic approach in training about tobacco smoking in their medical curriculum is a matter of concern. Interestingly, majority of the students indicated that contents of cigarette smoke, health effects of smoking and methods of smoking cessation and counseling as *'important'* in the tobacco module. Despite this only about half the students agreed that a separate tobacco module should be included in their curriculum.

Smoking rates among medical students in our survey were lower than those reported from previous surveys among medical students in Europe, North African and Middle Eastern countries [14-16]. Overall smoking rates in our survey were slightly higher than a previous survey in Asian countries [15]. The smoking rates among female students were lower in our study which is similar to the results reported from other surveys. In Asian countries, which are generally conservative societies, smoking is considered as unacceptable and thought to offend the social customs. However, as compared to previous surveys there is a slight increase in smoking rates among female students. This may be attributed to improvement in women's social status i.e. education, employment, urbanization and also marketing of lighter cigarettes meant for women by the tobacco industry [20]. We adapted questions about smoking habits from GHPSS while the studies cited above have adapted questions from WHO document. These studies varied from ours not only in classification of smokers and also the criteria used to define smokers.

Studies about smoking rates among practicing physicians are lacking. A survey from Kerala, India has reported that 10.8% of surveyed physicians were current smokers and 26% were *'ever smokers'* [21] which is higher than the smoking rates among students we surveyed from two medical schools in India. A survey from Lahore, Pakistan has also reported a higher smoking rates among physicians [22]. Though we did not find any literature about prevalence of smoking among physicians, we expect a similar pattern in other developing Asian countries. There is a need for leadership from the medical professionals by themselves being role models: *"doctor practice what you preach"* [23]. A smoking

Table 5 Rate the importance of following topics in tobacco education module in your curriculum

	Topic/contents of tobacco curriculum	Important	Very important
1	Epidemiology of tobacco smoking	322 (34.9)	195 (21.1)
2	Contents of cigarette smoke	356 (38.6)	323 (35.0)
3	Health effects of both active and passive smoking	230 (24.9)	595 (64.5)
4	Physical & psychological effects of nicotine addiction	255 (27.5)	557 (60.4)
5	Benefits from cessation of smoking	262 (28.4)	533 (57.8)
6	Clinical guidelines for smoking cessation	360 (39)	417 (45.2)
7	Types of cessation treatments available	384 (41.6)	378 (41.0)
8	Indications and contraindications for treatment	386 (41.9)	333 (36.1)
9	Counseling techniques to motivate patients quit smoking	331 (35.9)	416 (45.1)
10	Prevention of relapse and follow-up	387 (42.0)	331 (35.9)
11	Clinical postings in smoking cessation clinic	340 (36.9)	206 (22.3)
12	Tobacco control policies, regulations etc	310 (33.6)	306 (33.2)

doctor is a poor role model for the patient. Regrettably, anecdotal evidence suggests that professional assistance or facilities to quit smoking habit are barely available in these medical schools for smoking doctors or medical students. The results of our survey support our argument in accordance with a worldwide medical school survey [24].

One of the important shortcomings among practices of medical students we surveyed was advising about health effects, counseling and smoking cessation for smokers. This may be due to lack of knowledge among medical students about smoking-related diseases and smoking cessation techniques [25]. The worldwide survey of medical schools has reported that medical curricula of medical schools in low and middle income countries are deficient in training about cessation techniques [24] unlike in USA [11] and other developed countries [13]. These findings are not surprising considering the results of a survey among physicians in Kerala, India which reported that only a third of physicians had received training about cessation methods [21]. In another study from Bahrain primary care physicians reported about insufficient training during their medical school [17]. Both GHPSS and global medical school survey have underscored the importance of training medical students about cessation techniques [9,24]. Even in our survey, students agreed that all doctors should be competent in counseling and cessation methods and about having tobacco cessation clinics in university teaching hospitals. The students' perceptions about medical professionals' role in tobacco smoking was optimistic and they agreed about deficiencies in their current curricula. However, this optimism of students does not convert into inclusion of a separate tobacco education module including training about cessation techniques. Possible reasons for such difference could be vastness of syllabus, current methods of teaching and contents of medical curricula in these medical schools. It is also possible that students in traditional lecture-based curricula consider these topics as an additional burden. We justify this from the results of our previous studies in two of the five medical schools where our survey was carried out. The students reported that *'vast syllabus'* and *'frequent examinations'* were important sources of stress [26,27].

Though a majority of the students in our survey indicated that health effects, nicotine addiction, and its treatment as important contents in the module on tobacco education, they did not favor an additional clinical posting in cessation clinics. One reason could be an additional burden on an overloaded student. Another possibility is non-availability or unawareness of such facilities in the teaching hospitals of these medical schools. However, we feel that medical educators should seriously consider about clinical postings during curriculum review for adoption of tobacco education module. Experts working on training of medical students or health professionals in tobacco control have suggested about several obstacles or barriers to effective implementation of tobacco curriculum. They have also suggested some solutions to overcome these obstacles [5]. Tobacco control experts, medical educators, administrative staff of medical schools, universities, accreditation bodies should work together in this direction. Further studies in each of these countries about current content of medical curriculum, mode of delivery, teaching learning outcomes and facilities for counseling and cessation treatment in the medical schools could be beneficial for revision of the current curriculum or introduction of a separate integrated tobacco education module. Such an initiative has been undertaken as a pilot project in India and Indonesia by the Project Quit Tobacco International [28]. Results of our survey support the need for such an initiative.

The results of our exploratory survey should be interpreted in the light of some limitations we had. Due to exploratory nature of the survey on a convenient sample of medical schools our results can only provide a snapshot about the medical schools we surveyed. Therefore, our results cannot be applied to other medical schools. However, our study is expected to set a benchmark for further studies about medical professionals' role and training medical students in tobacco control. As smoking behavior among students was self-reported there could have been reporting bias. Verification of self-reported smoking behavior with cotinine tests was not possible since our survey was not funded. Although participation in our survey was not compulsory, we obtained acceptable response rates. However, we cannot rule out some selection bias.

Conclusions

Cigarette smoking was prevalent among medical students we surveyed. Counselling and cessation treatment is required for students who are smokers to quit their habit. Students were not practicing smoking cessation methods for their patients seen during clinical postings or clerkships. Though students have a positive perception towards medical professionals' role in tobacco control they were not encouraging about inclusion of a separate tobacco education module into their medical curriculum. However, they emphasised that health effects, counselling and treatment of nicotine addiction were important contents in the tobacco education module. Medical educators should consider about improving medical curricula to train tomorrow's doctors in

prevention and cessation of smoking. Our results should be supported by larger surveys in more medical schools in each country.

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Competing interests

The authors declare that they have no competing interests.

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Annexure

Kids and Adolescents

Smokeless tobacco consumption among school children

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Abstract

BACKGROUND: More than one-third of the tobacco consumed regionally is of smokeless form. **AIMS:** To determine the prevalence and pattern of smokeless tobacco use among school children. **SETTINGS AND DESIGN:** This cross-sectional study was conducted among children in 5 randomly selected high schools in Kannur district, Kerala, India. **MATERIALS AND METHODS:** This cross-sectional study was conducted among 1200 children. A self-administered questionnaire was used for data collection. **STATISTICAL ANALYSIS:** PASW 17 software was used for data analysis. **RESULTS:** The mean age of the students was 14.4 years with a standard deviation (SD) of 1.2 years, and 8.5% (CI, 7.1–10.2) of the participants were tobacco users. Smokeless tobacco was used by 2% (CI, 1.2–3.4) of the participants. None of the female students used tobacco products. Among the tobacco users, the mean age at the start of any tobacco use was 12.8 years with an SD of 1.1 years. The minimum age was 12 years and the maximum was 14 years. More than 50% smokeless tobacco users started their habit at the age of 12 years; 38.5% of them started at the age of 13 years and remaining at the age of 14 years. The 84.6% smokeless tobacco users were using it 2–3 times a week and 39% of them revealed that the tobacco products were purchased from shops located near the schools. Among the users, one used to keep the quid in the mouth for more than half an hour. **CONCLUSION:** The study concludes that there is a need to educate the children regarding the hazards associated with tobacco consumption.

Key words: Age at initiation, prevalence, school children, smokeless tobacco

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Introduction

Estimates show that in India, on existing trends, tobacco will kill 80 million males who are presently aged 0–34 years.[1] Different ways of tobacco consumptions are found all over the World. In India, smokeless tobacco use also is very common among both males and females. A study conducted in Kolkata, India, showed that about 38.3% of adult males were smokers and 35.7% were tobacco chewers. Among females, smoking habit prevalence was low, that is, 0.5% only. But 18.7% of females were tobacco chewers. The study also revealed that 52% of smokers were using cigarettes and 35% were using beedis for smoking.[2] A youth tobacco surveillance study reported that 68% of boys and 48% of girls had their first experience of tobacco before the age of 10 years. The current use of tobacco product was 57% among boys and 41% among girls.[3] A study by Horn *et al* showed that among youths, 31.8% were current tobacco smokers and 16.1% were current smokeless tobacco users. Among the students who were currently smokeless tobacco users, 63.2% were also current smokers.[4]

The traditional forms, such as betel quid, tobacco with lime, and tobacco tooth powder are commonly consumed in addition to the other forms of smokeless tobacco, and the use of new products is increasing. Usually men are the consumers but children, teenagers, women of reproductive age, and medical and dental students also consume the smokeless form.[5] The exact compositions of smokeless forms differ according to regional preferences. Smokeless tobacco forms are applied to the mandibular or labial groove for 10–15 min by most people and then they chew it slowly.[5] Consumption of processed areca nut products containing tobacco increases the chance of developing oral submucous fibrosis.[5] About 35–40%[5] of tobacco consumption in India is in smokeless forms. Moreover, smokeless form of tobacco use among

children, adolescents, women, and also immigrants of South Asian descent, wherever they have settled, has increased.[5,6] The major factors that persist to encourage people to use smokeless form of tobacco are its low price, ease of purchase or production, and the widely held misconception that it has medicinal value for improvement in tooth ache, headache, and stomach ache.[5] Furthermore, in contrast to smoking, there is no taboo against using smokeless tobacco[5] and the government's efforts have also focused more on eliminating cigarette use than tobacco as a whole.[5,7] All these, coupled with peer pressure and belief that using smokeless tobacco is less hazardous than smoking mean that these forms continue to be used by vast numbers of people, especially children.

Presently, tobacco use is the leading preventable cause of death globally,[8] and it is estimated that by 2030, it would account for over 10 million annual deaths worldwide,[9,10] 70% of which will be in the developing world.[11] All forms of tobacco carry serious health consequences, most importantly oral and pharyngeal cancers[5,12-15] and other malignancies of the upper aerodigestive tract.[5,9,16] Tobacco-related cancers account for about one-third of all cancers in South Asia,[5] while the emerging "epidemic" of oral submucous fibrosis[5,13] has been attributed to chewing of areca nut and its mixtures. There is also evidence that smokeless tobacco is a risk factor for hypertension and dyslipidemias.[5] This study was conducted to determine the prevalence and pattern of smokeless tobacco use among school children.

Materials and Methods

This cross-sectional study was conducted in the northern part of Kerala state in India in the year 2008. The participants were from Kannur district. Kannur district has a population of 24,08,956. Kannur district is one of the 14 districts in the state of Kerala. It is bound by Kasaragod district in the north, Kozhikode in the south, the Western Ghats in the east, and the Arabian Sea lies to the west.

A three-stage sample design was adopted to select the schools. In the first stage of the study, Kannur district was randomly selected among the districts in the northern part of Kerala. Line listing of higher secondary schools in Kannur district was done. Five schools were randomly selected from the list of schools in the second stage. The sampling unit in the study was class/division and total strength of students in each class varying from 30 to 40. In the third stage, classes were randomly selected from the selected schools.

Five high schools were randomly selected from the district. A total of 1200 students participated in the study. The response rate was 100% for schools and 81.4% for the students. Absence from the school on the day of study was the only cause for nonresponse. Students who were absent on the day of the study were excluded. No attempt was made to resurvey.

Informed consent was obtained from the school authorities before distributing the questionnaire. A self-administered, structured, open-ended pilot-tested questionnaire was used for data collection. The research tool included sociodemographic characteristics, type of tobacco habit, age at start, accessibility to tobacco products, reasons for using tobacco products, the use of spit tobacco, and the associated factors. Anonymity was maintained by asking them not to write their names in the questionnaire. The study was conducted over a period of 6 months.

After explaining the purpose of the study, all the students studying in the high schools were given the self-administered questionnaire. On the same day, the tool was collected back from the participants. The data were fed into an excel spread sheet and transformed to PASW 17 for statistical analysis. Descriptive analysis was done. Test of significance was done to find the association between variables, and a P value < 0.05 was considered statistically significant.

Results

In Table 1, the sociodemographic characteristics of the study participants are shown. A total of 1200 students studying in grade 8–12 participated in the study. With regard to the age of the participants, 31.1% were 14 years old, 28.7% have attained 13 years of age, 23.4% of them were 15 years of age, 9.8% were 16 years of age, and the remaining 7.1% were 17 years of age. In the present study, 52.5% were males and the remaining

Table 1: Sociodemographic characteristics of participants

Variable	Group	No.	%
Age (y)	13	344	28.7
	14	373	31.1
	15	281	23.4
	16	117	9.8
	17	85	7.1
Gender	Male	630	52.5
	Female	570	47.5
Religion	Hindu	633	52.8
	Christian	276	23.0
	Muslim	291	24.3
	Total	1200	100.0

were females. The sex ratio observed was 869 girls for 1000 boys. As far as religion is concerned, 52.8% were Hindu compared with those belonging to the other 2 religions. The mean age of the students was 14.4 years with an SD of 1.2 years. Age ranged from 13 to 17 years.

The prevalence and the type of tobacco products used by the school children are shown in Table 2. Among the participants, 91.5% were not tobacco users, whereas 8.5% (CI, 7.1–10.2) of them were tobacco users and were either smoking and/or using smokeless tobacco. As regards gender and tobacco use, 84.1% of male students were not tobacco users, whereas 15.9% (CI, 13.3–18.9) were tobacco users. Among the male students, 1.6% (CI, 0.9–2.8) were smokers. Smokeless tobacco alone was used by 2% (CI, 1.2–3.4) of the male students and 12.3% (CI, 10.0–15.1) of them were smoking as well as using smokeless tobacco. None of the female students were using tobacco products.

Age at start of tobacco use is depicted in Table 3. Among the tobacco users, the mean age at the start of any tobacco use was 12.8 years with an SD of 1.1 years. The minimum age of initiation was 11 years and the maximum age was 15 years; 52.0% of the users started tobacco consumption by 12 years. The age at initiation of smokeless tobacco habit is also shown in Table 3. The minimum age was 12 years and the maximum was 14 years. More than 50% of the smokeless tobacco users started their habit at the age of 12 years; 38.5% of them started at the age of 13 years and the remaining at the age of 14 years.

Of the total 92 smokeless tobacco users, 84.6% were using it 2–3 times a week. The remaining were using it once in a week. Of them, 39% revealed that the tobacco products were purchased from shops located near the schools. Also, 31% reported that they were getting this from petty shops. Among these users, one used to keep the quid in the mouth for more than half an hour. Most of them were using smokeless tobacco products because of their novelty and the misconception that they are safe form of tobacco and also they could be consumed much less conspicuously than the smoke form of tobacco products at home, in school, and other locations.

Table 2: Prevalence and type of tobacco use among school children according to gender

Habit	Gender				Total	
	Male		Female			
	No.	%	No.	%	No.	%
No habit	540	84.1	558	100.0	1098	91.5
Smoke form only	10	1.6	-	-	10	0.8
Smokeless tobacco only	13	2.0	-	-	13	1.1
Smoke and smokeless form	79	12.3	-	-	79	6.6
Total	642	100.0	558	100.0	1200	100.0

Table 3: Age at start of tobacco use

Age at start (y)	Any form of tobacco use		Smokeless tobacco use	
	No.	%	No.	%
11	2	2.0	1	1.1
12	53	52.0	47	51.1
13	21	20.6	20	21.7
14	14	13.7	14	15.2
15	12	11.8	10	10.9
Total	102	100.0	92	100.0

Discussion

The Global Youth Tobacco Survey reported that among adolescent children, smoking is the predominant form of tobacco use in the developed countries, whereas in the developing countries smokeless tobacco is equally prevalent.[18] In the current study, 8.5% of the total students were users of some form of tobacco. Among males, the prevalence observed was 15.9% and none of the female students in the study had the habit of tobacco use. As far as tobacco smoking is concerned, the prevalence was 1.6%, smokeless tobacco consumption was 2%, and both smoke and smokeless form was 12.3%. A study by Sinha *et al* observed that among students in the southern region of India in the age group of 13–5 years, the prevalence of any form of tobacco use was 8.2%. Among the males, the rate was 10.3% and among the females, the rate was 5.7%. With regard to smokeless tobacco use, the prevalence observed was 3.4% (4.5% among males and 2.0% among females).[18] This study supports the finding of prevalence of tobacco use among males in the present study. But a study among school children in Jaipur observed that any form of tobacco use in males was 2.06% and in females it was 1.7%. With regard to smokeless tobacco use, the same was 0.56% and 0.85%, respectively; this observation was not in accordance with the other studies[19,20] and also the present study. A study conducted in Goa reported that tobacco use among boys was 13.5% and among girls was 9.5%.[21] A study conducted in Mumbai by Jayant *et al* reported that the prevalence of tobacco use ranged from 6.9% to 22.5%[22] Another study conducted in Kerala observed that the prevalence of all types of tobacco use was 29% and smoking was 2%.[23] A study conducted in Gujarat by Makwana

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et al observed that the prevalence of tobacco chewing increases with age. The prevalence was 28.4% in the age group of 10–13 years, 33.6% in the age group of 14–16 years, and 36.3% in the age group of 17–19 years. The study also observed that among the users, 66.2% had the habit of only tobacco chewing, 14.6% had the habit of only smoking, and 19.2% had the habit of both smoking and tobacco chewing.[24] Another study conducted in Wardha reported that 68.3% boys and 12.4% girls had consumed some form of tobacco products in the last 30 days, with an overall prevalence of 39%.[25] A study conducted in Delhi observed that the prevalence of tobacco use was 5.4% (boys: 4.6%, girls: 0.8%).[26] Most of these studies support the observations made by the present study.

Regarding the age at initiation of tobacco habit, the present study observed that the mean age at start of any form of tobacco use was 12.8 years. The mean age at initiation of smokeless tobacco use also was found to be almost same, that is, 12.5 years. A study conducted in Mizoram observed that the mean age at the start of tobacco chewing and smoking was 17.2 years.[27] A study from Uttar Pradesh reported that the common age of experimenting with tobacco is 14–15 years.[28] The present study and other studies also observed that the initiation of tobacco use is usually in the teen period.

Conclusion

The present study demonstrated that there is no restriction on the sale of tobacco to school children in the study area. All children had easy access to tobacco products from shops near the schools. More than 90% of the students were nontobacco users. They need to be protected from the users. Based on the study findings, inclusion of tobacco control activities in the school curricula is very important for laying the foundation of healthy lifestyle practices among the school children. The habits injurious to health should be nipped in the bud itself. Also, these children can act as messengers by transmitting the desired message to members of his or her family and community. Children are the readily available and reachable population group in the context of primordial prevention. The study suggests that Students Advising and Guiding Units should be started in schools to offer counseling services to the needy children and those who are addicted to this habit.

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Annexure 25

Differences in tobacco use among young people in urban India by sex, socioeconomic status, age, and school grade: assessment of baseline survey data

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Summary

Background The epidemic of tobacco use is shifting from developed to developing countries, including India, where increased use is expected to result in a large disease burden in the future. Changes in prevalence of tobacco use in adolescents are important to monitor, since increased use by young people might be a precursor to increased rates in the population.

Methods 11 642 students in the sixth and eighth grades in 32 schools in Delhi and Chennai, India, were surveyed about their tobacco use and psychosocial factors related to onset of tobacco use. Schools were representative of the range of types of school in these cities.

Results Students who were in government schools, male, older, and in sixth grade were more likely to use tobacco than students who were in private schools, female, younger, and in eighth grade. Students in sixth grade were, overall, two to four times more likely to use tobacco than those in eighth grade. 24·8% (1529 of 6165) of sixth-grade students and 9·3% (509 of 5477) of eighth-grade students had ever used tobacco; 6·7% (413 of 6165) and 2·9% (159 of 5477), respectively, were current users. Psychosocial risk factors were greater in sixth-grade than in eighth-grade students. The increase in tobacco use by age within each grade was larger in sixth grade than in eighth grade in government schools, with older sixth-grade students at especially high risk.

Discussion The finding that sixth-grade students use significantly more tobacco than eighth-grade students is unusual, and might indicate a new wave of increased tobacco use in urban India that warrants confirmation and early intervention.

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Introduction

Tobacco use continues to be the leading cause of preventable death worldwide.[1] However, the burden of tobacco use is shifting from developed to developing countries.[2] By 2030, it is estimated that 10 million people per year will die from tobacco use, with 70% of those deaths occurring in developing countries.[1] In India, the proportion of all deaths that can be attributed to tobacco use is expected to rise from 1·4% in 1990 to 13·3% in 2020, which will result in enormous economic, emotional, and societal costs in a population of more than a billion people.[4]

Increased use of tobacco at the population level can often first be recognised by increased use among young people, since most people begin to use tobacco while they are teenagers, become addicted, and thereby become adult users, carrying the wave of increased use into the population over time.[5,6] This pattern was seen very clearly in the USA after the introduction and advertising of brands of cigarettes for women in the late 1960s. There were substantially increased initiation rates only among women younger than 18 years old, who remained smokers into adulthood, and increased the overall adult female smoking rates in the 1970s and 1980s.[7,8] In India, recent data suggest an increase in the prevalence of regular tobacco use among urban teens in Delhi and Mumbai since 2001.[9] Thus, we aimed to carefully examine current tobacco use in teenagers in urban India, and to explore whether particular subgroups used tobacco at higher rates, since these trends should be important for prediction of changes in future tobacco use and tobacco-related morbidity and mortality.[5,6]

Methods

Study design and participants

Project MYTRI (Mobilising Youth for Tobacco-Related Initiatives in India) is a randomised community trial with a long-term goal to prevent and reduce tobacco use among young people in the sixth to ninth grades (age 10–16 years) in Delhi and Chennai, India.[10] The trial involves a 2-year intervention to prevent tobacco use with two cohorts of students, those in the sixth and eighth grades in 2004. 32 schools with students in the sixth to 12th grades are participating in the trial. These schools were selected because they were representative of the range of types of schools in these urban cities, including government (low-to-middle income), private (middle-to-upper income), girls-only, boys-only, and co-educational schools. The study design is shown in figure 1. Schools were also selected that were not near to each other, to avoid contamination of the control schools in the trial, and that were willing to sign a cooperative agreement for 2 years of full participation.[10] In the present study, we assessed the baseline tobacco use data from sixth-grade

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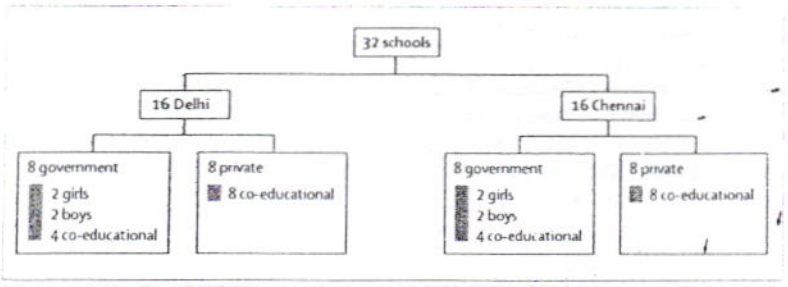

Figure: Project MYTRI study design

and eighth-grade students in the 32 schools. We postulated that students who were in government schools, boys, older in age, and in the eighth grade, would be using more tobacco than those who were in private schools, girls, younger in age, and in the sixth grade.

All students in the sixth and eighth grades (n=12 484) in the 32 schools were eligible and were invited to participate in the baseline survey in the summer of 2004. Informed passive parental consent and active student assent procedures were used. Letters were sent home from the schools to parents of all eligible students. Parents were asked to return a card if they did not want their child to participate in the survey. Students were read a form at the time of the survey ensuring confidentiality and also that their standing with their school and with the project would not be jeopardised by not participating. Every student signed an assent form if they agreed to participate. The institutional review board at the University of Minnesota (Minneapolis, MN, USA) and the Indian Independent Ethics Committee (Mumbai, India) approved the study protocol.

Procedures

The tobacco use survey was a self-administered paper and pencil survey administered in school classrooms by trained survey interviewers from the project. The questions about tobacco use were adapted from the Global Youth Tobacco Survey, which has been used in eighth-grade to tenth-grade students.[11,14] To ensure appropriate adaptation for sixth-grade students and our population, we did 48 focus groups with 435 students to gather information on their understanding of tobacco, tobacco use, and psychosocial predictive factors.[15] We then developed the questionnaire on the basis of this information, the Global Youth Tobacco Survey, and previous surveys. The draft questionnaire was translated from English and back-translated into Hindi and Tamil. All private schools in both cities had English versions. The government schools' versions were in Hindi in Delhi and in Tamil in Chennai. We administered the draft questionnaire to small groups of sixth-grade and eighth-grade students (n=60) in English, Hindi, and Tamil in government and private schools in Delhi and Chennai, and then discussed each question with them, and modified the questionnaire accordingly. Finally, we piloted the survey in English and Hindi with 235 students in private and government schools in Delhi in order to pilot survey implementation (including student questions and concerns during administration) and assess the psychometric properties of the survey.

Tobacco use items measured ever use and current use of chewing tobacco, cigarettes, and bidis (hand-rolled cigarettes). Current use of tobacco was measured by the questions: "During the last 30 days, did you (chew tobacco in any form?) (smoke one or more bidis?) (smoke one or more cigarettes?)". The response categories were "yes" or "no". Ever use of tobacco was measured by the questions: "How old were you when you first (chewed tobacco in any form?) (put a lit cigarette in your mouth?) (put a lit bidi in your mouth?)". The response categories were "I have never (chewed tobacco) (put a lit cigarette in my mouth) (put a lit bidi in my mouth)", or a specific age ranging from 7 years or less to 16 years or more. These response categories were collapsed to create a dichotomous variable: no use versus ever use of tobacco.

Additionally, psychosocial factors that are associated with tobacco use among young people in the USA were assessed with scales that measured intentions to use tobacco in the future, social susceptibility to use tobacco, reasons to use tobacco, and normative expectations concerning tobacco use.[8,16,17] All scales were created by adding up the scores of the responses to individual items. The two intentions scales each included four items: "Do you think you will try chewing tobacco (smoking cigarettes or bidis) in the next month? In the next year? When you enter college? When you are an adult?". Each item had four response categories including: "surely yes (3), maybe yes (2), maybe no (1), and surely no (0)". The scale range was 0–12 and the α coefficients for the intentions scales were 0·85 (chewing) and 0·87 (smoking). The two social susceptibility scales each included four items: "If one of your close friends gave you chewing tobacco (a cigarette or bidi), would you chew (smoke) it? If a group of friends gave you . . . ? If one of your family members gave you . . . ? If someone at a party gave you . . . ?" Each item had four response categories: "surely yes (3), maybe yes (2), maybe no (1), and surely no (0)." The scale range was 0–12 and the α coefficients for the two social susceptibility scales were 0·87 (chewing) and 0·88 (smoking). The reasons to use tobacco scale was measured by six items that addressed whether chewing or smoking was fashionable, fun to do with friends, grown up and brave, a way to reduce boredom, attractive to friends who are boys, and attractive to friends who are girls. Each item had four response categories: "surely yes (3), maybe yes (2), maybe no (1), and surely no (0)." The scale range was 0–18 and the α coefficient for the reasons to use tobacco scale was 0·73. The final scale addressed social norms (normative expectations) concerning tobacco use and was measured by six items: "If you were

to use tobacco, do you think . . . Your close friends would like it? Your parents would like it? Your teachers would like it? Your relatives/neighbours would like it? Boys in your school/neighbourhood would like it? Girls in your school/neighbourhood would like it?" Each item had four response categories: "surely yes (0), maybe yes (1), maybe no (2), and surely no (3)." The scale range was 0–18 and the α coefficient for the normative expectations scale was 0·91. To assess the validity of the psychosocial scales, the relations between the scales and tobacco use measures were assessed among all students using a series of regression models. All the scales were significantly associated with ever use of tobacco ($p<0·05$).

Trained survey interviewers from the Project MYTRI staff introduced the questionnaire in the classrooms, then allowed students to complete it at their desk with a pencil that we provided. Survey interviewers answered any questions as they arose during the survey administration, including queries related to the clarification of questions on the survey instrument. Students were given unique identification codes to assure confidentiality. Teachers remained in the classrooms but did not participate in the survey administration.

Statistical analysis

A series of mixed-effects regression models were used to assess differences in rates of tobacco use and psychosocial scales by relevant demographic factors, including city (Delhi *vs* Chennai), type of school (private *vs* government), sex (boys *vs* girls), grade (sixth *vs* eighth grade), and age (≤11 years *vs* 12 years *vs* 13 years *vs* ≥14 years). This kind of regression model is the most appropriate, in view of the nested study design, as it accounts for variability between both students and schools.[18] All comparisons between grade levels were adjusted for, when not stratified by, other demographic factors (city, school type, sex, age). In examining interactions between grade and other demographic factors, the only significant interaction was between age and grade, so comparisons between grade levels were additionally adjusted for the age*grade interaction. All analyses were done with SAS (version 8.80) statistical software.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

94% of the sample participated (n=11 748). Of the remainder, 4·4% were absent on the initial and make-up survey days (we came in on a second day to every school to survey those who were absent on the initial survey day); 1·5% did not participate because of parent or student refusal. After exclusion of inconsistent responders (<1%), that is, those with four or more inconsistent responses on the survey (such as reporting that they had used tobacco in the past month, but had not ever used in their lives), the analysis sample size was 11 642. The sample analysed included 5889 (50·6%) from Delhi, 4489 (38·6%) from private schools, 6386 (54·9%) who were male, and 6165 (52·9%) who were in the sixth grade. Mean age was 11·21 years (range 10–16 years) for students in the sixth grade and 12·92 years (10–16 years) for those in the eighth grade.

Overall, 1667 (14·7%) students had ever used tobacco; 1242 (10·8%) had chewed tobacco, 851 (7·4%) had smoked cigarettes, and 796 (7%) had smoked bidis. 520 (4·6%) were current tobacco users, with 346 (3%) currently using chewing tobacco, 163 (1·4%) cigarettes, and 180 (1·6%) bidis. Significant differences in ever use of any kind of tobacco were found by type of school, sex, age, and grade level. 1237 (17·3%) students at government schools and 476 (10·6%) at private schools had ever used tobacco. 1086 (17%) boys and 568 (10·8%) girls had used tobacco. Of students aged 10 years or younger, 96 (6%) had used tobacco, compared with 282 (9·3%) aged 11 years, 416 (14·9%) aged 12 years, 454 (17·6%) aged 13 years, and 346 (21·9%) aged 14 years or older. 1529 (24·8%) sixth-grade students had ever used tobacco, compared with 509 (9·3%) eighth-grade students.

These differences by demographic factors were in the expected direction except for the difference between sixth-grade and eighth-grade students. Students in the sixth grade were significantly more likely to use all forms of tobacco than students in the eighth grade (table 1), in each city, in government schools, and for both sexes (table 2). Sixth-grade students' tobacco use was, overall, two to four times that of eighth-grade students. Students in the sixth grade were overall using more tobacco than those in the eighth grade in every age group. The increase in tobacco use by age was greater in sixth-grade students than eighth-grade students ($p=0·0003$).

	Sixth grade (n=6165)	Eighth grade (n=5477)	Ratio*	p
Ever use of tobacco				
Chewing tobacco	19·0% (17·4–20·6)	6·8% (5·3–8·3)	2·8:1	<0·0001
Smoking bidis	11·9% (10·6–13·2)	3·4% (2·2–4·6)	3·5:1	<0·0001
Smoking cigarettes	12·5% (11·1–13·9)	4·7% (3·5–5·9)	2·7:1	<0·0001
Any kind of tobacco	24·8% (23·0–26·6)	9·3% (7·7–10·9)	2·7:1	<0·0001
Current use of tobacco				
Chewing tobacco	4·5% (3·7–5·3)	1·6% (0·9–2·3)	2·8:1	<0·0001
Smoking bidis	2·0% (1·4–2·6)	0·9% (0·4–1·4)	2·2:1	0·0009
Smoking cigarettes	2·0% (1·4–2·6)	0·9% (0·4–1·4)	2·2:1	0·0016
Any kind of tobacco	6·7% (5·6–7·8)	2·9% (1·9–3·9)	2·3:1	<0·0001

Data in parentheses are 95% CI. Estimates generated from mixed-effects models adjusted for city, school type, sex, age, and grade*age. *Compares prevalence of tobacco use in sixth grade with that in eighth grade.

Table 1: Differences in prevalence of tobacco use between sixth-grade and eighth-grade students (n=11 642)

	Sixth grade (n=6165)	Eighth grade (n=5477)	Ratio*	p
City				
Chennai	23·4% (20·1–26·7)	8·9% (6·7–11·1)	2·6:1	<0·0001
Delhi	25·4% (23·4–27·4)	9·0% (5·6–12·4)	2·8:1	<0·0001
School				
Private	10·8% (5·0–16·6)	8·9% (6·0–11·8)	1·2:1	0·5426
Government	28·7% (26·7–30·7)	11·0% (9·0–13·0)	2·6:1	<0·0001
Sex				
Girls	20·1% (17·6–22·6)	6·9% (5·1–8·7)	2·9:1	<0·0001
Boys	29·2% (27·0–31·4)	12·1% (9·5–14·7)	2·4:1	<0·0001
Age (years)				
≤11	16·6% (14·4–18·8)	8·3% (3·5–13·1)	2·0:1	0·0003
12	25·3% (22·8–27·8)	6·3% (4·4–8·2)	4·0:1	<0·0001
13	30·3% (26·7–33·9)	9·1% (7·5–10·7)	3·3:1	<0·0001
≥14	32·1% (25·9–38·3)	12·1% (8·0–16·2)	2·7:1	<0·0001

Data in parentheses are 95% CI. Estimates generated from mixed-effects models adjusted for (when not stratified by) city, school type, sex, age, and grade*age.
*Compares prevalence of tobacco use in sixth grade with that in eighth grade.

Table 2: Differences in prevalence of ever use of any kind of tobacco between sixth-grade and eighth-grade students, by city, type of school, sex, and age (n=11 642)

	Sixth grade (n=6165)	Eighth grade (n=5477)	p
Intentions to chew	1·55 (5·50)	0·76 (4·44)	<0·0001
Intentions to smoke	0·97 (3·93)	0·45 (2·96)	<0·0001
Susceptibility to chew	1·32 (5·50)	0·67 (4·44)	<0·0001
Susceptibility to smoke	0·92 (3·93)	0·39 (2·96)	<0·0001
Reasons to use	2·78 (7·07)	2·51 (5·92)	0·0041
Normative expectations	3·35 (10·49)	1·65 (9·62)	<0·0001

Data are mean (SD). Estimates are generated from mixed-effects models adjusted for city, school type, sex, age, and grade*age. High scores on these scales indicate more risk or less protective.

Table 4: Differences in psychosocial factors associated with tobacco use, by grade (n=11 642)

The only difference between grade levels that was not significant was for private schools. In further examining the interaction between age and grade by school type, the differences between sixth and eighth grades were significant for all ages in government schools, but only for 12-year-olds in private schools (table 3). However, in the private schools, only 33 students (1·4%) in the sixth grade were aged 13 years or older, and only 55 students (2·4%) in the eighth grade were aged 11 years or younger. In view of these small numbers, the comparisons by age for private schools were limited in meaning. Notably, in 12-year-olds at private schools, sixth-grade students' tobacco use was nearly four times that of eighth-grade students.

The significant age*grade interaction in government schools seemed to be driven by the clear increase in tobacco use by age in sixth-grade students; this trend was less apparent in eighth-grade students. In private schools, the significant interaction seemed to be driven by different relations between grade and tobacco use by age. In 12-year-olds, sixth-grade students used more tobacco than eighth-grade students, but in those aged 13 years or 14 years and older, the prevalence was actually higher in eighth-grade students (although not significantly so).

Analyses of psychosocial factors also showed consistently significant differences between grade levels (table 4). Students in the sixth grade also had greater intentions to use tobacco in the future, more social susceptibility to use, more positive reasons to use tobacco, and more positive normative expectations concerning tobacco use than those in the eighth grade. These psychosocial risk factors were all associated with significantly greater tobacco use in all students ($p<0·05$, data not shown).

	Sixth grade		Eighth grade		Ratio*	p
	Number	Prevalence	Number	Prevalence		
Private schools						
Total	2326		2143			
Age ≤11 years	2090	11·0% (8·4 to 13·6)	52	11·0% (2·3 to 19·7)	1·0:1	0·9939
Age 12 years	203	21·5% (17·2 to 25·8)	934	5·9% (3·8 to 8·0)	3·6:1	<0·0001
Age 13 years	22	3·0% (−8·9 to 14·9)	1018	7·6% (5·6 to 9·6)	0·4:1	0·4513
Age ≥14 years	11	3·8% (−16·9 to 24·5)	139	7·0% (−2·0 to 16·0)	0·5:1	0·7414
Government schools						
Total	3811		3306			
Age ≤11 years	2289	21·5% (18·2 to 24·8)	202	12·1% (6·0 to 18·2)	1·8:1	0·0008
Age 12 years	814	25·8% (23·1 to 28·5)	841	6·1% (3·3 to 8·9)	4·2:1	<0·0001
Age 13 years	426	32·5% (28·8 to 36·2)	1114	9·8% (7·4 to 12·2)	3·3:1	<0·0001
Age ≥14 years	282	36·2% (31·2 to 41·2)	1149	15·7% (13·3 to 18·1)	2·3:1	<0·0001

Data in parentheses are 95% CI. Estimates generated from mixed-effects models adjusted for city and sex. 56 students did not provide their age, so the analysis sample was 11 586. *Ratio compares prevalence of tobacco use in sixth grade with that in eighth grade.

Table 3: Differences in prevalence of ever use of any kind of tobacco, by grade, age, and type of school (n=11 642)

Discussion

Increased grade level in school has been thought to be the factor that most reliably predicts tobacco use among young people,[4] but we found the opposite in our data from Delhi and Chennai. Even though increased age was also associated with tobacco use, this trend was found within rather than across grade levels. In fact, increase in tobacco use by age was significantly greater in the sixth-grade than in the eighth-grade cohort. This difference was noted primarily in government schools, among students with lower socioeconomic status. These findings are highly unusual and suggest that this group of teenagers in urban India are just beginning to use tobacco at increased rates. Of particular concern is the very high prevalence of ever having used tobacco (>32%) in sixth-grade students aged 13 years and older in government schools. Since early use of tobacco predicts greater likelihood of addiction, longer lifetime use, and higher rates of lung cancer, these findings are of importance to public health.[5,6]

The results of the analyses of psychosocial factors are also consistent with greater use among sixth-grade than eighth-grade students, since these factors indicate that sixth-grade students have a significantly greater risk profile associated with onset of tobacco use in this age

group. Young adolescents are particularly likely to internalise messages from society.[3,4] Despite policies to control tobacco,[1] messages in a rapidly changing India may be increasingly pro-tobacco, with greater exposure to media from other countries, smoking in Bollywood movies, and images via the internet. For example, the Cigarettes and Other Tobacco Products Act was passed in India in 2003, prohibiting all direct and indirect advertising of tobacco products, smoking in public places, sales of tobacco products to people younger than 18 years, and sales of tobacco products near educational institutions.[1] In response, one tobacco company (Godfrey-Philips India) positioned air-conditioned lorries (Mobile Smoking Lounges) outside major attractions, such as a sports stadium and shopping malls, in four major cities in India, including Delhi, so smokers can sit in the lounge and smoke in comfort. Thus, although India is a leader in global tobacco control, the tobacco industry has also developed methods to counteract or ameliorate the effects of policy changes, and these actions may be of particular interest to young adolescents as they begin to explore the adult world.[4,5]

Notably, 10·8% of the sixth-grade students in our cohort had ever smoked cigarettes, compared with 4·2% (in Delhi) and 5·5% (in Tamil Nadu, the state where Chennai is located) of students in the eighth-to-tenth grades who participated in the Global Youth Tobacco Survey in 2001.[15] Likewise, 6·7% of sixth-grade students in our study were current users of tobacco, compared with 4% and 7·1% of students in the Global Youth Tobacco Survey in 2001. Even with the increase suggested by the recent Indian Cancer Association data,[9] our younger sixth-grade cohort of students was using tobacco at similar or substantially higher rates than students who were 2–4 years older. Clearly, surveys of tobacco use in students should begin before eighth grade (about age 13 years) if a true measure of early-onset rates is to be achieved.

The only demographic group in which sixth-grade students did not significantly differ from eighth-grade students was among those in private schools. However, the private schools had very little age dispersion, with small sample sizes in one of the grades for ages 11 years and younger, 13 years, and 14 years and older. The only age group with substantial numbers of students in both grades was 12-year-olds, in whom the rate of tobacco use was nearly four times greater for sixth-grade than for eighth-grade students. Thus, private schools might also be facing increased use in younger children, although the data from this study are inconclusive.

Other explanations for these outcomes include under-reporting or over-reporting by one grade level, lack of understanding of the survey items by the sixth-grade students, or differential school drop-out of tobacco users from sixth to eighth grades. Methods were used to ensure confidentiality in data collection; these methods have yielded valid responses in previous work.[7,8] An extensive process of survey development was undertaken to ensure that sixth-grade students understood the exact meanings of the questions on the survey. Moreover, the consistency of the data across different populations, and the reliability and predictive validity of the measures, suggest that confusion about the questions or over-reporting or under-reporting by one grade level would not account for the degree of differences noted between grades. Additionally, attrition rates are low (yearly, about 10–12%) between sixth and eighth grade in the Project MYTRI schools, compared with rates before sixth grade, and are not large enough to account for the differences seen between grades. For example, since 21·8% of sixth-grade and 6% of eighth-grade students have ever used tobacco (table 1), then even if disproportionately more tobacco users dropped out than non-users, about half of the tobacco users would have to drop out every year from sixth to eighth grade (and there could be no new users) in order to match the lower rates of eighth-grade students. Clearly, since this is a cross-sectional study, longitudinal data are needed to confirm the sustained increase in tobacco use rates in this cohort over time.

Limitations of this study include its cross-sectional design, the need for replication and follow-up of the cohort until adulthood, and the absence of physiological data as another measure of tobacco-use behaviour. The sample of schools was not randomly selected from the population, but was representative of the mix of types of schools in these cities and does provide a sample of students of lower to higher socioeconomic status and both sexes.

The difference in rates of tobacco use between the sixth and eighth grades, and the replication of this difference in two cities, in government schools, and for girls and boys, strongly suggests that sixth-grade students in urban India use tobacco at two to four times the rate that eighth graders do. Of particular concern are older sixth-grade students in government schools, who already report having used tobacco at high rates. These findings might indicate the initial wave of a large increase in tobacco use in India, which is alarming and warrants confirmation and early intervention in young students.

Contributors

K S Reddy is principal investigator of Project MYTRI in India. He worked on all aspects of survey development and design, data collection protocols, data management, and data analysis. He read, edited, and wrote portions of the manuscript. C L Perry is principal investigator of Project MYTRI and is responsible for the scientific integrity of the study. She worked on all aspects of survey development and design, data collection protocols, data management, and data analysis. She wrote the research article with input from the co-authors. M H Stigler is project director of Project MYTRI in Minnesota and is responsible for the ongoing management of the scientific components of the project. She worked on all aspects of survey development and design, data collection protocols, data management, and data analysis. She did data analyses for this paper and wrote sections pertaining to the study methods and results. M Arora is project director of Project MYTRI in India and was responsible for training the study staff, coordinating the ongoing management of all staff in India, and implementation of all aspects of

the project. She worked on all aspects of survey development and design, data collection protocols, data management, and data analysis. She read, edited, and wrote portions of the paper.

Conflict of interest statement

We declare that we have no conflict of interest.

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RESEARCH COMMUNICATION

Tobacco Use among Students and School Personnel in India

Dhirendra Narain Sinha*, Prakash C Gupta[1], P Gangadharan[2]

Abstract

Background: Tobacco usage is addictive and causative for several diseases and premature death. Concerted efforts by the individual and society are needed for control and for surveillance. The habit is initiated during early youth and this age group requires constant monitoring and timely appropriate action to curtail usage. The WHO FCTC has recommended actions to monitor and limit the tobacco use in young age groups. One of the actions is to examine the prevalence of tobacco habits in school children 13-15 years of age and of personnel employed in schools. Methods: WHO & CDC designed the study systems for Global Youth Tobacco Survey (GYTS) and Global School Personnel Survey (GSPS). In 2006 we conducted GYTS and GSPS in several parts of the country. The schools were chosen by strict sampling procedure and a well structured, self-administered questionnaire was used to obtain information on tobacco usage from 13 to 15 year old students of chosen schools and personnel of these schools. Results: Current use of any tobacco product was 14.1% among students (17.3% boys, 9.8% girls) and among school personnel it was 29.2%(35.0% males and 13.7% females). The prevalence was highest among male students in North East (34%) and the lowest was 4.9% among female students of western states. Cigarettes and Bidi smoking were more prevalent among boys. Smokeless tobacco use prevalence rate varied between 20% and 4.5% among boys and between 21.5% and 1.6% among girl students. Among male school personnel, the prevalence varied from 57.9% in NE to 25.7% in South. Among females 26.5% were tobacco users in the NE and in Western region it was 6.6%. Conclusion: It is essential to adopt forceful strategies, which are area specific, in order to undo the harm inflicted by tobacco use upon the individuals & society. Periodic surveys for surveillance of trends are essential to evaluate the outcome of programmes among students and school personnels.

Key Words: Tobacco use prevalence - GYTS - GSPS - India

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Introduction

India ratified the WHO FCTC on February 5, 2004 (World Health Organization, 2007). The WHO FCTC provides the driving force and blueprint to curtail tobacco-induced deaths and diseases through a coordinated action plan. An important feature of the WHO FCTC is the call for countries to establish programmes for national, regional, and global surveillance (Article 20) (World Health Organization, 2003). Research, Surveillance and Exchange of Information are integral components of FCTC. Among the important areas addressed by the WHO FCTC, strengthening education, communication, training and public awareness about the dangers of tobacco consumption are primarily focused in Article 12. Educators are specifically mentioned as important vectors of this information (World Health Organization, 2003).

The World Health Organization (WHO), the U.S. Center for Disease Control and Prevention (CDC), and the Canadian Public Health Association (CPHA) developed the Global Youth Tobacco Survey (GYTS) for youth, and the Global School Personnel Survey (GSPS) and the Global Health Professional Survey (GHPS) for adults as a part of Global Tobacco Surveillance System (GTSS) (Global Tobacco Surveillance System Collaborating Group, 2005).

The purpose of the current study is to use the data from GYTS and GSPS conducted in 2006 in India to examine the present status of tobacco use among students and school personnel.

Methods

The GYTS is a school-based survey of defined geographic sites, which can be countries, provinces, cities, or any other sampling frame including sub-national areas. The GYTS uses a two-stage cluster sample design that produces representative samples of students in grades associated with ages 13–15. The sampling frame includes all schools containing any of the identified grades. At

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the first stage, the probability of schools being selected is proportional to the number of students enrolled in the specified grades. At the second sampling stage, classes within the selected schools are randomly selected. All the students in the selected classes attending school on the day of the survey are eligible to participate. Student participation is voluntary and kept anonymous, by means of self-administered data-collection procedures. The GYTS sample design produces representative, independent, cross-sectional estimates for each site. For cross-site comparisons, data in this paper are limited to students aged 13–15 years old.

The GYTS and GSPS 2006 used self-administered, anonymous data-collection procedures. Names of schools or students or personnel were not collected and participation was voluntary. Trained and experienced personnel conducted the survey. The questionnaire was designed with no skip patterns to allow all respondents to answer all questions. The India GYTS and GSPS 2006 questionnaires were self-administered in classrooms, and school, class, student and school personnel anonymity was maintained throughout the GYTS and GSPS process. India questionnaire comprised a core set of questions asked in all countries and India-specific questions on bidi and smokeless tobacco. The final India questionnaires were translated into local languages and translated back into English to check for accuracy and pre tested.

Current use of tobacco for students was defined as use within 30 days of survey while current tobacco use/ current smoker for school personnel was defined by a complex variable definition from two questions (1) for ever used/smoked (Question 1) and (2) responded as daily or occasionally smoking/using tobacco now (Question 2).

A weighting factor is applied to each student record to adjust for non-response (by school, class, and student) and variation in the probability of selection at the school, class, and student levels. A final adjustment sums the weights by grade and gender to the population of school children in the selected grades in each sample site. SUDAAN, a software package for statistical analysis of correlated data, was used to compute standard errors of the estimates and produced 95% confidence intervals which are shown as lower and upper bounds (Shah et al., 1997).

India GYTS 2006 was performed region-wise, covering the Northern region, consisting of Chandigarh, Delhi, Haryana, Himaehal Pradesh, Jammu and Kashmir, Punjab, Rajasthan, Uttaranchal and Uttar Pradesh; the Southern region consisting of Andhra Pradesh; Karnataka, Kerala and Tamil Nadu; the Eastern region consisting of Bihar, Jharkhand, Orissa and West Bengal; the Western region consisting of Goa, Gujarat and Maharashtra; the Central region consisting of Chhattisgarh and Madhya Pradesh and finally the North-eastern region consisting of Arunachal Pradesh, Assam, Manipur, Meghalaya, Mizoram, Nagaland, Sikkim and Tripura. These regions represent 99.7% of India's total population. The school response rate was 96.7% and student response rate was 82.3%. In total, 12086 students from over 179 schools participated in the 6 regional surveys, with fieldwork completed during first half of 2006. The overall response was 81.8%.

The GSPS is a survey of all individuals working in schools selected to participate in the Global Youth Tobacco Survey (GYTS). All school personnel working in the selected schools were eligible to participate in the GSPS. The overall response rate was 80.6%. In total, 2926 school personnel participated in the 6 regional surveys, with fieldwork completed during the first half of 2006. The six regional GSPS have been combined into a national estimate to be identified as India GSPS 2006.

The report includes data from GYTS and GSPS 2006 data by region and country estimates.

Table 1. Prevalence of Current Tobacco Use Among Students Aged 13-15 Years, GYTS, 2006

Site	Any	Current smoking Cigarettes	Bidis	Current Smokeless Tobacco Use	Current Use of any Tobacco Products
India Overall	7.2 (6.0-8.6)	4.2 (3.4-5.1)	3.5 (2.7-4.6)	8.1 (6.5-10.0)	14.1 (11.9-16.7)
Male	9.7 (7.8-12.0)	5.9 (4.7-7.4)	5.1 (3.7-7.1)	9.9 (7.9-12.3)	17.3 (14.5-20.4)
Female	3.7 (2.9-4.8)	1.8 (1.1-2.8)	1.3 (0.9-1.9)	5.5 (4.0-7.7)	9.7 (7.2-12.8)
North	4.9 (2.5-9.1)	1.5 (0.7-2.8)	3.5 (1.6-7.4)	5.8 (3.1-10.7)	10.9 (6.6-17.5)
Male	7.5 (3.7-14.4)	2.4 (1.2-5.0)	5.7 (2.5-12.4)	7.7 (4.6-12.5)	14.5 (9.4-21.8)
Female	0.7 (0.3-1.7)	0.0 (-)	0.1 (0.0-1.0)	2.8 (0.6-12.9)	5.0 (1.4-16.3)
South	5.0 (3.2-7.8)	2.5 (1.3-4.7)	2.1 (1.2-3.6)	3.4 (1.8-6.3)	8.2 (5.4-12.1)
Male	6.2 (3.5-10.8)	3.6 (1.7-7.7)	2.5 (1.2-5.0)	4.5 (2.4-8.4)	10.3 (6.5-15.8)
Female	3.7 (2.4-5.8)	1.2 (0.4-3.5)	1.7 (0.9-3.1)	2.0 (1.1-3.8)	5.7 (3.8-8.6)
East	16.9 (14.4-19.7)	12.7 (10.2-15.8)	7.2 (5.2-9.8)	17.0 (14.1-20.5)	30.3 (27.0-33.9)
Male	21.5 (18.1-25.2)	16.5 (13.5-20.2)	9.6 (6.8-13.5)	17.5 (14.3-21.2)	32.4 (28.0-37.1)
Female	10.4 (8.0-13.3)	7.5 (4.6-11.8)	3.7 (1.9-7.2)	16.4 (12.3-21.5)	27.3 (23.0-32.1)
West	2.6 (1.1-6.1)	0.7 (0.3-1.6)	0.6 (0.3-1.1)	5.7 (2.1-14.5)	8.0 (3.3-18.0)
Male	2.7 (1.3-5.5)	1.2 (0.5-2.8)	0.7 (0.3-1.6)	8.7 (3.2-21.9)	10.2 (4.3-22.4)
Female	2.4 (0.6-8.9)	0.1 (0.0-0.6)	0.5 (0.1-2.9)	1.6 (0.6-4.1)	4.9 (1.6-14.1)
Central	9.8 (6.9-13.8)	4.8 (3.1-7.5)	6.7 (4.0-10.9)	14.4 (9.9-20.5)	21.4 (16.1-27.9)
Male	14.4 (10.0-20.2)	7.7 (5.1-11.6)	10.1 (6.0-16.4)	17.1 (11.0-25.5)	27.0 (19.5-36.2)
Female	2.2 (0.9-5.0)	0.2 (0.0-2.1)	1.2 (0.4-3.2)	9.8 (6.6-14.3)	11.9 (9.3-15.1)
Northeast	18.6 (14.1-24.0)	18.2 (11.8-27.1)	6.0 (4.3-8.3)	20.7 (13.7-30.0)	28.1 (20.4-37.4)
Male	26.7 (21.4-32.7)	28.0 (19.7-38.0)	9.2 (6.4-13.1)	20.0 (14.9-26.4)	34.0 (27.3-41.4)
Female	9.7 (5.9-15.3)	8.1 (3.4-18.5)	2.7 (1.1-6.3)	21.5 (11.0-37.8)	21.7 (12.7-34.4)

Table 2. Prevalence of Current Tobacco Use among School Personnel by Region and Sex, GSPS, 2006

Site	Current Smoking		Current Smokeless	Current Use of
	Cigarettes	Bidis	Tobacco Use	Any Tobacco Products
India Overall	12.8 (11.1-14.7)	10.7 (9.3-12.3)	17.5 (15.9-19.4)	29.2 (27.0-31.5)
Male	16.9 (14.7-19.4)	14.2 (12.3-16.4)	19.7 (17.8-21.7)	35.0 (32.2-38.0)
Female	2.4 (1.6-3.8)	2.1 (1.2-3.7)	11.9 (9.1-15.4)	13.7 (10.6-17.6)
North	11.9 (9.4-15.0)	11.5 (8.4-15.7)	23.0 (19.8-26.6)	30.8 (27.4-34.4)
Male	16.9 (13.2-21.4)	16.1 (11.6-21.9)	23.9 (20.2-28.0)	34.9 (29.8-40.3)
Female	2.0 (1.1-3.6)	2.5 (0.7-8.8)	21.3 (15.4-28.6)	22.2 (16.0-29.8)
South	10.3 (7.1-14.8)	6.8 (4.3-10.5)	6.6 (4.0-10.8)	20.9 (14.6-28.9)
Male	13.1 (9.1-18.4)	9.2 (5.8-14.4)	7.5 (4.3-12.9)	25.7 (18.5-34.5)
Female	3.1 (1.1-8.7)	1.1 (0.2-6.2)	3.8 (1.2-10.7)	8.2 (2.9-21.5)
East	17.1 (12.6-22.9)	22.9 (18.0-28.5)	24.4 (20.3-29.1)	39.4 (34.8-44.1)
Male	19.1 (14.5-24.8)	25.3 (20.4-31.0)	27.0 (22.1-32.6)	43.1 (38.9-47.3)
Female	4.2 (2.1-8.2)	6.6 (2.8-14.7)	6.1 (1.8-18.7)	12.9 (6.9-23.0)
West	10.8 (8.7-13.4)	8.1 (6.2-10.5)	16.2 (13.0-19.9)	25.7 (22.6-29.1)
Male	14.7 (11.9-18.1)	10.8 (8.0-14.3)	19.6 (16.1-23.6)	32.4 (28.8-36.1)
Female	0.0 (- -)	0.7 (0.1-6.0)	6.6 (3.2-13.0)	6.6 (3.2-13.2)
Central	8.6 (4.4-16.1)	6.0 (2.6-13.3)	14.8 (9.9-21.5)	21.1 (16.2-27.1)
Male	13.1 (7.4-22.0)	9.6 (4.3-20.2)	19.4 (12.0-29.9)	29.3 (22.5-37.1)
Female	1.8 (0.3-11.4)	0.3 (0.0-2.6)	8.0 (5.2-12.1)	8.0 (5.2-12.1)
Northeast	30.2 (20.0-42.7)	13.3 (9.4-18.5)	50.3 (41.1-59.4)	50.3 (41.1(59.4)
Male	36.7 (20.3-56.8)	14.8 (9.7-22.0)	57.9 (40.8-73.4)	57.9 (40.8-73.4)
Female	10.0 (3.7-24.7)	8.8 (3.1-22.2)	26.5 (10.8-51.8)	26.5 (10.8-51.8)

Results

Global Youth Tobacco Survey, 2006

In Table 1 the percentage prevalence and its standard error of various forms of tobacco used by school students are shown.

In India, 7.2% of students (9.7% boys; 3.7% girls) currently smoked any tobacco (Table 1). Across the regions, current smoking any tobacco ranged from 5% or less in 4 regions to over 15% in the east and northeast regions. In north, east, central and northeastern regions the rate for boys was significantly higher than girls (Table 1) but in south and west regions there was no significant difference in current any smoking between boys and girls.

Current cigarette smoking rate for all India was 4.2%, with the rate for boys (5.9%) significantly higher than in girls (1.8% in all regions) (Table 1). Across the regions, current cigarette smoking ranged from less than 1% in west to over 18.2% in the northeast regions.

Bidi smoking was prevalent in 3.5%, with the rate for boys (5.1%) significantly higher than in girls (1.3%) (Table 1). Across the regions, current bidi smoking ranged from 0.6 % (West) to 6.2% (East).

Current use of smokeless tobacco products was 8.1% among students (9.9% boys; 5.5% girls). Across the regions, smokeless tobacco use ranged from 3.4% (south) to 20.7% in the northeast regions. Across the 6 regions there was no significant difference in current smokeless tobacco use between boys and girls.

Among students 14.1% currently used any tobacco products (17.3% boys, 9.75 girls). Across the regions, any tobacco use ranged from less than 9 % (west and south) to nearly 30% in the northeast regions. Across the regions there was no significant difference in current any tobacco use between boys and girls in five regions (north, south, west, central and north eastern) whereas in east region the rate for boys was significantly higher than girls.

In figure 1 and 2 the percentage prevalence of tobacco smokers, non-smoking tobacco users and any tobacco users among boys and girls are shown. The relative importance of non-smoking tobacco use in certain regions is apparent in this.

Global School Personnel Survey, 2006

In Table 2 the prevalence and its standard error of various forms of tobacco used by school personnel are shown.

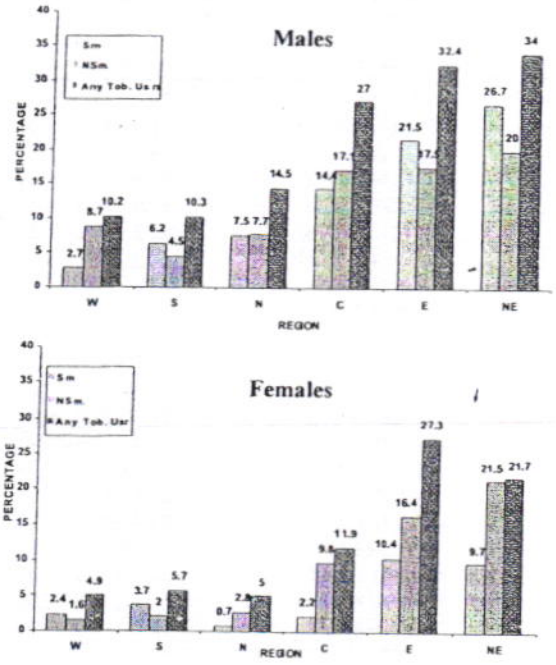
Among school personnel 12.8% currently smoked cigarettes (males 16.9%, females 2.4%) (Table 2). Across the regions, current cigarette smoking ranged from less than 12.0% in north, south west and central regions to over 30% in the northeast regions.

In India, 10.7% of school personnel currently smoked bidi (14.2% males, 2.1% females) (Table 2). Across the regions, current bidi smoking ranged from less than 12.0% in north, south west and central region to over 22% in the east region.

29.2% of school personnel used any tobacco product with male habituees 35% and females 13.7%. Across regions 50% of school personnel in north east used some form of tobacco and the lowest prevalence of 20.9% was seen in south.

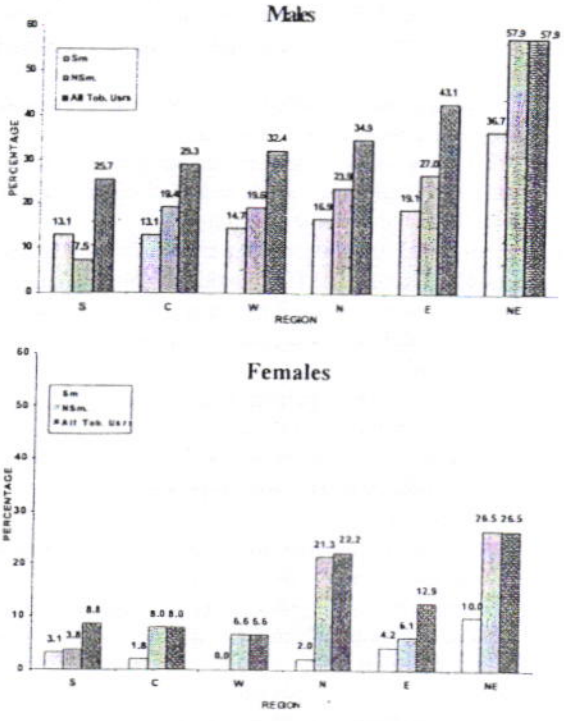
Among school personnel 17.5% currently used smokeless tobacco products (19.7% males, 11.9% females) (Table 2). Across the regions, current smokeless tobacco use ranged from 6.6% in south to 50.3% in the northeast region.

Among school personnel 29.2% currently used any tobacco products (35.0% males, 13.7% females) (Table 2). Across the regions, current any tobacco use ranged from 20.9% in south to 50.3% in the northeast regions. In east, west and central region the rate for males was significantly higher than females (Table 2) but in north, south and northeastern region there was no significant



West S-South N-North C-Central E-East NE-North East

Figure 1 and 2. Percentage Prevalence of Smoking (Sm), Non Smoking Tobacco Use (NSm) and Any Tobacco Use among 13 to 15 year Students in India – GYTS 2006



W-West S-South N-North C-Central E-East NE-North East

Figure 3 and 4. Percentage Prevalence of Smoking (Sm), Non Smoking Tobacco Use (NSm) and Any Tobacco Use among School Personnel (&) in India - GSPS-2006

difference in current any tobacco use between males and females.

Among different categories of school personnel, the prevalence of current use of any tobacco products ranged from 19.1% in any headmasters/principals to 45.7% in other teaching staff (the other categories consisted any teacher and office clerk).

In Figure 3 and 4 the prevalence of habit of smoking non-tobacco use and any tobacco use among males and females are shown. Any tobacco habit percent was double in north east male school personnel when compared to the prevalence in southern regions. A greater difference exists in female all tobacco use.

Discussion

The findings in this report are subject to at least three limitations. First the GYTS results do represent only school going population aged 13-15 years present on the day of survey. Second, GSPS sample design uses schools selected for the GYTS. Thus, GSPS is not an independent sample of schools and is dependent on the success of the GYTS. Fortunately, the GSPS school response rate has been greater than 80% in all sites. Third, findings are based on self-reports from school personnel who may under- or over-report their behavior and their knowledge of school policies. These limitation may affect the interpretation of results but perhaps only in a minor way.

Although as stated policy of all stakeholders including tobacco industry is that children should not use tobacco, in India across the six regions presented in this report, not a single site had a prevalence rate of current tobacco use equal to zero. Contrary to this ideal situation, the GYTS data documented here and in previous studies (Sinha et al., 2006; Sinha et al., 2003) show that tobacco use prevalence among students is quite high. As compared to other regions of the world, in India current cigarette smoking is on lower side (The Global Youth Tobacco Survey Collaborative Group, 2002;The Global Youth Tobacco Survey Collaborative Group, 2003) but current use of other tobacco products is the highest. Because of the deadly and addictive nature of tobacco products, and the high prevalence of its use among young people, it is clear that we need to change the ways in which tobacco products and their use are viewed by society, so as to begin to treat these products commensurate with the harm that they cause. Further, for India, the age group 13-15 that is currently in school represents 3% of population goes in terms of 33 million children. Among this at least 6 million currently use some form of tobacco. As the prevalence among out of school children is higher (Efroymson and Fitz, 2003), the non-school going group harbours more high-risk situations and this would enhance the total population estimates for tobacco related morbidities.

Use of tobacco products among youth in India presents a unique situation. The use of any form of tobacco by 13-15 year old students was greater than 20% in three regions presented in this report. Students reported using for various types of tobacco products, like bidi and various types of smokeless tobacco like Gutka, Pan Masala, Khaini etc

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In the present study, it was observed that tobacco use prevalence differed three-fold between the sites; highest rate was seen in northeastern region and lowest in west and in northern region. This is in concordance with previous round of GYTS which was conducted state wise and more conspicuous inter state difference was observed for current use of any tobacco product (62.8% in Nagaland, to 3.3% in Goa ,7). Such wide variations in responses within a country underscore the importance of sub-national data, and how national estimates can obscure important regional differences. This variation presents challenges and requires careful planning to develop, implement, and evaluate meaningful tobacco control programs. The prevalence and pattern of tobacco use variations seen in the country suggest that serious attention needs to be given to the development of country-specific tobacco control programs.

School personnel are role models for student, youth and public. The GSPS data document that tobacco use prevalence among school personnel is pretty high in India . Over three in 10 male and over one in 10 female school personnel are current tobacco users in India.

Equal female male ratio in current tobacco use among school personnel in 3 of 6 regions and among students in 5 of 6 regions is an indication of future increase in tobacco use in India. The results dispel the myth of tobacco use as taboo among middle class women and girls in India in so far as self administered, anonymous questionnaires revealed nearly 10% of girl students and over 10% of female school personnel reported current tobacco use. This social change is likely to be due to several factors such as female emancipation and role modeling from western media. The role of marketing strategies by cigarette companies however, cannot be underestimated. Almost all cigarettes and smokeless advertising imagery includes women and a cigarette and smokeless brand specially targeted at women with the name "Ms" is available in Indian market.

Despite minor limitations, the data clearly point out the extent of tobacco problem in India and the potential for its becoming a bigger problem in view of decreasing male female differences in use. This situation would certainly lead to a rise in tobacco related morbidity and mortality in India. The current study supports other similar studies (Warren et al., 2006). School level training and information dissemination for all anti tobacco activities should be initiated in school level curriculum. This would also have the school personnel to discard the habit if habituated to the use of tobacco.

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Annexure 37

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Popular perceptions of tobacco products and patterns of use among male college students in India

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Abstract

This paper examines popular perceptions of tobacco products and describes patterns of use among college youth in Karnataka, India. Data are drawn from 25 key informant interviews and six focus groups with male and female college students, interviews with shopkeepers, observational data on youth tobacco consumption, and a college-based survey. The survey was administered to 1587 males attending eleven colleges.

Forty-five percent ($n = 716$) of college students surveyed had used tobacco products. Thirty-six percent ($n = 573$) had tried cigarettes, 10% ($n = 157$) had tried *bidis*, and 18% ($n = 290$) had tried *gutkha*. Tobacco consumption among smokers was low; for daily smokers, the mean number of cigarettes smoked was 6 per day. Students attending professional colleges, including engineering, medicine, and law were significantly more likely to have ever smoked and to be daily smokers when compared to students enrolled in other courses of study.

In interviews, male students noted that smoking a cigarette enhanced one's manliness, relieved boredom, and eased tension. Although female students interviewed were non-smokers, several suggested that in the future, smoking might be an acceptable behavior among college-going females. When asked about their perceptions of smoking among youth in Western countries, the majority of students believed that three-quarters of male and female youth in the West smoked. This perception has been largely formed through media images, including satellite television and films.

With regard to addiction, it was widely believed that filter-tipped cigarettes were one of the most addictive products because they are made of better quality tobacco, and are milder and smoother to smoke. Therefore, a person could easily smoke more of them, which would lead to addiction. Another widely held belief was that the more expensive the cigarette, the less harmful it was for one's health.

Keywords: Tobacco products; Adolescent smoking; Initiation of smoking; India

Introduction

India is the third largest producer of tobacco in the world, and a country where tobacco is consumed in a wide variety of ways. Country-wide estimates of tobacco use suggest that tobacco prevalence is increasing in India. Also on the rise are tobacco-related diseases which presently account for one-half million deaths per year. By the year 2020, the annual number of tobacco-related deaths is projected to reach 1.5 million, accounting for approximately 13% of all deaths in the country (Kumar, 2000a, b). One distinctive feature of tobacco-related morbidity in India is that the incidence of oral cancers caused by the chewing of tobacco products exceeds that of lung cancer and is one of the highest in the world. Oral cancer accounts for 30–40% of all diagnosed cancer cases in the country (Gupta, 1999).

Five of the main ways in which tobacco is consumed in South India, the site of the present study, are the smoking of cigarettes and *bidi*, and the chewing of *pan*, *gutkha*, and *khaini*. Cigarette production has increased steadily in India. In 2000–2001, 91,400 million sticks were produced and this number is expected to exceed

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100,000 million sticks in 2001–2002 (Padmanabhan & Dikshit, 2001). The consumption of cigarettes is high in India with approximately 110 billion cigarettes sold each year (the equivalent of US$2 billion in sales). Between 1990–95, per capita consumption of cigarettes in India increased, a distinction it shares with only two other countries: China and Indonesia (The World Bank, 1999). During this time, the real price of cigarettes decreased by 45%. Even though India's cigarette tax is low by international standards, it contributes 90% of the government's revenue from tobacco[4] (Bose, Bamzai, Mohan, & Chawla, 2001). Importantly, more than 65% of cigarette sales in India are for single sticks. The cost of a single cigarette ranges from US$0.04–0.06, depending on the brand. Although relatively inexpensive, cigarettes are eight to ten times more expensive than *bidis*. Unlike *bidis*, cigarettes are a highly advertised product in which themes of sophistication, romance, sports, and adventure are prominent. As a result, cigarettes have come to be associated with higher socioeconomic status and sophisticated lifestyles (Gupta et al., 1992). Cigarettes are distributed by a highly sophisticated marketing network which reaches even the most remote village shops.

Bidis are small cigarettes consisting of indigenously grown tobacco wrapped in a *temburni* leaf (*Diospyros melanoxylon*). They are hand-rolled as a cottage industry in India and sold in packets of 20–30 *bidis*. Although smaller than cigarettes, smoking *bidis* yields more than three times as much carbon monoxide and more than five times as much nicotine and tar as cigarettes (Jayant & Pakhale, 1989). Since the leaf is not porous, the *bidi* smoker has to inhale often and deeply to keep it lit (Gupta & Ball, 1990). In fact, a *bidi* smoker must take three to four times as many puffs as one does with a cigarette. The topography of *bidi* use, in addition to the contents of *bidis*, make them particularly harmful for health. They are the most popular tobacco product on the Indian market, particularly among agricultural laborers, and account for 55% of tobacco consumption in India. *Bidis* do not carry warning labels.

Oral use of smokeless tobacco is very common in India, and is both prepared by the user as well as available prepackaged. *Pan*, also known as betel quid, is a product hand rolled at the time of consumption. It consists of one of several varieties of betel leaf (*Piper betle*) in which areca nut (*Areca catechu*) and slaked lime are added, often along with tobacco. Condiments and sweetening agents may also be added. *Pan* chewing is a widespread cultural practice engaged in at important events such as marriages, funerals, and ritual performances. In the study field site, it was common for guests to be offered a plate containing betel leaves, areca nut and tobacco shortly after entering a home.

Gutkha, a prepackaged mixture of chewing tobacco, areca nut, lime, and aromatic spices, is sold in small packets. It is widely available in small roadside shops and costs between Rs 1.50 and Rs. 4 (between US$0.04–0.11 per packet), depending on the size of the packet. *Gutkha* is a relatively recent product in the region of South India where the study was conducted. About 10 years ago, the product was introduced through tobacco distributors located in Mangalore, the district capital. Rapidly distributed through a network of agents, it has become popular among youth, manual laborers who find this product fast and convenient to use, and people in urban areas who wish to chew but do not want to stain their mouth red, which occurs as a result of chewing betel quid. *Gutkha* has been a source of public health concern because regular chewers of this product have been observed to experience a rapid progression to pre-cancerous oral lesions and submucuous fibrosis (Halarnkar, 1997). *Khaini*, a packaged chewing preparation containing tobacco flakes, slaked lime, and aromatic spices is cheaper than *gutkha*, costing only Rs. 1.50 (US$0.04) per packet. *Khaini* is stronger and harsher than *gutkha* and one packet contains sufficient tobacco for three chews.

Prevalence data on tobacco consumption in India is limited. It is estimated that 52–70% of males and 3–38% of females currently use tobacco in some form in different areas of India (Aghi, 1992; Bhonsle, Murti, & Gupta, 1992; Gupta, 1996; Gupta & Ball, 1990). In general, Indian men smoke as well as chew tobacco, whereas the vast majority of women who use tobacco are chewers (usually hand-rolled *pan* with tobacco). Cigarette smoking among women is not widely acceptable in India, although it is gaining some popularity among the elite in urban centers such as Mumbai and Delhi (Aghi, Asma, Yeong, & Vaithinathan, 2001; Kaufman & Nichter, 2001).

A review of the literature reveals that survey findings on tobacco use among adults often fail to differentiate which product is consumed and at what levels of consumption. Few studies provide information on patterns of use and age of initiation for tobacco; in addition, age groups used in estimating prevalence are broad, making age-specific examination of tobacco use over time difficult. Observational data suggest that patterns of tobacco use vary widely by age group, region (urban vs. rural), gender, and socioeconomic status.

The results of adult and several youth-based studies may be highlighted. A large cross-sectional study of adults in Mumbai found that 69% of males were tobacco users, with 24% using cigarettes or *bidi* (Gupta, 1996). Approximately one-half of those who smoked were cigarette smokers and one-half were *bidi* smokers. The median age of initiation for smokers was 21.5 years and the median number of cigarettes smoked per day was 5. Cigarette smoking showed a strong positive association with education, an association the author

links to sophisticated images of cigarette smoking promoted through advertising (Gupta, 1996).

A survey conducted among 1600 Mumbai youth, aged 14–15, found that 13% of boys and 1% of girls had used tobacco (Jayant, Notani, Gulati, & Gadre, 1991). Tobacco use was significantly more prevalent (23%) among students in private English-medium schools (a proxy for social class) when compared to those studying in regional-language public schools (Jayant et al., 1991). Among youth who had used a tobacco product, more than 85% had smoked cigarettes. The popularity of cigarettes among students in English-medium secondary schools lends credence to Gupta's findings about cigarette use among the educated. Less than 5% of these youth had experimented with any form of smokeless tobacco. A smaller study among 600 students (aged 15–22) in rural and urban Andhra Pradesh found that 12% of male students were occasional or daily cigarette smokers, and only one female smoked (Gavarasana, Doddi, Prasad, Allam, & Murthy, 1991). Among males who smoked, 60% were occasional smokers, and 40% defined themselves as regular smokers. The study did not report on use of smokeless tobacco products (Gavarasana et al., 1991). A study of college and school-aged students in Haryana found that 14% of males and 2% of females reported ever smoking (Kapoor, Anand, & Kumar, 1995). Results of the India Global Youth Tobacco Survey, sponsored by the Centers for Disease Control and Prevention (2000), reveal that among youth in standards 8–10 (aged 13–15) in the South Indian state of Tamil Nadu, only 6% of males and 4% of females report that they had ever smoked cigarettes.

What existing studies fail to provide is a sense of how tobacco consumption is changing among youth given the introduction of new products on the market (e.g., *gutkha*), changes in the modal age of initiation, patterns of consumption, perceived tobacco consumption among youth, and social factors influencing tobacco use. The researchers designed the present ethnographic and survey-based study of youth tobacco consumption bearing these issues in mind.

The study was conducted in Dakshina Kannaḍa District, Karnataka, where two of the authors (Nichter and Nichter) have conducted long-term ethnographic research (1974-present) on a range of health-related issues (Nichter & Nichter, 1996). These authors have fluency in the local language, Kannaḍa. Eleven key questions guided the study:

1. Among male college students in the district, what tobacco products are most commonly being consumed?
2. What factors account for the popularity and non-popularity of various products?
3. At what age are students initiating tobacco use?
4. Given the multitude of tobacco products available in India, can some products be characterized as starter products? Do some students use multiple products, and if so, do they progress from one to another?
5. What are the typical patterns of use among male college students, and do these vary in regard to school culture?
6. What are the perceived benefits of using various tobacco products?
7. Which tobacco products are considered most harmful and most addictive by youth and why?
8. What are the most important influences on tobacco use among college youth? To what extent do peers and family members serve as influences on youth smoking behavior?
9. What do youth think about tobacco advertisements and how do they affect their smoking behavior?
10. What are youths' perceptions of rates of tobacco use and how close are they to existing patterns?
11. Do youth view tobacco use as a problem in India?

Background of the study

The study was conducted from January to April 1998 in the coastal Karnataka district known as Dakshina (South) Kannaḍa. Unlike other regions of India, the district has a very high literacy rate of 77% (68% female; 85% male), with 32,000 students enrolled in colleges. The district has more private colleges than any other district in Karnataka, and is known around India as a center for higher education. Within the district, there is a wide range of public and private colleges which vary in the quality and medium of education, the courses offered, and their physical layout. While students from a range of socioeconomic classes attend these colleges, the course of study which students are enrolled in serves as a fair proxy for social class. That is, those students who come from wealthier families and have attended private English-medium schools and after-school tutorials tend to test (or buy) into more competitive and prestigious educational programs, such as medicine, engineering, and law.

For the purposes of this study, we chose a sample of eleven colleges reflecting the variability of these institutions in the region. College principals from Kannaḍa- and English-medium private and public schools and from technical and professional colleges were approached. All of the college principals who were approached agreed to participate. Of the 11 colleges surveyed, 2 were private Kannaḍa-medium, 3 were government Kannaḍa-medium (including one polytechnic), 3 were private English-medium (2 of which were Christian colleges), and 3 were English-medium professional colleges (medicine, engineering, and law). Seven of the colleges selected were located in the city of

Mangalore, the district capital, and four were in towns about an hour and a half from the city.

Given previous findings of a low prevalence of smoking among school- and college-aged women in India and the limited resources available for the present study, the researchers decided to focus the survey component of their research solely on college-aged males. Although all the colleges surveyed were coeducational, the researchers chose not to conduct the survey among young women because preliminary ethnographic research in the region had revealed that the prevalence of tobacco use among college-aged females was extremely low, a finding that has been corroborated in research studies around India. The researchers recognized that the survey instrument developed for male students would have been inappropriate for female college students. Thus, it was decided that the focus for the quantitative component of the project would be on those students who were most likely to be using tobacco products. To understand young women's perceptions of smoking, several focus groups were conducted with female college students.

Methods

Two months of focused ethnographic fieldwork were conducted to enable the researchers to gather data on how tobacco use was discussed by college students and to facilitate the development of the survey instrument. During the ethnographic component, twenty-five key informant interviews were conducted with male students attending colleges to be included in the survey. A semi-structured interview guide was developed based on two of the researchers' (Nichter and Nichter) previous ethnographic fieldwork in the region and observations of youth smoking in multiple contexts. Interviews were conducted on the college campus in English or Kannada (sometimes a combination of both languages), depending on the language which the student felt most comfortable speaking.

Five focus groups with males and three focus groups with females (mean size 6 participants) were also conducted to further explore issues related to perceptions of tobacco use, social norms regarding use, and the popularity of different products. Focus groups were held in a private room on the college campus after the completion of the school day, and were facilitated by two of the researchers. Students were assured of the confidentiality of their responses. Individual interviews and focus groups lasted about 30–45 min, and were tape-recorded and later transcribed. Taped interviews in Kannada were reviewed and notes were taken in Kannada and English on the language of smoking and important themes.

The research team carefully read through transcripts of the interviews and focus groups. To facilitate the process of data analysis, the authors discussed emergent themes. Interview data was useful in developing the appropriate language for the survey instrument and also provided clarification of the meaning of survey responses.

Twelve shopkeepers whose businesses were close to the colleges were interviewed about youth tobacco purchasing patterns and preferences. The researchers identified places where youth would and would not smoke, and conducted approximately 25 hours of observations of youth in spaces/times where free interaction and tobacco consumption was most likely to occur.

Design of the survey instrument drew on analysis of interview and observational data and required the identification of vernacular terms commonly used by youth to describe tobacco use. A process of translation and back translation from English into Kannada was utilized to ensure comprehension and comparability of the instrument administered in the two languages. The researchers (Nichter and Nichter) worked closely with a Professor of Kannada to ensure proper translation of the survey. The survey was pre-tested at two of the colleges, and students were given an opportunity to identify questions and responses that were not clear to them. Their suggestions were addressed in the final version of the survey.

Data collection

The principal at each of the colleges directed the researchers to a teacher who could help coordinate survey administration. Regardless of the medium of instruction, the survey was offered to students in either English or Kannada, and students were asked to select the language in which they wanted to complete the survey.

At each college, between one-quarter and one-half of the total male population enrolled at the institution participated in the survey. All male students attending class on the day the survey was administered were invited to participate. None of the students present declined participation. Prior to survey administration, one of the researchers provided a brief introduction in Kannada explaining that the purpose of the study was to understand changes in consumption behavior among youth, with a focus on tobacco. Confidentiality of responses was explained and questions from the students about the research were answered. At least two of the researchers and a teacher were present at each administration of the survey to answer any questions that might arise. Completion of the survey took approximately 45 minutes.

After administering surveys in each of the colleges, the researchers held informal group discussions with students who wished to discuss tobacco use behavior with them in greater depth. Typically, lively discussions ensued with 10–20 students wishing to ask questions or offer an opinion. These opportunistic group discussions often lasted 45–60 min and in many cases, students approached the researchers for advice on how to quit smoking.

Results from the surveys were entered into a database for analysis using SPSS (SPSS Inc., 1998). In addition to descriptive statistics, *t*-tests, and chi-square tests, analysis of variance (ANOVA) was used to test for significant differences in the mean values of variables such as age and age of initiation between subgroups. Follow-up Tukey's HSD was used to examine differences among all possible pairings. Logistic regression was used to analyze variables affecting cigarette smoking. All reported confidence intervals are 95% unless listed otherwise.

Results

Participants

The study sample consisted of 1587 male college students ranging in age from 16 to 23 years (mean age, 19.53 years old). The demographic charactersitics of respondents are summarized in Table 1. Sixty percent of respondents completed the survey in English, and 40% completed it in Kannada, generally reflecting the language of instruction at the college.

Prevalence and frequency of tobacco use

In response to the question "*Have you ever tried any tobacco products*?" 45% ($n = 716$) of informants responded "yes", and 55% ($n = 871$) responded "no". With regard to cigarette use, 64% ($n = 1014$) of students had *never tried*, while 36% ($n = 573$) had *ever tried* cigarettes. Ninety percent ($n = 1430$) of students reported that they had never tried smoking *bidis*.

The frequency of use of specific tobacco products is presented in Table 2. The term "experimented" which appears in the table refers to students who had tried a tobacco product on five or fewer occasions in their lifetime. The term "occasional" refers to a broad range of tobacco users who were not using tobacco on a daily basis.

The majority of tobacco users were cigarette smokers. The mean number of cigarettes smoked per week by *occasional smokers* was 6 (SD = 5.52). Of this group, 66% smoked a few times per month, and 33% smoked a few times per week (but not daily). For *daily smokers*, the mean was 39.72 cigarettes per week (SD = 31.48) (approximately 6 cigarettes per day). Of daily smokers, 32% smoked between 1 and 3 cigarettes per day, 32% smoked between 4 and 6 cigarettes per day, and 35% smoked 7 or more cigarettes per day.

Table 1
Characteristics of Respondents

	N	%	Mean age (SD)
Place of origin			
Village	639	40.26	19.63 (1.54)
Town	416	26.21	19.62 (1.40)
Urban	457	28.80	19.23 (1.48)
Missing	75	4.73	
Total	1587		
Religion			
Hindu	1142	71.96	19.59 (1.50)
Christian	240	15.12	19.42 (1.34)
Muslim	185	11.66	19.23 (1.74)
Other	16	1.01	19.75 (1.65)
Missing	4	0.25	
Total	1587		
Type of college and medium of instruction			
Private, Kannada-medium	346	21.80	19.68 (1.30)
Government, Kannada-medium	372	23.44	19.77 (1.25)
Private, English-medium	449	28.29	18.59 (1.64)
Professional, English-medium	420	26.47	20.16 (1.34)
Total	1587		
Age			
16–17	149	9.38	
18–19	583	36.73	
20–21	720	45.36	
22–23	135	8.5	
Total	1587		

Daily smokers were significantly older than occasional and experimental smokers ($f(3) = 6.47$, $p < 0.001$). The mean age of daily smokers was 20.18 (SD = 1.37), while the mean age of occasional smokers was 19.71 (SD = 1.55) and experimental smokers was 19.45 (SD = 1.53).

With regard to place of origin and level of smoking, it was found that daily smokers were 3.59 times more likely to be from urban and town areas than to be from villages (CI = 2.16, 6.04; $p < 0.0001$). The mean number of cigarettes smoked per week by students from town and urban areas (21.99; SD = 30.35) was significantly higher ($p < 0.01$) than that reported by their peers from village areas (12.01; SD = 17.47).

Table 2
Tobacco use among college students

	Cigarettes		Gutkha		Bidis		Pan with tobacco		Khaini	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%
Never tried	1014	63.89	1297	81.73	1430	90.11	1486	93.64	1506	94.90
Ever tried	573	36.11	290	18.27	157	9.89	101	6.36	81	5.10
Of those who had ever tried										
Experimented[a]	183	31.94	98	33.79	79	50.32	38	37.62	30	37.04
Occasional[b]	142	24.78	75	25.86	17	10.83	21	20.79	23	28.40
Daily	136	23.73	23	7.93	5	3.18	4	3.96	5	6.17
Quit	99	17.28	79	27.24	39	24.84	30	29.70	18	22.22
Unknown use[c]	13	2.27	15	5.17	17	10.83	8	7.92	5	6.17
Total	573		290		157		101		81	

[a] Experimented refers to students who used product on five or fewer occasions in lifetime.
[b] Occasional refers to a broad range of tobacco users who were not using tobacco on a daily basis.
[c] Unknown use refers to students who selected multiple responses for frequency of use.

Table 3
Prevalence of use of tobacco products, and mean age of initiation, by students attending different types of colleges

	Government Kannada	Private Kannada	Private English	Professional English	Total
Any tobacco product	Number (%)	Number (%)	Number (%)	Number (%)	Number (%)
Ever tried	174 (46.8)	131 (37.9)	192 (42.8)	219 (52.1)	716 (45.1)
Never tried	198 (53.2)	215 (62.1)	257 (57.2)	201 (47.9)	871 (54.9)
Cigarettes					
Ever tried	114 (30.6)	99 (28.6)	153 (34.1)	207 (49.3)	573 (36.1)
Never tried	258 (69.4)	247 (71.4)	296 (65.9)	213 (50.7)	1014 (63.9)
Mean age of initiation (SD)	16.95 (2.48)	17.06 (2.19)	16.19 (2.27)	16.84 (2.62)	
Gutkha					
Ever tried	94 (25.3)	64 (18.5)	60 (13.4)	72 (17.1)	290 (18.3)
Never tried	278 (74.7)	282 (81.5)	389 (86.6)	348 (82.9)	1297 (81.7)
Mean age of initiation (SD)	17.85 (1.74)	17.64 (1.85)	16.52 (2.47)	17.18 (2.48)	

Overall, Christian youth were 1.57 times more likely to have tried tobacco products than Hindu youth (CI = 1.18,2.09; $p<0.001$). Among those who smoked cigarettes, there were no significant differences in frequency of smoking between youth of different religions.

The prevalence of use of tobacco products, and mean age of initiation, by students attending different types of colleges is reported in Table 3. Differences in smoking status and levels of smoking were noted across colleges. Students attending professional colleges, including medicine, law, and engineering, were 2.13 times more likely to have ever smoked cigarettes than students attending all other colleges (CI = 1.69, 2.67; $p<0.0001$). Medical, law, and engineering students were significantly more likely to be daily smokers when compared to students enrolled in other types of colleges, even after controlling for age ($p<0.001$). Among students at professional colleges, engineering students were more likely to be daily smokers although the differences between professional college students were not significant.

Analyses of the survey question "*Does your best friend smoke*?" revealed that students who smoked were far more likely to have best friends who smoked. Of current smokers, 90% reported that they had a best friend who smoked. *Daily smokers* were 5.24 times more likely than non-smokers to have a best friend who smoked ($\chi^2_{(1)} = 45$; CI = 3.06, 9.58; $p<0.0001$).

To determine the relative influence of the variables contributing to cigarette use, further analysis was carried out on the use of cigarettes by students (ever use, never use) using logistic regression analysis (Table 4). Nine variables—including type of college, religion, survey language, having a best friend who smokes

Table 4
Ever use of cigarettes: multiple logistic regression model

Variable	B	Wald	Odds ratio	95% CI
Professional college*	0.4880	10.1770	1.629	1.21, 2.20
Age*	0.1042	6.7685	1.1098	1.03, 1.20
Christian*	0.3954	6.1012	1.4849	1.09, 2.03
English**	0.5375	14.1425	1.7116	1.29, 2.27
Best friend uses tobacco**	0.9900	53.3983	2.6912	2.06, 3.51
Household member uses cigarettes**	0.7713	38.6524	2.1625	1.70, 2.76
Constant	−4.0531	25.8159		

*$p<0.01$,
**$p<0.001$.

cigarettes, household member use of tobacco, and age—were entered into the regression. The variables with the greatest effect on ever use of cigarettes was having a best friend who smokes cigarettes (OR 2.69; CI = 2.06, 3.51, $p<0.0001$), followed by having a household member who used tobacco (OR 2.16; CI = 1.70, 2.76; $p<0.0001$).

Gutkha was not found to be popular among college students in the district. Eighty-two percent of respondents ($n = 1297$) had *never tried gutkha*, and 18% ($n = 290$) had *ever tried* (see Table 2). Students in professional colleges were significantly less likely (0.73 times; CI = 0.545, 0.971) to have ever chewed than students in other types of colleges. Responses to the survey question "*Does your best friend chew?*" showed that students whose best friend chewed *gutkha* were 3.12 times more likely to have chewed *gutkha* than students whose best friend did not chew (CI = 2.37, 4.096; $p<0.001$). Ninety-five percent of students ($n = 1506$) had never tried *khaini* (chewing tobacco). Similarly, *pan* with tobacco was unpopular with students; 94% ($n = 1486$) had never tried.

Age of initiation

Table 5 summarizes reported age of initiation by frequency of use of tobacco products and religion. The mean age of initiation for cigarette smoking among ever smokers was 17.01 (SD = 2.30). There were no significant differences in mean age of initiation by frequency of tobacco use. However, differences in age of initiation of cigarette smoking were found by religion. Christian youth began smoking cigarettes at younger ages than their Hindu and Muslim counterparts and were 1.7 times more likely than Hindu students to have initiated by age 17. There were no significant differences in age of initiation between students from villages and those from towns and urban areas.

The mean age of initiation of cigarette smoking and *gutkha* chewing among students at different types of colleges is presented in Table 3. Students enrolled in English-medium schools were 3.2 times more likely than Kannada-medium students to have initiated smoking by age 17 (CI = 1.81, 5.73; $p<0.001$) even when controlling for religion and type of college. As noted earlier, language of instruction may be considered a proxy for social class. There were no significant differences in age of initiation of smoking for students who had a household member who used tobacco (16.95 years; SD = 2.48), when compared to those students whose household members did not use tobacco (17.01 years, SD = 2.34).

Overall, the mean age of initiation for *gutkha* chewing ($n = 234$) was 17.26 years (SD = 2.18). The mean age of

Table 5
Age of initiation of tobacco use by frequency of use of product and religion

	N^a	Mean age	St. Dev.
Cigarette smoking			
Ever smokers	542	17.01	2.30
Occasional smokers	137	17.31	2.24
Daily smokers	134	16.97	2.19
Religion			
Hindu	384	17.24[a]	2.20
Christian	97	15.79[b]	2.76
Muslim	63	17.32[a]	1.70
Other	5	17.80[a]	1.64
Gutkha chewing			
Ever chewers	234	17.24	2.18
Occasional chewers	62	17.89	1.87
Daily chewers	21	17.57	1.91
Religion			
Hindu	197	17.36	2.06
Christian	31	16.32	2.70
Muslim	10	18.20	2.10
Other	1	18.00	2.70

Means with different letters are statistically significantly different from each other (at the level of $p< 0.05$).
[a] N represents number on whom age of initiation was available.

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initiation for chewing among youth from town and urban areas (17.72, SD = 1.85) was significantly older ($t(163) = -2.70$, CI for difference: −1.425, −0.221, $p<0.01$) than the mean age of initiation among youth from villages (16.89, SD = 2.19). Among students attending Kannada-medium colleges, the mean age of initiation for chewing (17.66, SD = 1.90) was significantly older (CI 0.375, 1.525; $p\leqslant 0.001$) than the mean age of initiation (16.71, SD = 2.42) for those attending English-medium colleges. Students in English-medium colleges were significantly more likely to have tried *gutkha* at an earlier age when compared to those studying in Kannada medium colleges (16.95 years vs. 17.69; $p<0.001$).

In interviews, college informants explained that *gutkha* had only recently become popular among youth (i.e., within the last five years) and that it was very popular among those younger than themselves. We will comment on this emergent trend later in the paper.

From survey data analysis, it appeared that younger students were initiating smoking at earlier ages when compared to older students. The design of the study did not permit us to answer this question directly. However, Fig. 1 shows that, for the most part, the proportion of students ages 17–23 (at the time of survey) initiating cigarette smoking by the ages of 16, 17, and 18 appears to have increased over the last 6–8 years.

Popularity of tobacco products

Why are cigarettes the most popular tobacco product among college youth? In focus groups, many young men explained that cigarettes make a young man appear attractive and are one of the few affordable avenues available to a young man to flaunt his manhood. The cost of a single cigarette was considered to be negligible by college students, with the most expensive cigarette costing approximately Rs. 2 (US$0.06). This was less than the cost of a cup of tea. In comparison, the cost of a single beer was several orders of magnitude greater, Rs. 40 (US$1.).

In addition to their affordability, cigarettes are a readily available substance outside the gates of college campuses. While smoking is forbidden on college campuses, directly outside the campus gates are small, often makeshift shops which sell inexpensive candies, soft drinks, and tobacco products. Discussion with shopkeepers who had stalls near college campuses revealed that up to one-quarter of their total profit came from the sale of cigarettes. At several shops, students did not require cash to buy cigarettes. Cigarettes were sold on credit to students who established monthly accounts in their name.

Cigarettes are generally sold by the single stick, and often smoked at the shop itself. During class breaks and

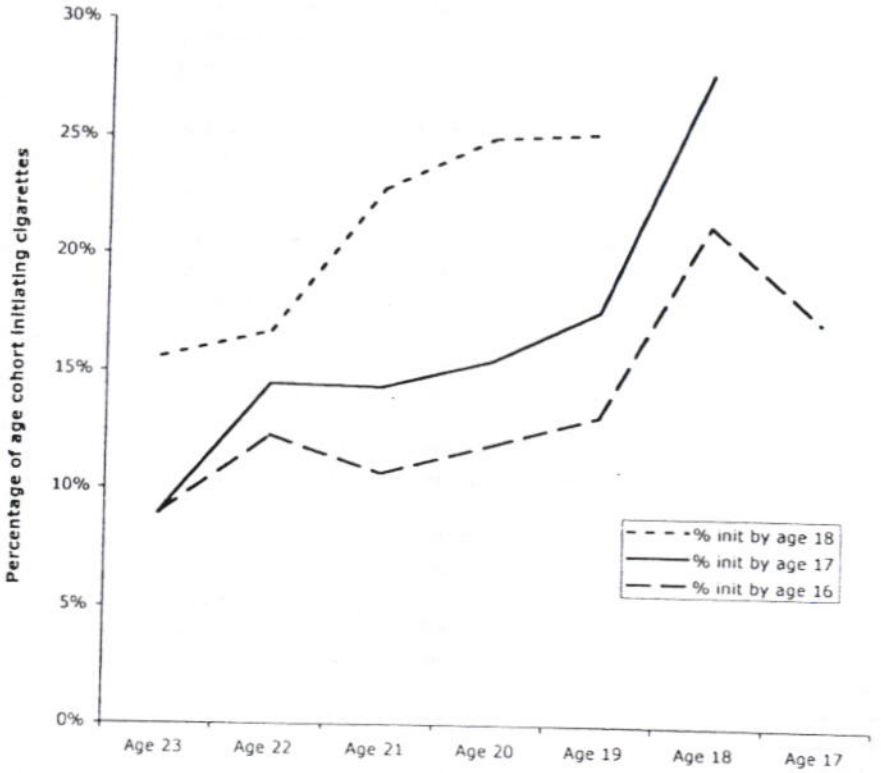

Fig. 1. Proportion of students of ages 17–23 (at time of survey) reporting initiation of cigarette use at ages 16, 17, and 18.

at lunchtime when students were allowed to leave the school, many of the male students gathered at these shops. Because students do not want college administrators and lecturers to see them smoking cigarettes, some shopkeepers provide a small private space inside their shops where students can sit and smoke without being seen by those walking on the road. Cigarettes are often shared among friends, in part because students have limited time to smoke between classes, or before they catch the bus to go home. After smoking or sharing a cigarette, 2 or 3 mint candies are commonly purchased and consumed to mask the smell of the cigarette. Eating mints after smoking was also considered important because it was widely believed that mints cooled the throat and the chest, and thus reduced the health risks of smoking. This reasoning was associated with notions of hot and cold foods, an important component of popular health culture. Specifically, it was believed that the effects of hot substances, such as tobacco, could be countered by ingesting cooling substances (Nichter, 1986). Utilizing similar reasoning, some students drank a glass of lemonade while smoking, as lemonade is thought to have cooling properties which can remove the negative and heating effects of tobacco. Shopkeepers offer these products to smokers as part of a consumption event.

Patterns of smoking are highly time/space sensitive (Mehl, Seimon, & Winch, 1999). Male students described feeling free to smoke in public places where they are anonymous or in front of female classmates. Smoking in front of one's parents or elders was considered a sign of disrespect. College lecturers sometimes threatened the students whom they had seen smoking, saying that they would inform their parents of their behavior. Young men did not smoke in their homes or in the homes of their friends.

Why are *bidis* smoked by so few college students (<10%)? In interviews, students explained that *bidis* are only smoked as an alternative to cigarettes if a person is "bankrupt", that is, out of cash. Several students noted that if they observe a well-dressed person smoking a *bidi*, they assume that he has only recently come into his money ("he's a late upstart") and has not yet cast off his lower-status habits. Even among college students who smoked *bidis*, it was rare to see them smoke *bidis* in public.

Although Dakshina Kannada District is one of the centers of *bidi* production in India, the smoking of *bidis* is becoming less common, particularly among young men. Rising wages in the district have led to increased disposable income, and have resulted in an increased purchase of cigarettes among this age group. Long-term ethnographic observation in the district suggests that beginning in the early to mid-1990s, young agricultural laborers, who smoked *bidis* while working in the fields, tended to shift their behavior to smoking cigarettes after work. At the end of the day, they would change clothes from a cloth tied around the waist (*lungi*) to pants and would put on a watch, also a symbol of being modern. Meeting their friends at the local tea or arrack shop, they would complete their identity shift by lighting up a cigarette. This pattern was also noted among some of the working class students in our study who attended colleges in the small towns. During school vacations when they engaged in agricultural labor in their villages, they would take a work break and smoke *bidis*, a behavior they would not engage in while at college.

Among certain segments of the Indian population, *bidis* make a political statement—that is, that the *bidi* smoker is a "son of the soil". For this reason, some leaders of the communist party as well as various nationalist parties smoked *bidis* in public in the 1970–1980s. As both of these groups are active in the district, we had expected *bidis* to be smoked by some young men as a political statement. We did not find this to be the case.

Use of multiple tobacco products

On the survey, we asked "*How many tobacco products have you tried?*" Fifty-seven percent ($n = 408$) of respondents who had ever used tobacco ($n = 716$) had used only one product; 27% ($n = 196$) had used 2 products; 10% ($n = 68$) had used 3 products, 4% ($n = 31$) had used 4 products, and 2% ($n = 13$) had used 5 products. Forty-eight percent of students who had used more than one product had tried cigarettes first, 18% ($n = 71$) had tried either *gutkha* or *bidis* first, and 9% had tried pan with tobacco tried first.

When asked if they considered one of these products to be a "starter" product from which one progressed to another tobacco substance, students did not identify such a trend across products. Several students did describe, however, how they had started smoking a "milder" cigarette (such as Wills Kings), which was easier to inhale, before moving on to a harsher cigarette.

Of those students who had used multiple products, the most commonly cited combination was cigarettes and *gutkha*. In-depth interviews with co-users revealed that some young men substituted *gutkha* for a cigarette during times and in spaces where it would not have been appropriate for them to smoke. To determine whether users of both consciously engaged in this behavior pattern, we asked "*Have you ever chewed gutkha when you wanted a cigarette and smoking was not permitted?*" Twenty-four percent replied "yes" to this question. In interviews, youth proposed another reason for using both cigarettes and *gutkha*. They explained that while cigarettes were relaxing and improved your status, *gutkha* gives you more of a kick and was good to consume when you were bored.

Another way in which multiple products were utilized among college students was for purposes of quitting. Some students noted that they chewed *gutkha* when trying to quit smoking cigarettes, and then switched to *pan masala* (betel leaf, areca nut, slaked lime, and aromatic spices) in an attempt to wean themselves off of chewing *gutkha*. Those who believed that *gutkha* was more addictive than cigarettes did not think this was a good idea.

Reasons for smoking cigarettes

While the researchers recognized the limitations of youth self-reports on reasons for smoking, because factors are often unconscious, we did feel it could be insightful to ask questions about social influences on smoking behavior. The most common reason noted for smoking was "for friendship," that is, to engage in similar behaviors to one's friends. Students explained that when they joined their classmates at restaurants it was a time when "you don't want to feel left out". As one student explained, "If your best friend is a smoker, you want to give him company."

During in-depth interviews and focus groups, we attempted to get a sense of peer selectivity (that is, the tendency of adolescents to choose friends who already share their interests and activities) as distinct from active peer influence related to smoking (Fisher & Baumen, 1988; Kandel, 1987; Kobus, 2003). In India, this proved to be a complex subject given caste and kinship ties which impact on, but do not determine, friendship circles. Our preliminary findings suggest that peer selectivity more commonly occurs around alcohol consumption (often co-occurant with smoking) than around smoking as an index behavior. Exclusion from a group because one does not smoke when friends do, does not commonly occur. However, friends do encourage friends to smoke in the form of teasing one about being overly conservative. For example, some students described that if you were offered a cigarette and you refused, others would tease you and call you a "Gandhi". Encouragement from friends to try tobacco increases in contexts where alcohol is consumed if one drinks but does not smoke. Notably, several students reported that once you were seen smoking, people would offer you drags off a cigarette making it hard to refuse if one was trying to quit.

Responses gained from interview data were used as closed-ended choices on the survey. In response to the question "*What were the reasons you first tried tobacco?*" (multiple responses allowed), the most common responses were "curiosity" (52%); "my friends encouraged me" (40%); and "to appear in style" (18%). Although 40% noted that their friends had encouraged them to smoke, in follow-up interviews many students explained that although they had been encouraged to smoke, decisions *not to* smoke were respected. Our overall impression is that indirect influence to smoke appeared to be greater than direct influence. That is, to choose *not* to smoke when one's friends were smoking would be uncomfortable as it would place the individual outside of the exchange relationship. In India, social connectivity at the site of the body is very visible (e.g., holding hands with one's friends), and an ideology of trust and reciprocity through the sharing of substances is widespread. One of the ways to show close friendship is to circumvent cultural rules, such as rules prescribing pollution from sharing food or drinks. Sharing a substance is an expression of both affection and closeness.

Beyond friendship, other reasons for smoking included: to reduce tension, to alleviate boredom, and to appear more fashionable. Smoking was thought to make a young man appear "more of a big shot", as well as more forward-minded. Although dating in this region of South India is rare, male college students believed that having a cigarette in hand "enhanced one's manliness" and helped to get one noticed by females. As one student explained, "If a boy wants to have something—either a cigarette or *gutkha*—he'll always go for a cigarette to impress girls."

Smoking to relieve tension and boredom

Table 6 summarizes responses to the survey question "*Which emotions lead a person to increase his use of tobacco products?*" Response choices were drawn from interview data, and multiple responses were allowed.

Experiencing tension was perceived to be the major reason for increasing one's use of tobacco. This response was cited by both ever-users of tobacco (54%) and never-users (55%). This is a script learned in part from popular culture, particularly films and advertisements, where lighting up a cigarette often signals that one is trying to cope with stress and tension. As one

Table 6
Which emotions lead a person to increase his use of tobacco products?

	Ever used tobacco ($N = 716$)	Never used tobacco ($N = 871$)
Tension	54%	55.4%
Boredom	45.2%	39.5%
Loneliness	36.5%	30.3%
Feeling like failure	32.8%	40.9%
Happiness	31.8%	30.7%
Feeling upset	28.8%	31.4%
Anger	18.2%	18.3%

student explained:

> We know from advertisements that we see in the newspaper and in the cinema that cigarettes help with tension. In cigarette ads, they show businessmen preparing their accounts and they always have a cigarette in one hand and a packet on the table. Smoking helps them to think through their problems. In Hindi films, when the hero loses his girlfriend or has a fight with her, he smokes a cigarette. Films and advertisements give us the reasons why we should smoke, and we follow.

Similarly, other students in a focus group explained:

> When you are tense, you can't think, then you smoke a cigarette and you get new ideas. Like when an engineer or an architect has to solve a problem, he becomes tense inside. Then he takes a break and smokes a cigarette and new thoughts enter his mind.

> In the cinema, a guy smokes when he is depressed, when he has tension. In Hindi movies, women also smoke—especially the modern wife.

It is not surprising that film images surface in youth narratives about tobacco use. Films are extremely popular in India, and smoking is widely viewed in Indian made films as well as in films imported from other countries. Of late, product endorsement (or "pseudo" advertising), including for cigarettes, is increasingly being seen in Indian films and television (Bosu, 2000).

Many students increased their smoking while studying for exams. Comments such as "smoking helps you think", "smoking keeps you alert" and "smoking relieves tension", were commonly noted. References to tension may also refer to symptoms of nicotine withdrawal. As one stressed student explained, "During exams I smoke more. When exams are over, in my mind, I don't want to smoke, but my nerves keep begging for it." Many students reported that their tobacco consumption also increased while waiting for exam results.

Boredom was reported as a common reason for youth to increase their tobacco consumption by both ever-users of tobacco (45%) and non-users (39%). In interviews, students talked about smoking with friends as a way to break up the boredom of the school day. In this region, it is not surprising that boredom emerges as a common discourse as there are few recreational activities for youth. Observational data and interviews with younger males (ages 14–15) suggest that *gutkha* is becoming more popular among this age cohort as a way to "pass time". Several college students observed that younger age cohorts used *gutkha* during school, something they had not done.

Perceived benefits of smoking cigarettes and chewing gutkha

Table 7 summarizes the responses of smokers and non-smokers to the survey question "*What are the benefits of smoking cigarettes?*" Notably, non-smokers were far more likely than smokers to report that cigarettes helped a person gain respect (50% vs. 24%), look more attractive (44% vs. 25%) look older (27% vs. 18%), and help one forget his problems (52% vs. 36%). Benefits commonly cited by smokers (and to a lesser extent, by non-smokers) include "it relieves boredom," "it's relaxing," and "it gives a person a kick."

In interviews, some students noted that smoking one cigarette a day was good for stamina for those engaged in sports, and several young men described how they had smoked at low levels when they were on sports teams. They were quick to explain, however, that if an athlete smoked three or four cigarettes a day, it could be harmful for health. The perception that smoking gives strength and improves athletic performance has been noted elsewhere in India (Vaidya, Naik, & Vaidya, 1996). Indian cricket, a sport which enjoys immense popularity, has a 3-year sponsorship contract with Wills Sport, a wholly owned subsidiary of ITC (Indian Tobacco Corporation) (Bose et al., 2001).

With regard to the benefits of chewing *gutkha*, the most common response of chewers and non-chewers was that "it gives a person a kick." Other attributes noted by chewers included "it relieves boredom" (49%), "it's a cheap way to enjoy" (38%), and "it removes bad taste from the mouth" (38%).

Table 7
What are the benefits of smoking cigarettes?

	Ever tried cigarettes ($N = 573$)	Never tried cigarettes ($N = 1014$)
Relieve boredom	58.5	55.4
Give a kick	51.9	42.7
Relaxing	48.6	47.8
Forget problems	35.9	51.5
Cheap way to enjoy	33.9	36
Helps one mix easily	32.6	37.4
Helps one stay awake	30.1	29.1
Helps one think	29	38.8
Look more attractive	24.8	44.1
Helps one gain respect	24.1	49.6
Increases confidence	23.3	29.2
Helps one look older	17.6	26.8
Reduce hunger	15	14.6
Good for digestion	12.1	7.7
Helps one work hard	12	18.2
Remove bad taste	8.9	12.4
Easy to conceal	6.7	12.1

Perceived prevalence of tobacco use

In the survey, we asked, "*What percentage of your classmates do you think smoke cigarettes?*" The mean response of *ever smokers* was 40%, compared to 32% for *never smokers*. Both smokers and non-smokers estimates of prevalence were fairly accurate; in this sample, 36% of youth had ever tried smoking. Estimates of smoking prevalence were similar across the three groups of smokers (experimenters, occasional smokers, daily smokers).

A widespread perception was that those who drink also smoke. In response to the question "*Do most young men who drink alcohol also use some tobacco product?*" 75% of the sample reported "yes". In interviews, students described how smoking while drinking helped enhance the kick, and how dropping ashes into a glass of beer served to further enhance the drinking experience.

Do young men associate tobacco use with particular professions? In interviews, students did cite several stereotypes. For example, it was widely believed that a majority of lawyers, architects, and engineers smoked cigarettes. These were stress-promoting jobs requiring intense thinking for which cigarettes were especially useful. Young agricultural laborers were widely believed to chew *gutkha*, while bus conductors chew *khaini* and smoke *bidis*.

In interviews, we also asked students about their perceptions of smoking among youth in Western countries. Importantly, the majority of students believed that three-quarters of youth in the West smoked, and that smoking was equally common among males and females. This perception has been largely formed through media images, including satellite television and films.

In response to the question "*What percentage of your classmates do you think chew gutkha?*" the modal response for the sample was 15%. Similar to the accuracy in perceived prevalence for smoking, students were quite accurate in their perceived prevalence for *gutkha* use—in this sample, 18% reported ever use of *gutkha*.

Perceptions of smoking among young women

Although cigarette smoking is extremely rare among female college students in the district, in focus group discussions with girls attending professional colleges in Mangalore, many noted that smoking behavior among females may change. As one 20-year-old female law student explained, "Now you only find women smoking at high status schools like the Indian Institute of Management. If you come back to India in ten years, you will find many professional women smoking!" When asked about what image is projected through cigarette smoking, young women were quick to note that "smoking is stylish, modern, and it says 'I'm mature, I'm grown up.'" Interestingly, male and female college students provided similar attributes, perhaps because both are exposed to the same cigarette advertisements which depict sophisticated and glamorous images of smokers. Several young women noted that some females who attend more progressive colleges in cosmopolitan cities such as Bangalore and Mumbai, already smoke (Upadhyay, 2001). Reasons cited for smoking included weight control, to appear stylish, because boys can, and to be free.

Importantly, the modal response of young women interviewed was that one-half to three-quarters of women their age in the United States smoke, at least socially. In reality, in the late 1990s, more than one in five adult women in the US report regular smoking and approximately 28% of high school senior girls report smoking within the last 30 days (US Surgeon General, 2001). Several Indian young women mentioned that they had gotten this impression from movies, from satellite television programs, and from film magazines.

Women are increasingly targets of the tobacco industry in Asia and overt attempts by the industry to legitimate and normalize smoking for women and to present it as a women's right have been documented (Kaufman & Nichter, 2001). Wills cigarette advertisements in India, for example, continually portray young, fashionably dressed couples with the tag line "Made for Each Other"—suggesting that the product could be used by either men or women. When asked if young Indian women were impressed with their male classmates who smoked, female students unanimously agreed that they were not, but said that this was an idea that young men got from the movies and from advertisements.

Perceptions of harmfulness of tobacco products

Of all tobacco products, *gutkha* was considered to be the most harmful for health by a large majority of students. Beyond the tobacco content, *gutkha* was thought to be adulterated with items (such as wall lizard or dolomite) for both coloration and to enhance its kick. Popular notions about this product changed while we were in the field following newspaper reports of *gutkha's* harmful effects. Rumors circulated that *gutkha* products were laced with various drugs ranging from codeine to marijuana. The size of the packet was another factor discussed in relation to potential harmfulness. Purchasing large packets of *gutkha* was considered to be better for health than purchasing small packets because a higher quality tobacco was used in the large packets. Smaller packets were thought to contain dust particles and leftover wastage tobacco which were harsher and thus, more harmful for health.

Bidis were also considered harmful for health because of the poorer quality of tobacco used and because they

Table 8
How many cigarettes or packets of *gutkha* can a person smoke/chew per week without it being harmful for health?

	Number of cigarettes or gutkha packets per week											
	All use is harmful		<5 cigarette packets		6–12 cigs/ packets		13–20 cigs/ packets		21–30 cigs/ packet		No response	
	%	N	%	N	%	N	%	N	%	N	%	N
Ever smoker	69.2	702	15.7	159	4.8	49	2.9	29	3.2	32	4.4	43
Never smoker	56.2	322	21.3	122	12.2	70	2.8	16	4.2	24	3.3	19
Total	64	1024	17.7	281	7.5	119	2.8	45	3.5	56	3.9	62
Ever chewer	66.6	193	19.3	56	6.6	19	2.1	6	2.1	6	3.4	10
Never chewer	71.1	922	12.9	167	3.9	50	1.8	23	1.6	21	8.8	114
Total	70.3	1115	14.1	223	4.3	69	1.8	29	1.7	27	7.8	124

do not have a filter. With regard to the relative harmfulness of cigarettes, non-filter-tipped cigarettes were considered more harmful for health than filter-tip cigarettes because they were harsher and made of poor quality tobacco. It was widely believed that the more expensive the cigarette, the less harmful it was for one's health. Thus, more expensive cigarettes like Kings (Rs. 2 per cigarette) were believed to be made of higher quality tobacco because they are more expensive, when compared to a cheaper brand, such as Bristol. It was believed that wealthier people smoked better quality cigarettes and suffered less from illness than the poor who smoked more harmful products. To mitigate the harmful effects of smoking and other side effects of tobacco use, some harm reduction behaviors were adopted.[1]

Table 8 reveals the range of student responses to the survey question "*How many cigarettes or packets of gutkha can a person smoke/chew per week without it being harmful for health*?" This question was included because in interviews and focus groups many students had asked the researchers if there was a level of "safe smoking" or "safe chewing". Ever smokers were 1.88 times more likely to report some level of safe use of smoking than were never smokers ($\chi^2(1) = 31.485$, CI: 1.50, 2.37, $p < 0.001$). With regard to *gutkha* chewing, 71% of non-chewers and 67% of chewers noted that "all use is harmful." Ever chewers were 1.59 times more likely to report some level of safe use of *gutkha* when compared to students who never chewed ($\chi^2(1) = 9.645$, CI: 1.181, 2.145, $p < 0.005$). These findings for both smoked and smokeless tobacco products indicate that the majority of college youth surveyed were aware of the harmful effects of both smoking and chewing tobacco.

Perceptions of addiction

In focus groups, interviews, and on the survey, we asked students their opinions about which tobacco products were more addictive, defined in terms of rapid progression to higher levels of use once one had tried a product a few times. *Ever smokers* reported that *gutkha* and filter-tip cigarettes were the most addictive tobacco products. In interviews, smokers explained that filter-tip cigarettes were more addictive than non-filter-tips because they are made of better quality tobacco, and are milder and smoother to smoke. Therefore, a person could more easily smoke more of them and become addicted. *Gutkha* was thought to be addictive because the manufacturers laced the product with unidentified addictive drugs.

During focus groups, we asked students if there was a particular kind of person who became dependent on tobacco more easily than others. We found that the concept of dependency was difficult to translate into Kannada. Kannada-speaking students were familiar with the English word addiction and preferred using it to describe tobacco use rather than local terms used by their parents. However, a semantic network analysis revealed that the word addiction had a range of meanings. Some informants identified tobacco addiction in terms of daily use and an inability to suspend use for more than a day, while others described addiction in relation to social behavior and needing to smoke at inappropriate times and in inappropriate spaces. For example, one informant noted, "Addiction means being

[1] Smoking cigarettes was recognized to have other negative side effects beyond being bad for health. One physical effect commented on by youth was the darkening of one's lips. To counteract this, some youth smoked cigarettes on the side of their mouth rather than the center. Alternatively, one could diminish the darkness by rubbing pan on their lips to turn them rosy. For lightening purposes, toothpaste was also applied to the lips, allowed to dry and then washed of, with the goal of reducing the blackish stain of tobacco. Some youth also described how eating pineapple helped to mitigate the harmful effects of tobacco. As one youth explained, "If you blow smoke on a cloth it will make a stain—pineapple juice removes the stain; like that, eating pineapple will remove the stain of tobacco on your lungs." People have heard about tobacco-related "stains" as a result of visiting doctors.

defeated, having to bow down to tobacco like some goddess...not being able to stop your habit even when you are someplace where others will think bad of you if you smoke." Another informant similarly noted: "To be addicted means that you cannot sit through an entire *puja* (ritual performance), because you feel that you must go outside the temple to have a smoke." For these informants, addiction is a concept defined less in terms of level of smoking (i.e., quantity), and more in terms of social deviance (Quintero & Nichter, 1996). As one daily cigarette smoker noted, "If I can control my need to smoke to regular timings, then it is just a habit (*abhiyasa*), not an addiction". Other informants described being addicted to needing to smoke to the extent that they would feel sick or nervous if they did not do so. It was recognized that such symptoms could be experienced by individuals smoking at different levels. Many youth believed that it was more harmful to experience symptoms of withdrawal (which could "shock" the body), than to continue smoking at low to moderate levels.

Given cultural practices, addiction was found to be a difficult concept to measure using standard instruments. We explored the use of the Fagerstrom scale normalized for western cultures during the pilot stage of the research, but rejected its use for a number of reasons (Fagerstrom, 1978). First, the majority of smokers, even daily smokers who report that they are addicted, are smoking at low levels (mean = 6 cigarettes per day). We found that responses to important questions on the Fagerstrom ("How soon after getting up do you smoke a cigarette?"; "What cigarette would be the most difficult to give up?") could be easily misinterpreted in India as signifying nicotine dependency. Many low-level daily smokers who were interviewed reported smoking soon after getting up. Of 25 interviewed, one-third stated that they smoked their first cigarette in the morning so they could go to the toilet. In India, cigarette and *bidi* smoking are widely believed to aid in the defecation process. Most of these smokers went on to state that their morning cigarette would be the hardest to give up because it helped them move their bowels. In order to use the scale, a series of questions about smoking and defecation behavior and the location of toilets (in house/outhouse) would need to be asked.

We decided not to administer the scale to informants and to instead ask one question on the survey to ascertain self-perception of addiction, broadly defined. In response to the question "*Have you ever felt you were addicted to a tobacco product?*" 71% of *daily smokers* responded "they had felt addicted", compared to 24% of *occasional smokers*. Irrespective of the relatively low levels of smoking, some of these youth considered themselves addicted. Of those youth who were *daily chewers*, 50% reported that they had felt addicted, while 37% of *occasional chewers* reported this. More sensitive measures of dependence that are able to tap into the multidimensionality of dependence (Edwards, 1986; Shiffman et al., 1995) and which are sensitive to the cultural use of tobacco are needed.

Familial influences on youth smoking

Overall, 52% of students had family members who used tobacco products at least once a week or more. Of those 52%, 51% had at least one adult male in the household who smoked cigarettes, 28% had a *bidi* smoker, and 39% had a household member who used smokeless tobacco. In focus groups, it was frequently noted that in Christian families, if the father smoked it was very likely that the son would also smoke. Notably, students commented that it was normative for Christian fathers and sons to smoke cigarettes and drink together. However, in Hindu families, such behavior was considered highly disrespectful.

On the survey we attempted to gain some understanding of parental attitudes to youth smoking with the question "*Have your parents told you not to use tobacco products?*" In response, over one-half of students responded that they had been told not to smoke or use *gutkha* by a family member. Another survey question, "*If your father came to know that you were using a tobacco product, how would he react?*" proved somewhat problematic because of the projective nature of the question. While 72% of respondents noted that their father would disapprove of any use, the remaining 28% answered, "I don't know how he would react."[2]

Effects of advertisements on youth tobacco use

During the time the survey was being administered, several important cricket matches were taking place and Wills Cigarettes was heavily involved with advertisements and sponsorship. Players' uniforms bore the Wills Sport logo and other advertisements were visible throughout the coverage. In response to the survey question "*Do you think tobacco advertising and sponsorship encourages young people to use tobacco products?*" 82% of respondents said "yes". In response to the question "*Have you ever tried a tobacco product as a*

[2]On a methodological note, despite great care in survey development and pretesting, a number of students expressed difficulty in answering projective questions on the survey, that required them to report on the possible attitude of another individual (e.g., "What would your father say if he found you smoking?"). Students who were non-smokers asked, "But I don't smoke, so how can I say what my father *might* think if I did smoke?" Although this difficulty did not arise during survey pretesting, we learned that this type of hypothetical reasoning was unfamiliar to college students. Future surveys need to be attentive to question design to ensure that items are sufficiently concrete to ensure comprehension and accuracy of answers.

result of an advertisement or promotion?" 40% of those who had tried tobacco products reported that they had.

Discussion

This paper moves beyond previous studies of adolescent tobacco use in India to more closely examine prevalence, patterns of tobacco consumption, and social factors influencing tobacco use. Survey findings and observational data confirm that among college students, cigarettes are the most popular form of tobacco consumption. Thirty-six percent of students ($n = 1587$) had ever tried cigarettes and 18% had ever tried *gutkha*. Only 10% had tried *bidis*, 6% had tried *pan*, and 5% had tried *khaini*. Daily cigarette smokers consumed a mean of 6 cigarettes per day. Similar patterns of low level smoking have been reported elsewhere in India and among youth in Sri Lanka (Bhonsle et al., 1992; Mehl et al., 1999).

School culture appears to be an important factor in determining patterns of tobacco use. Almost 50 percent of students attending professional colleges (medicine, law and engineering) had tried cigarettes, compared to 30% of students attending Government Kannada-medium colleges. The latter group was more likely to have tried *gutkha* when compared to professional college students.

Although the cross-sectional nature of the study does not allow for decisive findings about changes in the age of initiation for cigarette smoking, the data suggests that a greater proportion of students are initiating at younger ages. This raises the need for longitudinal studies that begin with students in secondary school and continue to follow them through college. Age of initiation to smoking should be considered as a key barometer to the understanding of changing youth consumption patterns, particularly in relation to the widespread idea that cigarette smoking helps one appear in style and fashionable (Appadurai, 1996). As alcohol consumption and cigarette smoking were behaviors that co-occurred, it will be important to track increases in drinking among youth which may be accompanied by increases in cigarette smoking.

Although it has been noted in the tobacco literature that youth in the West who smoke at the highest levels are those who begin at earlier ages, this pattern does not seem to hold true among Indian youth. The mean age of initiation for daily smokers was not significantly different than for those who smoked occasionally or those who had experimented with tobacco. Christian youth, who were significantly earlier initiators, were no more likely to be daily smokers than youth in other groups.

In response to the survey question "*Is tobacco use a problem among youth in India today*?" 77% of smokers and 85% of non-smokers replied "yes". Three-quarters of respondents reported that youth are beginning to consume tobacco products at younger ages. At present, however, there is little school-based tobacco prevention education available to students, and smoking is glamorized in films, magazines, and on television.

Although daily smokers consumed relatively few cigarettes per day, almost three-quarters reported that they felt addicted to tobacco. Many students noted that they would quit smoking after college, when they returned home or took up jobs. As one student explained, "Now we are not so mature so we don't understand what we are doing. Later, we will come to understand more about health and we may stop. People are more aware of the adverse effects when they are older." During focus group discussions and after administering the survey at colleges, students asked many questions about addiction to tobacco and requested information on how to quit. In addition, several female medical students voiced concern about the commonality of smoking among the next generation of Indian physicians. Clearly, there is a need in India for the development of cessation services for youth.

Future studies need to track *gutkha* use among youth; observational data and discussions in the rural areas revealed that *gutkha* has widespread appeal among young agricultural laborers who find its glossy, slick packaging as attractive as other "high tech" products—like Nescafe. Although *gutkha* was not a popular product among college students, several noted in interviews that the product was becoming increasingly popular with secondary school students. From ethnography, it appeared that secondary school students were using *gutkha* in ways that are different from college youth—early adolescents chew *gutkha* to break boredom. It will be important to determine whether *gutkha* is a starter product for them, and whether they continue to chew as they grow older or move on to other products. Notably, although there has been a lot of negative press coverage about the harmful effects of *gutkha*, it has not affected the supply and distribution of the product in local communities. Indeed, it is still widely available, despite its ban in some regions.

Concern with environmental pollution and additives in food and drink, a popular discourse in India today, was also apparent in discussions about tobacco. Just as *gutkha* was considered harmful because of unidentified additives, students explained that tobacco, in any form, is worse for health now than in previous times because of the insecticides used in the growing process. Importantly, a majority of students believed that smoking more expensive cigarettes offered protection from adverse effects because of the better quality tobacco used. Wealthier people who smoked better quality cigarettes were believed to suffer less than the poor who smoked cheaper and more harmful products.

Future research will need to carefully monitor the emergence of new tobacco products in the Indian marketplace and youth response to these products. New products are being marketed in the major urban areas of India, and it may not be long before they become available in other areas, including the study fieldsite. For example, a Swedish chew product in prepackaged pouches (called Click) was recently introduced into India, advertised as a safe alternative to tobacco use. Herbal cigarettes are also becoming available in the marketplace. It will also be important to follow emergent themes in the advertising of tobacco products, particularly in relation to the portrayal of women and tobacco. In order to develop culturally appropriate prevention and cessation interventions for youth, data is required on trajectories of tobacco use and non-use, changes in the age of initiation, and transition points to increased use. In this paper, we have attempted to address these issues.

Acknowledgements

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Special Report: National

Tobacco use among India's street children raises concern


HRIDAY

The Academy Award winning British film *Slumdog Millionaire* attracted global attention for presenting a romanticised story of life in the slums of Mumbai. However, the real-life problems of street children in India are far more serious, with new surveys indicating an alarmingly high use of various tobacco products among street children.

India has over 360 million children aged under 15 years. Although there are no official data on the number of street children, conservative estimates put the figure at over 10 million, most of whom earn a living through activities like rag picking, begging, vending, shoe shining, and sometimes petty crime.

A recent, unpublished survey of marginalised children in Mumbai and two other cities in north eastern India—Guwahati and Amsong—showed that over a quarter of children aged 5–19 years consumed tobacco in various forms. The survey—funded by the International Union Against Cancer (UICC)—was done by the Cancer Patients Aid Association (CPAA) in Mumbai. It noted that the average age at which children started using tobacco was 11·3 years for both boys and girls. In Mumbai, the most frequently used products were raw tobacco, gutkha (a blend of tobacco and flavourings), and cigarettes.

In Chandigarh, 70 street children out of 100 surveyed used one or more form of illicit stimulant, including cigarettes and bidi (small handrolled cigarettes), chewing tobacco, alcohol, and injectable drugs. 28 of them chewed one or two packets of tobacco a week, according to findings presented at the Multinational Association for Supportive Care in Cancer (MASCC) conference in June. Most children started chewing tobacco between 10 and 13 years of age.

Socio-economic status is a major factor in determining tobacco use. Several studies have shown that the poor and uneducated are at an increased risk of tobacco use. "Most tobacco-using children report chewing gutkha, confirming a countrywide trend of increasing gutkha use and an increasing incidence of oral cancer", says Umesh Kapil (All India Institute of Medical Sciences, New Delhi).

The high prevalence of chewing tobacco use is resulting in people presenting with oral cancers at increasingly younger ages, says Manoj Sharma (Maulana Azad Medical College, New Delhi). "We are definitely seeing more young people with pre-malignant, malignant and even aggressive malignant diseases of the oral cavity and oesophagus, and this is a direct result of chewing tobacco and gutkha", he says. Children get addicted to gutkha when they are young, and are at a high risk of developing oral cancers when they grow up unless they are helped to quit the habit early.

Because these children live on the streets and unauthorised urban slums, they have no access to government healthcare systems. They depend solely on voluntary bodies for any access to care. Awareness and early screening could help in the effort to detect oral cancers early, but no such programmes exist for street children.

The most common reason for children to start using tobacco is peer pressure. But the CPAA study also found that street children see tobacco as an alternative to food, because it "curbs hunger pangs and is inexpensive". "This is clear from the amount of money they spend on tobacco and related products—an average ranging anywhere from 0·5 Rupees to 200 Rupees", says Yogendra Kumar Sapru (CPAA).

"Voluntary bodies and other donors who work with street children pay much more attention to feeding them, giving them clothes and providing primary care. It has been reported that almost all their earnings get spent on tobacco since they feel other basic necessities would be taken care of", adds Prakash C Gupta (Healis Sekhsaria Institute for Public Health, Mumbai). CPAA works to reach out to marginalised children, either directly, or through voluntary agencies already working with them. "We find that even a small amount of schooling helps motivate children to quit and not to restart", notes Sapru.

The Delhi-based group Health-Related Information Dissemination Amongst Youth (HRIDAY) has noted that interventions through schools result in positive changes in behaviour and help prevent tobacco use. Now the group is collaborating with the University of Texas in the USA to conduct a community-based randomised trial among youths in seven low income communities in Delhi to see if the same interventions work with street children. Peer-led and interactive activities have been planned to spread awareness and influence norms regarding tobacco use.

"The idea is to prevent the onset of tobacco use among disadvantaged youth as well as provide support to those who wish to quit", comments Monika Arora (HRIDAY).

The government has taken several steps to curb tobacco use, but their impact is yet to be felt. Selling tobacco products to children younger than 18 years of age is prohibited, but retailers openly flout this regulation, and maximum fines only amount to the cost of a couple of packets of cigarettes. If this law is enforced and retailers penalised, it could cut out a major source of tobacco products to youth. Increased use of pictorial warnings and higher tax rates might also help to discourage the use of tobacco products.

Dinesh C Sharma

Annexe 39

The role of gutka chewing in oral submucous fibrosis: a case-control study.

Bathi RJ, Parveen S, Burde K

Quintessence Int. 2009 Jun;40(6):e19-25.

Abstract

OBJECTIVE: To learn about the use of various chewing substrates, such as areca nut and gutka, among subjects with oral submucosal fibrosis (OSMF) and controls with no oral mucosal lesions.

MATERIALS AND METHODS: In this hospital-based case-control study, 220 patients with OSMF were selected and compared with matched controls with regard to dietary habits, including spice use, smoking history, and preference for chewing substrates. Relative risk of various chewing habits was calculated using an odds ratio and logistic regression analysis to understand the influence of chewing habits, spices, and smoking on the development of OSMF. Discriminate analysis was employed to determine which risk factors were valid and reliable discriminators between individuals with or without OSMF.

RESULTS: The relative risk of developing oral submucosal fibrosis was highest with gutka-chewing habit (relative risk, 1,142.4), which was significant ($P < .01$) at 95% confidence interval. The next highest relative risk for development of oral submucosal fibrosis was observed for the combination of gutka with other chewing habits. The relative risk of developing submucosal fibrosis increased with the frequency of chewing habit up to 15 times daily with a duration of habit up to 4 years. The relative risk decreased with chewing frequency beyond 15 times daily and 4 years in duration. Logistic regression and discriminative analysis show that chewing areca nut and gutka, especially daily, greatly influence the development of submucosal fibrosis.

CONCLUSION: This study suggests that chewing commercially available areca-nut preparations such as gutka is strongly associated with the development of oral submucosal fibrosis.

Annexure 45

Oral submucous fibrosis: a clinicopathologic review of 205 cases in Indians.

Angadi PV, Rekha KP

Oral Maxillofac Surg. 2010 Apr 23. [Epub ahead of print]

Abstract

INTRODUCTION: Oral submucous fibrosis is a disease due to a chronic, insidious change in fibro-elasticity, characterized by burning sensation in the oral cavity, blanching, and stiffening of the oral mucosa and oro-pharynx leading to trismus and inability to open the mouth. The symptoms and signs depend on the progression of the lesions and number of affected sites. It is predominantly seen in Indians and other Asians. Once the disease has developed, there is neither regression nor any effective treatment. There are only few studies on the frequency and clinicopathological feature of oral submucous fibrosis in the Indian population in recent years.

MATERIAL AND METHODS: The present study evaluated 205 cases of oral submucous fibrosis for the age, sex, site of involvement, duration of disease at the time of diagnosis, associated habits and common presenting symptoms, presence of other mucosal lesions, malignant potential, and the histopathology.

RESULTS AND DISCUSSION: Oral submucous fibrosis was seen in younger age (20-30 years) than that reported in literature and showed a characteristic male preponderance. A strong association with smokeless tobacco use especially arecanut in the form of gutkha was established and was related to earlier development of oral submucous fibrosis (OSMF), i.e., within a year of the habit. A total of 11.6% of cases were associated with malignancy and occurred predominantly in males.

CONCLUSION: This article gives an insight into OSMF in this part of southern India and adds to its biologic profile.

1.

Annexure 41

ORIGINAL RESEARCH
Oral Epidemiology

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Prevalence of oral lesions in relation to habits: Cross-sectional study in South India

ABSTRACT

Background: Smoking, drinking and chewing tobacco product, common habits in India have been positively associated with oral lesions. No study has been conducted in this part of Tamilnadu regarding the prevalence of oral lesions in relation to habits.

Methods: A hospital based cross-sectional study was carried out at Ragas Dental College, Chennai. Already existing data of two thousand and seventeen consecutive patients from sub-urban areas of Chennai, who attended the outpatient department, at Ragas Dental College, for dental complaints during a period of three months in 2004, who underwent oral examination and interviewer based questionnaire was used.

Results: Oral soft tissue lesions were found in 4.1% of the study subjects. The prevalence of leukoplakia, OSF and oral lichen planus was 0.59%, 0.55%, and 0.15% respectively. The prevalence of smoking, drinking alcoholic beverages and chewing was 15.02%, 8.78% and 6.99% respectively. Smoking and chewing were significant predictors of leukoplakia in this population.

Discussion: The prevalence of leukoplakia, OSF and oral lichen planus in our study population is similar to those found in other populations. The prevalence of consumption of alcoholic beverages in our study population was higher when compared to the Indian National Sample Survey study. However the prevalence of smoking and chewing was found to be lower. Smokers were more likely to develop smoker's melanosis compared to other lesions. Among those who consumed alcoholic beverages alone, the prevalence of leukoplakia was higher compared to other lesions. OSF was the most prevalent lesion among those who chewed panmasala or gutkha or betel quid with or without tobacco.

Keywords: Betel quid, areca nut, panmasala, unfiltered cigarette, oral submucous fibrosis, lichen planus, leukoplakia, Tamilnadu India, chewer's mucosa, oral lesions.

INTRODUCTION

Chewing, smoking and consumption of alcoholic beverages have become common social habits in India. According to the study conducted by Neufeld and his coworkers, using National Sample Survey (NSS) which is a representative sample of India, conducted in 1995-96, constituting 4,71,143 people 10 years and older, the prevalence of regular use of alcohol is 4.5%, smoking tobacco is 16.2%, and chewing tobacco is 14% (1). The prevalence of these habits was found to be more among men when compared to women. Also, the prevalence was higher among the rural population and those with no formal education (1).

Smoking, drinking, and chewing have been positively associated with oral lesions such as oral submucous fibrosis (OSF), leukoplakia, and oral lichen planus, which has the potential for malignant transformation (2-9). The prevalence of OSF in India varies between 0.03% and 3.2% according to various studies conducted here (7,10-14). Also, higher occurrence of leukoplakia and cancer are observed in OSF patients and it is believed to be an important risk factor for oral cancer among youths (15,16). Prevalence of oral leukoplakia in India varies from 0.2%-5.2% (7,10,12,13). According to an Indian study at four urban centers, the prevalence of oral lichen planus varies between 0.02%-0.4% (10,14,17). In yet another door-to-door survey of 7639 Indian villagers, the prevalence varies from 0.1%-1.5% (18). However, no study has been conducted in Tamilnadu in this regard to our knowledge. We wanted to know the scenario of oral lesion's relation to habits in this part of the state. Therefore, a pilot hospital based cross-sectional study was carried out using already existing data collected during a period of three months at Ragas Dental College, Uthandi, Chennai, India.

MATERIALS AND METHODS

Two thousand and seventeen consecutive patients from sub-urban and rural areas near Chennai, who attended the outpatient department, at Ragas Dental College, for dental complaints during a period of three months from 16th of August to December 2004 formed our study group. Trained dental surgeons collected the data using a combination of clinical oral examination and standardized questionnaire. Information on habits and other characteristics of the study participants were acquired using the standardized, interviewer based questionnaire.

Analyses

Prevalence of oral lesions and habits were estimated using STATA statistical software version 7.0 (STATA Corporation 2001). Logistic regression was used to estimate the effects of different variables on oral lesions. Univariate analysis was done to find the effect of each variable on the prevalence of leukoplakia among the study subjects

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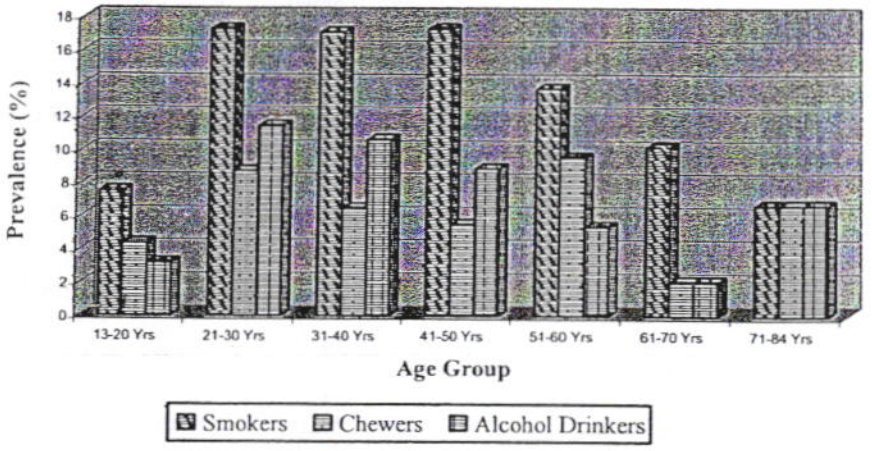
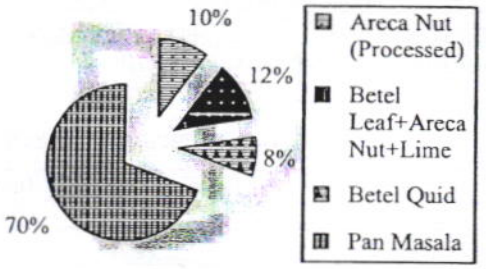
Graph 1
Prevalence of habits by age group



Graph 2
Prevalence of different type of chewing habits



Graph 3
Prevalence of different types of alcohol consumption

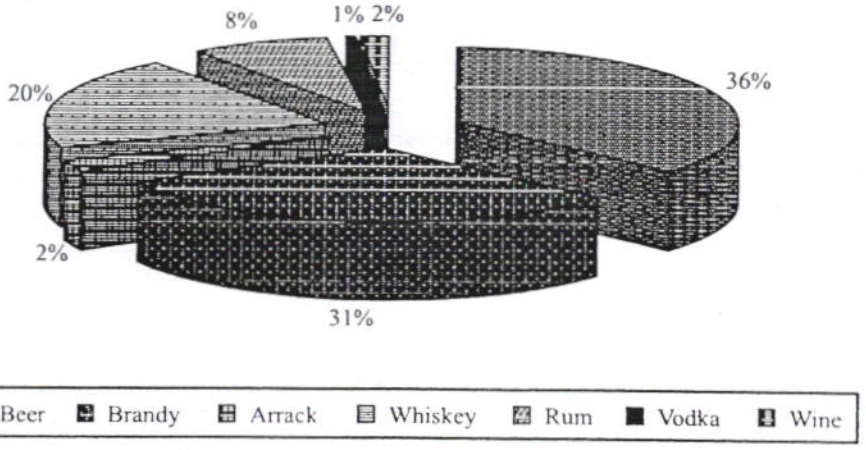


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Table 1
Variable definitions and distribution of study subjects by basic characteristics

Characteristics	Males (%)	Females (%)	Total (%)
Age Group			
13yrs - 20yrs	17.34	16.85	17.15
21yrs - 30yrs	40.36	34.25	38.13
31yrs - 40yrs	19.44	25.07	21.47
41yrs - 50yrs	10.81	13.42	11.75
51yrs - 60yrs	8.32	8.36	8.33
61yrs - 70yrs	2.95	1.51	2.43
71yrs - 84yrs	0.78	0.55	0.74
Education			
Illiterate	21.41	13.69	18.59
Primary	8.93	4.56	7.34
High School	18.56	16.18	17.69
Higher Sec	29.23	25.45	27.84
Diploma	17.69	29.18	21.91
Degree	4.19	10.93	6.63
Family Income			
< 5000 Rs	3.11	2.71	2.96
5000Rs	11.63	6.99	9.96
5000Rs – 10000Rs	82.87	88.87	85.03
> 10000Rs	2.39	1.43	2.04
Number of study Participants *	**1287**	**730**	**2017**

* The number of study participants varies slightly for individual variables depending on the number of missing values.

Table 2
Prevalence of soft tissue lesions by gender

Lesions	Prevalence in Men (%)	Prevalence in Women (%)	General Prevalence (%)
Smoker's Melanosis	1.63	0.27	1.14
Leukoplakia	0.7	0.41	0.59
Stomatitis Nicotina Palatini	1.24	0.27	0.89
Leukedema	0.39	0	0.25
Chewer's Mucositis	0.23	0.27	0.25
Oral Submucous Fibrosis	0.62	0.41	0.55
Median Rhomboid Glossitis	0.38	0	0.25
Lichen Planus	0.23	0	0.15
Candidiasis	0.07	0	0.05
Number of study Participants	**1287**	**730**	**2017**

Table 3
Effects of different predictor variables on the prevalence of leukoplakia

Characteristics	Odds Ratio	95% Confidence Interval
Chewing		
Non Chewer	1.0 *	-
Chewer	5.08	(3.75, 6.41)
Smoking		
Non Smoker	1.0 *	-
Smoker	6.82	(5.63, 8.01)
Alcohol Drinking		
Non Alcohol Drinker	1.0 *	-
Alcohol Drinker	2.33	(0.79, 2.33)

* Reference Category

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RESULTS

Profile of the study subjects

Table 1 shows the distribution of study subjects by basic characteristics. There were more males (63.75%) in the study population than females (36.25%). 17.15% of the study participants were in the age group of 13 to 20 years, 38.13% were in the age group of 21 to 30years, 21.47% were in the age group of 31 to 40 years, and the remaining 23.25% were in the age group of 41 to 84 years. About 28.54% of the participants were either degree or diploma holders and remaining participants have had only school education or were illiterates. More than 85% of the study subjects come from families with monthly income between Rs 5,000 and Rs 10,000 per month, whereas less than 3% belonged to families with income less than Rs 5,000 per month.

Prevalence of habits

The overall prevalence of smoking, drinking alcoholic beverages and chewing were 15.02%, 8.78% and 6.99% respectively. Graph 1 shows the prevalence of habits by age. The prevalence of smoking was higher among men (23.25%) when compared to women (0.55%). Also, the prevalence of smoking is higher among the age group of 20 to 50, highest being in the age group of 20 to 31 (17.3%) and 40 to 51 (17.3%). More than 7 out of 10 smokers use unfiltered cigarettes, as compared to the other types namely filtered cigarette, cigar, and beedi. In this population, alcohol consumption was more common among men (13.37%) when compared to women (0.55%), with the prevalence being highest (11.44%) in the age group of 21 to 30. The use of beer, brandy and whisky was more prevalent compared to other alcoholic beverages consumed in this study group, namely arrack, wine, vodka, and rum.

The chewing habit was more prevalent in men (8.55%) as compared to women (4.25%), with highest being in the age group of 51-60. In women, the chewing habit was more prevalent when compared to the other two habits; wherein, in men it was the smoking habit that was more prevalent. The study participants were more likely to chew pan masala (commercially available processed areca nut product without tobacco) or gutkha (commercially available processed areca nut product without tobacco) (70%) as compared to other products namely betel quid, betel leaf with areca nut and lime, unprocessed and processed areca nut alone as can be seen in graph 2.

Prevalence of lesions

Oral soft tissue lesions were found in 4.1% of the study subjects. In this study, smoker's melanosis was found to be the most common soft tissue lesion with the prevalence being 1.14%. Stomatitis nicotina palatini (0.89%) and leukoplakia (0.59%) were the second and third most common lesions. Table 2 shows that the prevalence of all lesions is more common in men when compared to women, but for chewer's mucosa. Among men, smoker's melanosis and stomatitis nicotina palatini were more prevalent compared to other soft tissue lesions, whereas among women leukoplakia and OSF were more prevalent. Majority of the oral soft tissue lesions were found among people aged from 41 to 60 years.

Prevalence of lesions in relation to habits

Study subjects who smoked had much higher prevalence of soft tissue lesions compared to those who did not. Same was the case among those who consumed alcoholic beverages and chewers. Smokers were more likely to develop smoker's melanosis compared to other lesions. Among those who consumed alcoholic beverages alone, the prevalence of leukoplakia was higher compared to other lesions. OSF was the most prevalent lesion among those who chewed panmasala or gutkha or betel quid with or without tobacco.

Effect (Univariate) of predictor variables on prevalence of leukoplakia

Table 3 shows the effect of different predictor variables on the prevalence of leukoplakia among the study subjects. The odds of having leukoplakia is 6 times higher for those who smoke [OR=6.82; 95% CI, (5.63, 8.01)] as compared to those who do not. The odds of suffering from leukoplakia is about 5 times higher among those who chew as compared to those who do not [OR= 5.08; 95% CI, (3.75, 6.41)]. The consumption of alcoholic beverages alone is not significantly associated with the prevalence of leukoplakia i.e., prevalence of leukoplakia did not differ between those who consumed alcoholic beverages and those who did not.

DISCUSSION

Cross-sectional studies are important in estimating the prevalence of a disease in the population and identifying the high-risk sub population. In this sample the prevalence of oral lesions was 4.1%, with the prevalence being greater for males than females. The prevalence of leukoplakia (0.59%), OSF (0.55%) and oral lichen planus (0.15%) in our study population is similar to those found in other previous studies conducted in India (7,10,12,13, 15,17,18).

The prevalence of alcohol consumption (8.78%) in our study population was higher when compared to the results reported by Neufeld and his coworkers using the Indian National Sample Survey sample (1). However the prevalence of smoking (15.02%) and chewing (6.99%) was found to be lower. Smoking, and chewing were significant predictors of leukoplakia in this population. However the association between alcohol consumption and presence of leukoplakia was not statistically significant.

In the present study, females were more likely to chew when compared to the other two habits (this goes with the finding that chewer's mucosa is the most prevalent soft tissue lesion among them). Also, the study shows that smoking is more prevalent in men when compared to the other two habits. Findings from the present study are similar to that of Hashibe et al (19) with regard to chewing and smoking habit being significant predictors of leukoplakia. However consumption of alcoholic beverages (any amount and all types mentioned in Graph 3) did not prove to be a significant predictor as found in the studies by Hashibe et al and Gupta (19,20).

Data was collected as a chair side procedure, which involved oral examination and questionnaire administration. Since the information on the habits was gathered through questionnaire, there could be information bias, but this could only bias our results towards the null. In this study detailed information could not be gathered on other predictors of oral lesions such as nutritional status and BMI (Body Mass Index); a more detailed and case control study is required to better understand the oral lesions and habits association in this population.

The findings from this study can be used to design case control or cohort studies to further understand the relation between habits and oral lesions. Studies of this nature could potentially help clinicians in identifying high-risk population and which would be most beneficial for providing better oral hygiene programs. Programs to improve oral health should be conducted regularly to promote oral health care in the population.

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Annexe 4

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RISK FACTORS FOR MULTIPLE ORAL PREMALIGNANT LESIONS

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Oral leukoplakia, oral submucous fibrosis and erythroplakia are 3 major types of oral premalignant lesions. Multiple oral premalignant lesions may possibly develop due to field cancerization, where carcinogenic exposures can cause simultaneous genetic defects to the upper aerodigestive tract epithelium, putting the epithelium at high risk for development of premalignant lesions at different stages of carcinogenesis. There have been no epidemiological studies on risk or protective factors of the disease. A case-control study was conducted with data from the baseline screening of a randomized oral cancer screening trial in Kerala, India. A total of 115 subjects with multiple oral premalignant lesions (8–10% of oral premalignant lesions in our case series) were included: 64 subjects with oral leukoplakia and oral submucous fibrosis, 19 subjects with oral leukoplakia and erythroplakia, 22 subjects with oral submucous fibrosis and erythroplakia and 10 subjects with all 3 lesions. Individuals without oral lesions were considered controls (n=47,773). The odds ratio (OR) for ever tobacco chewers was 37.8 (95% confidence interval (CI)=16.2–88.1) when adjusted for age, sex, education, BMI, smoking, drinking and fruit/vegetable intake. Dose-response relationships were seen for the frequency (p<0.0001) and duration of tobacco chewing (p<0.0001) with the risk of multiple oral premalignant lesions. Whereas alcohol drinking may possibly be a risk factor for multiple oral premalignant lesions, smoking was not associated with the risk of multiple oral premalignant lesions (OR=0.9, 95%CI=0.5–1.7). The results suggest that tobacco chewing was the most important risk factor for multiple oral premalignant lesions and may be a major source of field cancerization on the oral epithelium in the Indian population.

Key words: *precancerous conditions; oral leukoplakia; oral submucous fibrosis; erythroplakia; chewing tobacco*

Oral premalignant lesions such as oral leukoplakia, oral submucous fibrosis and erythroplakia can occur together as multiple oral premalignant lesions. A potential mechanism for the development of multiple oral premalignant lesions is explained by the field cancerization theory,[1] which proposes that carcinogenic exposures can cause simultaneous genetic defects on the epithelium of the upper aerodigestive tract, putting the epithelium at high risk for the development of multiple lesions. The lesions are considered to be independent of each other, with the assumption that they arise from separate genetic events. A competing theory is that multiple lesions occur due to the migration of transformed cells to adjacent areas. For gastrointestinal cancers, clones appear to spread by crypt or gland fission.[2] Migration may also be a possible mechanism for oral lesions that are close to one another. However, for head and neck tumors that are far from one another, studies have reported that lesions are usually not clonally related according to microsatellite alterations, loss of heterozygosity patterns, cytogenetic characteristics and p53 mutations.[3] In fact, a study on patients with multiple oral premalignant lesions such as hyperplasia and dysplasia reported that the majority of these multiple lesions arose from clonally independent cells.[4]

There have been no studies focusing on the epidemiologic risk factors of multiple oral premalignant lesions, to our knowledge. Risk factors for such multiple lesions may be considered a mixture of risk factors for single premalignant lesions. Tobacco chewing is a major risk factor for all 3 lesions, while tobacco smoking may be a risk factor for oral leukoplakia.[5–7] Alcohol drinking may increase the risk by 1.5-fold for oral leukoplakia,[5] by 2-fold for oral submucous fibrosis[6] and by 3-fold for erythroplakia.[7]

Nevertheless, it is possible that subjects with multiple lesions are a distinct group with respect to the degrees of tobacco and alcohol exposures and genetic susceptibility. When exposed to a common carcinogenic exposure, more genetic abnormalities may occur in these individuals who may have weakened DNA repair capabilities in comparison to other individuals who have normal DNA repair capabilities. Examining risk factors for multiple oral premalignant lesions may help to identify the major exposure that leads to field cancerization of the oral cavity. The aim of our study is to examine tobacco chewing, smoking, alcohol drinking, fruit/vegetable intake, vitamin/iron supplements and body mass index (BMI) as potential risk or protective factors for multiple oral premalignant lesions. We will also explore interactions among these potential risk and protective factors.

MATERIAL AND METHODS

Study population and data collection

A case-control study design was employed to evaluate the risk factors for multiple oral premalignant lesions. Data from the first round of intervention from an on-going randomized oral cancer screening trial in Kerala, India were used. The analysis included only the intervention group since subjects from this group had been screened with oral visual inspections and their disease status was known. The objective of the randomized oral cancer screening trial is to evaluate the efficacy of oral visual inspections by trained health workers in preventing death from this cancer.[8] The randomization unit was the panchayath (n=13), which is a rural administrative structure. Subjects who were over the age of 35 years and living in one of the specified panchayaths were eligible for the trial. The intervention group included a total of 59,894 eligible subjects who lived in 1 of 7 panchayaths, where the total resident population was 172,567. In the first round of intervention, 49,179 (82.1%) subjects were interviewed and screened in their houses by trained health workers. A total of 115 multiple oral premalignant

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lesions cases and 47,773 controls were identified from this intervention group for this case-control study.

The health workers, who were college graduates and residents of the area, were trained in the management of oral precancers and cancers as described previously.[8] They interviewed subjects about demographic information, tobacco chewing, smoking and alcohol drinking habits by using a structured questionnaire. Information on the duration (years) and frequency (times per day or week) of the alcohol and tobacco habits were collected. The subjects were also asked whether they kept the chewing tobacco in their mouth overnight and whether they swallowed the chewing tobacco fluid. Health workers then asked whether fruits were taken frequently, vegetables were taken daily and vitamin/iron supplements were taken currently or in the past. After the interview, blood pressure, body weight and height were measured.

The health workers then identified lesions suggestive of oral leukoplakia, erythroplakia, submucous fibrosis or oral cancer by inspecting the buccal and labial mucosa, gingivae, bucco alveolar sulci, tongue, palate and the floor of the mouth. Subjects with positive or suspicious findings were referred to the dentists and oncologists who made the final diagnosis. Among the 3,585 subjects with suspicious oral lesions who were referred by the health workers, 1,877 subjects (52.4%) complied with the referral and were examined by the dentists or oncologists. Compliance was somewhat higher among subjects with more severe lesions.[8] Overall, the subjects who complied were generally representative of the subjects who were referred. Differences were not observed in the distribution of age, sex, education, occupation, smoking or alcohol habits between the groups of subjects who complied and subjects who were referred (according to χ^2 statistics). For tobacco chewing, there was a slightly higher percentage of current tobacco chewers in the referred group (66%) than in the complying group (60%).

For our study, cases were defined as subjects without oral cancer, diagnosed with more than one of the following oral premalignant lesions: oral leukoplakia, oral submucous fibrosis and erythroplakia. One subject who had a homogenous leukoplakia lesion and 2 oral submucous fibrosis lesions was excluded since this subject also had oral cancer. Thus, we had a total of 115 multiple oral premalignant lesions cases, which represented 8–10% of oral premalignant lesions in our case series. The controls were defined as subjects who were diagnosed to be free of oral diseases by the health workers (n=47,773).

Statistical analysis

Logistic regression was used to estimate odds ratios (OR) and their 95% confidence intervals (95% CI), to evaluate the effects of potential risk factors on the risk of multiple oral premalignant lesions. To estimate ORs for each category of exposure, dummy variables were created for the categories and included in the logistic regression model. Trend tests for ordered variables were performed by assigning the score j to the jth exposure level of a categorical variable (where j=1, 2, . . .) and treating it as a continuous predictor in unconditional logistic regression. Chi-square tests were conducted to determine whether there were associations between disease status and demographic/risk factor distributions. BMI was categorized into quartiles, based on the distribution of BMI among the controls.

For the crude analysis, the first model did not include any covariates. In the second model, potential confounders were included: age (continuous, in years), sex (F/M) and education (categorical as shown in Table I). In the third model, we further adjusted for the following potential risk or protective factors of multiple oral premalignant lesions: BMI (kg/m^2, continuous), tobacco chewing (continuous, duration in years), smoking (continuous, pack-years), alcohol drinking (continuous, duration in years), fruit intake (low/high) and vegetable intake (low/high) by including these variables in the logistic regression model where appropriate.

RESULTS

We identified 115 subjects with multiple oral premalignant lesions: 64 subjects had oral leukoplakia and oral submucous fibrosis, 19 subjects had oral leukoplakia and erythroplakia, 22 subjects had oral submucous fibrosis and erythroplakia and 10 subjects had all 3 lesions. In addition to having multiple types of oral precancers, some subjects had more than one of each oral precancer: 18 subjects had 2 or more homogenous leukoplakias (15.6% of all homogenous leukoplakia cases), 3 subjects had 2 ulcerated leukoplakias (2.6% of all ulcerated leukoplakia cases), 73 subjects had 2 or more oral submucous fibrosis (63.5% of all

TABLE I – GENERAL CHARACTERISTICS OF MULTIPLE ORAL PREMALIGNANT LESION CASES AND CONTROLS

	Cases		Controls		
	N (n = 115)	%	N (n = 47,773)	%	χ^2 p-value
Age groups					
35–44 years	18	15.7	18,748	39.2	<0.0001
45–54 years	44	38.3	12,777	26.8	
55–64 years	33	28.7	9,804	20.5	
≥65 years	20	17.4	6,444	13.5	
Sex					
Female	73	63.5	29,876	62.5	0.8351
Male	42	36.5	17,897	37.5	
Education					
None and illiterate	42	36.5	8,351	17.5	<0.0001
None and literate	13	11.3	3,078	6.4	
Primary	35	30.4	10,758	22.5	
Middle	11	9.6	8,399	17.6	
≥High school	14	12.1	17,178	36.0	
Religion					
Hindu	76	66.1	32,968	69.0	0.0047
Muslim	16	13.9	9,555	20.0	
Christian	23	20.0	5,250	11.0	
Occupation					
Manual	100	87.0	39,918	83.6	0.4709[1]
Teacher/office worker	2	1.7	2,577	5.4	
Business	2	1.7	1,227	2.6	
Retired	8	7.0	2,801	5.9	
Others	3	2.6	1,250	2.6	

[1]manual *vs.* nonmanual.

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oral submucous fibrosis cases) and 12 subjects had 2 or more erythroplakia lesions (10.4% of all erythroplakia cases). Subjects with nodular or verrucous leukoplakias only had one leukoplakia lesion, in addition to the oral submucous fibrosis or erythroplakia lesion.

Table I shows the distribution of the general characteristics by case and control status. Chi-square tests were performed to determine whether the distribution of these factors was related to disease status. Multiple oral premalignant lesions cases were more likely to be in the 45–54 year age group while controls were more likely to be in the youngest age group of 35–44 years. The distribution of sex was fairly similar among cases and controls. The level of education was higher among the controls than the cases; the highest percentage of cases were in the no education and illiterate category. Most subjects were Hindu among both cases and controls, but the percentage of Muslims was higher among controls and the percentage of Christians was higher among cases. The majority of cases and controls held a manual occupation. Controls had a higher percentage of teachers and office workers.

The distribution of potential risk and protective factors stratified by disease status and by sex is shown in Table II. Among both men and women, the majority of cases were tobacco chewers, while the majority of controls were nonchewers. Most men smoked whether they were a case or control but very few women smoked. Almost no women reported alcohol use, while 31% of male cases and 15% of male controls drank alcohol. Fruit and vegetable intake was consistently higher among the controls for women and men. Past and current vitamin/iron supplement use was higher in the cases than in controls. Most female cases were in the lowest quartile for BMI, while the male cases were more likely to be in the 3rd quartile.

Only 6 multiple oral premalignant lesions cases were nonchewers, while the other 109 cases were either past, occasional or current tobacco chewers (Table III). Tobacco chewing was associated with an increased risk of multiple oral premalignant lesions (OR=37.8, 95%CI=16.2, 88.1) when adjusted for age, sex, education, BMI, smoking, drinking and fruit/vegetable intake. Past chewers had a higher OR then current and occasional tobacco chewers. Most tobacco chewers preferred "pan with tobacco", for which the adjusted OR was 52.8 (95%CI=22.4, 124.4). The OR for chewers of "tobacco only" appeared higher than for pan with tobacco, but there was only 1 case who chewed "tobacco only" limiting the statistical precision for this category. Dose-response relationships were observed for both the frequency (p for trend<0.0001) and duration of tobacco chewing (p for trend<0.0001) in the crude as well as adjusted models. Swallowing the tobacco fluid seemed to elevate the risk of multiple oral premalignant lesions among tobacco chewers. Keeping the tobacco chewing fluid overnight did not elevate the ORs further among tobacco chewers, according to the model adjusting for risk and protective factors.

An association between tobacco smoking and the risk of multiple oral premalignant lesions was not observed (Table IV). The adjusted OR for ever smoking was 0.9 (95%CI=0.5, 1.7). Occa-

TABLE II – DISTRIBUTION OF POTENTIAL RISK AND PROTECTIVE FACTORS AMONG MULTIPLE ORAL PREMALIGNANT LESION CASES AND CONTROLS BY SEX

	Male		Female		Total	
	Cases n = 42 (%)	Controls n = 17897 (%)	Cases n = 73 (%)	Controls n = 29876 (%)	Cases n = 115 (%)	Controls n = 47773 (%)
Chewing						
No chewing	4.8	69.0	5.5	73.7	5.2	72.0
Occasional	4.8	7.6	1.4	4.2	2.6	5.5
Past	21.4	3.7	16.4	2.1	18.3	2.7
Current	69.1	19.7	76.7	20.0	73.9	19.9
p-value*	<0.0001		<0.0001		<0.0001	
Smoking						
No smoking	33.3	35.7	94.5	97.7	72.2	74.5
Occasional	11.9	4.0	1.4	0.2	5.2	1.6
Past	14.3	9.6	0.0	0.3	5.2	3.8
Current	40.5	50.7	4.1	1.8	17.4	20.1
p-value*	0.0366		0.0575		0.0158	
Alcohol drinking						
No drinking	42.9	61.4	100.0	99.8	79.1	85.4
Occasional	9.5	15.2	0.0	0.1	3.5	5.7
Past	16.7	8.1	0.0	0.1	6.1	3.1
Current	31.0	15.3	0.0	0.0	11.3	5.8
p-value*	0.0034		0.9860		0.0118	
Fruit						
Low intake	23.8	12.2	12.3	9.2	16.5	10.3
High intake	76.2	87.8	87.7	90.8	83.5	89.7
p-value*	0.0224		0.3519		0.0292	
Vegetable						
Low intake	33.3	9.7	16.4	6.7	22.6	7.8
High intake	66.7	90.3	83.6	93.3	77.4	92.2
p-value*	<0.0001		0.0009		<0.0001	
Vitamin/ iron supplements						
No	45.2	73.1	46.6	57.9	46.1	63.6
Yes	7.1	3.8	5.5	3.1	6.1	3.3
Past	47.6	23.2	48.0	39.0	47.8	33.1
p-value[1]	0.0003		0.1068		0.0004	
Body Mass Index (kg/m^2)						
Quartile 1	16.7	26.9	44.4	24.0	34.2	25.1
Quartile 2	26.2	27.5	29.2	23.5	28.1	25.0
Quartile 3	31.0	26.0	16.7	24.3	21.9	24.9
Quartile 4	26.2	19.6	9.7	28.3	15.8	25.0
p-value*	0.3952		<0.0001		0.0366	

[1]* χ^2 test.

TABLE III – CHEWING TOBACCO HABITS AND RISK OF MULTIPLE ORAL PREMALIGNANT LESIONS (ODDS RATIOS AND 95% CONFIDENCE INTERVALS)

	Cases	Controls	Crude OR (95% CI)	Adjusted OR[1] (95% CI)	Adjusted OR[2] (95% CI)
Chewing tobacco					
No chewing	6	34,373	1.0	1.0	1.0
Ever chewing	109	13,400	46.6 (20.5, 106.0)	40.8 (17.6, 94.2)	37.8 (16.2, 88.1)
Chewing tobacco					
No chewing	6	34,373	1.0	1.0	1.0
Occasional	85	2,625	6.5 (1.6, 26.2)	6.3 (1.6, 25.2)	7.1 (1.8, 28.6)
Past	3	1,276	94.2 (38.0, 233.9)	103.3 (40.4, 264.4)	93.9 (35.9, 245.9)
Current	21	9,499	51.2 (22.4, 117.3)	48.1 (20.6, 112.5)	43.5 (18.5, 102.7)
Type of chewing tobacco					
No chewing	6	34,373	1.0	1.0	1.0
Pan with tobacco	100	9,477	60.5 (26.5, 137.8)	58.5 (25.1, 136.6)	52.8 (22.4, 124.4)
Pan without tobacco	5	1,157	24.8 (7.5, 81.2)	22.7 (6.8, 75.6)	22.2 (6.6, 74.0)
Tobacco only	1	43	133.2 (15.7, ---)	132.7 (15.5, ---)	177.0 (20.3, ---)
Frequency of chewing (Times per day)					
No chewing	6	34,373	1.0	1.0	1.0
1–10	79	8,991	50.3 (21.9, 115.4)	49.2 (21.0, 115.4)	45.7 (19.4, 108.1)
11–20	19	1,443	75.4 (30.1, 189.0)	71.6 (27.8, 184.3)	63.0 (24.1, 164.2)
≥20	8	271	169.0 (58.3, 490.4)	154.2 (51.3, 464.0)	112.8 (35.0, 363.8)
p for trend			<0.0001	<0.0001	<0.0001
Duration of chewing (years)					
No chewing	6	34,373	1.0	1.0	1.0
1–20	52	5,971	49.9 (21.4, 116.2)	47.5 (20.1, 112.4)	43.9 (18.4, 104.6)
21–40	44	3,470	72.6 (30.9, 170.6)	77.3 (31.5, 189.9)	67.1 (27.0, 167.1)
≥40	10	1,217	47.1 (17.1, 129.7)	62.8 (20.3, 194.3)	56.2 (17.8, 177.3)
p for trend			<0.0001	<0.0001	<0.0001
Swallow chewing tobacco fluid					
No chewing	6	34,373	1.0	1.0	1.0
Chewing/no swallowing	94	10,117	53.3 (23.4, 121.7)	51.9 (22.2, 121.1)	47.8 (20.3, 112.5)
Chewing/swallowing	7	291	138.0 (43.1, 413.1)	121.3 (39.4, 373.8)	89.6 (27.0, 297.3)
Occasionally swallow	5	303	94.7 (28.7, 311.8)	90.0 (26.4, 307.1)	85.7 (23.6, 310.7)
Keep chewing tobacco in mouth overnight					
No chewing	6	34,373	1.0	1.0	1.0
Chewing/don't keep	101	10,351	55.9 (24.5, 127.4)	53.8 (23.1, 125.4)	49.2 (20.9, 115.5)
Chewing/keep	5	310	92.4 (28.1, 304.4)	81.3 (20.3, 209.4)	49.6 (13.1, 187.6)

[1]OR adjusted for age (continuous), sex (M/F), education (categories).–[2]OR adjusted for age, sex, education, body mass index (continuous, kg/m^2), smoking (continuous, pack-years), drinking (continuous, years), fruit intake (low/high) and vegetable intake (low/high).

sional smoking appeared to be a risk factor for multiple oral premalignant lesions in the crude analysis but when adjusted for age, sex, education, BMI, tobacco chewing, drinking and fruit/vegetable intake the confidence interval crossed the null value. A trend was not observed between the frequency of smoking and the risk of multiple oral premalignant lesions. The *p* for trend for the duration and pack-years of smoking was small but may have indicated an inverse dose-response relationship. The small number of cases in the upper categories of duration and pack-years of smoking may have been responsible for this unexpected trend.

The adjusted OR for ever drinking was 1.4 with a confidence interval overlapping the null value (95%CI=0.7, 2.7) (Table V). Subjects who drank toddy, arrack and foreign liquor had an elevated adjusted OR (2.5, 95%CI=1.1, 5.4). Dose-response trends were observed in the crude analysis and in the models including age, sex and education. However, the trends were not apparent when further adjusted for BMI, smoking, tobacco chewing and fruit/vegetable intake.

High fruit intake was not associated with a lower risk of multiple oral premalignant lesions, but high vegetable intake may be protective against multiple oral premalignant lesions (Table VI). Vitamin and iron supplements appeared to be risk factors, with larger ORs for current users. A trend was observed between BMI and the risk of multiple oral premalignant lesions (*p* for trend=0.0011) in the crude analysis but when adjusted for various factors, the association was no longer seen. Subjects with a high BMI of more then 35 kg/m^2 had a crude OR of 0.5 (95%CI=0.3, 0.8).

The interaction between tobacco chewing and alcohol drinking could not be assessed because there were no subjects who drank but did not chew tobacco. The analysis for exploring interactions between vegetable intake/tobacco chewing and vegetable intake/alcohol drinking was conducted. There did not appear to be any interactions on the multiplicative scale between either pair of factors. The ORs were 1.5 (95%CI=0.7, 3.3) for drinkers, 3.0 (95%CI=1.5, 6.0) for subjects with low vegetable intake and 3.4 (95%CI=1.3, 8.9) for drinkers with low vegetable intake when adjusted for age, sex, education, BMI, tobacco chewing, smoking, drinking and fruit intake. Tobacco chewers had an OR of 41.6 (95%CI=16.5, 104.8), while subjects with low vegetable intake had an OR of 5.0 (95%CI=0.6, 44.7) and tobacco chewers with low vegetable intake had an OR of 100.4 (95%CI=33.8, 298.1), when adjusted for risk/protective factors. This analysis may be considered exploratory since the sample size was limited.

DISCUSSION

Tobacco chewing was associated with the strongest increase in the risk of multiple oral premalignant lesions and may be the major source of field cancerization of the oral cavity in the Indian population. The elevated risk of multiple oral premalignant lesions for ever chewing (OR=37.8, 95%CI=16.2, 88.1) was intermediate

TABLE IV – SMOKING AND RISK OF MULTIPLE ORAL PREMALIGNANT LESIONS (ODDS RATIOS AND 95% CONFIDENCE INTERVALS)

	Cases	Controls	Crude OR (95% CI)	Adjusted OR[1] (95% CI)	Adjusted OR[2] (95% CI)
Smoking					
No smoking	83	35,567	1.0	1.0	1.0
Ever smoking	32	12,206	1.1 (0.7, 1.7)	1.0 (0.6, 1.8)	0.9 (0.5, 1.7)
Smoking					
No smoking	83	35,567	1.0	1.0	1.0
Occasional	6	769	3.3 (1.5, 7.7)	3.4 (1.3, 8.4)	2.3 (0.8, 6.1)
Past	20	1814	1.4 (0.6, 3.3)	1.3 (0.5, 3.4)	1.4 (0.5, 3.4)
Current	6	9623	0.9 (0.5, 1.5)	0.8 (0.4, 1.5)	0.7 (0.4, 1.4)
Type of smoking					
No smoking	83	35,567	1.0	1.0	1.0
Bidi	8	818	1.2 (0.6, 2.5)	0.7 (0.3, 1.6)	0.5 (0.2, 1.3)
Cigarette	5	3,217	0.7 (0.3, 1.6)	0.7 (0.3, 2.0)	0.9 (0.3, 2.9)
Bidi + cigarette	10	5,321	0.8 (0.4, 1.5)	0.7 (0.3, 1.5)	0.7 (0.3, 1.7)
Churuttu	1	39	10.7 (1.5, 79.1)	4.6 (0.6, 35.9)	2.0 (0.2, 16.7)
Frequency of smoking (times per day)					
No smoking	83	35,567	1.0	1.0	1.0
1–20	22	8,366	1.1 (0.7, 1.8)	1.0 (0.5, 1.8)	0.8 (0.5, 1.6)
>20	4	2,972	0.6 (0.2, 1.6)	0.5 (0.2, 1.4)	0.6 (0.2, 1.9)
p for trend			0.3019	0.0843	0.4098
Duration of smoking (years)					
No smoking	83	35,567	1.0	1.0	1.0
1–20	19	4,550	1.8 (1.1, 2.9)	1.9 (1.0, 3.5)	1.7 (0.9, 3.2)
>20	7	6,758	0.4 (0.2, 1.0)	0.3 (0.1, 0.7)	0.3 (0.1, 0.7)
p for trend			0.0916	0.0020	0.0072
Packyears of smoking					
No smoking	83	35,567	1.0	1.0	1.0
1–20	18	3,638	2.1 (1.3, 3.5)	2.0 (1.1, 3.6)	1.6 (0.8, 2.9)
>20	8	7,635	0.4 (0.2, 0.9)	0.3 (0.1, 0.8)	0.3 (0.1, 0.8)
p for trend			0.0698	0.0058	0.0290

[1]OR adjusted for age (continuous), sex (M/F), education (categories).–[2]OR adjusted for age, sex, education, body mass index, chewing tobacco (continuous, duration in years), drinking (continuous, duration in years), fruit intake (low/high) and vegetable intake (low/high).

TABLE V – ALCOHOL DRINKING HABITS AND RISK OF MULTIPLE ORAL PREMALIGNANT LESIONS (ODDS RATIOS AND 95% CONFIDENCE INTERVALS)

	Cases	Controls	Crude OR (95% CI)	Adjusted OR[1] (95% CI)	Adjusted OR[2] (95% CI)
Alcohol drinking					
No drinking	91	40,801	1.0	1.0	1.0
Ever drinking	24	6,972	1.5 (1.0, 2.4)	1.9 (1.0, 3.5)	1.4 (0.7, 2.7)
Alcohol drinking					
No drinking	91	40,801	1.0	1.0	1.0
Occasional	4	2,743	0.7 (0.2, 1.8)	1.0 (0.4, 3.1)	1.1 (0.4, 3.2)
Past	7	1,475	2.1 (1.0, 4.6)	2.2 (0.9, 5.2)	1.8 (0.7, 4.5)
Current	13	2,754	2.1 (1.2, 3.8)	2.3 (1.1, 4.8)	1.3 (0.6, 3.0)
Type of alcohol					
No drinking	91	40,801	1.0	1.0	1.0
Arrack	5	952	2.4 (1.0, 5.8)	1.9 (0.7, 5.2)	0.9 (0.3, 2.6)
Toddy, arrack and foreign liquor	15	2,230	3.0 (1.7, 5.2)	3.4 (1.7, 6.8)	2.5 (1.1, 5.4)
Frequency of drinking (days per week)					
No drinking	91	40,801	1.0	1.0	1.0
1–3	5	1,359	1.7 (0.7, 4.2)	1.9 (0.7, 4.9)	1.2 (0.4, 3.4)
4–7	15	2,760	2.5 (1.4, 4.3)	2.5 (1.3, 4.9)	1.9 (1.0, 4.0)
p for trend			0.0012	0.0088	0.1546
Duration of drinking (years)					
No drinking	91	40,801	1.0	1.0	1.0
1–20	8	2,318	1.5 (0.8, 3.2)	1.9 (0.8, 4.4)	1.7 (0.7, 4.0)
>20	12	1,811	3.0 (1.6, 5.4)	2.8 (1.3, 5.8)	1.8 (0.8, 4.0)
p for trend			0.0009	0.0240	0.8421

[1]OR adjusted for age (continuous), sex (M/F), education (categories).–[2]OR adjusted for age, sex, education, body mass index, smoking (continuous, packyears), chewing tobacco (continuous, duration in years), fruit intake (low/high) and vegetable intake (low/high).

to those reported previously for single lesions of oral leukoplakia (OR = 7.0, 95%CI = 5.9, 8.3), oral submucous fibrosis (OR = 44.1, 95%CI = 22.0, 88.2) and erythroplakia (OR = 19.8, 95%CI = 9.8, 40.0).[5–7] The results are also consistent with lab-based studies that have shown that genetic alterations such as chromosome aberrations, cytokeratin expression, focal overexpression of *p53* as well as increased proliferation are associated with tobacco exposure.[3] The major carcinogens identified in chewing tobacco include tobacco-specific N-nitrosamines (TSNA) such as N'-Nitrosonornicotine (NNN) and 4(methylnitrosamino)-1-(3-pyridyl)-1-butanone

TABLE VI – NUTRITIONAL INTAKE AND RISK OF MULTIPLE ORAL PREMALIGNANT LESIONS (ODDS RATIOS AND 95% CONFIDENCE INTERVALS)

	Cases	Control	Crude OR (95% CI)	Adjusted OR[1] (95% CI)	Adjusted OR[2] (95% CI)
Fruits					
Low intake	19	4,930	1.0	1.0	1.0
High intake	96	42,821	0.6 (0.4, 1.0)	0.8 (0.5, 1.3)	1.0 (0.6, 1.8)
Vegetables					
Low intake	26	3,473	1.0	1.0	1.0
High intake	89	44,010	0.3 (0.2, 0.5)	0.4 (0.3, 0.7)	0.5 (0.3, 0.9)
Vitamins/iron supplements					
No	53	30,352	1.0	1.0	1.0
Past	7	1,590	2.0 (1.4, 2.9)	2.0 (1.4, 3.0)	1.5 (1.0, 2.3)
Yes	55	15,800	2.5 (1.1, 5.6)	2.3 (1.1, 5.1)	2.7 (1.2, 5.9)
Body Mass Index					
<15	39	11,869	1.0	1.0	1.0
15–20	32	11,835	0.8 (0.5, 1.3)	1.0 (0.6, 1.6)	1.0 (0.6, 1.6)
21–35	25	11,791	0.7 (0.4, 1.1)	1.0 (0.6, 1.5)	0.9 (0.5, 1.6)
>35	18	11,852	0.5 (0.3, 0.8)	0.8 (0.4, 1.3)	0.7 (0.4, 1.3)
p for trend			0.0011	0.1631	0.1356

[1]OR adjusted for age (continuous), sex (M/F), education (categories).–[2]OR adjusted for age, sex, education, body mass index, chewing tobacco (continuous, duration in years), smoking (continuous, packyears) and drinking (continuous, duration in years), (body mass index was not controlled for the BMI ORs)

(NNK).[9] Some areca-nut specific nitrosamines suspected to be carcinogenic are 3-Methylnitrosaminopropionaldehyde (MNPA), 3-Methylnitrosaminopropionitrile (MNPN), N-Nitrosoguvacine (NGC) and N-Nitrosoguvacoline (NGL). MNPA in particular can cause DNA single-strand breaks and DNA protein cross-links.[10] We observed in our study that chewing pan without tobacco also elevated the risk of multiple oral premalignant lesions.

Smoking did not appear to be a risk factor for multiple oral premalignant lesions in the Indian population. Analysis of smoking among nonchewers could not be conducted since there were only 2 cases who smoked but did not chew tobacco. Perhaps tobacco smoking is a weak risk factor relative to smoking because of the direct exposure of the chewing tobacco with the inside of the mouth for long periods. In the Indian population, some subjects swallow the chewing tobacco fluid or keep the chewing tobacco in the mouth overnight. Tobacco smoking involves the inhaling of smoke, which may have less contact with the mouth and more contact with the throat and lung than tobacco chewing. Even though some of the carcinogens from chewing tobacco and cigarettes are the same, perhaps the amount of exposure between these tobacco habits is different in the Indian population. Tobacco smoking is considered a risk factor for oral leukoplakia (OR=3.0, 95%CI=2.5, 3.7) but is not yet strongly associated with oral submucous fibrosis (OR=0.7, 95%CI=0.4, 1.3) or erythroplakia (OR=1.6, 95%CI=0.9, 2.9) in India.[5–7] For multiple oral premalignant lesions, the results of our study suggest that tobacco smoking may not be a major risk factor.

Alcohol drinking has been associated with elevated risks of oral leukoplakia,[5] oral submucous fibrosis[6] and erythroplakia.[7] Our analysis suggested that alcohol drinking is possibly a risk factor for multiple oral premalignant lesions. Though the association was not evident after adjusting for tobacco habits, dose-response trends were observed for alcohol drinking and the risk of multiple oral premalignant lesions. We may have had limited statistical power in the fully adjusted model due to the small number of alcohol drinkers. Since alcohol drinking is not socially accepted in India, especially for women, reporting bias may lead to bias toward the null. Analysis among nonchewers would be necessary to support the possible association between alcohol drinking and multiple oral premalignant lesions. In our data, we were unable to carry out such an analysis because only 2 male cases were nonchewers who drank alcohol.

High fruit and vegetable intake are considered protective factors for oral leukoplakia and possibly for oral submucous fibrosis.[11] According to our previous studies, high fruit and vegetable intake were protective against oral submucous fibrosis and erythroplakia in the crude analyses. However, when we adjusted for factors such as tobacco chewing, smoking and drinking, the inverse association with high fruit/vegetable intake was no longer present for oral submucous fibrosis and erythroplakia.[6,7] In our study, we observed that high vegetable intake was protective against multiple oral premalignant lesions but that high fruit intake was not.

Vitamin/iron supplements appeared to be a risk factor for multiple oral premalignant lesions. In our study, there was a higher percentage of cases who had vitamin/iron supplement use compared to the controls. The high proportion of vitamin use in these cases may actually have reflected treatment of oral submucous fibrosis. Administering high dosages of vitamins is part of the oral submucous fibrosis treatment modality,[12] since a combination of micronutrients (vitamins A, B complex, C, D and E) and minerals (iron, calcium, copper, zinc and magnesium) has been shown to alleviate some oral submucous fibrosis symptoms.[13] Among the multiple oral premalignant lesion cases, 96 (83.5%) subjects had oral submucous fibrosis as one of their lesions. Thus, the elevated OR for vitamins on the risk of multiple oral premalignant lesions may reflect that these cases were taking vitamins as part of their treatment.

We have previously reported an inverse association of BMI with oral leukoplakia[5] and oral submucous fibrosis.[6] Though an inverse relationship was suggested in the crude analysis, high BMI did not appear to decrease the risk of multiple oral premalignant lesions after adjustment for tobacco chewing, smoking, drinking and fruit/vegetable intake. Furthermore, owing to the cross-sectional design of our study, we are unable to exclude the possibility that the oral disease may have caused a decrease in BMI.

The 52.4% compliance of subjects with suspicious lesions to visit dentists and oncologists may lead to selection bias. However, the subjects who were examined by the dentists and oncologists were generally representative of the subjects who were referred. Furthermore, since subjects with severe lesions were more likely to comply, we may expect that multiple oral premalignant lesions cases were compelled to participate. Since this is a case-control study, recall bias may also have occurred. Subjects with multiple oral premalignant lesions are likely to have known about their disease status and may have recalled their exposure history with more effort compared to subjects without oral disease. Such recall bias can cause bias away from the null. Detection bias is also a potential limitation since the health workers were aware of the tobacco and alcohol habits of the subjects who were undergoing oral visual inspections. This bias may be minimized since the dentists and oncologists who

made the final diagnosis did not know the tobacco/alcohol habits of the subjects.

In conclusion, tobacco chewing was identified as a major risk factor for multiple oral premalignant lesions. Tobacco chewing may be a major source of field cancerization of the oral cavity in the Indian population. Tobacco smoking did not appear to be associated with an increased risk of multiple oral premalignant lesions, whereas alcohol drinking may possibly be a risk factor. Further studies are necessary to clarify the relationship of tobacco smoking and alcohol drinking with multiple oral premalignant lesions.

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Annexe 43

Oral mucosal disorders associated with habitual gutka usage: a review

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Objective. The aim of this study was to investigate the oral mucosal disorders associated with habitual gutka consumption.

Methods. Databases were searched from 1956 to June 2009 using the following terms: "gutka," "gutkha," "ghutka," "guttkha," "smokeless tobacco," "areca nut," "betel nut," "slaked lime," "dental," "oral," "periodontal," "inflammation," "submucous fibrosis," "carcinoma," and "cancer." The eligibility criteria included: human and experimental studies, use of control subjects, and articles published in English. Unpublished data were not sought. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed.

Results. Twelve studies were included. Three studies associated gutka consumption with periodontal inflammation (ORs 1.64 [CI 1.2-2.1], 2.20 [CI 1.1-4.9], and 3.56 [CI 1.9-5.5]). Five studies showed a direct relationship between gutka usage and oral submucous fibrosis (ORs 1.65 [CI 1.2-2.3], 2.33 [CI 1.9-4.5], 2.98 [CI 1.5-3.9], 3.56 [CI 1.3-4.7], and 5.08 [CI 3.7-6.4]). An increased frequency of gutka usage was associated with malignant transformations in oral submucous fibrosis by 2 studies (ORs 4.59 [CI 2-5.6] and 18 [CI 5.8-61.6]). Two studies showed an extension of oral submucous fibrosis into the hypopharynx and esophagus in gutka users (ORs 4.59 [CI 2-5.6] and 33 [CI 2.2-46.6]).

Conclusions. Habitual gutka usage is associated with severe oral mucosal disorders, and the consequences may extend beyond the oral cavity. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;109:857-864)**

Gutka (a form of smokeless tobacco) is chiefly a mixture of powdered tobacco, areca nut (fruit of *Areca catechu*), and slaked lime (aqueous calcium hydroxide).[1] Other components of gutka include perfumery compounds such as sandalwood and musk ketones. The easy availability, low cost, and extensive marketing of gutka has resulted in an increase in its usage. Gutka is commercially available in colorful and glittery tins and sachets. Unlike cigarettes, gutka is commercially sold without a health warning, and lack of awareness of its negative impact on health increases its consumption.[1] Gutka is initially placed between the teeth and gently chewed. It is then held against the buccal mucosa over a long duration and continued to be lightly chewed and sucked occasionally. The constituents may either be swallowed or spat out when desired.[1] Other forms of smokeless tobacco products commonly used in the Indian subcontinent include betel quid/paan (a blend of areca nut, slaked lime, artificial sweeteners, and sometimes tobacco wrapped in *Piper betel* leaf) and khaini and zarda (mixtures of powdered tobacco and slaked lime).[1-3]

Gutka usage is not restricted to the Indian subcontinent, but is also enjoyed by immigrant communities settled in Europe and the United States.[2-5] The actual prevalence of gutka usage in southeast Asia and other countries is yet to be documented; however, varying results have been reported from community surveys. In a recent study, 46% of the residents of a local community in Karachi, Pakistan, reported using gutka habitually.[1] Similarly, another study reported 35% of the patients visiting a health care center in Karachi to be habitual gutka users.[2] In the Indian State of Wardha, the prevalence of gutka usage by men and women was reported to be 46.4% and 20%, respectively.[3] In Tanzania, 6.9% of the native inhabitants have been reported to use gutka on a daily basis.[6]

Habitual gutka use has been associated with the occurrence of several oral mucosal disorders, including oral submucous fibrosis (OSF), oral cancer, and periodontal disease.[1,7] OSF is a chronic premalignant condition, characterized by progressive accumulation of

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collagen fibers in the oral submucosa, and its clinical presentation depends on the stage of the disease at detection.[8,9] Most patients with OSF present with an intolerance to spicy food, with rigidity of lips, tongue, and palate leading to varying degrees of limitation of mouth opening and tongue movement.[8,9] Habitual gutka users have also been shown to present with OSF at earlier ages compared with traditional betel quid users.[10-16] This may be explained by the average weight and moisture content in a gutka sachet/pouch.[15,17] A gutka sachet weighs ~3.5 g and contains 7% moisture, whereas the net weight of a betel quid is nearly 4 g (with ~1.14 g of tobacco) and contains 70% moisture.[15] Because gutka users tend to consume more dry weight of tobacco, areca nut, and slaked lime, they may be exposed to oral mucosal disorders at earlier ages compared to betel quid users.

Oral cancer is the fifth most common cancer worldwide, and tobacco use has been thought to account for 30% of the global cancer load.[18] In Karachi, oral cancer (mainly squamous cell carcinoma) ranks second in all malignancies among both men and women, with the highest reported incidence in the world.[19] Bhurgri et al. identified areca nut and tobacco (which are also chief ingredients of gutka) as significant risk factors for the high oral cancer incidence in Pakistan.[19] In a longitudinal study performed in India, 66 individuals with OSF were followed-up for malignant transformations over a period of 17 years.[7] The results showed that oral cancer developed in 7.6% of the individuals, and the malignant transformation rate in the study group was reported to be 4.5% over a 15-year observational period.[7] Malignant transformation rates up to 19.1% have also been reported in patients with OSF.[20,21] Those results showed that a high degree of malignancy can be observed in patients with OSF.[7]

Periodontal inflammatory parameters have also been reported to be higher among gutka users compared to control subjects (individuals not using tobacco in any form). In a recent study, Javed et al.[1] measured the plaque index (PI), bleeding on probing (BOP), and periodontal probing depth (PPD) among habitual gutka users and control subjects. The results showed a significantly higher PI, BOP, and PPD (4-6 mm) in habitual gutka users compared with control subjects.[1] In that study, self-perceived gingival bleeding also was more often reported by the gutka users than the control subjects.[1] Similar results were reported in the study by Parmar et al., that showed an increased incidence of BOP, PPD, gingival recession, and oral ulceration in subjects chewing a mixture of areca nut and tobacco.[22] Slaked lime is a strong alkali and has been shown to promote hyperplasia and irritation in the oral mucosal tissues.[23] Chewing a mixture of slaked-lime, areca nut, and powdered tobacco has also been shown to facilitate the development of oral cancer.[24,25]

It may be postulated that gutka use intensifies the severity of oral mucosal disorders and exposes the consumers to severe oral health risks at earlier ages. Because gutka usage is increasing worldwide and its ingredients are hazardous to oral mucosal health, the aim of the present review was to evaluate the oral mucosal diseases associated with habitual gutka consumption.

MATERIALS AND METHODS

Rationale and focus question

Individuals who consumed ≥1 gutka sachet daily for ≥6 months were designated as "habitual gutka users/chewers."[15] The objective of the present review was to assess the negative effects of habitual gutka consumption on oral mucosal health. Therefore, our focus question was: What are the deleterious effects of habitual gutka consumption on oral mucosal health?

Eligibility criteria

The following eligibility criteria were imposed: 1) human studies; 2) test group: individuals consuming ≥1 gutka sachet/pouch daily for ≥6 months; 3) control group: individuals not using tobacco in any form; and 4) articles published in English.

The reference lists of potentially relevant original and review articles were also searched to identify articles that were not located in the original search. Table I presents the list of pertinent studies that were retrieved during the data extraction process. Letters to the editor, historical reviews, and unpublished articles were excluded. Table II shows the 13 studies that did not comply with the eligibility criteria and were excluded.

Search strategies

As a first step, the authors searched the National Library of Medicine, Washington, DC (Medline-Pubmed), for appropriate articles addressing the focus question. Databases were searched from 1956 up to and including June 2009 using the following terms in different combinations: "gutka," "gutkha," "ghutka," "guttkha," "smokeless tobacco," "areca nut," "betel nut," "slaked lime," "dental," "oral," "periodontal," "inflammation," "submucous fibrosis," "carcinoma," and "cancer."

The second step was to hand search the reference lists of original and review studies that were found to be relevant in the first step. Titles containing words suggesting smokeless tobacco consumption as an adjunct to oral health disorders were also sought.

After final selection of the papers, those studies that fulfilled the selection criteria were processed for data extraction. Full texts of the selected articles were re-

Table I. Investigators (year), study design, age, sample size, odds ratios, duration of gutka use and daily intake, and main results of selected studies

Investigator(s), year	*Study design*	*Age range (yrs)*	*Sample size*	*Male:female ratio*	*OR*	*95% CI*	*Duration of gutka use*	*Daily intake of gutka**	*Main results*
Periodontal inflammation									
Javed et al., 2008[1]	Case-control	45-64	1,000	1:1	2.20	(1.1-4.9)	~8 years	~8×	Periodontal inflammation was higher in gutka chewers than in nonchewers.
Doifode et al., 2000[13]	Case-control	14-59	110	1:1	3.56	(1.9-5.5)	NA	NA	Gutka chewing was significantly associated with OSF* and periodontal disease.
Parmar et al., 2008[22]	Case-control	31-33	365	4:1	1.64	(1.2-2.1)	NA	NA	Periodontal inflammation and oral ulcers were higher in gutka-chewers compared to nonchewers.
Oral submucous fibrosis									
Bathi et al., 2009[10]	Case-control	10-64	220	26.5:1	2.98	(1.5-3.9)	3-4 yrs	1-15×	Gutka is strongly associated with the development of OSF.*
Hazarey et al., 2007[11]	Cross-sectional	9 to <50	1,000	4.9:1	2.33	(1.9-4.5)	2-~5 yrs	~4×	Gutka consumption was a major pre-malignant lesions associated with OSF* and oral cancer.
Saraswathi et al., 2006[12]	Cross-sectional	13-84	2,017	1.7:1	5.08	(3.7-6.4)	NA	NA	OSF*was the most prevalent lesion among gutka chewers.
Doifode et al., 2000[13]	Case-control	14-59	110	1:1	3.56	(1.3-4.7)	NA	NA	Gutka-chewing is associated with periodontal disease and OSF.*
Misra et al., 1998[14]	Case-control	20-42	110	5.8:1	33	(2.2-46.6)	~6 yrs	NA	Gutka usage was associated with oesophageal subepithelial fibrosis.
Babu et al., 1996[15]	Case-control	20-30	90	NA	1.65	(1.2-2.3)	~3 yrs	~4×	Gutka consumption was associated with the presentation of OSF.*
Bansode, 2002[16]	Retrospective	31-40	336	2:1	3.33	(2.5-5.3)	NA	10-12×	Gutka usage was associated with OSF,* oral ulceration and stomatitis.
Ahmad et al., 2006[17]	Case-control	11-54	292	2.7:1	9.25	(3.1-15.5)	2-4 yrs	2-10×	Gutka chewing was positively associated with OSF*
Oral cancer									
Gangane et al., 2007[26]	Cross-sectional	29-70	520	2.1:1	18	(5.8-61.6)	20-49 yrs	NA	Gutka consumption was significantly associated with oral cancer cases.
Sapkota et al., 2007[27]	Case-control	34-75	1,742	14.3:1	4.59	(2-5.6)	≥1 yr	NA	Gutka use was associated with an increased risk of hypopharyngeal cancer.

OR, odds ratio; *CI*, confidence interval; *OSF*, oral submucous fibrosis; *NA*, not available.
*Each sachet/pouch contains ~3.5-3.8 g dry weight gutka.[1,15]

trieved. The following data were extracted from all the selected studies: investigators and year of publication of the study, study design, age/age range of the participants, gender of the participants, total number of study participants, number of male and female participants (male:female ratio), daily frequency of gutka usage (number of times gutka was consumed daily), duration of gutka usage (years), oral mucosal disorders associated with habitual gutka usage, and odds ratio (OR) and 95% confidence interval (CI). The structure of this review was customized to mainly summarize the relevant information.

Statistical analysis

The statistical analysis was performed using a software program (statistica v. 6.0; Statsoft, Tulsa, OK).

Table II. Excluded studies and main reasons for exclusion

Investigator(s), year	*Title*	*Main reason for exclusion*
Chaturvedi, 2009[a]	Gutka consumption	Letter to the editor
Chaturvedi, 2009[b]	Gutka or areca-nut chewer's syndrome	Letter to the editor
Tilakaratne et al., 2006[c]	Oral submucous fibrosis: review on aetiology and pathogenesis	Review article
Reichart and Philipsen, 2006[d]	Oral submucous fibrosis in a 31-year-old Indian women: first case report from Germany	Article in German
Avti et al., 2006[e]	Smokeless tobacco impairs the antioxidant defense in liver, lung, and kidney of rats	Focus question not addressed
Changrani and Gany, 2005[f]	Paan and gutka in the United States: an emerging threat	Review article
Mishra et al., 2005[g]	Indian youth speak about tobacco: results of focus group discussions with school students	Focus question not addressed
Gupta and Ray, 2004[h]	Epidemiology of betel quid usage	Review article
Nair et al., 2004[i]	Alert for an epidemic of oral cancer due to use of the betel quid substitutes gutkha and pan masala: a review of agents and causative mechanisms	Review article
Gupta and Ray, 2003[j]	Smokeless tobacco and health in India and south Asia	Review article
Tobacco Free Initiative, World Health Organization, 2002[k]	Tobacco and youth in the south east Asian region	Review article
Pai, 2002[l]	Gutkha banned in Indian states.	News desk
Warke et al., 1999[m]	Irradiation of chewable tobacco mixes for improvement in microbiological quality	Focus question not addressed

[a]Br Dent J 2009;206:397.
[b]Indian J Cancer 2009;46:170-2.
[c]Oral Oncol 2006;42:561-8.
[d]Mund Kiefer Gesichtschir 2006;10:192-6.
[e]Toxicol Sci 2006;89:547-53.
[f]J Immigr Health 2005;7:103-8.
[g]Health Educ Behav 2005;32:363-79.
[h]Ann Acad Med Singapore 2004;33:31-6.
[i]Mutagenesis 2004;19:251-62.
[j]Respirology 2003;8:419-31.
[k]Indian J Cancer 2002;39:1-33.
[l]Lancet Oncol 2002;3:521.
[m]J Food Prot 1999;62:678-81.

The ORs were computed and 95% CIs were constructed using logistic regression to assess the association between oral mucosal diseases among gutka chewers and control subjects.

RESULTS

Characteristics of the publications

The initial Medline-Pubmed search resulted in 25 citations. Titles of all articles obtained were screened by each author and all abstracts of related articles were screened further. The full text of articles fulfilling the eligibility criteria was assessed. Eventually, 12 studies (which varied by population characteristics and research methodology) were included in the present review (Table I). Thirteen studies, which did not comply with the selection protocol, as shown in Table II, were excluded.

All of the 12 studies[1,10-17,22,26,27] included in the present review were carried out at either universities or health care centers. The sample sizes ranged from 90 to 5,061 individuals. The ages of the participants varied between ≥9 years to ≤75 years. In 2 studies,[1,13] the male:female ratio was 1:1; and in the remaining 10 studies[10-12,14-17,22,26,27] there were at least twice as many men than women in the study population.

The duration of gutka-chewing habit was reported in 8 studies[1,10,11,14,15,17,26,27] and ranged between ≥1 year and 49 years. Daily gutka consumption by participants was reported by 5 studies.[1,10,11,15,17] In those studies, the daily consumption of gutka by its consumers ranged from 1 time to 15 times.

Eleven studies[10-17,22,26,27] were performed in India and 1[1] was conducted in Pakistan. Eight studies[1,10,13-15,17,22,27] were clinical and 4[11,12,16,26] were epidemiologic. Three studies[1,13,22] showed a significant association between habitual gutka consumption and periodontal inflammatory conditions, including gingivitis, gingival recession, and formation of periodontal pockets (ORs 1.64 [CI 1.2-2.1], 2.20 [CI 1.1-4.9], and 3.56 [CI 1.9-5.5]). Results by Javed et al.[1] also reported self-perceived gingival bleeding to be significantly higher in gutka chewers than in nonchewers (OR 2.20 [CI 1.1-4.9]). Seven stud-

ies[10-13,15-17] (4 clinical[10,13,15,17] and 3 epidemiologic[11,12,16]) showed that OSF was more common in gutka chewers than in nontobacco users (ORs 1.65 [CI 1.2-2.3], 2.33 [CI 1.9-4.5], 2.98 [CI 1.5-3.9], 3.33 [CI 2.5-5.3], 3.56 [CI 1.3-4.7], 5.08 [CI 3.7-6.4]s and 9.25 [CI 3.1-15.5]). Hazarey et al.[11] (OR 2.33) and Gangane et al.[26] (OR 18 [CI 5.8-61.6]) reported oral cancer to be more prevalent in gutka users than in individuals not using tobacco products. An increased frequency of gutka usage was associated with malignant transformations in OSF cases in 2 studies (ORs 2.33 [CI 1.9-4.5] and 1.65 [CI 1.2-2.3]).[11,15] Studies by Misra et al.[14] (OR 33 [CI 2.2-46.6]) and Sapkota et al.[27] (OR 4.59 [CI 2-5.6]) demonstrated an extension of oral mucosal fibrosis into the hypopharynx and esophagus in gutka users. Two studies demonstrated an association between gutka consumption and oral mucosal ulcerations (ORs 3.33 [CI 2.5-5.3] and 1.64 [CI 1.2-2.1]).[16,22]

DISCUSSION

The deleterious effects of areca nut, smokeless tobacco, and slaked lime on oral health have been well documented; however, a more severe and intense pathogenic response may be expected when these substances are consumed as a mixture (gutka).[28,29] A summary of the oral pathophysiologic events induced by habitual gutka chewing is presented in Fig. 1.

The duration of smokeless tobacco usage has been associated with the development of oral mucosal disorders. The Eipe study[30] reported that habitual use of betel quid for ≥5 years predisposes the oral mucosa to oral premalignant disorders including OSF. Maher et al.[31] also reported that individuals using smokeless tobacco products for up to a decade are more susceptible to develop OSF compared with subjects using such products for a shorter duration. However, habitual gutka use has been shown to expose its consumers to OSF at a much faster pace compared to betel quid usage.[15] Results by Babu et al.[15] showed that gutka users with OSF had consumed it for ~3 years compared with betel quid users with OSF who had started the habit nearly 8 years before. Similarly, a recent case-control study reported that gutka-chewing habit for up to 4 years increases the relative risk of developing OSF.[10] A possible explanation for this may be that habitual gutka users consume more dry weight of tobacco, areca nut, and slaked lime, which causes nicotine to act synergistically on the cytotoxicity induced by arecoline (a major areca nut alkaloid), thereby increasing the vulnerability of buccal mucosal fibroblasts to damage and enhanced collagen production (up to 170%).[15,32-37]

To our knowledge from the indexed literature, there is no consensus regarding the influence of daily frequency of gutka consumption on the occurrence of oral

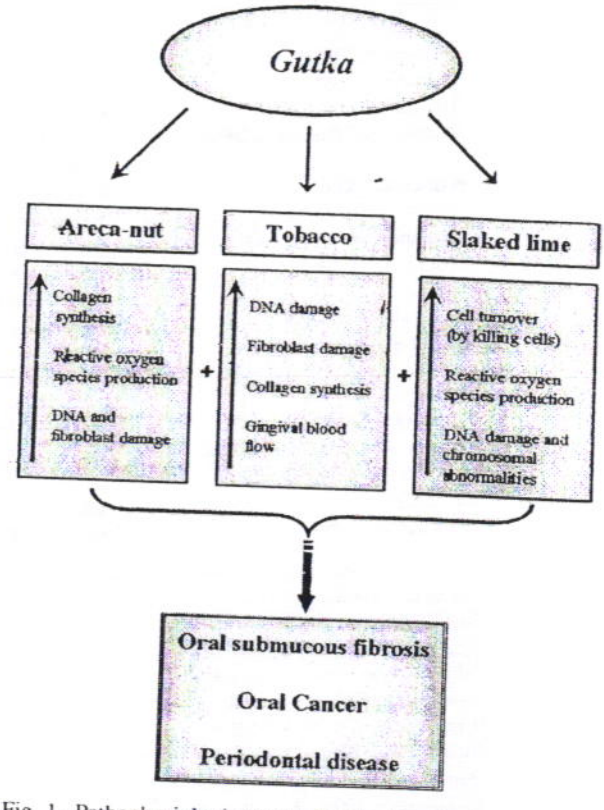

Fig. 1. Pathophysiologic events (mechanisms) of gutka's effect on oral soft tissues.

mucosal disorders. According to results by Javed et al.,[1] the frequency of gutka consumption among individuals with oral mucosal disorders ranged from once a day to 10 times daily (average frequency 8 times daily). On the other hand, Bathi et al.[10] reported that the risk of developing OSF is significantly higher in individuals consuming gutka at least 15 times daily.

A direct association between oral inflammatory conditions and age of the subject has been reported.[38] However, it seems that gutka can expose its consumers to severe oral mucosal disorders at any age. In a study by Javed et al.,[1] gutka chewers presenting with periodontal inflammation had a mean age of ~51 years (range 45-64 years). In the study by Bathi et al.,[10] the mean age of gutka users was <34 years and ranged from 10 to 64 years. OSF has also been reported in children as young as 4 and 11 years of age who rapidly developed submucosal fibrosis within 3 years of starting the chewing abuse.[17,37,39]

Gutka contains fine grains of areca nut, which besides causing mechanical injury to oral tissues, also allow ground tobacco to adhere to the traumatized mucosa, leading to morphologic changes and membrane damage. Thus, areca nut in combination with

tobacco may cause cross-links and accelerate the onset of OSF in habitual gutka chewers. This may be an explanation for clinical reports that have shown habitual gutka users to present with OSF at earlier ages compared with traditional betel quid users.[10-15] However, there are several other factors that may influence the induction of OSF at younger ages regardless of the frequency and quantity of daily gutka usage. Rajendran[40] reported that vitamin and iron deficiency together with malnourished state of the host leads to derangement in the inflammatory reparative response of the lamina propria, resulting in impaired healing and scarification, which eventually leads to OSF. Nutritional deficiency, deprived socioeconomic status (SES), poor education, as well as the duration of placement of gutka in the oral cavity may play cumulative roles on the induction and severity of oral mucosal disorders.[13,17,38-41] In studies by Ahmad et al.[17] and Shiau and Kwan,[41] the majority of gutka users presenting with OSF were malnourished and had a deprived SES. In the study by Javed et al.,[1] gutka users cited the chewing habit to be "beneficial" because it helped them to control hunger. Simultaneously, the role of a poor education status, which may compel tobacco chewers to continue with the abuse despite being aware of their impaired oral mucosal health, can not be overlooked. In the Eipe study,[30] individuals with OSF were aware of their oral mucosal disorder, but they continued the tobacco-chewing habit until the diagnosis of oral cancer was made. Regarding duration of placement of gutka in the oral cavity, Ahmad et al.[17] reported that 74.5% of the individuals with OSF were placing gutka in their buccal vestibule for 2-10 minutes. In another study, individuals with oral inflammatory disorders were placing gutka in their buccal vestibule for 5-30 minutes.[1] Therefore, it seems that the duration of the insult (in combination with the factors mentioned above) may also influence the occurrence and progression of oral mucosal disorders among gutka users. Although OSF is irreversible and persists even after cessation of the chewing habit, it may be hypothesized that cessation of the gutka-chewing habit may help to reduce the severity of the condition and may also prevent its progression to malignancy. However, gutka prevention and cessation research and interventions are not yet documented.

A relationship between oral inflammatory conditions and gender has been reported.[42] However, the influence of gender in relation to oral mucosal disorders among gutka chewers remains debatable. Anwar et al.[43] conducted a pilot study which aimed to investigate the attitudes and practices concerning habitual gutka use in a town in India. That study reported gutka usage to be more common among men than women.[43] Similarly, results by Saraswathi et al.,[12] Ahmad et al.[17] and Gangane et al.[26] have reported oral mucosal diseases (including OSF and oral cancer) to be more prominent among male than female gutka chewers. However, it is noteworthy that there were at least twice as many men than women in those studies.[12,17,26] It may therefore be argued that the reported gender might have been due to the increased number of male compared with female participants. However, results by Hazarey et al.[11] showed that the severity of OSF was more prevalent in women than men even though the male:female ratio was 4.9:1. In that study, an underprivileged SES and poor education was significantly higher in women than men.[11] These factors may have contributed to the increased severity of OSF in women compared with men with OSF participating in that study.[11] From the literature reviewed, we believe that the question "Does gender have any influence on oral mucosal disorders among gutka chewers?" is yet to be answered and further studies are warranted to investigate this relationship.

A study that investigated the effect of smokeless tobacco on blood flow responses showed that smokeless tobacco significantly increases the heart rate, arterial blood pressure, and gingival blood flow.[44] Furthermore, gutka chewers have been shown to have reduced salivation and mucous formation, thereby reducing the normal commensal oral microflora and exposing their oral cavities to pathogens (*Aspergillus* species).[45] Thus, a reduced salivary flow may allow the pathogenic bacteria to stagnate in the supra- and subgingival areas, thereby inducing periodontal inflammation in gutka chewers compared with nonchewers. Areca nut extracts have also been associated with the expression of matrix metalloproteinase 9 in gingival epithelial cells, which might help to promote periodontal pathosis in gutka users compared with control subjects.[46] These might be possible explanations for the raised periodontal inflammatory parameters (including PI, BOP, PPD, and self-perceived gingival bleeding) among gutka users compared with controls.[1,22] Nevertheless, the role of confounding factors such as a low SES and poor education that may also trigger periodontal inflammation can not be overlooked.[40]

In conclusion, it is apparent that habitual gutka consumption can rapidly devastate the oral mucosa, and the consequences may extend beyond the oral cavity.

RECOMMENDATION

It is highly recommended that the department of health and consumer protection should restrict access to gutka for adolescents and prohibit its sale to minors to curtail gutka usage. There should also be a health hazard label on gutka products. By raising public awareness about the negative effects and health hazards

of gutka, the prevalence of oral cancer and other mucosal disorders might decrease among gutka users. This may also assist in improving the quality of life in these individuals.

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Annexure 4

The Prevalence of Oral Lesions in Smokeless Tobacco Users and an Evaluation of Risk Factors

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Background. The widespread use of smokeless tobacco (ST) has prompted concern in regard to the development of oral lesions in long-term users.

Methods. For inclusion in the current study, a subject must have used an ST product, either snuff or chewing tobacco, for at least 6 months. The subjects were recruited by advertising, and none was referred for the evaluation of an oral lesion. The following were performed on all subjects: assessment of exposure to ST, cigarettes, and alcohol; examination of the oral cavity; a biopsy, if an oral lesion was found; and analysis of a blood sample for beta-carotene. The dietary intake of most of the subjects was analyzed.

Results. Of the 347 ST users, all of whom were white male subjects, 45 (13.0%) had an oral lesion. Thirty-five of the lesions were hyperkeratosis and 10 were epithelial dysplasia.

Conclusions. Snuff exposure was associated significantly with the presence of an oral lesion ($P < 0.0001$). A decreased vitamin C intake also was found among the ST users with oral lesions ($P < 0.01$). The ST users with epithelial dysplasia, as compared with those with hyperkeratotic lesions, were slightly older, had a lower intake of vitamin C ($P < 0.05$), and were more likely to have used chewing tobacco than snuff. *Cancer* 1992; 70:2579–85.

Key words: ascorbic acid, beta-carotene, leukoplakia, oral cancer, smokeless tobacco.

The use of smokeless tobacco (ST), defined as either snuff or chewing tobacco, is a popular habit in the United States, with an estimated six million regular users.[1] The association between ST use and the development of oral lesions is well established.[2–6] Some of this evidence is from retrospective studies that evaluated ST exposure in patients in whom an oral lesion already had been diagnosed. Typical of this type of study were those by Rosenfeld and Callaway[2] and Brown et al.,[3] which together included 919 patients in whom squamous cell carcinoma was diagnosed between 1937 and 1963, that showed an association between squamous cell carcinoma and the long-term use of ST in elderly women.

As the popularity of ST surged in the early 1970s, researchers documented the increase in ST use among adolescents and reported the prevalence of ST-associated oral lesions.[7–15] The prevalence of oral lesions has ranged from 9.5% to 58.9% because of the variability in the age of the population surveyed and the definition of a lesion.[6–8,16–21] Most of the lesions diagnosed in recent studies were hyperkeratosis, with only a small number of epithelial dysplasias or carcinomas.[17–20,22–26] In a preliminary study, we found that 29 of 127 (22.8%) adult ST users had an oral lesion at the time of examination and that, of the 29 patients with a lesion, 6 (4.7%) had an epithelial dysplasia and none had a carcinoma.[27]

To resolve this apparent contradiction between earlier reports showing a strong link of ST with cancer and recent findings, we expanded our preliminary study of a group of adults who were predominantly long-term ST users. One purpose was to determine the prevalence of oral lesions in ST users and obtain histopathologic diagnoses to grade the severity of the mucosal changes. In addition, for each subject, we assessed exposure to cigarettes and alcohol, calculated dietary intake, and measured serum beta-carotene levels to determine whether this antioxidant vitamin provided a protective effect.

Materials and Methods

ST users were recruited by advertising that offered payment for their participation. None of the subjects was

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referred for the evaluation of an oral lesion or had a lesion diagnosed previously. The subjects were from a mixture of urban, suburban, and rural settings within several different areas of Virginia. Because of the nature of ST use, most subjects were (greater than 99%) white and male. The subjects who did not fit this description were excluded from the analysis because the number was so small. For inclusion of a subject in the study, the minimum duration of ST use was 6 months. Ninety-one nonusers of ST with no oral lesions were recruited to act as a comparison group. The following were performed on all subjects: (1) assessment of ST, cigarette, and alcohol use; (2) clinical examination of the oral cavity; (3) biopsy, if an oral lesion was present; and (4) analysis of a blood sample for beta-carotene.

An oral lesion was defined as a visible alteration of the oral mucosa that persisted for at least 7 days after discontinuation of ST use; an alteration with little probability of resolving within 7 days, in the opinion of the clinical investigator (G.E.K.); or an alteration occurring in a subject who was unable to return for a recall visit.

Subjects completed a questionnaire in regard to their use of snuff, chewing tobacco, cigarettes, and alcohol during the previous 12 months. Use during the previous year or last year of usage was applied to estimate lifetime exposure, which was computed with the following formula:

$$\frac{0.5 \text{ hours}}{\text{"dip"}} \times \frac{\#\text{dips}}{\text{day}} \times \frac{365 \text{ days}}{\text{year}} \times \text{years} = \text{hours of snuff use}$$

In a similar fashion, exposure to chewing tobacco was calculated:

$$\frac{1 \text{ hour}}{\text{"chaw"}} \times \frac{\#\text{chaws}}{\text{day}} \times \frac{365 \text{ days}}{\text{year}} \times \text{years} = \text{hours of chewing tobacco use}$$

A "dip" and a "chaw" were defined as the typical portion size of either snuff or chewing tobacco, respectively, used by the subject. The figures of 0.5 hours per snuff dip and 1 hour per chewing tobacco chaw were based on popular usage patterns.[8,14,28] Total ST exposure equalled the combined estimated hours of snuff and chewing tobacco exposure.

Cigarette consumption was determined by the following:

$$\frac{\#\text{packs}}{\text{day}} \times \frac{365 \text{ days}}{\text{year}} \times \text{years} = \#\text{ packs in lifetime}$$

Whiskey equivalent units were used to standardize the alcohol consumption of subjects. Twelve ounces of beer contains 10.08 g of ethanol, 4 ounces of wine has 11.32 g, and 1 ounce of whiskey has 10.24 g.[29] Consumption was computed as follows:

$$\frac{\#\text{WE}}{\text{episode}} \times \frac{\#\text{episodes}}{\text{week}} \times \frac{52 \text{ weeks}}{\text{year}} \times \text{years} = \text{lifetime WE}$$

For both cigarettes and alcohol, the lifetime consumption was computed even if the habit had been discontinued at the time of entry into the study.

High-performance liquid chromatography was used to measure serum beta-carotene levels. A 10-ml blood sample was drawn from a subject and stored in a refrigerator for a maximum of 2 hours. The serum was separated by centrifugation and stored in cryostat tubes at −70°C. The serum samples were extracted from ethanol–ascorbate solutions with hexane, evaporated under nitrogen, and injected into a C18, 5-μm, 25-cm column as a 200-μl sample that was taken up in the 80:20 (methanol:toluene) mobile phase. Beta-carotene levels were determined at 454 nm, and the retention time was 10.3 minutes at a flow rate of 1.5 ml/min.

The dietary questionnaire of the National Cancer Institute was used to measure the dietary intake of 75% of the subjects. The questionnaire is self-administered, and the answers were examined before data entry to exclude responses that were obviously erroneous. Only the results for the intake of beta-carotene, vitamin A, vitamin C, and total calories were analyzed for this study.

Results

A total of 347 ST users, all of whom were white males, were included in the analysis. The mean age was 29.3 (±13.0) years (range, 14–77 years). Of the 347 users, 45 (13.0%) had an oral lesion as previously defined. All oral lesions were at the site of the ST placement. The histopathologic diagnoses for the 45 oral lesions were as follows: hyperkeratosis, 35 cases; and epithelial dysplasia, 10 cases (4 cases were focally mild; 3 mild; 2 moderate; 1 severe).

No squamous cell carcinomas or verrucous carcinomas were diagnosed. Table 1 compares the ST exposure in the group of users without oral lesions with that of users with lesions. ST users with lesions had higher levels of ST use for both snuff and chewing tobacco than those without a lesion. This difference, however, was particularly large for lifetime snuff use (13,760 versus 5893 mean hours, respectively), with ST users with lesions reporting 2.3 times more snuff use than ST users without lesions.

Table 2 compares exposure to cigarettes and alcohol. The mean age for nonusers with no lesions was

Table 1. Smokeless Tobacco Exposure

	ST users without lesions	ST users with lesions
No. of patients	302	45
Age in yr (mean)	28.9 (±12.3)	30.8 (±16.1)
Snuff use in lifetime hours (mean)	5893 (±13,120)	13,760 (±16,780)*
Chewing tobacco use in lifetime hours (mean)	19,310 (±43,490)	23,300 (±44,300)
Total ST use in lifetime hours (mean)	25,200 (±46,150)	37,060 (±41,777)
Snuff users	66.9%	75.6%
Chewing tobacco users	65.2%	40.0%

ST: smokeless tobacco.
*$P < 0.0001$.

23.3 years. The role of alcohol was apparently nonexistent in the 33.3% of subjects who did not drink and had lesions, and cigarettes were not a factor in the 73.3% who did not smoke. In comparing the ST users with the nonuser group, the ST users were more likely to smoke cigarettes but less likely to drink alcohol. However, the ST users who drank alcohol had a higher number of whiskey equivalent units than the ST nonusers.

To determine whether any significant differences existed between the ST users with and without lesions, analyses of variance were performed to compare lifetime exposure to snuff, chewing tobacco, cigarettes, and alcohol. Only snuff exposure was significantly different ($P < 0.0001$). To assess the importance of ST, cigarettes, and alcohol, controlling for the intercorrelation between these variables, a discriminant function analysis was done with the following predictor variables: hours of snuff use, hours of chewing tobacco use, number of packs of cigarettes smoked, and whiskey equivalents. Consistent with the previous finding, snuff use was the only significant predictor ($t = 2.98$, $P < 0.002$) for the presence of an oral lesion.

The serum levels of beta-carotene are shown in Table 3, and an analysis of variance on lesion status did not show a significant difference ($f = 2.04$, $P = 0.15$). The direction of the difference was contrary to the hypothesis because ST users with lesions had a slightly higher mean value (15.5 μg/dl for users with lesions versus 12.6 μg/dl for users without lesions). However, the median value was the same for both groups (9.5 μg/dl).

In regard to dietary intake (Table 4), a significant difference ($P < 0.01$) was observed between the two groups of ST users by analysis of variance for vitamin C intake. Dietary levels of vitamin C were 1.5 times greater in those without lesions than in those with lesions. Discriminant function analyses of the dietary factors were performed separately from those of the risk factors because of the difference in sample size and the general lack of significant correlation between the sets of variables. With the use of discriminant function analysis, two significant predictors for the presence of a lesion were identified: vitamin C intake ($t = -2.34$, $P < 0.02$) and calories consumed ($t = 2.17$, $P < 0.03$). Given the lack of a significant univariate difference between lesion groups regarding calories and the 0.56 correlation between vitamin C and calories, it appears that the calories variable is a suppressor variable, improving the variance accounted for by vitamin C by controlling for total caloric intake. All analyses also were performed on log-transformed independent variables because of the skewed distribution of the independent variables, but the results were similar.

Table 5 separates the 45 ST users with lesions into

Table 2. Cigarette and Alcohol Exposure

	ST users without lesions	ST users with lesions	Nonusers without lesions
No. of patients	302	45	91
Smokers	40.4%	26.7%	11.0%
Lifetime no. of cigarette packs (mean)	2568 (±6299)	3473 (±13,050)	937 (±7531)
Drinkers	77.8%	66.7%	89.0%
Lifetime no. of whiskey equivalents (mean)	8260 (±14,860)	9069 (±20,390)	3930 (±4637)

ST: smokeless tobacco.

Table 3. Serum Beta-Carotene Levels

	ST users without lesions	ST users with lesions	Nonusers without lesions
No. of patients	295	45	88
Serum beta-carotene in μg/dl (mean)	12.6 (±9.7)	15.5 (±19.9)	17.3 (±10.5)

ST: smokeless tobacco.

two groups: those with hyperkeratosis (n = 35) and those with epithelial dysplasia (n = 10). Analyses of variance indicated that the subjects with dysplastic lesions had a lower intake of vitamin C ($f[1,43] = 3.87$, $P < 0.05$) and higher serum levels of beta-carotene ($f[1,43] = 4.52$, $P < 0.05$). Those with dysplastic lesions were older and more likely to use chewing tobacco than snuff, but these differences did not reach the 0.05 level of significance, possibly because of the small number of subjects with lesions. The smallest number of lifetime ST exposure hours associated with the development of a hyperkeratotic lesion was 2190 hours, and for a dysplastic lesion it was 7300 hours.

Discussion

It is difficult to compare the prevalence of oral lesions with those in previously published studies because of the variability in how investigators defined an oral lesion and the characteristics of the subject population. Our definition of a lesion, which required a 7-day waiting period in most cases, is a conservative one because of the percentage of lesions that resolve if ST use is discontinued for a short time.[24] Also, our choice of an adult population, as compared with an adolescent one, is more indicative of changes that develop with chronic ST use. Recruitment bias is a consideration in the current study because the subjects were found through advertising that offered payment for participation. Because of our selection criteria, we excluded neophyte ST users who might have been interested only in getting some extra money. Many of the subjects were encouraged to participate by wives or girlfriends who had read the advertisements. None of the subjects had been referred for the evaluation of an oral lesion; therefore, we believe that our study population is representative of adult ST users.

Without question, the topical application of ST causes mucosal alteration. Based on our survey of adult ST users, the prevalence of oral lesions was 13.0% and the prevalence of epithelial dysplasia was 2.9%. Assuming that the cases diagnosed as focal mild epithelial dysplasia are a reactive change,[30] then the prevalence of epithelial dysplasia among the ST users decreases to 1.7%. The aforementioned problem with comparison with other studies is demonstrated by the range of reported values. Greer and Poulson[7] found that 42.7% (50 of 117) of high school ST users had oral lesions. A survey of teenage football players showed that 13% of regular ST users had oral lesions.[6] Surveys of professional baseball players found that 34%,[26] 40.9%,[19] 46.3%,[23] and 53%[25] of the ST users in these studies had oral lesions. If we add the previously reported complete resolution rate of 15% when ST use is discontinued for 1–21 days,[24] then our prevalence of 13% is only slightly lower than that found in other studies. As a comparison with the general population, Bouquot[31] found that 4.5% of a large population of men (mean age, 55.9 years) had oral leukoplakia. It is uncertain how many of these men were ST users.

Histopathologic examination of the oral lesion is necessary to determine the severity of the mucosal change. The studies that have obtained tissue from ST users for histologic examination[16,23,32–35] and the current study have evaluated 707 ST-associated oral lesions and found 27 (3.8%) cases of epithelial dysplasia and 1 (0.1%) squamous cell carcinoma. However, the degree of histologic severity of epithelial dysplasia is significantly milder in ST users as compared with nonusers. This was shown in another study, which identified 108 ST-associated cases of epithelial dysplasia, with most (83.8%) being either focal mild or mild.[36] It is not known with certainty why early studies showed a

Table 4. Dietary Intake

	ST users without lesions	ST users with lesions	Nonusers without lesions
No. of patients	205	36	88
Calories/day (mean)	3099 (±1381)	2902 (±1481)	3184 (±1610)
Vitamin A/day in IU (mean)	13,450 (±11,240)	11,420 (±6457)	12,550 (±10,860)
Vitamin C/day in mg (mean)	253.1 (±183.7)	176.5 (±122.3)*	232.1 (±129.5)
Beta-carotene/day in μg (mean)	5232 (±5702)	4341 (±3134)	4691 (±5881)

ST: smokeless tobacco.
*$P < 0.01$.

Table 5. Comparison of Smokeless Tobacco Users Who Have Lesions

	ST user, hyperkeratosis	ST user, epithelial dysplasia
No. of patients	35	10
Mean age (yr)	29.2	39.2
Snuff use in lifetime hours (mean)	16,280 (±17,870)	6424 (±7247)
Chewing tobacco use in lifetime hours (mean)	17,840 (±38,120)	38,870 (±59,230)
Total ST use in lifetime hours (mean)	34,120 (±36,880)	45,300 (±55,090)
Snuff users	82.9%	50.0%
Chewing tobacco users	34.3%	60.0%
Smokers	22.9%	40.0%
Lifetime no. of cigarette packs (mean)	3952 (±14,840)	5384 (±11,340)
Drinkers	62.9%	80.0%
Lifetime no. of whiskey equivalents (mean)	7876 (±18,930)	13,600 (±24,290)
Serum beta-carotene in μg/dl (mean)	12.5 (±8.4)	26.5 (±38.6)
Calories/day (mean)	3092 (±1559)	2243 (±959.0)
Vitamin A/day in IU (mean)	11,240 (±6259)	11,170 (±7035)
Vitamin C/day in mg (mean)	193.5	108.8
Beta-carotene/day in μg (mean)	4427 (±2819)	3865 (±3846)

ST: smokeless tobacco.

strong link of ST use with carcinoma and more recent ones show low prevalence rates for even hyperkeratosis. One possibility is that the composition of the tobacco or its processing changed over the last 50 years. Unfortunately, this information is proprietary and not available (Traystman K. Smokeless Tobacco Research Council, Inc., May 21, 1991). A plausible reason is that the mean age of the populations studied is different. As an example, the mean age for the ST users with oral lesions in our study was 30.8 years, but, in the study by Winn et al.,[4] 89% of the patients with oral cancer were older than 49 years of age. In the analysis by McQuirt[37] of 57 oral cancers associated with ST use, 80.7% of the patients were 60 years of age or older. Many of the ST studies done in the last 15 years surveyed adolescents or young baseball players and, therefore, might not be comparable to earlier studies that had older populations.

The transition time from the first use of ST to development of an oral lesion is important. Our data showed a minimum of 2190 hours of ST use by the time a hyperkeratotic lesion was diagnosed and 7300 hours for an epithelial dysplasia. If 3 hours of ST use per day is assumed, then it would have taken a minimum of 2 years (730 days) for the development of hyperkeratosis and 6.6 years (2433 days) for epithelial dysplasia. It is necessary to use caution in interpreting these numbers because they are based on estimates by subjects and it is unknown how long the lesions were present before diagnosis. Our mean of 37,060 hours of ST exposure for the 45 subjects with lesions is equivalent to 33.8 years (12,353 days) of use at 3 hours per day. The 302 subjects with no lesions had a mean of 25,200 hours of ST use, equivalent to 23.0 years (8400 days) of use at 3 hours per day. In a study of 32 Danish snuff users, the mean exposure time was 33.8 years at the time an oral lesion was diagnosed,[32] which is similar to our data. Winn et al.[4] found that half of their nonsmokers in whom oral cancer developed had been dipping snuff for 50 years or more. McQuirt[37] reported that 75% of his patients had used snuff for more than 40 years. Our previous study reported a range of 23.9–47.6 years of ST use before a lesion evolved into an epithelial dysplasia or carcinoma and was diagnosed.[27] From the accumulated evidence, it is reasonable to state that, for lesions that do progress, it often takes 5–10 years of ST use for development of hyperkeratosis and 40 or more years for development of a carcinoma. It should be emphasized that oral lesions develop in only a minority of ST users.

It has been convenient to consider snuff and chewing tobacco as comparable, but there are adequate differences to indicate that they should be analyzed separately. The early reports of cancer and ST use mentioned snuff but not chewing tobacco,[2,3,5,37] which may be indicative of a greater prevalence of snuff-related lesions. In a survey of baseball players, Greene et al.[20] found that 55% of the snuff users had oral lesions, as compared with 14% of the chewing tobacco users. Although there are differences in the types of tobacco, the processing, and how the products are used, it is still unclear why snuff is associated more often with an oral lesion than is chewing tobacco.

Interest in beta-carotene was generated by reports that showed an increased incidence of various carcinomas associated with low intake or serum levels of

beta-carotene.[38–41] In addition, beta-carotene supplements have been used effectively to treat oral lesions.[42–44] The protective and therapeutic functions of beta-carotene might be related to its role as an extremely efficient quencher of free oxygen radicals[45,46] or its ability to enhance the immune system.[47] In the current study, neither the dietary nor serum levels of beta-carotene were lower in those with an oral lesion; instead, serum beta-carotene levels were higher in those with lesions, particularly in subjects with epithelial dysplasia. A difference in the predicted direction might have been found if more of the lesions had been carcinomas instead of hyperkeratosis.

A significant correlation between low vitamin C intake and the presence of an oral lesion was found (Table 4). Others have shown that the antioxidant properties of vitamin C are useful in reducing the incidence of carcinoma,[48] which suggests the possibility of using vitamin C in either a preventive or therapeutic role for ST users. The variables not significantly associated with the presence of an oral lesion in ST users also are important: age, cigarette smoking, and alcohol use. Other authors also have observed that the use of alcohol or cigarettes is not a significant factor in the development of oral lesions in ST users.[6]

Comparison of hyperkeratotic versus dysplastic lesions (Table 5) showed that chewing tobacco, and not snuff, was more likely to be associated with epithelial dysplasia. Exposure to ST, cigarettes, and alcohol was increased in the group with epithelial dysplasia, whose mean age also was 10 years greater. Of possible importance is the significantly lower intake of vitamin C among patients with epithelial dysplasia.[49]

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Annexe 4

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Smokeless tobacco use and oral pathology in a professional baseball organization.

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Abstract

BACKGROUND: Smokeless tobacco has been implicated as a risk factor for numerous oral conditions. Since baseball players are known to have a high incidence of smokeless tobacco use, they are an excellent group in which to study the effects of smokeless tobacco on the oral cavity. We report our findings in 206 of 220 eligible men during spring training of a professional baseball organization. Major and minor league ballplayers, coaches, and management personnel were included.

METHODS: Participants completed a 2-page, 23-item questionnaire on smokeless tobacco use. This was followed by a detailed examination for oral leukoplakia, periodontal disease, and dental caries performed by a physician who was blinded to the results of the questionnaire. Oral leukoplakia was graded I, II, or III according to severity.

RESULTS: Eighty-eight of 206 participants (42.7%) reported current use of smokeless tobacco; 62 of these men used smokeless tobacco year round, while 26 used smokeless tobacco only during the baseball season. The 88 smokeless tobacco users often used more than one form of tobacco. Moist snuff was the most common form (73.9% of users) followed by loose leaf tobacco (53.4%) and plug tobacco (9.1%). Oral leukoplakia was found in 25 of 88 current users (28.4%). Only the year-round users, however, had an incidence rate (37.1%) that was significantly different from all others (odds ratio = 9.35, 95% CI = 3.46 to 26.21). Year-round users were also more likely to have a higher grade of oral leukoplakia. Periodontal disease and dental caries were no more prevalent among smokeless tobacco users than nonusers.

CONCLUSIONS: We conclude that the use of smokeless tobacco products is a significant risk factor for the development of oral leukoplakia, and that this risk is greatest in those individuals who use smokeless tobacco continuously throughout the year.

Annexure 46

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Tobacco chewing and female oral cavity cancer risk in Karunagappally cohort, India

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This study examined oral cancer in a cohort of 78 140 women aged 30 – 84 years in Karunagappally, Kerala, India, on whom baseline information was collected on lifestyle, including tobacco chewing, and sociodemographic factors during the period 1990 – 1997. By the end of 2005, 92 oral cancer cases were identified by the Karunagappally Cancer Registry. Poisson regression analysis of grouped data, taking into account age and income, showed that oral cancer incidence was strongly related to daily frequency of tobacco chewing ($P < 0.001$) and was increased 9.2-fold among women chewing tobacco 10 times or more a day. The risk increased with the duration of tobacco chewing during the first 20 years of tobacco chewing. Age at starting tobacco chewing was not significantly related to oral cancer risk. This is the first cohort study of oral cancer in relation to tobacco chewing among women.
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Keywords: tobacco chewing; oral cancer; India

Globally, oral cancer is the 11th most common cancer and is responsible for about 200 000 deaths each year (IARC, 2003), two-thirds of which were in economically developing countries. Tobacco chewing as a cause for oral cancer was suggested as early as the beginning of the last century (Niblock, 1902; Orr, 1933). To date, epidemiological studies conducted in South Asia, west Europe and North America have clearly shown the relationship between oral cancer risk and tobacco chewing among men (Critchley and Unal, 2003; IARC, 2007). However, to our knowledge, the corresponding risk in women has been examined only by a few studies.

In this study, we analysed the oral cancer risk among women in relation to tobacco use, and socioeconomic status (SES) in a rural cohort in Kerala. To our knowledge, this is the first cohort study to examine the association of oral cavity cancer risk with tobacco chewing among women. It is relevant that smoking and alcohol drinking were rare in this women population.

SUBJECTS AND METHODS

In the early 1990s, a cohort was established of virtually all the residents in Karunagappally (Nair *et al*, 1999), a rural coastal area in Kollam district of Kerala, south west India. This taluk consisted of 12 panchayats at taluk being an administrative unit, corresponding to a county, with panchayats as subunits. According to the 1991 Census, this taluk had a population of 385 103 (191 149 males and 193 954 females) residing in an area of 192 km^2 All the households ($N = 71\,674$) in Karunagappally taluk were visited by 12 – 14 trained interviewers, starting from 1 January 1990 and ending on 31 December 1997 (Jayalekshmi *et al*, 2008). Using a 6-page standardised questionnaire, they collected information on sociodemographic factors, religion, family income in rupees, education, occupation, lifestyles and other factors. Residents were asked if they never chewed tobacco, habitually chewed it in the past or habitually chewed it currently. For those who ever habitually chewed tobacco, further questions were asked on the daily frequency, age at starting and the duration. For ex-chewers, age at stopping was also asked. The same types of questions were asked to beedi and cigarette smokers.

In total, this household survey collected personal information on 359 614 subjects in 71 674 households, which correspond to 93% of population and 94% of households in Karunagappally by the 1991 census. There were 81 514 women aged 30 – 84 years old at the time of interview. We excluded the following from analysis: those younger than 30 years of age, as cancer risk is low in this age range; those aged 85 years or older; workers employed in the local Rare Earth factory, who might have various occupational exposures ($N = 29$); 166 subjects who had died or been diagnosed as cancer before the base-line interview; and those who died within 3 years of interview, as their lifestyles might have been affected by their health conditions. Thus, there were 79 593 subjects for statistical analysis.

The entry into the cohort was 1 January 1990 or the date of interview, which was started on 1 January 1990 and ended on 31 December 1997. A cohort member was censored when she was (i) diagnosed as cancer other than oral cancer, (ii) died of causes other than oral cancer or (iii) migrated from the study area. Thus, the end of follow-up was the date of diagnosis for cancer cases, of death for those deceased, of the end of follow-up (31 December

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Table 1 Tobacco chewing and sociodemographic factors

	Tobacco chewing				
	Yes[a]	No[a]	Odds ratio[b]	95% CI	
Total	18612 (100%)	59221 (100%)			
Age at interview (years)					$P<0.001$
30–	1889 (7%)	25964 (93%)	1	Reference	
40–	4108 (21%)	15377 (79%)	3.67	3.47–3.89	
50–	4757 (35%)	8734 (65%)	7.49	7.06–7.94	
60–	5060 (44%)	6414 (56%)	10.84	10.22–11.51	
70–	2411 (50%)	2411 (50%)	13.74	12.77–14.79	
80–	387 (55%)	321 (45%)	16.57	14.19–19.35	
Religion					$P<0.001$
Hindu	13960 (25%)	41969 (75%)	1	Reference	
Moslem	3953 (26%)	11047 (74%)	1.18	1.13–1.23	
Christian	699 (10%)	6205 (90%)	0.31	0.28–0.33	
Family income (Rs.)[a]					$P<0.001$
<500	1943 (34%)	3797 (66%)	1	Reference	
501–1200	6407 (28%)	16422 (72%)	0.79	0.74–0.84	
1201–2500	6766 (24%)	21920 (76%)	0.60	0.56–0.63	
2501–3500	2405 (18%)	10703 (82%)	0.40	0.37–0.42	
3500+	1091 (15%)	6379 (85%)	0.27	0.25–0.29	
Education					$P<0.001$
Illiterate	6144 (47%)	6917 (53%)	1	Reference	
Primary school	7272 (33%)	14803 (67%)	0.67	0.64–0.70	
Middle school	3750 (20%)	14983 (80%)	0.45	0.42–0.47	
High school	1257 (7%)	18094 (94%)	0.22	0.21–0.24	
College	70 (2%)	4081 (98%)	0.12	0.11–0.14	
Unknown	119 (26%)	343 (74%)	0.45	0.37–0.54	
Occupation					$P<0.001$
Fishermen and farmers	1180 (53%)	1060 (47%)	1	Reference	
Unemployed	548 (13%)	3522 (87%)	0.29	0.27–0.32	
House wives/students	7523 (18%)	34023 (82%)	0.40	0.37–0.43	
Skilled workers	9349 (32%)	20297 (68%)	0.67	0.62–0.72	
Others	12 (4%)	319 (96%)	0.18	0.14–0.22	

[a]Those who chew tobacco currently or in the past. Those whose tobacco chewing status was unknown were excluded from analysis. [b]Odds ratio and 95% CI (confidence interval) were obtained by logistic analysis adjusting for age at interview (5-year category). In the analysis of association with age, univariate analysis logistic analysis was conducted.

2005), of moving out, or reaching the age of 85 years. In person-year calculation, we used the information on migration of cohort members even though this was available only for a part of our observation period; this caused only small changes in relative risk estimates.

In this study, we analysed cancer incidence in the period 1990–2005. Cancer cases among the cohort were ascertained by the cancer registry in Karunagappally, which was officially initiated as of 1 January 1990 and has been reported in 'Cancer Incidence in Five Continents', vols. VII–IX (Nair *et al*, 1997, 2002; Jayalekshmi and Rajan, 2007). As there was no dedicated cancer centre in this rural area, we had to pursue an active registration method by visiting all health-care facilities of the taluk and outside where cancer patients are seen (Jayalekshmy *et al*, 2008).

Death reports were obtained from the death registers kept in the vital statistics division of each panchayat. House visits of the deceased, to supplement information on cause of death, were started in 1997. The proportion of DCO cases in Karunagappaly cancer registry was 14% during 1990–1994 (Nair *et al*, 1997), 10% during 1993–1997 (Nair *et al*, 2002) and 4% during 1998–2002 (Jayalekshmi and Rajan, 2007). The ratio of incidence to mortality (M/I percent) for all cancer among women was 39% during the period between 2002–2003 (Jayalekshmi *et al*, 2005), similar to those in other major cancer registries in India (Nandakumar *et al*, 2005).

The extent of migration among cohort members was assessed by conducting a door-to-door survey of all the households in the six panchayats (Chavara, Neendakara, Panmana, Alappad, Oachira and Thevalakkara) and in the remaining six panchayats in 2001 and 2003, respectively. The survey findings were linked to incident cases through name, address, age, house number and so on; it showed that migration was negligible.

Statistical analysis

Statistical analysis of tobacco chewing in relation to socio-demographic factors were conducted using logistic analysis, adjusting for age at interview. For the association with age, univariate logistic analysis was used.

Analyses of sociodemographic factors and tobacco chewing were based on the data in cross-classifications by attained age (5-year category), and other covariates. Relative risk (RR) and 95% confidence intervals (95% CI) were obtained from Poisson regression analysis of grouped survival data (Breslow and Day, 1987), using the DATAB and AMFIT procedures of Epicure programme (Preston *et al*, 1993). In the analysis of risk associated with tobacco

chewing, which has the three categories (never, former and current), the following model was used to estimate the RRs of former tobacco chewers (represented by S_2) and current-chewers (represented by S_3): H_0 (attained age, income) exp $(\beta_2 S_2 + \beta_3 S_3)$, where H_0 represents the baseline, or background oral cancer incidence (among never smokers) for cross-classified strata by attained age and sociodemographic variables. Attained age at the time of the midpoint of 1-year interval during the observational period (1990–2005) was calculated for each cohort members by the DATAB procedure of EPICURE programme. Heterogeneity test was based on a global *P*-value for a set of indicator variables. Trend test for, for example, duration of tobacco chewing was conducted by assigning the mean duration of tobacco chewing to its each category.

RESULTS

Among the 79 593 eligible women aged 30–84 years, 102 female cases of oral cancer (ICD9: 140, 141, 143–145) were identified by the end of 2005. After restricting the examination to women who do not smoke beedis or cigarettes and do not drink alcohol, there were 78 140 women and 92 oral cancer cases. Table 1 shows the distribution of tobacco chewers according to sociodemographic factors. All the factors examined were strongly related to tobacco chewing. Table 2 presents sociodemographic features of study subjects and the RRs for those factors obtained by the analysis stratified on attained age. The lowest family income group had a higher risk than higher income groups ($P<0.001$, the lowest income *vs* other groups).

Tables 3 and 4 summarise the results of risk analysis with respect to tobacco chewing. The analyses were stratified on attained age and family income. Tobacco chewing increased oral cavity cancer risk by 5.5-fold. Former tobacco chewers had an RR even larger than current tobacco chewers. The duration of tobacco chewing was related to incidence ($P<0.001$), particularly in the first 20 years. Among those who had chewed tobacco for 20 years or longer by the time of baseline study, no further risk increase was observed.

Table 4 summarises the results examining the effects of the daily frequency of tobacco chewing and age starting tobacco-chewing on incidence. In those analyses, those who stopped chewing tobacco by the time of interview were excluded. Oral cancer incidence was strongly related to daily frequency of tobacco chewing ($P<0.001$) and was increased 9.2-fold among women chewing tobacco 10 times or more a day. The effect of age starting tobacco chewing did not evidently modify risk. Oral cavity cancers were grouped into cancers of the tongue (ICD9: 141) and gum and mouth (ICD9: 143–145), there were only four cases in the other location, which were cancer of the lip. As shown in Table 5, tobacco chewing was significantly associated with cancers of the mouth ($P<0.001$) and the tongue ($P<0.001$).

DISCUSSION

This study showed that daily frequency of tobacco chewing was strongly related to oral cancer incidence among women, and the risk among women chewing tobacco 10 times or more a day was 9.2-fold higher than that of non-tobacco chewers. Moreover, it increased with duration of chewing during the first 20 years.

Former tobacco chewers had an RR even larger than current tobacco chewers, as also found by a case–control study in Trivandrum, India (Muwonge *et al*, 2008). Although former chewers may include those who stopped because of precancerous lesions, the increase of risk among those who stopped 10 or more years before the interview is difficult to explain in this way.

Table 2 Sociodemographic features of study subjects (women only)

	Subjects (%)	Person-years	Cases[a]	RR	95% CI	
Total	78 140 (100%)	921 051	92			
Religion						
Hindu	56 147 (72%)	665 846	67	1	Reference	$P>0.5$
Moslem	15072 (19)	176 024	18	1.1	0.7–1.9	
Christian	6921 (9)	79 181	7	0.9	0.4–1.9	
Family income (Rs.)[a]						
<500	5768 (7)	71 639	13	1	Reference	$P=0.401$
501–1200	22 939 (29)	275 136	25	0.5	0.3–1.0	
1201–2500	28 806 (37)	334 910	30	0.5	0.3–1.0	
2501–3500	13 144 (17)	150761	16	0.6	0.3–1.2	
3500+	7483 (10)	88 605	8	0.5	0.2–1.2	
Education						
Illiterate	13 105 (17)	147 362	20	1	Reference	$P>0.5$
Primary school	22 187 (28)	259 572	35	1.2	0.7–2.1	
Middle school	18 810 (24)	225 008	22	1.2	0.6–2.2	
High school	19 420 (25)	234 263	11	0.9	0.4–2.0	
College	4155 (5)	49 570	4	2.0	0.6–5.9	
Unknown	463 (1)	5276	0			
Occupation						
Fishermen and farmers	2252 (3)	24 710	3	1	Reference	$P>0.5$
Unemployed	4079 (5)	47 914	3	0.7	0.1–3.4	
House wives/students	41 698 (53)	491 971	39	1.0	0.3–3.2	
Skilled workers	29 780 (38)	352 557	46	1.3	0.4–4.1	
Others	331 (0.4)	3899	1	3.3	0.3–32.3	

Relative risk (RR) and 95% CI (confidence interval) were obtained from the following model: $H = H_0 \exp(\beta X)$, where background hazard, H_0, was stratified by attained age (5-year category), and X_i are categorical variables for one of sociodemographic factors. [a]Oral cancer cases.

Table 3 Tobacco chewing and oral cancer among women

Tobacco chewing	Oral cancer case[a]	Person-years	RR	95% CI	
Chewing habit					$P<0.001$
Never	25	706 872	1	Reference	
Former	14	26 804	9.2	4.6 - 18.1	
Current	53	183 749	5.5	3.3 - 9.0	
Unknown	0	3629			
Duration					P for trend[a] <0.001
Never	25	706 872	1	Reference	
1 - 9	9	63 998	3.1	1.5 - 6.8	
10 - 19	17	38 927	8.9	4.8 - 16.8	
20 - 29	18	41 867	7.8	4.2 - 14.5	
30 - 39	14	31 489	7.1	3.6 - 14.1	
40+	7	31 203	3.2	1.3 - 7.8	
Unknown	2	6747	6.5	1.5 - 27.4	
Years since stop tobacco chewing					
Current smokers	53	183 849	1	Reference	
1 - 9	7	13 817	1.7	0.8 - 3.7	
10+	4	4819	2.6	0.9 - 7.2	
Never	25	706 872	0.2	0.1 - 0.3	
Unknown	3	11 796	0.8	0.2 - 3.3	

Relative risk (RR) and 95% confidence interval (CI) were obtained from the following model: $H = H_0 \exp(\beta_i X_i)$, where background hazard, H_0, was stratified by attained age (5-year category) and family income; and X_i are categorical variables for tobacco chewing. [a]The category of 'unknown' was excluded when calculating P for trend.

Table 4 Tobacco chewing and oral cancer among women—former tobacco chewers are excluded from analysis

Times	Oral cancer cases	Person-years	RR	95% CI	
Daily frequency					
Never	25	706 872	1	Reference	
1 - 4	16	95 614	3.3	1.7 - 6.4	
5 - 9	25	62 143	7.8	4.4 - 13.9	
10+	12	25 063	9.2	4.5 - 18.7	
Unknown	0	4558			P for trend[a] <0.001
Starting age (years)					
<20	4	21 989	3.8	1.9 - 7.5	
20 -	15	46 775	7.8	4.2 - 14.4	
30 -	18	49 953	6.4	3.3 - 12.4	
40+	14	60 799	3.5	1.2 - 10.1	
Never	25	706 872	1	Reference	
Unknown	2	7862	5.7	1.3 - 24.3	
					P for trend[b] >0.5

Relative risk (RR) and 95% confidence interval (CI) were obtained from the following model: $H = H_0 \exp(\beta_i X_i)$, where background hazard, H_0, was stratified by attained age (5-year category) and family income; and X_i are categorical variables for tobacco chewing. [a]The category of 'unknown' was excluded when calculating P for trend. [b]The categories of never-tobacco chewers and unknown were excluded when calculating P-value.

Socioeconomic status is suspected to be related to oral cancer risk, but the results from studies have been mixed. A review concluded that most incidence studies did not show a clear association, whereas oral cancer mortality was elevated in lower SES sections of various populations (Faggiano *et al*, 1997). Recently, a case–control study in Kerala, India, showed that lower levels of education and income were related to relatively high prevalence of oral premalignant lesions (Hashibe *et al*, 2003). However, inconsistent results on SES are not unexpected, as this is most likely a surrogate marker of oral cancer, and the factors related to SES may differ from society to society. In this study, oral cancer risk among women was related to very low family income but not to education levels.

In India and Pakistan, almost 100 million people use smokeless tobacco (Reddy and Gupta, 2004), and in many ways (IARC, 2007). In most Asian countries, the widely used method is to chew 'pan' - a bolus made of betel leaf, areca nut or slaked lime smeared on betel leaf and tobacco. IARC has classified areca nut as a human carcinogen (group 1) (IARC, 2004). In the study area, tobacco chewing was almost always associated with chewing pan, and only a small number chewed tobacco alone, so that it was difficult to determine which was more harmful, the use of pan alone or pan together with tobacco.

A limitation of our study is the fact that the lifestyle of cohort members, may have changed during follow-up and no attempt was made to re-interview subjects. Some never-chewers at baseline may have started tobacco chewing during our follow-up period, first as some who chewed tobacco at interview may have stopped the habit during the follow-up. Our RRs for tobacco chewing may therefore be underestimated. In addition, duration of tobacco chewing and years after cessation of chewing is probably underestimated, as we used the periods until the time of interview.

Table 5 Tobacco chewing and location-specific oral cancer incidence

Site of cancer	Tobacco chewing	Oral cancer cases	RR	95% CI	
Tongue (ICD9: 141)					
					$P<0.001$
	Never	13	1	Reference	
	Former	5	6.7	2.3–19.4	
	Current	20	3.9	1.9–8.0	
	Unknown	0			
Gum and mouth (ICD9: 143–145)					
					$P<0.001$
	Never	9	1	Reference	
	Former	9	16.7	6.3–44.0	
	Current	32	10.0	4.6–21.8	
	Unknown	0			

Relative risk (RR) and 95% confidence interval (CI) were obtained from the following model: $H = H_0 \exp(\beta_i X_i)$, where background hazard, H_0, was stratified by attained age (5-year category) and family income; and X_i are categorical variables for tobacco chewing.

This study, the first cohort study of the question among women, showed that frequent tobacco chewing strongly increases oral cancer incidence ($P<0.001$).

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RESEARCH COMMUNICATION

Role of Tobacco in the Development of Head and Neck Squamous Cell Carcinoma in an Eastern Indian Population

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Abstract

Head and neck squamous cell carcinoma (HNSCC) accounts for about 30-40% of all cancer types in India and the subcontinent in general. HNSCCs are primarily not hereditary, but rather a disease of older and middle aged adults. Many etiological factors like tobacco, alcohol and HPV infection are known to play important roles. Eastern India, particularly Kolkata, has a population heavily exposed to various types of smoked and smokeless tobacco, with only limited exposure to alcoholic beverages. Since there have been no previous epidemiological studies on tobacco as the main risk factor for head and neck carcinogenesis in Kolkata, we here carried out a hospital based case control study in the city and its adjoin regions. Data from 110 patients diagnosed with HNSCC and a similar number of matched control samples were analyzed using chi-square ($\chi 2$) test. Survival status of the patients was also analyzed using the Kaplan-Meier method. A tobacco habit was significantly correlated with the incidence of HNSCC and persons with current addiction had a 2.17 fold increased risk of cancer development. Dose-response relationships were seen for the frequency ($p=0.01$) and duration ($p=0.02$) of tobacco exposure with the risk. No significant difference in impact was found with smoked as opposed to smokeless tobacco in the development of the disease. Among HNSCC patients, significant poor survival in cases with tobacco habit than in those with no addiction and in cases with >10 years of addiction than in those with ≤ 10 years of addiction. Our data suggest that tobacco in both smoked and smokeless forms is the most important risk factor for both development and prognosis of HNSCCs and may be a major source of field cancerization on the head and neck epithelium in the eastern Indian population.

Key Words: Head and neck squamous cell carcinoma - epidemiology - tobacco - Eastern India

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Introduction

Head and neck squamous cell carcinoma (HNSCC) is an epithelial malignant disease arising from the mucosa of the upper aerodigestive tract (oral cavity, larynx, oropharynx and hypo pharynx) (Nagai, 1999). It is the fifth most common cancer worldwide (Parkin et al., 1993). In some parts of the world, these cancers represent the most common malignancies found in men. For example, in South-Central Asia (India, Pakistan, Bangladesh, Iran, Afghanistan, and the Central Asian Republics), that accounts for one fifth of the world's population, head and neck cancer accounted for approximately 1,55,400 new cases of cancer in 1990 (17% of all cancers and 25% of all cancers occurring in men) (Parkin et al., 1999). Although in most regions of the world, laryngeal and naso-pharyngeal cancers account for between one third and one half of all head and neck malignancies, in South-Central Asia, 80% of head and neck cancers are found in the oral cavity and oropharynx (Sankaranarayanan et al., 1998; Parkin et al., 2005). Cancers of the oral cavity accounted for 2,74,000 cases in 2002, with almost two-third of them in men (Parkin et al., 2005). In most regions of India, cancer of the oral cavity is the leading malignancy diagnosed in men, accounting for up to 20% of cancers in men, and oral cavity cancer is the third most common cancer in Indian women (Sen et al., 2002).

HNSCCs are primarily not hereditary, but a disease of older and middle aged adults with a long history of tobacco smoking (Cann CI et al., 1985). Tobacco smoking has long and consistently been identified as the major risk factor for HNSCC. Actually head and neck regions like oral cavity, larynx, oropharynx and hypopharynx, as directly exposed to tobacco smoke, have a relatively higher risk of developing cancer than other regions like the pancreas and urinary bladder, for example (Vineis et al., 2004).

A recent report found a 20 fold increased risk of oral and pharyngeal cancer below age 46 for heavy smokers, and a 5-fold increase for heavy drinkers; the combination of heavy smoking and drinking led to an almost 50 fold increased risk (Rodriguez et al., 2004). Oral cancer is also increased by tobacco chewing (Cullen et al., 1986; Chen et al., 1990) and is prevalent in communities such as India

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and Indonesia where chewing of betel quid – betel nut (Areca catechu) wrapped in betel leaf, sometimes mixed with lime - is prevalent (Muir & Kirk, 1960). Use of snuff also increases the risk of developing oral cancer (Winn et al., 1981).

Population based screening and early detection programs are rare or nonexistent and in spite of surgical advances, these cancers remain a disfiguring disease associated with a relatively low survival rate (Berrino et al., 1998; Forastiere et al., 2001). But despite the clear role of tobacco in the etiology of HNSCCs, this association has not been assessed clearly among the eastern Indian population. In the present study, we therefore explored the role and impact of tobacco in head and neck carcinogenesis and for this, data were analyzed in a large, hospital-based, case control study of head adn neck cancer. The aim was to establish the association of tobacco with development of HNSCCs, focusing on: a) the tobacco habit as a major risk factor; b) the contribution of various characteristics related to tobacco habit (i.e. dose and duration; smoking and chewing); c) the survival status.

Materials and Methods

Samples:

We have categorized our samples into two broad groups. Case samples were patients, histologically diagnosed in the participating hospital with invasive cancer of head and neck region. A total of 110 cases were studied for our analysis. Equal numbers of control samples were identified from Kolkata matched with the cases by gender age and also the locality (out of total 465 HNSCC patients visited to the hospital for treatment between 1998 to 2006, 110 from the greater Kolkata region were only selected as case samples for our study). Individuals with an admission diagnosis related to tobacco consumption were not accepted as controls.

Sources:

The detailed clinical history of the case samples was collected from the record section of the Chittaranjan National Cancer Institute, Kolkata. The written consent of the hospital authority was taken prior to our study. The control samples were selected from both North and South Kolkata. Normal healthy individuals willing to participate in our study were selected randomly at the first round. Finally among the participating individuals, control samples were selected on the basis of sex, age group and other criteria.

Methodology:

Questionnaire: All the controls were interviewed properly to collect the necessary data for our study. The questionnaire elicited detailed information on demographic, educational and socioeconomic characteristics, on the characteristics of tobacco habit [i.e.- type of the tobacco habit (smoking/chewing/both smoking and chewing), duration of each habit and also age of starting, average number of cigarettes smoked / average number of chewing per day etc.], tobacco related illness and also the family history of cancer (If any). In our study, current smokers/chewers were defined as those having the habit at the time of interview, as well as those stopping the habit within the year before the date of the interview.

Table 1. Clinicopathologic Characteristics (110 cases)

Characteristics	No. of patients		Median age	Age range
Primary Site				
Orofacial (28)	Maxilla	15	49	32-76
	Mandible	12		
	Nasal cavity	1		
Oralcavity (60)	BM	23	48	30-74
	Tongue	16		
	Alveolus	8		
	Tonsil	6		
	Palate	5		
	Lip	2		
Larynx (15)		15	58	50-75
Thyroid (7)		7	55	40-70
Tumor Stage	Stage-I	15	60	58-62
	Stage-II	28	46	40-76
	Stage-III	33	50	39-75
	Stage-IV	34	54	45-70
Tumor Differentiation				
Well Differentiated		45	52	40-77
Moderately Differentiated		40	50	41-65
Poorly Differentiated		25	44	35-75
Lymph Node Involvement				
	No	60	50	40-70
	Yes	50	52	45-76
Gender	Male	80	50	38-68
	Female	30	45	40-65

Statistical analyses: 2x2 Chi-square analysis was performed to determine the association of tobacco habit and HNSCC development. Chi-square for trends was also performed to determine the significance of various parameters of tobacco habit like dose, duration etc. For analysis of the survival status of the case samples, Survival curves were calculated according to Kaplan-Meier method. Post-operative overall survival was measured from the date of surgery to the date of last follow-up or death (up to 5 years). Probability value (P-value) ≤ 0.05 was considered statistically significant. All the statistical analysis was performed using statistical program SYSTAT-9.0(Binary Semantics).

Results and Discussion

Subjects' Characteristics:

The detail clinical histories of the case samples are presented in Table 1. Out of total 110 cases, 60 were from oral cavity (55%), 15 from larynx (14%), 28 from orofacial region (25%) and 7(6%) from thyroid. Among oral cavity, buccal mucosa seems to be the most commonly affected site (39%; 23/60) followed by tongue (26%; 16/60), alveolus (13%; 8/60), tonsil (10%; 6/60), palate (8%;5/60) and lip (3%;2/60). Among orofacial regions, maxillae and mandibles are the most common (53%; 15/28 and 43%; 12/28), however one nasal cavity tumor was also reported. All the tumors are of invasive category, no dysplasia has been recorded among the case samples. The tumors were clinically staged (I, II, III & IV) according to UICC TNM classification and the histopathological

Table 2. Subject Details

	Cases	Controls	χ^2 p-Value
Age Group			
35-44 Years	15 (14%)	35 (32%)	0.2
45-54 years	49 (44%)	30 (27%)	
55-64 years	35 (32%)	30 (27%)	
≥65 years	11 (10%)	15 (14%)	
Sex			
Male	80 (73%)	70 (64%)	0.147
Female	30 (27%)	40 (36%)	
Education			
Illiterate	5 (5%)	1 (1%)	0.0001
Primary	15 (14%)	5 (5%)	
Secondary	50 (45%)	30 (27%)	
≥Higher	40 (36%)	74 (67%	
Religion			
Hindu	55 (50%)	60 (55%)	0.6
Muslim	45 (41%)	30 (27%)	
Christian	10 (9%)	20 (18%)	
Occupation			
Manual	45 (41%)	40 (36%)	0.4
Teacher/office worker	15 (14%)	25	23%
Business	10 (9%)	18 (16%)	
Retired	30 (27%)	20	18%
Others	10 (9%)	7 (7%)	
Tobacco History			
Nonaddicted	58 (53%)	76 (69%)	0.027
Addicted	52 (47%)	36 (31%)	

grades (WDSCC, MDSCC & PDSCC) were also assessed.

Table 2 shows the distribution of study participants according to their case control status, selected socio-demographic characteristics and main descriptive statistics of tobacco habit. Chi-square ($\chi 2$) tests were performed to determine whether the distribution of these factors was related to disease status. The cases were more likely to be in the 45-54 year age group while the controls were more likely to be in the youngest age group of 35-44 years. Males were the predominating sex among cases and controls. The level of education was higher among the controls than the cases: the highest percentages of cases were in the secondary education category. We did not find any correlation (Neither positive nor negative) between education and tobacco habit; however the chewers and bidi (raw tobacco) smokers mostly belonged to the no education and illiterate category (Data not shown). Most subjects were Hindu among both cases and controls but the percentage of Muslims was higher among cases and the percentage of Christians was higher among controls. The majority of the cases and controls held a manual occupation. Controls had a higher percentage of teachers and office workers.

Effect of tobacco habit:

The tobacco habit and its' related characteristics were stratified as the main potential risk factor by the disease status in Table-3. The overall prevalence of tobacco habit was higher among case subjects than among the controls. We explored the relationship of all the parameters of tobacco habit (dose or amount of intake per day, duration of the habit, type of tobacco etc.) and cancer risk. An increased risk for head and neck cancer was detected

Table 3. Cancer Risk Relative to Smoking History

Variables	Cases	Controls	OR (95%CI)
Status of the tobacco habit			
Never addicted	40	60	1
Ex- addiction	18	14	1.93
Current addiction	52	36	2.17
p value for trend test			0.0087
Type of tobacco habit			
Smoked tobacco	30	20	1
Non smoked tobacco	13	10	0.87
Mixed	9	6	1
p value for trend test			0.92
Type of smoked tobacco habit			
Cigarette	19	15	1
Bidi	20	10	1.58
Cigar	0	1	0
p value for trend test			0.7
Type of Non smoked tobacco habit			
Khaini	11	8	1
Snuff	8	6	0.97
Gutkha	3	2	1.02
p value for trend test			0.96
Amount of tobacco intake (Avg. no of smoking/chewing/day)			
1-10	22	22	1
11-20	16	12	1.33
≥21	14	2	7
p value for trend test			0.01
Duration of tobacco intake (Avg. year of smoking/chewing)			
1-10	19	20	1
11-20	22	14	1.65
≥21	11	2	5.79
p value for trend test			0.02

among the tobacco-addicted individuals compared to those with no addiction. Risk for HNSCC also increased with both dose and duration of the habit. No associations were found with age at start or age at quitting tobacco habit (Data not shown). Smokers of cigarettes with filters had the same risk as smokers of bidis and also the chewers.

Tobacco products contain a diverse array of chemical carcinogens that cause cancers of various types (Hecht, 2003). More than 60 known carcinogens have been detected in cigarette smoke and 16 in smokeless tobacco. Among these, tobacco specific nitrose amines (NNK, NNN etc), polycyclic aromatic hydrocarbons (benzo[a]pyrene), and aromatic amines seem to have important role as causes of cancer. Most carcinogens in tobacco undergo metabolic activation process initiated by cytochrome p450 enzymes (Part of normal mammalian systems designed to respond to the foreign compounds).

Metabolic activation makes the carcinogens electrophilic that now react with DNA to form DNA adducts. Cellular repair system remove DNA adducts and return DNA structure to its normal state, but if the adducts persist and escape repair, mutation arise. It has been established conclusively that DNA adducts of tobacco cause miscoding – most frequently G-T and G-A mutations. If these permanent mutations occur in crucial regions of oncogene like RAS and MYC or in tumor suppressor gene p53, CDKN2A, pRB, FHIT etc; this resulting disruption of cell cycle check points leading to loss of normal cellular growth control mechanism and development of cancer.

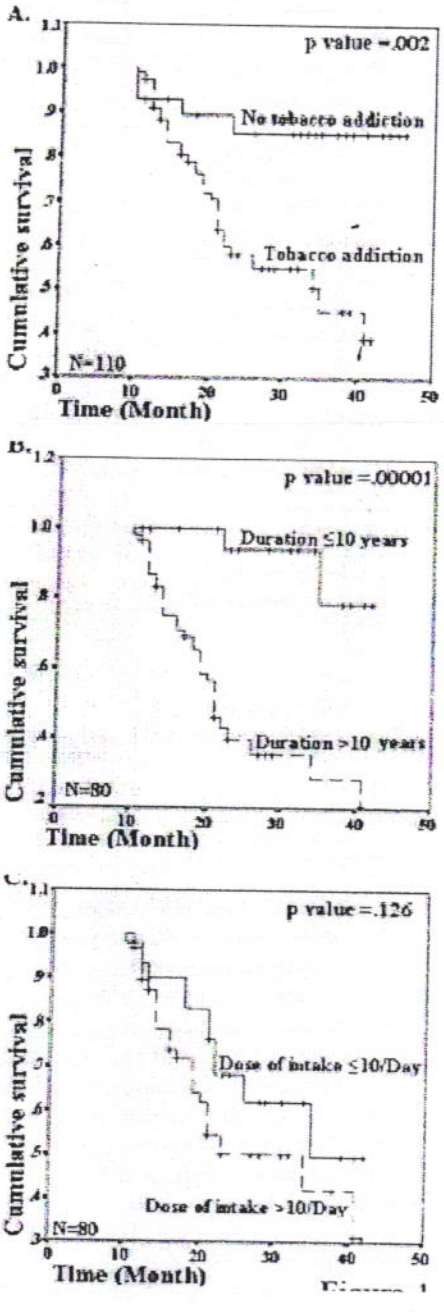

Figure 1. Survival Curves Relative to Tobacco Exposure

Survival status of the case samples:

The overall disease-free survival of the HNSCC patients was analyzed i.e. Patients died due to the disease or patients with recurrence of the disease at same or different site were considered as same category and designated by the value-"1"; while patients reported to be alive in the hospital follow-up record with no recurrence of the disease were designated by "0". Two approaches were taken to determine the association of tobacco (if any) with the poor survival of the HNSCC patients and also the bad prognosis of the disease.

A). Survival status of the patients not addicted to tobacco (designated by "0") Vs. those addicted to the tobacco (designated by "1"), (Supplement-1). As evident from the figure-1A, the tobacco addicted HNSCC patients showed significant poor survival/ bad prognosis of the disease compared to tobacco non-addicted patients.

B). Survival status among the tobacco addicted patients i.e. -a. Tobacco addicted HNSCC patients were grouped on the basis of duration of the habit (Patients addicted to tobacco for 10 years or less were designated by "0", while those for more than 10 years were designated by "1"), (Supplement-2A). Figure-2B clearly showed that duration of the tobacco habit was positively correlated with the poor patient survival and also the bad prognosis of the disease.

The addicted HNSCC patients were also grouped on the basis of daily tobacco intake (Patients having 10 or less bidi/cigarette/chewing habit were designated by "0" and those having more than 10, were designated by 1), (Supplement-2B). But surprisingly, the dose of the daily tobacco intake was shown to have no significant impact upon the survival status of the patients (Figure-1C).

At CNCI, the cancer patients receive a quality treatment. They visit to the outdoor first for the diagnosis of the disease. Spot admission on emergency bed depends upon the severity of the disease. In case of HNSCC, the disease is diagnosed by punch biopsy (in case of oral cavity), endoscopy based biopsy (in case of esophagus and larynx) or by FNAC /Fine Niddle Aspirate Cytology (in case of salivary gland, thyroid etc.). If the disease was diagnosed previously, slides are crosschecked in pathology department and the test is repeated if necessary. After that a medical board is constructed including the attending onco-surgon, radiotherapist and also chemotherapist to determine the proper treatment procedure. If the tumor remains confined to the primary site, then it's surgical removal followed by radiotherapy (by cobalt or Linac Accelerator) / chemotherapy is recommended. In general, surgery removes 70-80% of the tumor cells and the rests destroyed by ray / chemotherapeutic agents. For this the disease free survival of this category of patients should be higher compared to those in which the tumor cells get metastasizes from the primary site. But surprisingly we found poor survival/ recurrence in some patients instead of surgical removal of their tumor followed by chemo/ radiotherapy. About 90% of these patients were also addicted to tobacco for a long duration of time (>10 years). Actually x-rays/chemotherapeutic agents impose genotoxic stress upon the cell by creating irreversible DNA damage. This damage is sensed by some master genomic element like p53 that induces the cell to commit apoptosis. Tobacco containing carcinogens form DNA adducts and thus inducing mutation and other types of alterations of p53 and other crucial genetic elements during malignant transformation of a cell. As a result, these cells become resistant to ray / chemotherapeutic agents resulting recurrence of disease and poor survival of the patients.

Limitations of the study:

Case control studies have some important limitations and are subject to bias, and our study is no exception. Selection bias might be an issue but this potential bias is

somehow minimized by the fact that: i) Controls were selected from the same sex and age groups as the patients; ii) Control individuals with a history of hospitalization for diagnoses related to tobacco consumption were carefully excluded and iii) The public hospital (Chittaranjan National Cancer Institute) from where the patients were selected, provides quality cancer care.

Concluding remarks:

Out of 110 cases, no dysplastic/ premalignant lesions of head and neck were included. It indicates that the common people are not aware about the early symptoms of the HNSCC. So in most of the cases, the disease was diagnosed at an advanced stage and therefore the probability of complete cure of the disease and disease free survival of the patients got reduced.

∑ Education has no positive impact against the tobacco habit. Therefore a greater part of the mass is addicted to tobacco after being acknowledged completely about its' harmful effects.

∑ Both smoked & nonsmoked tobacco and both dose & the duration of the exposure of tobacco seems to be equally important in the development of this disease.

∑ The duration of exposure of body tissue to the tobacco carcinogens seems to be more important over the dose in the survival of patients. Therefore long duration of exposure may have some positive impact on the process of development of drug resistance by tumor cells.

From our findings, it may conclude that, tobacco in all forms is a potential risk factor for both HNSCC development and also for the development of drug resistance of malignant cells; common people in majority are unaware about the early symptoms of HNSCC but are aware about the carcinogenic role of tobacco.

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Annexe 48

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ORAL ONCOLOGY

Role of tobacco smoking, chewing and alcohol drinking in the risk of oral cancer in Trivandrum, India: A nested case-control design using incident cancer cases

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KEYWORDS
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Pan chewing;
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Prevention;
Control

Summary Oral cancer is one of the most common cancers in the world, with two-thirds of the cases occurring in developing countries. While cohort and nested case-control study designs offer various methodological strengths, the role of tobacco and alcohol consumption in the etiology of oral cancer has been assessed mainly in case-control studies. The role of tobacco chewing, smoking and alcohol drinking patterns on the risk of cancer of the oral cavity was evaluated using a nested case-control design on data from a randomized control trial conducted between 1996 and 2004 in Trivandrum, India. Data from 282 incident oral cancer cases and 1410 matched controls were analyzed using multivariate conditional logistic regression models. Tobacco chewing was the strongest risk factor associated with oral cancer. The adjusted odds ratios (ORs) for chewers were 3.1 (95% confidence interval (CI) = 2.1–4.6) for men and 11.0 (95%CI = 5.8–20.7) for women. Effects of chewing pan with or without tobacco on oral cancer risk were elevated for both sexes. Bidi smoking increased the risk of oral cancer in men (OR = 1.9, 95%CI = 1.1–3.2). Dose-response relations were observed for the frequency and duration of chewing and alcohol drinking, as well as in duration of bidi smoking. Given the relatively poor survival rates of oral cancer patients, cessation of tobacco and moderation of alcohol use remain the key elements in oral cancer prevention and control.

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Introduction

Oral cancer is one of the most common cancers in the world, with approximately 274 300 new cases and 127 500 deaths occurring each year.[1] Two-thirds of those cases occur in developing countries and the majority are over the age of 40 years at the time of diagnosis. The highest incidence rates have been observed in the Indian sub-continent.[1] Five-year relative survival for oral cancer patients is approximately 30% in selected regions of India.[2] The poor overall survival reflects the advanced stage at diagnosis for the vast majority of these patients.

Findings from case-control studies have suggested chewing tobacco, smoking and alcohol drinking as risk factors for oral cancer and its precancerous lesions.[3–11] However, case-control studies have methodological weaknesses that limit the interpretation of findings such as selection bias and exposure misclassification. The role of tobacco and alcohol consumption in the etiology of oral cancer has rarely been assessed using cohort or nested case-control designs. These two designs avoid or minimize most of the limitations of case-control designs. The aim of our study was to evaluate the role of tobacco chewing, smoking and alcohol drinking patterns on the risk of cancer of the oral cavity, using a nested case-control design on data from a randomized control trial carried out between 1996 and 2004 in Trivandrum, southern India.

Methods

Study design

The study design of the Trivandrum Oral Cancer Screening study has been described elsewhere.[12–14] The objective of this screening trial study was to evaluate the effectiveness of oral visual inspection by trained health workers in reducing mortality from oral cancer. Study participants were apparently healthy individuals aged 35 years and above living in 13 clusters called 'panchayaths' (municipal administrative units in rural areas of India, with total populations of 20 000–50 000) in Trivandrum district. Subjects diagnosed with oral cancer prior to entry into the study were excluded. The study protocol was reviewed and approved by the Regional Cancer Centre (RCC), Trivandrum, India and the International Agency for Research on Cancer (IARC), Lyon, France.

At the beginning of the study, non-medical health workers were trained in enumerating all eligible subjects; in explaining the study and obtaining informed consent; in interviewing subjects to obtain information on socio-demographic, pan chewing (with or without tobacco), smoking (bidi or cigarette) and alcohol drinking habits in terms of duration, frequency and type used using a structured questionnaire. Pan chewing subjects were also asked whether they kept the quid in their mouth overnight and whether they swallowed the chewing fluid. Follow-up information on the oral cancer cases diagnosed and deaths due to oral cancer during the study period was obtained both for the screening and control arm subjects using data from the Trivandrum population based cancer registry, hospital cancer registry of the RCC, medical departments of local hospitals, histopathology registers of pathology laboratories, municipal mortality registration offices and death records from churches and mosques. Information was also obtained from active follow-up by home visits and telephone inquiries.

Definitions of terms used for tobacco smoking, chewing and alcohol drinking

Individuals were categorized into never and ever (subdivided into self reported past and current) smokers, chewers or alcohol drinkers as follows: never smokers were individuals who had never engaged in any type of tobacco smoking; smokers of cigarettes were those who had smoked the classical industrial cigarettes; smokers of bidi were those who smoked a locally made cigarette containing 0.5 g of coarse tobacco dust rolled in a dried temburni leaf. Chewers were classified as follows: never chewers were individuals who had never engaged in any type of chewing; pan chewers were those who chewed a quid consisting of betel leaves (*Piper betel*), areca nut (*Areca catechu*) and aqueous lime (*calcium hydroxide*); chewers of pan with tobacco were those who used the quid with an additional ingredient of locally cured tobacco leaves plus or minus stems. Alcohol categories were as follows: never alcohol drinkers were individuals who had never consumed any type of alcohol; ever alcohol drinkers were those who consumed either 'toddy' (a locally fermented distilled sap from palm trees), another locally brewed liquor called 'arrack' (approximately 40% ethanol) or foreign liquor (locally made liquor similar to that brewed in western countries) or a combination of at least two of the above types.

Case definition and selection of controls

A nested case-control study was conducted within the framework of this study, with all subjects with oral cancer diagnosed during the study period from both arms taken as cases (ICD 10 code: C001- C009, C020, C021, C022, C023, C028, C029, C030, C031, C039, C040, C041, C048, C049, C050, C059, C060, C061, C062, C068, C069). These cancer cases were either histologically confirmed or diagnosed by doctors. Only incident cases were included in the analysis (i.e. oral cancer cases whose date of diagnosis was after the date of first interview). Five controls were randomly selected for each case from all other subjects aged 35 years and above not diagnosed with oral cancer during the study period. Controls for a particular case were selected from the non-cancer individuals enumerated in the screening round in which the case was diagnosed. These controls were matched on sex, age (±1 year), panchayaths and response status (that is if they were interviewed or not at the particular round and at the previous round(s) for the cases diagnosed in the second and third screening rounds). For 12 cases for which enough controls could not be obtained with the above matching criteria, additional controls were selected matching on age (±2, ±3, ±4 or ±5 years) with all other matching variables remaining the same.

Statistical analysis

Socio-demographic characteristics, tobacco chewing and smoking, and alcohol drinking habits of subjects were com-

pared between cases and controls using χ^2 or Fisher's exact test. The effects of pan chewing, tobacco smoking and alcohol drinking on the risk of oral cancer were estimated with odds ratios (ORs) and their 95% confidence interval (CIs), derived from conditional logistic regression analysis. Continuous variables such as years of chewing, smoking or drinking, and frequency of use were categorized by dividing the distributions among exposed controls into approximate tertiles. Trend tests for ordered variables were performed by assigning the score j to the jth exposure level of a categorical variable (where $j = 1,2,\ldots$) and treating it as a continuous predictor in conditional logistic regression. For the calculation of pack-years, the amount of tobacco was estimated as 1 g per cigarette, 0.5 g per bidi and 2 g per other types.[15,16]

Exposure effects of the three habits (smoking, chewing or alcohol) were assessed in the logistic regression model with statistical adjustment for education (categorical; nil, primary, middle school, high school and above), and religion (Hindu, Muslim, Christian). Religion was adjusted for because it is generally known that individuals of different religions in India differ in their habit patterns. Odds ratios corresponding to one habit were obtained after adjusting for the other two habits (categorized into never and ever).

Attributable fractions (AFs) for each habit[17] and a combination of habits[18] were obtained using ORs estimates from the conditional regression models. ORs estimates for a combination of two habits were obtained after adjusting for the third habit.

Because very few women reported smoking and drinking habits, evaluation for these two habits in the logistic regression analysis was restricted to men. All data analysis was performed using STATA Version 9.2.[19]

Results

During the study period, 282 (163 males and 119 females) incident oral cancer cases were identified. The intra-oral site distribution was buccal mucosa (143 [50.7%]); tongue (76 [27.0%]); gum (25 [8.9%]); palate (22 [7.8%]); floor of month (11 [3.4%]); and lip (5 [1.8%]).

The distribution of the socio-demographic characteristics at first interview of cases and controls is shown in Table 1. Around 58% of the cases were males and 80% of the cases were aged between 45–74 years. The level of education was lower among the cases compared to the controls. This difference was also apparent in the distribution of occupation, as a larger proportion of cases were manual laborers compared to controls (84% versus 77%). The proportion of Hindus was 71% among cases and 70% among controls.

Compared to never smokers, a higher proportion of men among both cases (66%) and controls (59%) had ever smoked. Only 27 women (7 cases and 20 controls) reported

Table 1 General characteristics of incident cancer cases and controls at first interview

	Cases	Controls	*p*-Value	Crude OR (95%CI)		*p* for trend
Number	282	1410				
Sex						
Males	163 (57.8%)	815 (57.8%)	1.000			
Females	119 (42.2%)	595 (42.2%)				
Age (in years)						
35–44	32 (11.3%)	167 (11.8%)	0.920			
45–54	71 (25.2%)	387 (27.4%)				
55–64	87 (30.9%)	403 (28.6%)				
65–74	68 (24.1%)	335 (23.8%)				
75+	24 (8.5%)	118 (8.4%)				
Education[a]						
Nil	116 (41.1%)	437 (31.1%)	<0.001	1.0		<0.001
Primary	69 (24.5%)	313 (22.3%)		0.8	(0.5–1.1)	
Middle	47 (16.7%)	258 (18.4%)		0.6	(0.4–0.9)	
High school+	50 (17.7%)	396 (28.2%)		0.4	(0.3–0.6)	
Religion						
Hindu	199 (70.6%)	974 (69.1%)	0.135	1.0		
Muslim	32 (11.3%)	221 (15.7%)		0.7	(0.5–1.0)	
Christian	51 (18.1%)	215 (15.2%)		1.3	(0.9–2.1)	
Occupation[a]						
Manual	237 (84.3%)	1078 (76.7%)	0.022	1.0		
Teacher/office worker	7 (2.5%)	99 (7.0%)		0.3	(0.1–0.7)	
Business	8 (2.8%)	48 (3.4%)		0.7	(0.3–1.5)	
Retired/unemployed	27 (9.6%)	160 (11.4%)		0.7	(0.4–1.2)	
Other	2 (0.7%)	21 (1.5%)		0.4	(0.1–2.1)	

OR: Odds ratio; CI: Confidence interval.
[a] Six control missing information on education.

ever having smoked. In both men and women, a majority of cases (61% and 87%, respectively) were ever chewers, while the minority of controls (31% and 41%, respectively) were ever chewers. Among both cases and controls, the proportions of chewers were higher for women than men. Only one woman from the controls reported alcohol use, while 41% of the male cases and 28% of the male controls were current alcohol drinkers.

Our data showed no effect of having ever smoked on the risk of oral cancer in males after adjusting for chewing and alcohol drinking (Table 2). The adjusted OR for past and current smokers was 1.0 (95%CI = 0.5–2.1) and 1.2 (95%CI:0.8–1.8), respectively. There was a significant increased risk of oral cancer for smokers of bidi alone (OR = 1.9, 95%CI = 1.1–3.2) compared to never smokers. After adjustment, dose-responses relations were not apparent for frequency, duration and pack-years of smoking overall, but when the analysis was restricted to smokers of bidi compared to never smokers, a dose-response was observed in duration of bidi smoking ($p = 0.045$).

Of the 282 incident cases, only 80 had never chewed, while 160 were currently chewing and 42 were past chewers (Table 3). In all categories of chewing, significantly increased estimates of oral cancer risk were obtained. Stratifying by gender (Table 3) showed that estimates of oral cancer risk among females were higher than those observed in males in all categories of chewing. The highest increased risk estimates were observed among past chewers (OR = 5.9, 95%CI = 3.0–11.7 for males and OR = 39.0, 95%CI = 15.0–101.8 for females), chewers of pan with tobacco (OR = 3.4, 95%CI = 2.2–5.2 for males and OR = 11.8, 95%CI = 6.0–23.3 for females), individuals who had chewed more than five times a day and those had those who had chewed for 20 years or more (Table 3). An increased risk of oral cancer was still seen among those chewing pan without tobacco (borderline significance for males with OR = 3.3, 95%CI = 0.9–12.0 and significant for females with OR = 5.4, 95%CI = 2.1–14.1).

Increased risks of oral cancer were observed in the chewers not swallowing the tobacco fluid (Table 3), with risk estimates still even higher among females. Even with the small-observed numbers of chewers swallowing the fluid, high risks were obtained in female chewers. Both keeping and not keeping the quid in the mouth overnight increased the effect of chewing further among both male and female chewers (Table 3).

We observed a statistically non-significant increased risk of oral cancer among the males who had ever consumed

Table 2 Smoking and risk of oral cancer among males using incident cases[a]

	Cases ($n = 163$)	Controls ($n = 815$)	Adjusted[b] OR (95%CI)		p for trend
Never smoked[c]	55	335	1.0		
Smoking					
Ever smoked	108	480	1.2	(0.8–1.8)	
Past	14	72	1.0	(0.5–2.1)	0.412[d]
Currently	94	408	1.2	(0.8–1.8)	
Type of cigarettes[e]					
Cigarettes	19	113	1.0	(0.6–1.9)	
Bidi	40	129	1.9	(1.1–3.2)	
Cigarettes + bidi	44	211	1.0	(0.6–1.7)	
Others	1	3	0.9	(0.1–9.9)	
Frequency (times/day)[e]					
1–10	39	170	1.3	(0.8–2.1)	0.263
11–20	32	167	1.0	(0.6–1.7)	
>20	33	118	1.6	(0.9–2.9)	
Duration (years)[e]					
<20	19	96	1.0	(0.5–2.0)	0.200
20–39	55	232	1.3	(0.8–2.1)	
40+	30	124	1.4	(0.8–2.5)	
Pack-years[e]					
<20	66	290	1.2	(0.8–1.9)	0.461
20–39	28	122	1.4	(0.8–2.4)	
40+	10	39	1.3	(0.6–3.0)	

OR: Odds ratio; CI: Confidence interval; n: Total number.

[a] Smoking among females not considered because only 27 females reported ever smoking.

[b] Adjusted for education, religion, chewing and alcohol drinking habits (both habits categorized into never and ever).

[c] Reference category.

[d] p for trend for never, past and current categories.

[e] Numbers do not add up to total because of missing information.

Table 3 Chewing habits and risk of oral cancer using the incident cases by sex

	Males			Females			Overall		
	Cases (n = 163)	Controls (n = 815)	Adjusted[a] OR (95%CI)	Cases (n = 119)	Controls (n = 595)	Adjusted[a] OR (95%CI)	Cases (n = 282)	Controls (n = 1410)	Adjusted[a] OR (95%CI)
Never chewed[b]	64	561	1.0	16	354	1.0	80	915	1.0
Chewing									
Ever chewed	99	254	3.1 (2.1–4.6)	103	241	11.0 (5.8–20.7)	202	495	5.0 (3.6–6.9)
Past	21	32	5.9 (3.0–11.7)	21	18	39.0 (15.0–101.8)	42	50	11.9 (7.0–20.4)
Currently	78	222	2.7 (1.8–4.2)	82	223	9.5 (5.0–18.0)	160	445	4.3 (3.1–6.1)
p for trend[c]			<0.001			<0.001		<0.001	
Type chewed[d]									
Pan without tobacco	5	16	3.3 (0.9–12.0)	8	28	5.4 (2.1–14.1)	13	44	3.5 (1.7–7.1)
Pan with tobacco	81	197	3.4 (2.2–5.2)	85	186	11.8 (6.0–23.3)	166	383	5.4 (3.8–7.7)
Areca nut/lime + tobacco	5	18	1.5 (0.4–5.0)	4	11	9.1 (1.2–67.0)	9	29	2.4 (0.9–6.4)
Frequency (times/day)[d]									
1–5	28	99	2.0 (1.2–3.5)	74	188	8.5 (4.2–17.6)	62	196	3.7 (2.4–5.5)
6–10	39	77	4.5 (2.7–7.7)	23	33	10.3 (5.1–20.8)	79	168	5.8 (3.9–8.7)
>10	24	54	4.0 (2.0–7.8)	4	3	18.8 (8.5–41.6)	51	90	7.8 (4.8–12.7)
p for trend			<0.001				<0.001		<0.001
Duration (years)[d]									
<20	24	98	1.9 (1.1–3.3)	44	98	8.0 (3.8–16.7)	55	182	3.4 (2.2–5.1)
20–39	44	80	4.9 (2.8–8.5)	39	75	15.4 (7.4–32.1)	87	149	7.5 (5.0–11.4)
40+	25	52	5.4 (2.7–10.8)	15	51	9.9 (4.2–23.3)	49	123	6.5 (3.9–10.8)
p for trend		<0.001			<0.001			<0.001	
Swallow chewing tobacco fluid[d]									
Chewing/no swallowing	88	198	3.4 (2.3–5.2)	94	218	11.0 (5.7–21.2)	182	416	5.2 (3.7–7.3)
Chewing/swallowing	5	32	1.2(0.4–3.6)	2	1	25.3(6.8–94.6)	12	39	4.0(1.8–8.8)
Keep chewing tobacco in mouth overnight[d]									
Chewing/don't keep	82	208	3.2 (2.1–4.8)	97	218	11.5 (6.0–22.4)	179	426	5.1 (3.6–7.1)
Chewing/keep	9	15	5.8 (2.0–16.7)	3	5	10.0 (2.1– 48.0)	12	20	7.4 (3.1–17.5)
Occasionally keep	1	7	0.9 (0.1–8.9)	1	2	12.4 (1.0–155.2)	2	9	3.0 (0.6–15.4)

n: Total number; OR: Odds ratio; CI: Confidence interval.

[a] Adjusted for education, religion, smoking and alcohol drinking habits (both habits categorized into never and ever).

[b] Reference category.

[c] p for trend for never, past and current categories.

[d] Numbers do not add up to total because of missing information.

alcohol after adjusting for the other two habits (OR = 1.4, 95%CI = 0.9–2.0). Both past and current male drinkers had a similar non-significant elevated risk of oral cancer (Table 4). Increased, but statistically non-significant effects were observed in consumers of any type of alcohol. Increased risk of oral cancer was associated with increased amount of alcohol consumed and increased duration of consumption. Dose-responses were observed for both frequency (p for trend = 0.050) and duration (p for trend = 0.010) of drinking.

Table 5 shows the joint effects of smoking, chewing and drinking habits among males only. It was noted that chewing induced a significant increase of risk for oral cancer even for subjects who were never exposed to other habits. The joint effect of the combination of any of the two habits in the development of oral cancer appeared to be multiplicative. However, our study did not have enough statistical power to test for interactions between habits, hence the joint effects results should be interpreted with caution. The estimated attributable fractions in males having ever smoked, ever chewed or ever consumed alcohol were 9.0%, 42.6% and 12.2%, respectively and 81.2% for having ever chewed in females (Table 6). The attributable fraction for all the three habits among males was 62.0% (Table 6).

Discussion

Our study showed chewing of pan as the strongest risk factor for oral cancer with the highest risk estimates observed

Table 4 Alcohol drinking and risk of oral cancer using the incident cases (only males considered)

		Cases (n = 163)	Controls (n = 815)	Adjusted[a] OR (95%CI)		p for trend
Alcohol	Never taken	74	508	1.0		
	Ever taken	89	307	1.4	(0.9–2.1)	
	Past	23	79	1.3	(0.7–2.4)	0.152[b]
	Currently	66	228	1.4	(0.9–2.2)	
Liquor type[c]						
	Toddy	3	6	2.5	(0.6–10.9)	
	Arrack	16	32	2.0	(0.9–4.4)	
	Foreign liquor	9	30	2.1	(0.9–5.2)	
	Combination of at least two	48	154	1.5	(0.9–2.5)	
Frequency (days/week)[c]						
	1–3	17	68	1.5	(0.7–2.9)	0.050
	4–7	56	154	1.7	(1.0–2.7)	
Duration (years)[c]						
	<20	22	76	1.4	(0.7–2.6)	0.010
	20–39	38	123	1.5	(0.9–2.6)	
	40+	14	24	3.3	(1.4–7.7)	

OR: Odds ratio; CI: Confidence interval; n: Total number.
[a] Adjusted for education, religion, smoking and chewing habits (both habits categorized into never and ever).
[b] p for trend for never, past and current categories.
[c] Numbers do not add up to total because of missing information.

Table 5 Combined effects of smoking, chewing and alcohol drinking among males

Ever smoked	Ever chewed	Ever taken alcohol	Cases (n = 163)	Controls (n = 815)	Adjusted[a] OR (95%CI)	
No	No	No	18	226	1.0	
Yes	No	No	17	182	1.3	(0.6–2.6)
No	Yes	No	16	46	4.8	(2.2–10.5)
No	No	Yes	2	21	1.2	(0.3–6.0)
Yes	No	Yes	27	132	2.6	(1.4–5.0)
No	Yes	Yes	19	42	6.4	(2.8–14.6)
Yes	Yes	No	23	54	5.5	(2.6–11.4)
Yes	Yes	Yes	41	112	4.8	(2.5–9.3)

n: Total number; OR: Odds ratio; CI: Confidence interval.
[a] Adjusted for education, religion.

Table 6 The adjusted population attributable fractions for smoking, chewing and alcohol drinking

Factor	Attributable fractions (%)	
	Men	Women
Smoking	9.0	
Chewing	42.6	81.2
Alcohol drinking	12.2	
Smoking and chewing	58.0	
Smoking and alcohol drinking	26.9	
Chewing and alcohol drinking	56.3	
Smoking, chewing and alcohol	62.0	

among female chewers in this population. Bidi smoking among men also appeared as an independent risk factor in this study. Alcohol drinking was suggested as a risk factor among men, with dose-response trends observed for frequency and duration of consumption. Our tobacco chewing, bidi smoking and alcohol drinking results are consistent with those from many epidemiological studies carried out in India.[15,20,21] However, the results we obtained for cigarette smoking and/or alcohol drinking are different from those obtained other regions of the world.[22–26]

In our study, overall tobacco smoking among men did not appear to increase the risk of oral cancer, while bidi smoking emerged as an independent risk factor for it. Bidi smoking is the predominant form of tobacco use practiced in India and is 8–10 times more commonly smoked than cigarettes countrywide.[27] Bidi smoking is also practiced in neighboring countries and there are reports of its availability and popularity also in the USA, especially among young individuals. The result of bidi smoking (OR = 1.6, 95%CI = 1.0–2.7) is in line with results from previous studies,[15,20,21,28–30] in which an elevated risk among bidi smokers (OR range = 1.4–2.9) was shown. In this study, like in some previous studies in India, no association was found between smoking of cigarettes only[15,20,21,28,29] or combined bidi plus cigarette smoking[15,21,28] and the risk of oral cancer. An increased effect on oral cancer risk as a result of cigarette and/or pipe smoking[22,23,30] or combined bidi plus cigarette smoking[20,30] has, however, been previously reported. It is possible that the result in our study is because the most prevalence type smoked is bidi not cigarettes. It might also indicate the qualitative difference between bidi and cigarette smoke due to the additional burning of the dried temburni leaf.

Our study confirmed the previous findings[15,20,21,28–31] that showed chewing of tobacco as the strongest risk factor for oral cancer. Overall, women had substantially higher ORs at any level of chewing than men. This difference remained when further analysis was carried out including only men and women without the other two habits (for ever compared to never chewers, OR for men = 7.2, 95%CI = 1.4–37.3 versus OR for women=11.0, 95%CI = 5.7–21.2, data not shown). The overall finding was similar to what was observed in two previous studies.[15,30] However, in the three studies carried out by Sankaranarayanan et al.[21,28,29] 20 years ago, no difference in ORs between sexes was found. By pan chewing, a greater vulnerability to oral damage in females might be possible, as has been reported already for alcohol drinking.[8,32] It is also noteworthy to mention that women reported chewing on average 3 years more than the men. Women appear to have a higher prevalence of chewing in many rural areas due to the beliefs that tobacco has many magical and medicinal properties; keeping the mouth clean, getting rid of a foul smell, curing toothache, controlling morning sickness, and minimizing labor pains.[33]

Chewing of pan with or without tobacco was shown to be a very important independent risk factor of oral cancer as indicated in previous studies.[15,20,21,28,29,31] Some of the most important carcinogens have been identified in tobacco.[34] One of the major components of betel quid is the areca nut. In vitro evidence suggests that areca-nut-related agents extracted or formed in saliva evoke alterations of normal cell morphology, growth and differentiation, as well as formation of DNA damage.[35] Furthermore, a higher risk was seen in chewers who kept the tobacco chew overnight. These findings might be part of the explanation why tobacco chewing emerged a stronger risk factor than smoking since there is a direct exposure of tobacco chewing with the inside of the mouth for long periods. Tobacco smoking involves the inhaling of smoke, which may have less contact with the mouth and more contact with the throat and lung than tobacco chewing. The high risk observed in past chewers of tobacco compared with that obtained among current chewers is most like artificial and due to 'reverse causality' – that is the tendency for some individuals who have developed symptoms of a life-threatening disease to quit chewing.

Alcohol drinking among men was associated with an increased, but not statistically significant, risk of oral cancer (OR = 1.4, 95%CI = 0.9–2.0). This is consistent with previous evidence from case-control studies that reported ORs ranging from 1.8 to 2.6.[15,20] Our study found a statistically increased risk of oral cancer among heavy drinkers. A similar finding was observed in three previous cohort studies that looked at cancers of the upper aerodigestive tract.[24,25,36] However, the result observed in our study might be an overestimation due to the disproportionate loss of controls, which is due to missing information (8% cases versus 10% controls with missing information on frequency and duration of drinking).

The impact of tobacco chewing was higher in females than in males, as the AFs were 81.2% and 42.6%, respectively. The impact of tobacco smoking was similar to that of alcohol drinking among males (AFs = 9.0% and 12,2%, respectively). Up to 62.0% of the cancers among males can be attributed to the joint exposure to the three habits, due to the relatively high prevalence of males simultaneously exposed to at least two of the habits (67%) and the strong association found with cancer risk in these males. Based on these estimates, it can be concluded that the high prevalence of females exposed to chewing and the high prevalence of males exposed to at least two of the habits largely explain the oral cancer incidence in India.

One of the limitations of our study might have been under-reporting of tobacco smoking and alcohol drinking habits, especially among women, which might have distorted the true associations between these factors and oral cancer risk. However, we think that this is quite unlikely when men

alone were considered given the magnitude and statistical significance of the associations and the internal consistence of the results (i.e. positive associations were found for intensity and duration).

Given the strength of the associations and the refined statistical adjustments performed, residual confounding, although always possible, would need to be exerted by a risk factor very strongly related to both exposures of interest and to cancer status in order to explain the strong reported associations. We adjusted for most of the relevant risk factors reported in the literature and we further performed stratified analyzes excluding cases and/or controls that could potentially distort the results (for tobacco chewing using cases and controls without the other two habits and for tobacco smoking, redefining the ever smokers' category; data not shown), and the findings were minimally altered.

Our study was a nested case-control study that measured data on exposure and confounders before diagnosis of the disease, thus reducing potential recall bias and temporal ambiguity. In addition, cases and controls were drawn from the same cohort, decreasing the likelihood of selection bias into this study. This was different from previous case-control studies carried out in India[15,20,21,28–30] that used hospital-based controls from non-tobacco-related cancer patients, which might not be representative of the general population where the cases come from. Selection bias into the original Trivandrum Oral Cancer Screening study cohort could not have happened since all eligible individuals were enumerated into the study regardless of whether they participated in screening or not. This nested case-control study retained all the advantages of a cohort study. The additional limitations of case-control studies, such as non-participation and differential misclassification (that comes from recall bias), were avoided or minimized.[37]

To our knowledge, in India, no cohort or nested case-control study looking at the risk factors of oral cancer incidence had been published to date. However, one cohort study from India looking at the association of tobacco with oral cancer mortality has been published.[38] Elsewhere in the world, one cohort study looking at oral cancer incidence among women[39] and four cohort studies[24,25,36,40] similar to ours have been published to date, but because of the small numbers of cancer of the oral cavity, all four studies presented analysis combining all cancers of the aerodigestive tract.

Our study shows that the risk of developing oral cancer is modulated by bidi smoking, chewing and alcohol drinking patterns, especially smoking of bidi for a long period, chewing any type of pan and the exposure to chewing at any amount or duration and alcohol consumption at high amounts and duration. Attention should be given to these aspects of smoking, chewing and alcohol habits. In India, chewing pan without tobacco is not considered dangerous and is often practiced by women and children. Our data suggests that it is not only chewing pan with tobacco, but also pan without tobacco, that leads to the development of oral cancer. Our findings give emphasis to public health initiatives targeted to prevent smoking and chewing and/or prevent and reduce alcohol drinking exposures. The public should be aware of the high risk of oral cancer attributed to chewing, bidi smoking as well as a combination of tobacco smoking, chewing and alcohol consumption. Given the relatively poor survival rates of patients diagnosed with oral cancer, moderation or cessation of tobacco and alcohol use remain the key elements in effectively preventing and controlling oral cancer.[41]

Conflict of Interest Statement

None declared.

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RESEARCH COMMUNICATION

Reassessment of Risk Factors for Oral Cancer

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Abstract

A total of 140 cases of histologically confirmed oral cancer were evaluated for their demographic details, dietary habits and addiction to tobacco and alcohol using a pre-designed structured questionnaire at the Mahatma Gandhi Institute of Medical Sciences, Sevagram, in Central India. These cases were matched with three sets of age and sex matched controls. Oral cancer was predominant in the age group of 50-59 years. Individuals on a non-vegetarian diet appeared to be at greater risk of developing oral cancer. Cases were habituated to consuming hot beverages more frequently and milk less frequently than controls. Consumption of ghutka, a granular form of chewable tobacco and areca nut, was significantly associated with oral cancer cases. Cases had been using oral tobacco for longer duration than controls, and were habituated to sleeping with tobacco quid in their mouth. Most cases were also addicted to smoking tobacco and alcohol consumption. Bidi (a crude cigarette) smoking was most commonly associated with oral cancer. On stratified analysis, a combination of regular smoking and oral tobacco use, as well as a combination of regular alcohol intake and oral tobacco use were significantly associated with oral cancer cases. Synergistic effects of all three or even two of the risk factors - oral tobacco use, smoking and alcohol consumption- was more commonly seen in cases when compared to controls.

Key Words: Oral cancer - epidemiology - oral tobacco - smoking - risk factors

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Introduction

Cancers of the oral cavity accounted for over 274,000 cases in 2002 and were the cause of death in over 127,000 cases (Parkin et al, 2002). In India, cancer of the oral cavity is one of the five leading sites of cancer in either sex. It is estimated that 75,000-80,000 new oral cancer cases develop in India annually. Only 15% of patients are diagnosed when the disease is in a localized stage (Gupta and Nandakumar, 1999).

Over 90% of oral cancer among men in India could be attributed to tobacco (WHO, 1997). Tobacco is smoked, chewed, sucked or applied to gums in diverse ways (Bhonsle et al, 1992). Chewing of betel-quid with tobacco is widespread and a dose response relationship has been established as measured with duration of chewing, frequency of chewing and period of time chewed (Sankaranarayanan et al, 1989).Smoking of cigarettes or bidi (a crude cigarette with about 0.2 gm coarsely ground tobacco wrapped in a specific tree leaf) have also been shown to be risk factors (Bhonsle et al, 1992).

However, the emergence of newer, chewable flavoured tobacco preparations, called ghutka, which are packaged attractively and easily available in the market has changed the scenario and their role in oral cancer needs to be assessed. The present study was carried out to ascertain the newer epidemiological risk factors involved in causation of oral cancer and to emphasize the role of each risk factor individually. The study also seeks to determine the statistical association and synergistic effect of various known risk factors like oral tobacco use, smoking and alcohol consumption.

Materials and Methods

This hospital based study was carried out in 2001-2002 in the Department of Pathology, Mahatma Gandhi Institute of Medical Sciences (MGIMS), Sevagram. The study area mainly comprised of Wardha and adjoining districts, in the state of Maharashtra in central India, where majority of the population is rural.

Epidemiological evaluation of 140 adult cases with histologically confirmed oral cancer (ICD- OC02 to ICD-OC 069) was carried out. The anatomical sites included in this study were: buccal mucosa, alveolus and gingival, palate, tongue (excluding base of tongue) and floor of mouth. Patients with carcinoma of the lip, tumours of the salivary gland and sarcomas were excluded from this study.

These 140 cases of oral cancer were age and sex matched with three sets of controls: Control Group 1: 140 'healthy' subjects i.e. persons with no apparent clinical disease. These subjects were recruited from visitors to the hospital, blood donors and people outside the hospital

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area.Control Group 2: 140 subjects who were diagnosed with cancers other than oral cancers. These controls were taken from patients admitted in various wards of the hospital. Control Group 3: 100 subjects who were habituated to tobacco consumption in any form were recruited. These subjects were visitors to the hospital and subjects from outside the hospital.

All the cases and controls were interviewed in depth according to a pre-designed structured questionnaire. Complete demographic details were obtained. The oral cavity was thoroughly examined in good illumination for the carcinoma site in cases and for any other possible pathological lesion in all the three sets of controls. Tobacco chewers in all groups were specifically asked about the site of placing tobacco or betel quid in their mouth.

Detailed information was obtained about dietary habits and tobacco use according to the questionnaire format (Table 1). All data was compiled, quality checks were carried out for consistency of information, and analysis was done using EPI Info 6 software

Table 1. Questionnaire used to obtain Dietary and Addiction Information

A. Dietary Habits:
1. Food:
1. Vegetarian 2. Non-Vegetarian
If non-vegetarian, how frequently do you take non-vegetarian food:
1. Regular 2. Occasional
Staple food: 1. Rice 2. Wheat 3. Coarse Grains
2. Seasonings frequently used:
1. Green chillies 2. Red chillies 3. Pepper
4. Garlic 5. Onion 6. Ginger
7. Cloves 8. Tamarind
3. Nature of cooking utensils.
1. Iron 2. Aluminium 3. Copper
4. Brass 5. Copper-zinc coated 6.Zinc
4. Do you take milk?
1. Daily 2. Occasionally 3. No.
5. Do you take hot beverages? :
1. Tea 2. Coffee

B. Addictions/Habits:
6.Do you use tobacco:
1. Yes 2. Occasionally 3.No
7. Type of tobacco:
1. Mainpuri 2. Pattiwala 3. Ghutka
4. Kharra 5. Pan Parag 6. Zarda
8. Age at which started chewing tobacco:.....years.
9. Quantity daily consumed: ...packets.
10. Do you sleep with tobacco quid in mouth:
1. Yes 2.No.
11.Do you smoke:
1. Yes 2. Occasionally 3. No.
12. Type:
1. Bidi 2. Cigarette 3. Hukkah
4. Cigar 5. Chilum
13. Age at which started smoking:.....years.
14. Do you drink alcohol:
1. Regularly 2. Occasionally 3. No.
15.Do you use:
1. Pan 2. Betel Nut 3. Lime
16.Do you use:
1. Opium 2. Ganja 3. Bhang
4. Charas

Results

Most cases of oral cancer (77.1%) as well as control groups belonged to rural areas. Maximum cases (30.7%) were present in the age group of 50-59 years (Table 2). Males were twice as commonly affected by oral malignancies than females in the ratio of 2.1:1. The most common site of occurrence of oral cancer was the cheek mucosa (34.28%), followed by floor of mouth (17.85%) and gums (11.42%)

On analysis, the consumption of non vegetarian food was found to be significantly higher in oral cancer cases compared to controls (p value = 0.03 between cases and control group 1, p value = 0.00004 between cases & control group 2, p value = 0.0000 between cases and control group 3). It was observed that though regular milk consumption was not frequent in all the categories, oral cancer cases had least frequent (4.3%) habit of milk consumption. This was found to be statistically significant (p value < 0.04).

All subjects of the study group consumed hot beverages regularly, with tea drinkers being the most predominant (99.6%). Oral carcinoma cases were habituated to consuming hot beverages more frequently (more than 4 times a day) than the controls and the difference was found to be highly significant (p value < 0.002)

It was observed that cases and control group 3 (these were selected for their habit of tobacco consumption) regularly used oral tobacco (Table 3). Ghutka chewing was more common (74.3%) in cases than controls. Ghutka is a generic name for a product which contains tobacco, areca nut and several other substances in a powdered or granulated form. It is sold in commercially prepared attractively coloured sachets. It is generally chewed, sucked and spat out or sometimes swallowed.

It was observed that most cases had been using oral

Table 2. Age Distribution of Cases with Oral Cancer

Age group	No. of cases	Percentage
0-29	05	3.6%
30-39	06	4.3%
40-49	28	20.0%
50-59	43	30.7%
60-69	39	27.9%
> 70	19	13.6%
Total	140	100%

Table 3. Correlation of Study Group with Oral Tobacco Use

Category	Regular user	Occasional user	No habit	Total
Cases	136 (97.1%)	4 (2.9%)	0 (0.0%)	140 (100%)
Control 1	18 (12.9%)	26 (18.6%)	96 (68.6%)	140 (100%)
Control 2	0 (0.0%)	24 (17.1%)	116 (82.9%)	140 (100%)
Control 3	95 (95.0%)	5 (5.0%)	0 (0.0%)	100 (100%)
Total	249 (47.9%)	59 (11.3%)	212 (40.8%)	520 (100%)

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Table 4. Criteria for Division into Groups

Group A: Occasional or no use of any one of the risk factors i.e. oral tobacco use, smoking, alcohol intake.

Group B: Regular use of one of the risk factors. It includes the following 3 subgroups:

1) a) Occasional or no oral tobacco use.
   b) Occasional or no habit of smoking.
   c) Regular habit of alcohol intake.
2) a) Occasional or no oral tobacco use.
   b) Regular habit of smoking.
   c) Occasional or no habit of alcohol intake.
3) a) Regular habit of oral tobacco use.
   b) Occasional or no habit of smoking.
   c) Occasional or no habit of alcohol intake.

Group C: Regular use of two out of three risk factors. It includes the following three subgroups:

1) a) Regular habit of oral tobacco use.
   b) Regular habit of smoking.
   c) Occasional or no habit of alcohol intake.
2) a) Regular habit of oral tobacco use.
   b) Occasional or no habit of smoking.
   c) Regular habit of alcohol intake.
3) a) Occasional or no habit of oral tobacco use.
   b) Regular habit of smoking.
   c) Regular of habit of alcohol intake.

Group D: Regular use of all the risk factors i.e. oral tobacco use, habit of smoking and alcohol intake.

tobacco for 20 - 49 years. Controls in group 3 were also regular tobacco users, but had been using oral tobacco for 1-29 years. This difference was found to be highly statistically significant between the cases and control group 2 and was also significant with the other control groups. It was observed that a very high number of cases (42.9%) had the habit of keeping quid in mouth and falling asleep as compared to control groups and this finding was found to be highly statistically significant (Odds Ratio = 18 (CI 5.88 < OR < 61.65)).

Most of the cases (62.9%) were regular smokers, whereas more than 50% of controls in all groups did not smoke. Bidi smoking was most common in cases and control groups 1 and 2, whereas cigarette smoking was commonly seen in control group 3.

It was observed that alcohol intake, whether occasional (22.1%) or regular (30.0%), was more common in cases as compared to all the controls.

Further analysis was done to observe the effects of multiple risk factors. On stratified analysis between the habit of smoking and oral tobacco use, it was observed that regular smoking and regular oral tobacco use was the commonest combination in patients with oral carcinoma; whereas in control group 1, the commonest combination was regular smoking with no oral tobacco use. In control group 2, the commonest combination was occasional smoking without oral tobacco use; whereas in control 3, the commonest combination was non smoker with oral tobacco use. The difference was highly significant in all subgroups between cases and control groups 1 and 2. On comparing cases and control group 3, no statistical significance was found in non smokers, whereas in regular, occasional smokers, the difference was minimally significant with p value = 0.21 and 0.30 respectively.

Stratified analysis between the habit of alcohol intake and oral tobacco use, showed that regular alcohol intake and regular oral tobacco use was the commonest combination in patients with oral cancers. In control groups 1 and 2 the commonest combination was regular alcohol intake and no oral tobacco use. In control group 3 commonest combination was regular tobacco use and no habit of alcohol intake. Highly significant difference was seen between cases and control groups 1 & 2 (p value = 0.0000).

Table 5. Synergistic Effects of Oral Tobacco Use, Smoking and Alcohol Intake

Category	Group A	Group B	Group C	Group D	Total
Cases	01 (0.7%)	51 (36.4%)	49 (35.0%)	39 (27.8%)	140
Control 1	80 (57.1%)	51 (36.4%)	09 (6.4%)	0 (0.0%)	140
Control 2	120 (85.7%)	19 (13.6%)	1 (0.7%)	0 (0.0%)	140
Control 3	2 (1.41%)	75 (53.6%)	22 (15.7%)	01 (0.71%)	100
Total	203 (39.0%)	196 (37.7%)	81 (15.6%)	40 (7.69%)	520

To study the synergistic effect of important risk factors in oral cancer, all the subjects of the study were divided into 4 groups (Table 4). It was observed that regular use of all the three risk factors was significantly seen in patients of oral cancer. Even regular use of two risk factors was associated with increased risk of developing oral cancer (Table 5). The synergistic effect of risk factors was highly significant.

Discussion

Oral cancer is the fifth most common cancer worldwide (Parkin et al, 1993). The age standardized rates per 100,000 population in India were estimated to be 12.8 in men and 7.5 in women. An increase in the incidence of mouth cancer was reported among those aged less than 50 years (Gupta, 1999). This is consistent with the hypothesis of an increase in oral cancer among young people due to increased consumption of the alternative chewing products like ghutka and pan masala. The consumption of these newer forms of flavoured oral tobacco has widespread social sanction, and hence in this study, we have tried to refocus on the role of all tobacco products which are available in market and their association with oral cancer.

Most of the cases and control subjects were from rural areas. The present study has a rural bias since Wardha district has a predominantly rural population. This may also indicate that the urban lifestyle influences may not play a major role in the causation of oral cancers.

The disease was predominantly seen in middle aged persons (50-59 years) and was common in males (67.5%). Other studies from India (Padmavathy and Reddy, 1960; Gandagule and Agarwal, 1969) have reported highest incidence in the fourth and fifth decades. A comparison of age specific incidence rates during 1983-87 and 1995 in Ahmedabad, India, shows that the incidence has

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significantly increased in the younger population (Gupta, 1999). We found a significant number of cases of oral cancer presenting at younger ages. Since oral cancer is a disease related to environmental influences, early exposure to these influences may lead to development of malignancy at an early age. The fact that a large incidence of oral cancer is being observed in younger age groups, it is definitely a matter of great concern as it stems from increasing use of tobacco by adolescents, youth and women.

The high incidence of oral cancers in males in this study and those of other authors (Padmavathy and Reddy, 1960; Gandagule and Agarwal, 1969) can be attributed to high prevalence of tobacco chewing, smoking and alcohol intake in them. However, a large number of women (30.7%) in our study were housewives who were accustomed to oral tobacco use.

The commonest site of occurrence of oral cancer in the present study was cheek mucosa, (34.28%) followed by floor of mouth (17.85%). In countries such as Australia, the USA, Denmark, tongue is the commonest site of oral cancer (Pinholt et al 1997, Hibbert et al 1983, Oliver et al, 1996). However, the buccal mucosa is the commonest site of oral squamous cell carcinoma in countries where the use of oral tobacco is more common such as India, Malaysia and New Guinea (Ng et al 1985, Thomas and MacLennan, 1992). This is probably due to the fact that location of cancer in oral cavity has direct bearing by the type of tobacco use, the majority of the lesions corresponding with the site of maximum exposure to betel quid and also to other related habits.

This study showed a significant association between oral cancer cases and non vegetarian food. In a hospital based case control study done in China, Zheng et al (1993) found that dietary fibre derived from food and vegetables had a strong negative association with risk of oral cancer. They also observed that dietary fibre had protective effect on both leukoplakia and oral submucous fibrosis. Analysis obtained from three simultaneous case control studies conducted in the USA, Italy, China (MacFarlane et al, 1995) has observed that high consumption of vitamin C and dietary fibre leads to lower risk.

While non-vegetarians appeared to be at greater risk than vegetarians in developing oral cancer, other factors like staple food and seasonings were not significantly associated with cancer. Macfarlane et al (1995) did not observe any consistent effect of levels of intake of micronutrients, fats, proteins and carbohydrates on risk of developing oral cancer. However, Nandakumar et al (1990) observed that there was markedly elevated risk of oral cancers in persons who consumed ragi as a staple cereal in their diet. As this particular cereal is not used in diets of the local resident population of Wardha district, we did not observe any association of staple food with oral cancer.

Regular milk consumption was not frequent in all the categories of study group. However, the cases of oral cancer consumed milk least frequently and this was statistically significant. Findings of our study are similar to Levi et al (1998) who showed that milk has some protective effect in development of oral cancer.

Most of the subjects in the present study were habituated to hot beverage consumption, especially to drinking tea (99.6%). We observed that oral carcinoma cases were habituated to consuming hot beverages more frequently than the controls. Chutta is a kind of cigar often smoked in a reverse pattern, where the burning end is placed inside the mouth. This pattern of smoking, seen in certain coastal districts of Andhra Pradesh (India), is commonly associated with squamous cell carcinoma of palate and dorsum of tongue. This is because the mucosa is exposed to pyrolyzed tobacco products and intense heat. It has been shown that heat functions as co-carcinogen and accelerates the neoplastic process (Daftary et al, 1992). Although there are no studies in available literature which have observed the association of hot beverages in oral cancer, a similar mechanism maybe responsible for statistically significant association of oral cancer with frequent intake of hot beverages observed in our study.

We observed highly significant association of oral tobacco use with oral cancer when cases were compared with controls from groups 1 and 2. However, the difference was not of statistically significant when cases were compared with control group 3, as these subjects were selected because of their habit of tobacco consumption. Padmavathy and Reddy (1960) observed that the habit of chewing tobacco alone or with betel was seen more commonly in oral cancer cases when compared to controls. Samuel et al (1969), Gandagule and Agarwal (1969), Nandakumar et al (1990), Ko et al (1995), Wasnik et al (1998), Hayes et al (1999) and Dikshit and Kanhere (2000) demonstrated the association of oral tobacco use with carcinoma of oral cavity. However, the absence of a statistically significant difference between controls and cancer patients having history of regular use of tobacco indicates that there are additional factors which may also be involved in the development of oral cancers.

We observed that consumption of ghutka was significantly high in cases of oral cancer when compared with control groups 2 and 3. The findings of our study are significant as ghutka, which is a preparation without betel quid, is significantly associated with malignancy when compared to other forms which are consumed along with betel quid. This is probably due to the fact that the betel leaf (paan) contains compounds such as eugenol, and hydroxychavicol. These compounds are probably anti-mutagenic or anti-carcinogenic (Amonkar et al, 1986; Padma et al, 1989). The findings of our study do substantiate earlier observations regarding partial protection given by paan which may negate the carcinogenic effects of areca nut, tobacco and lime mixture.

Oral cancer cases were found to have been using oral tobacco for longer duration than the controls in this study. Gandagule and Agarwal (1969) and Nandakumar et al (1990) also observed a statistically significant dose response based on duration of tobacco consumption. Muscat et al (1996) observed that cumulative life time measure of exposure to cigarette is associated with linear increase in the risk of oral cancer. We also found that history of sleeping with tobacco quid in the mouth was a highly significant risk factor in development of oral cancer.

We observed that most cases (62.9%) of oral cancer were regular smokers, whereas more than 50% of controls did not smoke. The difference between cases and controls was highly significant. Padmavathy and Reddy (1960) observed that smoking was seen in highly significant number of cases than controls. Graham et al (1977) observed high risk of developing oral cancer associated with heavy smoking. Nandakumar et al (1990) found only slightly elevated risk of developing oral cancer with smoking. MacFarlane et al (1995) observed high risk for smokers having smoked more than 33 pack years as compared to smokers having smoked less than 33 pack years.

We observed that bidi smoking was more common in patients of oral cancer and control groups 1 and 2; whereas cigarette smoking was more common in control group 3. The statistical difference was found to be highly significant on comparison between control groups 2 and 3. Rao and Desai (1998) observed that bidi smoking was a significant risk factor for cancer from the base of tongue, whereas tobacco chewing was risk factor for cancer from anterior portion of tongue. Bidis are the most popular form of tobacco consumption, accounting for 34% of tobacco produced in India (Lee, 1975). The mainstream smoke of bidi contains much higher concentration of toxic agents as compared to cigarettes. Thus smoking bidi is even more hazardous than cigarette smoking in the development of tongue and oral cancer (Jayant and Pakhale, 1985). The findings of our study also corroborate the increased risk associated with bidi smoking when compared with cigarette smoking. Control group 3 subjects who were regular oral tobacco users used cigarettes more frequently than bidis.

Alcohol intake, whether occasional (22.1%) or regular (30%), was more common in cases when compared to controls in this study and this difference was found to be highly significant. Padmavathy and Reddy (1960) and Graham et al (1977) observed that alcohol has a role in development of oral cancer.

We found that the combination of regular smoking and regular oral tobacco use was a significant risk factor on comparing cases with control groups 1 and 2. However, there was no statistically significant association on comparison with control group 3. No studies in available literature have performed stratified analysis in relation to smoking and use of oral tobacco in comparison with the controls who are regular tobacco users. Our findings indicate that though this association is significant in comparison with groups who may be regular oral tobacco users or non users (control groups 1 & 2), it is not a statistically significant association in comparison with the group having regular or occasional oral tobacco users (control group 3). Therefore the habit of smoking may not have significant association with oral cancer.

Another factor which may be more important than this combination of habits is our observation that controls had been using oral tobacco for a lesser duration than cases. So, the duration of oral tobacco use is perhaps more important than the association of oral tobacco use with smoking.

On stratified analysis, we found that regular alcohol intake with regular oral tobacco use caused significant risk to cases compared to all the control groups. According to Sankaranarayanan et al (1990), although alcohol consumption alone is not independently associated with oral cancer, it did seem to enhance the risk of developing disease when used in combination with tobacco chewing and cigarettes smoking. The findings of our study have also shown that in patients of oral cancer, all non-alcoholics were regular oral tobacco users. Similarly it was also observed that none of the cases were non-tobacco users but regular alcoholics. This indicates that alcoholism itself may not be an independent risk factor in the development of oral cancer, but may enhance the risk of developing disease.

To study the synergistic effect of important risk factors i.e. oral tobacco use, smoking and alcohol consumption in development of oral cancer, we divided the study subjects into four subgroups based on regular, occasional or no use of the risk factors. It was observed that regular use of all the three risk factors was significantly seen in oral cancer cases and even regular use of two risk factors was common in cases as compared to controls. Similar observations were made by Sankarnarayanan et al (1990), Ko et al (1995) and Hayes et al (1999). Our findings indicate that the combination and regular use of important risk factors shows a significant synergistic effect on development of oral malignancy.

In last few decades, small, attractively packed commercial preparations of tobacco and non-tobacco betel quid substitutes have become widely available. These are being aggressively marketed by the concerned companies, often claiming to be safer products. These are being consumed widely by people of all ages and sexes as well from all social strata of society. Hence the consequences of these habits are expected to be significant and intense in the future. Although recently some attempts have been made to curb the sale of these products, urgent action is needed to permanently ban these products

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Annexure 50

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REVIEW

Alert for an epidemic of oral cancer due to use of the betel quid substitutes *gutkha* and *pan masala*: a review of agents and causative mechanisms

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In south-east Asia, Taiwan and Papua New Guinea, smoking, alcohol consumption and chewing of betel quid with or without tobacco or areca nut with or without tobacco are the predominant causes of oral cancer. In most areas, betel quid consists of a mixture of areca nut, slaked lime, catechu and several condiments according to taste, wrapped in a betel leaf. Almost all habitual chewers use tobacco with or without the betel quid. In the last few decades, small, attractive and inexpensive sachets of betel quid substitutes have become widely available. Aggressively advertised and marketed, often claimed to be safer products, they are consumed by the very young and old alike, particularly in India, but also among migrant populations from these areas world wide. The product is basically a flavoured and sweetened dry mixture of areca nut, catechu and slaked lime with tobacco (*gutkha*) or without tobacco (*pan masala*). These products have been strongly implicated in the recent increase in the incidence of oral submucous fibrosis, especially in the very young, even after a short period of use. This precancerous lesion, which has a high rate of malignant transformation, is extremely debilitating and has no known cure. The use of tobacco with lime, betel quid with tobacco, betel quid without tobacco and areca nut have been classified as carcinogenic to humans. As *gutkha* and *pan masala* are mixtures of several of these ingredients, their carcinogenic affect can be surmised. We review evidence that strongly supports causative mechanisms for genotoxicity and carcinogenicity of these substitute products. Although some recent curbs have been put on the manufacture and sale of these products, urgent action is needed to permanently ban *gutkha* and *pan masala*, together with the other established oral cancer-causing tobacco products. Further, education to reduce or eliminate home-made preparations needs to be accelerated.

Introduction

It has been estimated that, world wide, ~600 000 000 people chew areca nut (Nelson and Heischober, 1999). A causal association between tobacco and betel quid (BQ) chewing habits and oral mucosal diseases such as leukoplakia, oral submucous fibrosis and oral cancer has been established and heavy users have a significantly increased mortality rate. Oral cancer is the fifth most common cancer world wide (Parkin *et al.*, 1993). A 2- to 3-fold increase in mortality has been recorded in eastern and central European countries in recent decades (Coleman *et al.*, 1993) and upward trends in several other areas of Europe have been reported (Franceschi *et al.*, 2000). Tobacco use has been estimated to account for 30% of the worldwide cancer burden. Tobacco smoking and heavy alcohol consumption are the main risk factors for oral cancer in the developed countries (La Vecchia *et al.*, 1997), where over 80% of cases are attributable to these causes (Negri *et al.*, 1993; Boyle *et al.*, 1995).

Of the 390 000 oral and oro-pharyngeal cancers estimated to occur annually world wide, 58% occur in south and south-east Asia. In India there are 75 000–80 000 new cases of oral cancer each year and the incidence rates of cancers of the oral cavity in both males and females in all urban cancer registries are among the highest in the world. Age-standardized incidence rates per 100 000 population in India were estimated to be 12.8 in men and 7.5 in women (Ferlay *et al.*, 2001). Time trend analysis of cancers at all sites for the period 1990–1996 showed a decrease in cancers of the oral cavity in Indian population-based registries (ICMR, 2001), but an increase in the incidence of mouth cancer was reported among those aged <50 yr between 1983–1987 and 1995 (Gupta, 1999b), consistent with the hypothesis of an increase in oral cancer among the young due to increased consumption of the alternative chewing products *gutkha* and *pan masala*. In this review we focus on these commercially available products and summarize what is known about their cancer-causing components and the mechanisms involved.

Description of betel quid

Chewing of BQ and areca nut is an ancient custom in several parts of south-east Asia, the south Pacific islands and Taiwan. This practice dates back several thousand years and is deeply entrenched in the culture of the population. A ceremonial gift of dried tobacco leaves given to Columbus by Native Americans in 1492 led to the introduction of tobacco into the rest of the world. It arrived in India in the 16th century; a sample was presented to the Emperor Akbar, who patronised smoking, rapidly spreading the habit in the sub-continent. An attempt to ban it in 1619 had little effect, as the revenues from tobacco were already considerable. BQ chewing was already a socially well accepted practice and the introduction of tobacco reinforced this practice. The BQ is a mixture of areca nut (*Areca catechu*), catechu (*Acacia catechu*) and slaked lime (calcium oxide and calcium hydroxide) wrapped in a betel leaf (*Piper betle*) (Figure 1A). Condiments, sweetening agents and spices may be added according to individual preferences. In India, most habitual chewers of BQ add tobacco. In some countries, such as Papua New Guinea and China, tobacco is not added. BQ chewing has been related mainly to oral, pharyngeal and oesophageal cancer (IARC, 1985, 2004).

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Commercial betel quid substitutes: *pan masala* and *gutkha* (Figure 1B)

Betel leaf is perishable and preparation of BQ is somewhat complex or requires visits to shops selling *pan*/BQ. With the emergence of commercial *pan masala* and *gutkha* about three decades ago, not only did the Indian market witness massive growth in the sales of smokeless tobacco and areca nut products, but also a huge worldwide export market developed. The packaging revolution has made these products portable, cheap and convenient, with the added advantage of a long shelf-life. Tobacco products which were usually consumed by a small section of the population are today part of the modern urban and rural lifestyle.

The web site (www.newindia.com/kothari/) of the first major manufacturer of *pan masala* and *gutkha* presents their strategy as '... to prepare convenient anytime, anywhere substitute for pan ... give some respectability to a habit that was considered low in image by the genteel'. The product was put on the market in 1985 as 4 g sachets. Today sachets and bulk packages are produced and sold in India and exported to markets in the USA, Europe, the Middle East, Australia and many other countries.

Pan masala is basically a preparation of areca nut, catechu, cardamon, lime and a number of natural and artificial perfuming and flavouring materials. *Gutkha* is a variant of *pan masala*, in which in addition to these ingredients flavoured chewing tobacco is added. Both products are often sweetened to enhance the taste.

Promoted by a slick, high profile advertising campaign and aggressive marketing, *pan masala* and *gutkha* have become very popular with all sections of Indian society, including school children. For most children, teenagers and women, cigarette smoking still remains taboo in India. These alternative tobacco products are often advertised as being safer than conventional cigarettes, leading to a much higher frequency of use, so that these younger chewers constitute an alarming *avant garde* for a new epidemic of oral cancer. Further, these habits and preparations have spread to Europe and the USA, wherever there are Asian migrant communities.

Although the actual prevalence of this habit is unknown, its popularity can be gauged by commercial estimates valuing the Indian market for *pan masala* and *gutkha* at several hundred million US dollars (Gupta, 1999a). These products are typically consumed throughout the day. A number of small surveys conducted in schools and colleges in several states of India have shown that 13–50% of students chew *pan masala* and *gutkha* on a regular basis (Gupta and Ray, 2003). A large proportion of migrant ethnic groups resident in the UK practice various chewing habits (Warnakulasuriya *et al.*, 2002); population studies conducted among Asian ethnic groups in the UK suggest that chewing habits are prevalent in 14–15% of 11–15 yr old children, with *pan masala* having the highest average frequency of use (Farrand *et al.*, 2001). Areca nut chewing is an addictive habit (Chu, 2001) and evidence from the UK shows that the use of *pan masala* and *gutkha* is also addictive (Winstock, 2002).

Oral cancer and precancerous conditions

Oral cancer, a malignancy of the lip, mouth or tongue, is predominantly a squamous cell carcinoma. The prognosis is poor and severe functional and cosmetic defects accompany its

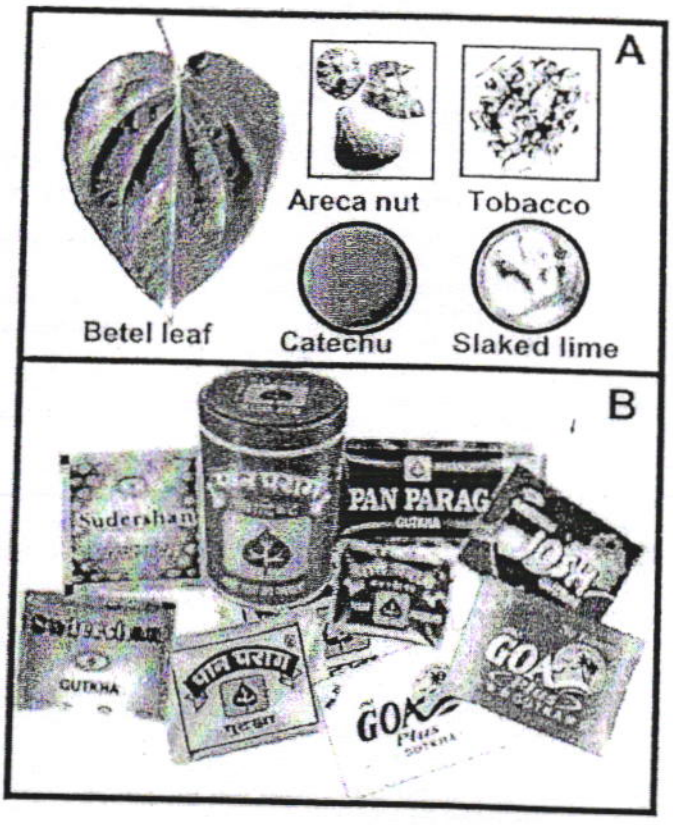

Fig. 1. Traditional betel quid chewing ingredients (**A**) and the commercial examples of betel quid chewing substitutes, *pan masala* and *gutkha* (**B**).

treatment. As an early sign of damage to the oral mucosa, chewers of BQ with or without tobacco often develop clinically visible whitish (leukoplakia) or reddish (erythroplakia) lesions and/or stiffening of the oral mucosa and oral submucous fibrosis (OSF). All these well-established precancerous lesions are easily diagnosed and present an important indicator of oral cancer risk. Some 2–12% of these lesions have been reported to turn malignant over several years. The malignant transformation of non-homogeneous lesions involving erythroplakia and nodular leukoplakia is particularly high, reportedly ranging from 15 to 40% depending upon the time period (Sankaranarayanan *et al.*, 1997). Almost every BQ/tobacco chewing-related oral malignancy is preceded by a clinically distinct premalignant stage at the site of cancer development (WHO, 1984; Gupta *et al.*, 1989; Murti *et al.*, 1995).

OSF is predominantly caused by the use of areca nut (Murti *et al.*, 1995). Besides being regarded as a precancerous condition, it is a seriously debilitating and progressive disease. Marked by stiffening of the oral mucosa and development of fibrous bands, loss of elasticity of the mucosa results in a progressive restriction of mouth opening. Affected users experience a burning sensation of the oral mucosa, occasional mucosal ulceration, a peculiar marble-like blanching of the mucosa and palpable fibrous bands of the buccal mucosa, soft palate and lips. OSF does not regress and there is no known cure.

In recent years, studies in India, China, south-east Asia and South Africa and on Asian migrants in the UK have shown a clear link between areca nut chewing and OSF. Several case–control studies in India have shown a high risk for OSF among

areca nut chewers; over 70% of the cases were under 35 yr old (Gupta and Ray, 2003). Several studies have reported relative risks of from 29 to 154 for developing OSF due to chewing of areca nut (Sinor *et al.*, 1990; Maher *et al.*, 1994; Gupta *et al.*, 1998; Hazare *et al.*, 1998). A dose–response relationship has been suggested by an increasing relative risk with increasing frequency of areca nut chewing (Sinor *et al.*, 1990; Hazare *et al.*, 1998; Lee *et al.*, 2003).

Oral cancer was hitherto considered a disease of the elderly, appearing after several decades of the causal lifestyle habits. Although no epidemiological studies on *pan masala* or *gutkha* have yet been reported, several surveys showing an increase in the incidence of OSF attributed to their use, especially among youngsters, portend an epidemic of oral cancer. As with tobacco and areca nut, the addictive nature of *pan masala* and *gutkha* results in a high frequency of chewing. A relative risk of 489 has been reported for OSF in *pan masala* chewers compared with non-users (Hazare *et al.*, 1998). In a survey of 236 consecutive cases of OSF and 221 matched control subjects, chewing of areca nut, BQ or *pan masala* was directly related to OSF. *Pan masala* was chewed by a comparatively younger age group and was associated with OSF changes earlier than areca nut or BQ chewing. Moreover, the frequency of chewing rather than the total duration of the habit was directly correlated with OSF (Shah and Sharma, 1998). In a clinico-pathological study in current chewers, chewers of *pan masala* or *gutkha* presented with OSF after a significantly shorter duration of the habit (2.7 ± 0.6 yr) than BQ chewers (8.6 ± 2.3 yr) (Babu *et al.*, 1996a). Symptoms of cancer appeared at an early age in youngsters (Babu *et al.*, 1996b).

Oesophageal subepithelial fibrosis, an extension of oral submucosal fibrosis, was seen more frequently in patients who had consumed *pan masala*, *gutka*, areca nut, tobacco or a combination of some or all of these, with or without betel leaf, for ≥5 yr than in those consuming these products for a shorter period (91 versus 46%, $P < 0.001$), suggesting that submucosal fibrosis is not a disease confined to the oral cavity, but that the oesophagus may also be involved in about two-thirds of patients. (Misra *et al.*, 1998). *Mawa*, a preparation similar to *gutkha*, containing tobacco, lime and areca nut slivers, has also been linked to OSF, oral cancer and oesophageal cancer. A study carried out in the Bhavnagar district in India, where chewing of *mawa* has mushroomed in recent years, showed a corresponding increase in OSF (Gupta *et al.*, 1998).

A malignant transformation rate of 7.6% in an Indian cohort over a period of 17 yr has been reported (Murti *et al.*, 1985). Based on three new oral cancer cases arising among 25 OSF cases and four new cases among 10 145 persons in an 8 yr follow-up, the relative risk of malignant transformation of OSF was reported to be 397 compared with lesion-free controls with tobacco habits (Gupta *et al.*, 1989). In Pakistan, the malignant transformation rate was reported to be 19 times higher (95% CI 4.2–87.7) in patients with OSF than in subjects without any lesion (Merchant *et al.*, 2000).

Carcinogens in *pan masala* and *gutkha* ingredients

The main carcinogens in *pan masala* and *gutkha* are derived from their ingredients areca nut, lime, catechu and tobacco. Although carcinogens present in *pan masala* or *gutkha* have not been systemically analysed, studies of the ingredients and their mixtures provide indications of the carcinogenic potential of these commercial products (Table I).

Table I. Major carcinogenic and genotoxic agents in *pan masala* and *gutkha*

Products	Ingredients	Genotoxic agents/carcinogens[a]
Gutkha	Tobacco	NNN, NNK
	Areca nut	arecoline, MNPN
	Areca nut + lime	ROS
	Catechu + lime	ROS
Pan masala	Areca nut	Arecoline, MNPN
	Areca nut + lime	ROS
	Catechu + lime	ROS

NNN, *N*′-nitrosonornicotine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; MNPN, 3-(methylnitrosamino)propionitrile; ROS, reactive oxygen species, $O^{\cdot}$, H_2O_2, $OH^{\cdot}$.
[a]For structures and pathways see Figures 2 and 3.

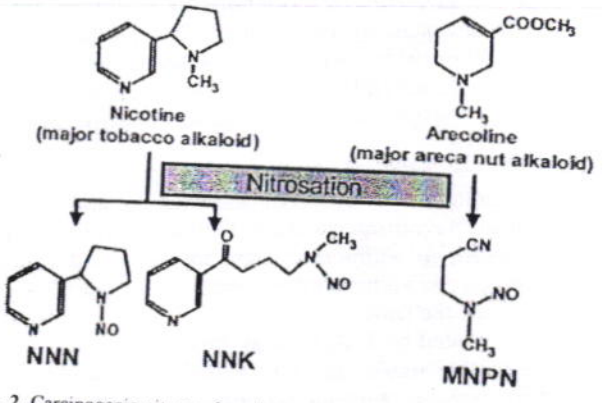

Fig. 2. Carcinogenic nitrosamines that could be derived from major ingredients of *pan masala* (areca nut) and *gutkha* (areca nut and tobacco). NNN, *N*′-nitrosonornicotine, which could also be formed from the minor tobacco alkaloid nornicotine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; MNPN, 3-(methylnitrosamino)proprionitrile.

Several carcinogens are derived from tobacco but also from areca nut (Hoffmann *et al.*, 1994). Chewing of tobacco with BQ results in high exposure to carcinogenic tobacco-specific nitrosamines (TSNAs), to ~1000 µg/day (Nair *et al.*, 1999), compared with ~20 µg/day in smokers (Hoffmann and Hecht, 1985), as well as leading to exposure to nitrosamines derived from areca nut alkaloids (Figure 2). The carcinogenic TSNAs *N*′-nitrosonornicotine (NNN), 4-(*N*-methyl-*N*-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and *N*-nitrosoanabasine (NAB), as well as the volatile nitrosamines *N*-nitrosodimethylamine and *N*-nitrosodiethylamine, have been detected in the saliva of chewers of BQ with tobacco (Wenke *et al.*, 1984; Nair *et al.*, 1985, 1987a; Bhide *et al.*, 1986).

TSNAs undergo metabolic activation by cytochrome P450s and other enzymes. NNK, a major carcinogenic TSNA, is activated by either methylene hydroxylation to generate an intermediate that decomposes to a DNA-methylating agent, resulting in the formation of 7-methylguanine, O^6-methylguanine (O^6-MeG) and O^4-methylthymidine in DNA or via methyl hydroxylation to form bulky pyridyloxobutyl DNA adducts. NNK is also converted metabolically to 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, which can also be activated by α-hydroxylation to yield methyl and pyridylhydroxybutyl adducts in DNA (Hecht, 2003). 2′-Hydroxylation of NNN, another important TSNA, can give rise to the same

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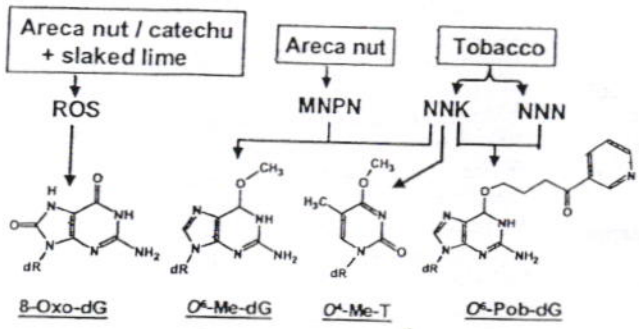

Fig. 3. Miscoding DNA adducts derived from genotoxic agents that are present or formed from major ingredients of *pan masala* and *gutkha*. 8-oxo-dG, 8-oxodeoxyguanosine; O^6-Me-dG, O^6-methyldeoxyguanosine, O^4-Me-T, O^4-methylthymidine; O^6-Pob-dG, O^6-[4-oxo-4-(3-pyridyl)butyl]-deoxyguanosine.

intermediate as is formed by methyl hydroxylation of NNK, resulting in pyridyloxobutylation of DNA (Figure 3).

The areca nut-specific nitrosamines (ASNAs) *N*-nitrosoguvacoline (NG) (Wenke *et al.*, 1984; Nair *et al.*, 1985, 1987a; Stich *et al.*, 1986) and the carcinogenic 3-(methyl-*N*-nitrosamino)propionitrile (MNPN) (Prokopczyk *et al.*, 1987) were also detected in the saliva of chewers of BQ without tobacco (Table II). ASNAs were not detected in BQ containing areca nut. Nitrosation of BQ with nitrate and thiocyanate *in vitro* at neutral pH resulted in the formation of NG (Nair *et al.*, 1985). Nitrosation of arecoline at neutral pH yielded approximately four times more NG than at acidic or alkaline pH (Wang and Peng, 1996). Hence the reported presence of ASNAs in the saliva of BQ chewers could arise from their formation during chewing of BQ. The highest levels of an ASNA (NG) were found in the sediment of saliva collected from Taiwanese BQ chewers (Stich *et al.*, 1986), whereas the highest levels of TSNAs have been found in saliva samples collected in India (Bhide *et al.*, 1986).

Formation of *N*-nitroso compounds in the oral cavity

Volatile nitrosamines and tobacco-specific nitrosamines in the saliva of chewers are derived from leached-out preformed nitrosamines present in tobacco, but can also be formed endogenously from abundant precursors during chewing. Secondary and tertiary amines present in areca nut and tobacco can be nitrosated during BQ chewing when they react with available nitrite in the presence of catalysts such as thiocyanate (Nair *et al.*, 1985, 1987a). Using a modified *N*-nitrosoproline (NPRO) test (Ohshima and Bartsch, 1981), it was clearly shown that NPRO, a marker of endogenous nitrosation, is formed during chewing of BQ with or without tobacco (Nair *et al.*, 1987a). Further, nitrosation was significantly more extensive in subjects with poor oral hygiene, as determined by dental plaque, compared with those with good oral hygiene (Nair *et al.*, 1996). The enhanced nitrosation in subjects with poor oral hygiene may be due to greater conversion of nitrate to nitrite and bacterial enzyme-mediated formation of nitrosamines or both (Calmels *et al.*, 1996; Ziebarth *et al.*, 1997). Elevated levels of nitrite and nitrate reductase activity have been reported in the saliva of Indian chewers of BQ with tobacco (Murdia *et al.*, 1982). There is increased nitric oxide and nitrite formation in subjects during deposition of dental plaque (Carossa *et al.*, 2001). Thus, in view of the availability

Table II. Carcinogenic tobacco- and areca nut-specific nitrosamines detected in saliva of chewers of betel quid with and without tobacco

Carcinogenic agent	BQT (range, ng/ml)	BQ (range, ng/ml)	Reference
Tobacco-specific nitrosamines			
NNN	1.2–3.8	NR	Wenke *et al.* (1984)
	1.6–14.7	NR	Nair *et al.* (1985)
	3.0–85.7	NR	Bhide *et al.* (1986)
	4.9–48.6	NR	Nair *et al.* (1987a)
NNK	1–2.3	NR	Wenke *et al.* (1984)
	0–2.3	NR	Nair *et al.* (1985)
	0–14.3	NR	Bhide *et al.* (1986)
	0–9.4	NR	Nair *et al.* (1987a)
Areca nut-specific nitrosamines			
MNPN	NR	0.5–11.4	Prokopczyk *et al.* (1987

NNN, *N*'-nitrosonornicotine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; MNPN, 3-(methylnitrosamino)propionitrile; BQ, betel quid; BQT, betel quid with tobacco; NR, not reported.

of nitrosatable amines from areca nut and tobacco, increased formation of nitrosamines might be expected in the oral cavity of BQ, tobacco, *pan masala* and *gutkha* chewers with poor oral hygiene.

Endogenous nitrosation in BQ chewers

Many chewers swallow the quid that contains precursors of nitrosamines. The acidic pH of the stomach would favour the nitrosation of secondary and tertiary amines in the quid. Urinary levels of NPRO were 4- to 6.5-fold higher in chewers of BQ with or without tobacco following ingestion of L-proline compared with non-chewers (Nair *et al.*, 1986; Chakradeo *et al.*, 1994). Detection of NG and its metabolite *N*-nitrosonipecotic acid in the urine of Syrian hamsters fed areca nut and nitrite (Ernst *et al.*, 1987; Ohshima *et al.*, 1989) also supports the notion that exposure to carcinogenic nitrosamines formed by endogenous nitrosation is likely to be higher in BQ chewers who swallow the quid.

Reactive oxygen species

Reactive oxygen species (ROS), implicated in multistage carcinogenesis, are generated in substantial amounts in the oral cavity during chewing (Nair *et al.*, 1992, 1995). Nair *et al.* (1987b) first demonstrated that aqueous extracts of areca nut and catechu were capable of generating superoxide anion and hydrogen peroxide at pH > 9.5. The areca nut-induced production of ROS was enhanced by Fe^{2+}, Fe^{3+} and Cu^{2+}, but inhibited by Mn^{2+}. These results show the importance of pH for the formation of ROS that is likely to occur due to autoxidation, redox cycling via quinone/semiquinone radical- and iron-catalysed Haber–Weiss and Fenton reactions (Figure 4).

When calf thymus DNA was incubated with an aqueous extract of areca nut under alkaline conditions, 8-oxodeoxyguanosine (8-oxo-dG) was formed, and more so in the presence of Fe^{2+} and Fe^{3+}. The presence of $Ca(OH)_2$ in slaked lime leads to alkaline conditions in the oral cavity, favouring ROS generation. Slaked lime used by chewers was collected in a region of Papua New Guinea where the incidence of oral cancer is high (Nair *et al.*, 1990). In 25 lime samples, the free calcium hydroxide content and pH were highly correlated with the generation of ROS from areca nut extract *in vitro* and DNA damage *in vitro* measured as 8-oxo-dG. Fe^{2+} and Mg^{2+} levels in

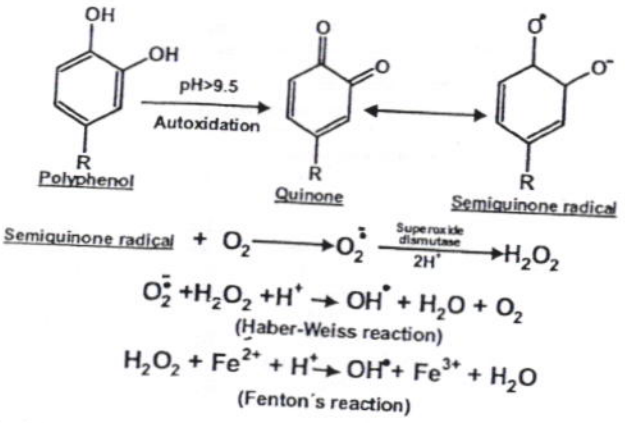

Fig. 4. Pathways of formation of superoxide anion, hydroxy radical and hydrogen peroxide from areca nut and catechu in the presence of slaked lime, which are the major ingredients of *pan masala* and *gutkha*

the lime samples were too low to modify the formation of ROS, but hydrogen peroxide formation was almost entirely inhibited by addition of Mg^{2+} to the reaction mixture. These results suggest that the calcium hydroxide content of lime in the presence of areca nut is a major factor responsible for the formation of ROS which cause oxidative damage in the DNA of buccal mucosa cells of BQ chewers. Decreasing the slaked lime content of BQ should therefore reduce its toxicity. Extracts of tender areca nut caused more 8-oxo-dG formation in DNA than ripe areca nut extract when incubated with Fe^{2+} under alkaline conditions (Liu *et al.*, 1996).

Hydroxyl radicals ($OH^{\cdot}$) were shown to be generated *in vitro* using L-phenylalanine as substrate together with some ingredients of BQ and *pan masala*. Therefore, the formation of *o*- and *m*-tyrosine from L-phenylalanine can be measured as a marker of $OH^{\cdot}$ generation. Both *o*- and *m*-tyrosine were formed *in vitro* in the presence of extracts of areca nut and/or catechu, transition metal ions (Cu^{2+} and Fe^{2+}) and alkaline pH (slaked lime or sodium carbonate). Omission of any of these ingredients from the reaction mixture significantly reduced the yield of tyrosines. Scavengers of $OH^{\cdot}$ such as ethanol, D-mannitol and dimethylsulphoxide inhibited the hydroxylation of phenylalanine in a dose-dependent manner (Nair *et al.*, 1995).

Direct evidence for the generation of ROS in the oral cavity during BQ chewing was obtained by measuring *o*- and *m*-tyrosine formation from L-phenylalanine in human saliva by HPLC with fluorescence detection (Nair *et al.*, 1995). The tyrosine levels were significantly higher than in saliva of subjects who kept phenylalanine in the oral cavity without BQ. These studies demonstrated that $OH^{\cdot}$ are formed in the oral cavity of BQ chewers and probably implicated in the genetic damage observed in oral mucosal cells of chewers. By the same method, OH formation was monitored in Taiwanese subjects chewing tender areca nut and lime with either *Piper betle* inflorescence or betel leaf (Chen *et al.*, 2002). Levels of *o*- and *m*-tyrosine were increased but were lower than those detected in Indian chewers, perhaps due to differences in the BQ ingredients.

Iron and copper are the transition metal ions that are involved in the catalytic process of ROS generation. Copper content in various BQ ingredients has been reported to range from 3 to 108 μg/g in areca nut and from 8 to 53 μg/g in *pan masala* (Trivedy *et al.*, 1997; Ridge *et al.*, 2001; Zaidi *et al.*, 2002). The iron levels measured were 75 ng/g in areca nut, 132 ng/g in betel leaf, 5.2 ng/g in catechu and 22–256 ng/g in slaked lime samples (Nair *et al.*, 1990; Zaidi *et al.*, 2002). *In vitro*, not only was areca nut-induced ROS production enhanced by Fe^{2+}, Fe^{3+} and Cu^{2} (Nair *et al.*, 1987b), but formation of 8-oxo-dG in calf thymus DNA was also increased in the presence of Fe^{2+} and Fe^{3+} (Nair *et al.*, 1990, 1995). Significant superoxide anion production, assayed by cytochrome c reduction and lipid peroxidation by formation of thiobarbituric acid-reactive substances, was demonstrated in normal human oral keratinocytes following exposure to commercially available *gutkha* and *pan masala* extracts (Bagchi *et al.*, 2002). Thus, some of the cytotoxic effects of these chewing products appear to be mediated through production of ROS.

Genotoxicity and mutagenicity of *pan masala* and *gutkha* ingredients

The mutagenic, clastogenic and carcinogenic properties of areca nut, the major constituent of *pan masala*, have been extensively studied in a variety of experimental systems (Jeng *et al.*, 2001). Areca nut contains 5–40% polyphenols and several alkaloids including arecoline, arecaidine, guvacine and guvacoline. Arecoline, the most important areca nut alkaloid, is present at 1% of the dry weight and has been shown to be genotoxic (Dave *et al.*, 1992a). Areca nut extract was mutagenic to *Salmonella typhimurium* strains in the presence and absence of an exogenous metabolic activation system (Shirname *et al.*, 1983, 1984). Exposure to aqueous areca nut extract induced mitotic gene conversion at pH > 10 (Rosin *et al.*, 2002). Recently, areca nut chewing has been classified as carcinogenic to humans (IARC, 2004).

Pan masala and *gutkha* have been reported to be genotoxic and mutagenic in several short-term assays. Aqueous extracts of various brands of *pan masala* were mutagenic in *S.typhimurium* strains (Polasa *et al.*, 1993). Aqueous extracts of both *pan masala* and *gutkha* induced chromosomal aberrations, sister chromatid exchange and micronucleated cells in Chinese hamster ovary cells in the presence or absence of an exogenous metabolic system, although metabolic activation markedly inhibited the chromosome damaging effect, implicating the presence of direct-acting mutagens (Dave *et al.*, 1991). A significant dose-dependent increase in sister chromatid exchange was observed in bone marrow cells of Swiss albino mice injected i.p. with *pan masala* suspensions. Higher doses caused significant delay in cell cycle progression of bone marrow cells (Mukherjee and Giri, 1991).

Oral feeding of *pan masala* caused significantly elevated frequencies of sperm head abnormalities and chromosomal aberrations in male mice, indicating its clastogenic potency (Mukherjee *et al.*, 1991). Chronic feeding of *pan masala* impaired liver function in rats, as indicated by changes in marker enzyme activities and decreased organ weights of the gonads and brain (Sarma *et al.*, 1992). *Pan masala* reduced testis weight in mice and enhanced the frequency of morphological abnormalities in mouse sperm (Kumar *et al.*, 2003). *Pan masala* applied to the palate and cheek mucosa of albino Wistar rats resulted in keratosis, thickening of the submucosal collagen, an inflammatory reaction and changes in tissue vasculature, similar to those observed in oral submucous fibrosis and leukoplakia in humans (Khrime *et al.*, 1991).

Gutkha and *pan masala* have been shown to be carcinogenic in experimental animals, causing tumours in various organs. *Pan masala* acts as a tumour promoter in mice (Ramchandani *et al.*, 1998). Mice fed *pan masala* developed tumours of the lung, liver, stomach and testis (Bhisey *et al.*, 1999). Swiss mice fed *gutkha* or *pan masala* in the diet developed tumours affecting various organs such as lung, stomach, liver, testis, ovary and adrenal gland, *gutkha* being more potent than *pan masala* (Nigam *et al.*, 2001).

Catechu, another constituent of pan masala, has mutagenic (Stich *et al.*, 1983) and clastogenic activity (Giri *et al.*, 1988), while lime is known to cause irritation and hyperplasia of the oral mucosa (Dunham *et al.*, 1966).

Genotoxicity in humans

The frequency of micronucleated cells was measured to assess genotoxic damage in BQ chewers. Significantly elevated frequencies of exfoliated human oral mucosal cells were observed in chewers of BQ with tobacco (4.83/1000 cells) and of tobacco with lime (5.20/1000 cells) compared with the control group (2.59/1000 cells). In addition, chromosome breaks have been reported in oral exfoliated cells in chewers of BQ with or without tobacco. Micronucleus formation has been observed in precancerous lesions of the oral cavity of chewers (Nair *et al.*, 1991).

Sister chromatid exchange and chromosome aberrations were examined in peripheral blood lymphocytes and the frequency of micronucleated cells was scored in exfoliated buccal mucosa cells of *pan masala* and *gutkha* consumers. All three cytogenetic end-points showed a statistically significant increase among the habit groups as compared with the controls (Dave *et al.*, 1991; Desai *et al.*, 1996).

Healthy individuals and OSF patients from several parts of India who were regularly using either areca nut alone, *mava* or tobacco with lime were investigated. Compared with 'no chewing habit' healthy controls, all the habit groups, irrespective of their type of chewing, had significantly higher frequencies of micronucleated cells in exfoliated oral mucosal cells (Kayal *et al.*, 1993). The frequencies of sister chromatid exchanges and chromosome aberrations in peripheral blood lymphocytes and the percentage of micronucleated cells in exfoliated cells of buccal mucosa were significantly increased among areca nut chewing controls, OSF and oral cancer patients compared with those of non-chewing controls (Dave *et al.*, 1992b).

Areca nut and oral submucous fibrosis (OSF)

There is conclusive evidence for the role of areca nut as the major risk factor in the development of OSF, but the mechanisms by which this occurs are not fully understood. *In vitro* studies with cultured fibroblasts have shown that areca nut alkaloids such as arecoline and its hydrolysed product arecaidine stimulate proliferation and collagen synthesis in a dose-dependent manner (Canniff and Harvey, 1981; Harvey *et al.*, 1986), higher concentrations being cytotoxic (van Wyk *et al.*, 1994; Jeng *et al.*, 1996). Flavonoids, catechins and tannins in areca nuts cause collagen fibres to crosslink, making them less susceptible to collagenase (Scutt *et al.*, 1987). This can cause increased fibrosis due to increased collagen production and decreased collagen breakdown. OSF is irreversible and persists even after cessation of the chewing habit, suggesting that components of the areca nut initiate OSF and then affect gene expression in the fibroblasts, which then produce greater amounts of normal collagen (Meghji *et al.*, 1987; de Waal *et al.*, 1997). In OSF patients with a habit of chewing areca nut or *pan masala*, a significant increase in total serum protein was observed with lower levels of ascorbate and iron, which are used in collagen synthesis. The total tissue collagen content increased significantly in patients with advanced disease and with progression of the disease, leading to hypomobility of the tongue, lips, cheeks, soft palate and faucial pillars (Anuradha and Devi, 1993).

Copper appears to play a significant role in the pathogenesis of OSF. Considerable amounts of copper have been found in areca nut products (Trivedy *et al.*, 1997) and copper salts significantly increased the production of collagen by oral fibroblasts *in vitro* (Trivedy *et al.*, 2001). Areca nut chewing for up to 20 min releases significant amounts of soluble copper into the saliva (Trivedy *et al.*, 1999) and mucosal biopsies taken from OSF subjects had a higher copper concentration than those from controls (Trivedy *et al.*, 2000). Activity of the copper-dependent enzyme lysyl oxidase was increased in fibroblasts cultured from OSF (Ma *et al.*, 1995). Copper was found to up-regulate collagen production in oral fibroblasts (Trivedy *et al.*, 1999), indicating that the increased tissue copper may increase the activity of lysyl oxidase, which catalyses the crosslinking of collagens and elastin and is implicated in the pathogenesis of OSF.

OSF is a collagen-related disorder induced by cumulative exposure to BQ/areca nut chewing. Specific genotype combinations of six collagen-related genes situated on different chromosomes (collagen 1A1 and 1A2, collagenase-1, transforming growth factor β1, lysyl oxidase and cystatin C) were associated with risk for OSF in a low exposure group, while a different configuration was associated with risk in a high exposure group of OSF patients in Taiwan (Chiu *et al.*, 2002). Tissue inhibitors of metalloproteinases (TIMPs) and matrix metalloproteinases (MMPs) are the major gelatinolytic proteinases secreted by human mucosal fibroblasts. Arecoline treatment alters the balance in favour of matrix stability by elevating TIMP-1 expression and inhibiting MMP-2 activity, which could lead to development of fibrosis in chewers (Chang *et al.*, 2002).

Possible mechanisms of carcinogenicity of *gutkha* and *pan masala*

The salient points of the postulated mechanism of oral premalignant lesions and oral carcinoma development due to *gutkha* and *pan masala* are summarized in Figure 5.

Pan masala and *gutkha* have been shown to be clastogenic and carcinogenic in animal studies and a battery of *in vitro* test systems, the tobacco-containing *gutkha* being more potent. Increased cytogenetic damage has been observed in peripheral blood lymphocytes and exfoliated buccal mucosal cells of *pan masala* chewers. These genotoxic effects are most likely caused by tobacco- and areca nut-specific nitrosamines (Figure 2) and ROS generated by areca nut and catechu polyphenols and slaked lime (Figure 4).

Gutkha and *pan masala* are dry products and one can assume that the ROS concentration will increase in the oral cavity of chewers as soon as the areca nut and catechu polyphenols together with slaked lime dissolve in the saliva, similar to the reaction observed *in vitro* (Nair *et al.*, 1987b). This could result in the formation of high levels of ROS close to the buccal

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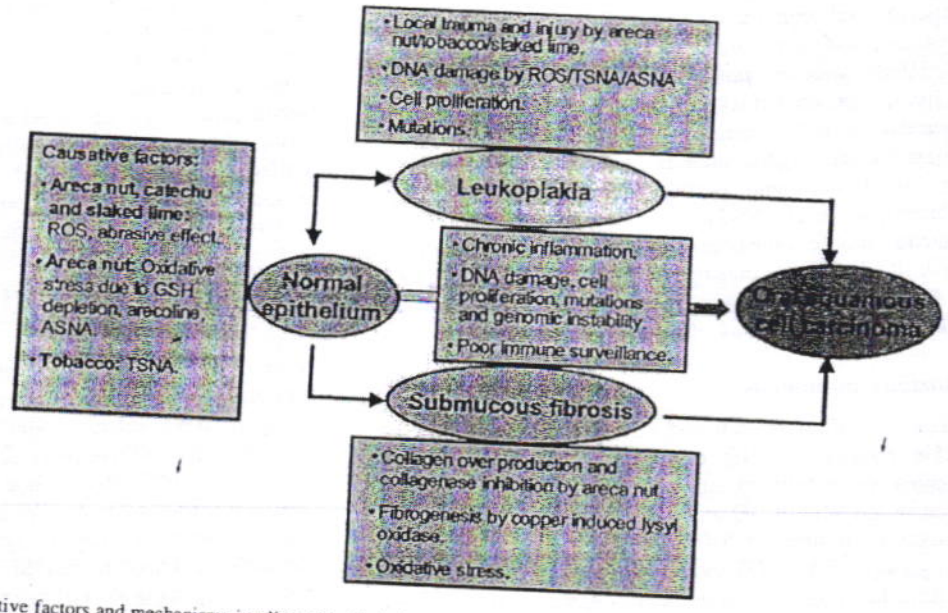

Fig. 5. Postulated causative factors and mechanisms implicated in the induction of leukoplakia/submucous fibrosis and oral squamous cell carcinoma due to *pan masala* and *gutkha* use.

mucosa, overwhelming the protective enzymes and thus causing direct damage to the tissue. High copper and iron content in these products would further add to the load through their action as catalysts via the Haber–Weiss and Fenton reactions. This has been demonstrated in primary human oral keratinocytes, where *pan masala* induced superoxide radical production and lipid peroxidation.

Areca nut chewing is known to cause local trauma and injury to the oral mucosa due to its abrasive nature. This could be more severe in users of *pan masala* and *gutkha* due to their fine particulate nature, with the high probability of particle adhesion to the traumatized mucosa, leading to morphological changes and membrane damage. Areca nut, present in these mixtures, can disturb collagen homeostasis, cause crosslinks and accelerate the onset of OSF, a collagen-related disorder, in habitual chewers. This continuous local irritation by *pan masala*, *gutkha* or areca nut can lead to injury-related chronic inflammation, oxidative stress and cytokine production. Oxidative stress and subsequent ROS generation can induce cell proliferation, cell senescence or apoptosis, depending upon the level of ROS production. During chronic exposure, these events can lead to preneoplastic lesions in the oral cavity and subsequently to malignancy.

Pan masala and *gutkha*, developed and marketed as BQ substitutes, are mixtures of the individual components of the BQ but without the betel leaf. The fresh betel leaf itself has been shown to be non-genotoxic and contains several compounds such as chlorophyll, chavicol and hydroxychavicol, thought to be possible chemoprotective agents (Amonkar *et al.*, 1986; Nagabhushan *et al.*, 1987, 1989; Bhide *et al.*, 1994). Betel leaf extracts act as potent scavengers of ROS (Jeng *et al.*, 2002) and have antimutagenic and anticarcinogenic activity against the TSNAs NNN and NNK (Amonkar *et al.*, 1989; Padma *et al.*, 1989a,b).

Depletion of the cellular antioxidant glutathione and reduced glutathione *S*-transferase activity has been demonstrated in arecoline-treated cultured human oral keratinocytes and fibroblasts (Jeng *et al.*, 1996; Chang *et al.*, 2001). Reduced glutathione content and enhanced CYP450 activity, which was observed in the liver of mice treated with areca nut (Singh and Rao, 1995), could cause increased oxidative metabolism of carcinogens and reduced detoxification. Glutathione depletion leads to increased oxidative stress that can cause DNA damage and trigger several response signals implicated in the carcinogenic process. Glutathione *S*-transferases M1 and T1 are enzymes known to detoxify ROS, lipid peroxidation products and tobacco-derived carcinogens that have been found in the saliva of BQ/tobacco chewers. Null genotypes for *GSTM1* and *GSTT1* increase the risk of developing leukoplakia in chewers (Nair *et al.*, 1999). So far, no similar studies on gene–environment interactions in *pan masala*, *gutkha* or areca nut chewers have been reported.

A key initiating step in the carcinogenic process is the formation of DNA adducts. Some miscoding DNA adducts that could be formed by use of *pan masala* or *gutkha* are shown in Figure 4. Persistence of these adducts during DNA replication can cause miscoding, leading to mutations and derangement of cellular growth control processes. The tobacco-specific nitrosamines NNN and NNK induce miscoding DNA adducts, including O^6-pyridyloxobutyl and O^6-MeG adducts (Hecht, 2003), that could initiate the tumourigenic process in the oral cavity of BQ/tobacco and *gutkha* chewers. The areca nut-specific nitrosamine MNPN also forms O^6-MeG, which causes G→A transitions following DNA replication (Horsfall *et al.*, 1990). In Thai betel chewers who neither smoked nor drank alcohol, such G→A transition mutations were observed exclusively in the *p53* gene (Thongsuksai *et al.*, 2003). Moreover, BQ extracts also inhibit the DNA repair activity of O^6-methylguanine-DNA methyltransferase in buccal mucosal tissue and cell cultures *in vitro* (Liu *et al.*, 1997). Generation of ROS from polyphenols can oxidize DNA bases, e.g. deoxyguanosine to yield 8-oxo-dG (inducing G→T transversions), promoting the tumourigenic process in the oral cavity.

Generation of prostaglandins and overexpression of cyclo-oxygenase 2 (COX-2) have been implicated in several human cancers. Areca nut extract-enhanced COX-2 expression and prostaglandin production in cultured human gingival keratinocytes and human buccal mucosa fibroblasts (Jeng *et al.*, 2000). Up-regulation of COX-2 expression was also observed in human submucous fibrosis tissue samples (Tsai *et al.*, 2003). Chewers of BQ could have impaired immune surveillance, in view of the inhibition by arecoline of both humoral and cell-mediated immune responses in mice (Shahabuddin *et al.*, 1980).

A genetic progression model for head and neck squamous cell carcinoma (HNSCC) to explain the field cancerization theory has been proposed, by which an entire epithelial surface is primed for neoplastic changes following prolonged carcinogen exposure, leading to focal areas that progress at different rates towards invasive cancer (Califano *et al.*, 1996; Oh and Mao, 1997). Microsatellite analysis in HNSCC for allelic loss at 10 major chromosome loci demonstrated that the spectrum of chromosomal deletions progressively increases at each histopathological step from benign hyperplasia to dysplasia to carcinoma *in situ* to invasive cancer (Califano *et al.*, 1996). The most common gains in BQ and/or tobacco chewing associated oral cancers are on chromosomes 8p, 9p, 9q, 11q, 17q and 20q and the most frequent losses are in chromosome arms 3p (genes *FHIT* and *RARB*), 4q, 5q, 9q and 18q (Mahale and Saranath, 2000; Lin *et al.*, 2002b; Pai *et al.*, 2002).

HNSCCs that develop in patients from India frequently have abnormalities of *ras* oncogenes, including mutations, loss of heterozygosity (H-*ras*) and amplification (K- and N-*ras*), in contrast to the low prevalence of mutations in these genes in the same malignancies from developed countries. A high incidence of H-*ras* mutations (35%) has been reported (Saranath *et al.*, 1991). The *p53* tumour-suppressor gene is found in mutated form in many common human cancers, but in India *p53* mutations are infrequent in BQ-associated oral premalignant lesions and squamous cell carcinomas (Heinzel *et al.*, 1996; Ralhan *et al.*, 2001; Saranath *et al.*, 1991). Although *p53* mutations have been reported in 43% of oral cancers in BQ chewers from Sri Lanka, several subjects were also smokers (Chiba *et al.*, 1998). On the other hand, a high frequency of p53 protein overexpression was reported in premalignant and malignant oral lesions of Indian patients who were heavy consumers of betel, areca nut and tobacco (Ranasinghe *et al.*, 1993b; Kaur *et al.*, 1994; Kuttan *et al.*, 1995; Pillay *et al.*, 2003). This effect could be used as a marker to identify lesions that are more likely to progress to malignancy. However, a lack of correlation between p53 protein expression and mutations (Ranasinghe *et al.*, 1993a) suggests that other mechanisms are involved in oral tumourigenesis in BQ chewers. Interactions of p53 with other cellular proteins such as murine double minute 2 (MDM2), 70 kDa heat shock protein (HSP70) and/or E6 protein of human papilloma virus (HPVE6) have been identified in some of these lesions (Agarwal *et al.*, 1999; Ralhan *et al.*, 2000; Nagpal *et al.*, 2002; Pande *et al.*, 2002).

Gutkha and *pan masala* are marketed as substitutes for several prevalent chewing habits. Compelling evidence has led to a classification of oral use of tobacco mixed with lime (khaini) (group 1) and BQ containing tobacco (group 1) as carcinogenic to humans (IARC, 1985). Recently, chewing BQ without tobacco (group 1) and areca nut (group 1) have also been found to be carcinogenic to humans (IARC, 2004).

Overall, although specific studies on these comparatively recent BQ substitutes are lacking, an association and similarity of mechanisms can be convincingly projected from the large body of data on chewing tobacco, areca nut and BQ to hold true for the commercial preparations *pan masala* and *gutkha* and sound a red alert for their carcinogenic potential to humans. In addition, the submucous fibrosis observed after short use of these preparations, especially in the very young, points to a high susceptibility to an irreversible and debilitating disease.

Perspectives

Banning of *gutkha* and *pan masala* has been strongly advocated by oncologists as a preventive measure to reduce oral cavity cancers. Recently, a number of States in India have banned the manufacture and sale of both products and this should reduce the incidence rate. Similar regulations regarding other health-impairing tobacco products which have been on the market for centuries, together with cigarettes and bidis (an indigenous smoking product), should also be reinforced.

However, for those who are addicted to these products or are already affected by premalignant lesions, educational interventions to encourage stopping the habit are essential. Additionally, chemopreventive interventions are being explored. Retinoids, NSAIDS and green tea are among the promising agents (Garewal, 1994; IUSHNCC, 1997; Papadimitrakopoulou and Hong, 1997; Lin *et al.*, 2002a). Although a large percentage of lesions did respond to treatment, recurrence after terminating the chemopreventive regime was also observed (Sankaranarayanan *et al.*, 1997), perhaps due in part to continuation of the addictive habit.

As with all cancers, early diagnosis is important for successful treatment of oral cancer, as its prognosis is still very poor. There is, nowadays, a strong drive to apply proteomics technology to molecular diagnosis of cancer. Expression profiling of tumour tissues, molecular classification of tumours and identification of markers to allow early detection, sensitive diagnosis and effective treatment are now being explored for oral cancers. Genes with significant differences in expression levels between normal, dysplastic and tumour samples have been reported and this should help in better understanding the progression of oral squamous cell carcinoma (Kuo *et al.*, 2002; Leethanakul *et al.*, 2003).

DNA aneuploidy in oral leukoplakia in Caucasian tobacco users has been found to signal a very high risk for subsequent development of oral squamous cell carcinomas and associated mortality (Sudbo and Reith, 2003; Sudbo *et al.*, 2004). A risk assessment model to predict progression of premalignant lesions that includes histology and a score combining chromosomal polysomy, p53 expression and loss of heterozygosity on 3p or 9p has also been described (Lee *et al.*, 2000; Rosin *et al.*, 2002). Once diagnosed, these premalignant lesions could be treated at a much earlier stage by chemopreventive agents, surgery, chemotherapy and/or intense radiotherapy to prevent new lesions and premalignant lesions from progressing to invasive cancer.

Conclusions

Gutkha and *pan masala* have flooded the Indian market as cheap and convenient BQ substitutes and become popular across all age groups wherever this habit is practised. There is sufficient evidence that chewing of tobacco with lime, BQ with tobacco, BQ without tobacco and areca nut are carcinogenic in

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humans (IARC, 1985, 2004). These evaluations in conjunction with the available evidence on the BQ substitutes *gutkha* and *pan masala* implicates them as potent carcinogenic mixtures that can cause oral cancer. Additionally, these products are addictive and enhance the early appearance of OSF, especially so in young users who could be more susceptible to the disease. Although recently some curbs have been put on the manufacture and sale of these products, urgent action needs be taken to permanently ban *gutkha* and *pan masala*, together with the other well-established oral cancer-causing tobacco products. Finally, as the consequences of these habits are significant and likely to intensify in the future, an emphasis on education aimed at reducing or eliminating the use of these products as well as home-made preparations should be accelerated.

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Annexure 57

ORIGINAL RESEARCH

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Trends in the epidemiology of oral squamous cell carcinoma in western UP: An institutional study

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ABSTRACT

Objective: The purpose of the study was to identify trends in incidence rates of oral squamous cell carcinoma (OSCC) at specific anatomic sites or within specific age or sex groups in the Western Uttar Pradesh population.

Materials and Methods: The study covers the period from January 2004 through April 2009. OSCC cases were retrospectively analysed for site, age, gender and habits and the findings were formulated to chart the trends in Western U.P.

Results: The study revealed a male to female ratio of 2.2:1 with the largest number of OSCCs developing in the fourth and fifth decades of life. Overall, the most common site was the buccal mucosa (63.75%), followed by retromolar area (15%), floor of the mouth (11.25%), lateral border of the tongue (3.75%), labial mucosa (3.75%), and palate (2.5%). Smokeless tobacco habit was more prevalent than smoking tobacco in both men as well as women. Karl – Pearson's correlation coefficient was calculated to find the degree of association between the two variables i.e. between gender to buccal mucosa and gender to smokeless and smoking tobacco habits, which were found to be positively correlated with respect to the age.

Conclusion: Oral cancer is an important cause of morbidity and mortality worldwide with an incidence rate that varies widely by geographic location. Even within one geographic location, the incidence varies among groups categorized by age, sex, site or habit.

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Squamous cell carcinoma (SCC) is the most common malignant neoplasm of the oral cavity and represents about 90% of all oral malignancies.[1] Oral squamous cell carcinoma (OSCC) is an important cause of morbidity and mortality worldwide with an incidence rate that varies widely by geographic location.[2] In India, oral cancer represents a major health problem constituting up to 40% of all cancers and is the most prevalent cancer in males and the third most prevalent in females. Even within one geographic location, the incidence varies among groups categorized by age, sex or race.[1,2] Recent publications have highlighted variations in oral cancer trends by geographical location, anatomic site, race, age and sex.[2,3] Thus, descriptive oral cancer data for each specific geographic area are important for many reasons, including understanding the extent of the problem, determining which groups within the population are at highest and lowest risk, and relating the burden of oral cancer to that of other cancers to evaluate the allocation of resources for research, prevention, treatment and support services.[3,4] Despite several diagnostic and therapeutic advances, the overall incidence and mortality associated with OSCC are rising, with current estimates of age-standardized incidence and mortality being 6.6/100,000 and 3.1/100,000 in men and 2.9/100,000 and 1.4/100,000 in women, respectively.[5]

There have been studies reported on the incidence and pattern of OSCCs from various parts of the world.[4-7] However, very few studies have been reported on the incidence and trends of OSCC in the Western U.P population. The purpose of this retrospective study was to identify any trends in the number of cases or incidence rates at specific anatomic sites or within specific age or sex groups in the Western U.P. population and also to compare their trends with reports from other studies in which figures were made specifically on OSCC.

MATERIALS AND METHODS

Histologically verified cases of OSCCs diagnosed in the period from January 2004 to April 2009 were extracted from the archives of Subharti Dental College, Meerut. The anatomic sites included in the study were - tongue, floor of the mouth, hard palate, buccal mucosa, labial mucosa and retromolar area. As the pathophysiologic and epidemiologic

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behaviour of lip cancer is believed to be substantially different from the oral cavity sites, cancers originating in the lip were not included in this study. Charts were made listing the age, sex, site and habits of eighty OSCC patients. A comprehensive analysis was done on the data collected and the results were formulated.

RESULTS

Of the 80 OSCC patients, men represented a higher proportion (68.7%) of OSCCs than women (31.2%). Large number of cases were seen to develop in the fourth and fifth decades of life. Overall, buccal mucosa was the most common site involved (63.75%) while the palate showed the least incidence in this belt of U.P. (2.5%). The study also revealed that larger number of patients had the smokeless tobacco habit (60%) than the bidi or cigarette smoking habit (36.25 %) [Table 1, Figures 1-3].

Statistically, Karl - Pearson's correlation coefficient was calculated to find the degree of association between the two variables i.e. gender to buccal mucosa and gender to smokeless and smoking tobacco habits, which were found to be positively correlated with respect to the age. All of the above said correlations were found to be significant at 5% and 1% level of significance respectively; i.e. $P<0.05$ and $P<0.01$.

DISCUSSION

The incidence of OSCC seems to be increasing and is a global health problem with increasing incidence and mortality rates; around 300,000 patients are annually estimated to have oral cancer worldwide.[4,7,8] OSCC is known to show geographical variation with respect to the age, site, sex and habits of the population.[1,2,4,8,9] The present study revealed a male to female ratio of 2.2:1 with the largest number of OSCCs developing in the fourth and fifth decades of life. This is consistent with an earlier report by Mehrotra and coworkers[8] confirming that oral cancer in Northern India was a disease of the middle aged men. An epidemiologic study on palatal changes in reverse smokers conducted in Andhra Pradesh (Southern India) by Mehta FS *et al*[10] showed a predominance of females in the middle age group (35-54 years).

As regards the site of preference for intra-oral SCC, our study showed some degree of variation from most of the studies conducted at Spain, Canada, Scandinavia and some parts of India.[11-13] A retrospective study conducted by S. Manuel and co-workers,[14] in 2003, at the Regional Cancer Centre (RCC), Thiruvananthapuram, Kerala analysed one of the largest series of young patients under the age of 45 years having SCC of the oral tongue.

In the present study, the buccal mucosa and retromolar pad

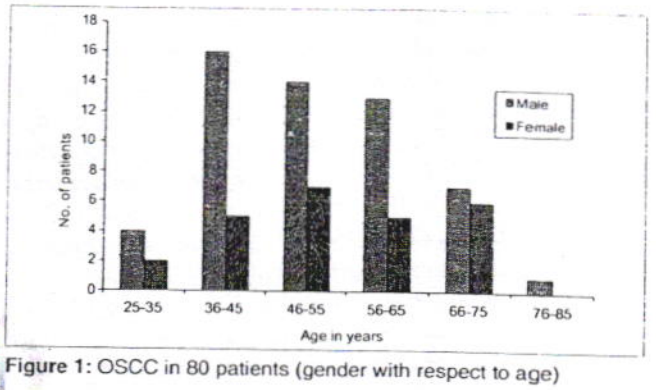

Figure 1: OSCC in 80 patients (gender with respect to age)

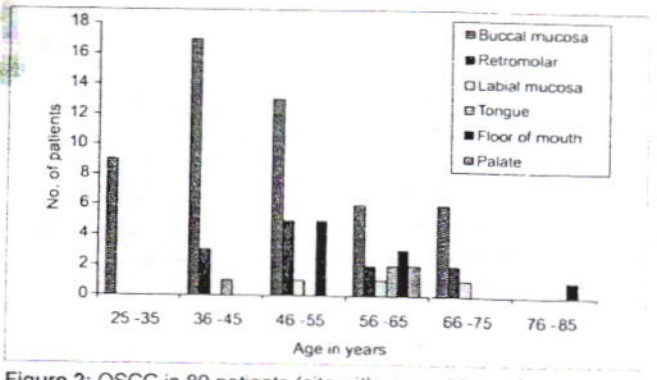

Figure 2: OSCC in 80 patients (site with respect to age)

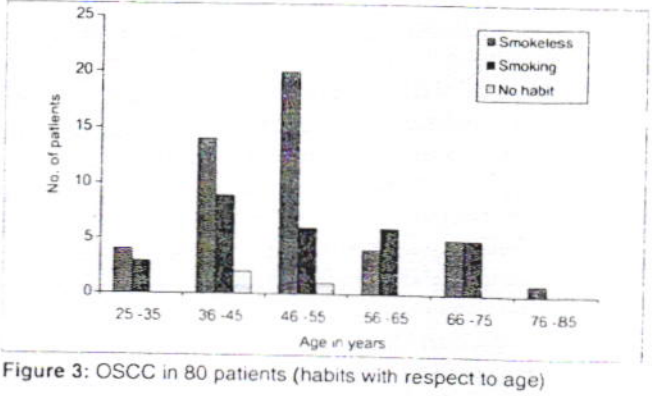

Figure 3: OSCC in 80 patients (habits with respect to age)

Table 1: Oral squamous cell carcinoma trends in western U.P population according to age, sex, site, habit

	Sex		Site						Habit		
Age (yrs)	M	F	BM	LM	RA	T	FM	P	SL	ST	NH
25-35	4	2	9	0	0	0	0	0	4	3	0
36-45	16	5	17	0	3	1	0	0	14	9	2
46-55	14	7	13	1	5	0	5	0	20	6	1
56-65	13	5	6	1	2	2	3	2	4	6	0
66-75	7	6	6	1	2	0	0	0	5	5	0
76-85	1	0	0	0	0	0	1	0	1	0	0
Total patients	55	25	51	3	12	3	9	2	48	29	3

M: Male, F: Female, BM: Buccal mucosa, LM: Labial mucosa, RA: Retromolar area, T: Tongue, FM: Floor of mouth, P: Palate, SL: Smoke less, ST: Smoking tobacco, NH: No habit

were the most frequently involved sites (63.75 and 15% respectively), while the palate was the least commonly involved site (2.5%). These regional differences may be attributed to the exclusive use of chewing tobacco in the Indian subcontinent compared to smoking in the West.[12-14] SCC of buccal mucosa is one of the most common cancers along a geographical belt extending from Central to South East Asia because of the practice of chewing "pan", a combination of tobacco, nut and lime.[15] In contrast, the lateral tongue and floor of mouth are the more commonly involved sites in the West.[11-13] The anterior two-thirds of the tongue is commonly involved in India, while the posterior lateral border and ventral surfaces are frequently involved in the United States.[8]

In 1969, the results of the first epidemiologic survey of palatal changes in reverse smokers in the Srikakulam district of Andhra Pradesh in India were reported by Mehta FS *et al*,[10] who later emphasized that the palatal changes seen in reverse smokers exhibited greater clinical variations than the leukokeratosis nicotina palati known from the Western countries. Earlier, OSCC was thought to be a disease primarily of the elderly.[1,2] Some recent studies conducted in United States, South East of England, Spain and Scandinavia have, however, shown that the incidences of oral cancer are increasingly being reported in the young (<40 years of age) also, particularly younger male patients.[13,14,16,17] Our study, finds increasing number of OSCC cases being recorded in the fourth and fifth decades of life. This may be related to the habits like tobacco and alcohol.

Men represented a higher proportion of OSCCs than women simulating the trends in many recent publications.[3,6,11,18] Some studies show the opposite trend with the increased incidence among women, which may be due to the changing social habits in high socioeconomic groups or cultural habits of some rural areas of India.[10,16] Interestingly, 3.75% of the patients were not associated with any habits like tobacco smoking or chewing in our study which may be attributed to other etiological factors of OSCCs like certain viruses (such as human papilloma virus), low consumption of fruits and vegetables, genetic predisposition, etc.[16]

"Pan" chewing or Gutkha chewing were the most prevalent habits recorded in our study, the incidence being highest at mucosal sites with prolonged contact with carcinogens. There has been strong evidence that smokeless tobacco can cause oral cancer and precancerous oral lesions like leukoplakia.[8] Smokeless tobacco is thought to induce cancer in regions where it is held in direct contact, such as the cheek or gum.[8] The clinicopathologic profile of Indian oral cancers shows significant differences from oral cancer in several developed countries of world, including the USA, UK, France and Japan, where it is associated with tobacco smoking with or without alcohol consumption.[19]

CONCLUSION

As useful clinical information on the trends of OSCCs among Western U.P. population is limited, this retrospective study was undertaken to present a comprehensive data on the trends of OSCC in Western U.P population. Different levels of tobacco and alcohol exposure, diet, socio economic circumstances, age, gender and sites are the causative factors in the differences seen in the incidence rates of OSCC in various populations globally. Because of the magnitude of the oral cancer problem and the trends reported, serious thought should be given to plans for prevention and early detection of premalignant and malignant oral diseases in Western U.P. Race, ethnicity and age cannot be altered; however, lifestyle behavior such as use of tobacco and alcohol are amenable to change and increased intake of fruits and vegetables must be addressed. The dental profession has a well-deserved reputation for preventing other oral diseases. Now is time to focus on the prevention and early detection of oral cancer.

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Annexure 52

Oral cavity cancer risk in relation to tobacco chewing and bidi smoking among men in Karunagappally, Kerala, India: Karunagappally cohort study.

Jayalekshmi PA, Gangadharan P, Akiba S, Koriyama C, Nair RR.

Cancer Sci. 2010 Oct 26. doi: 10.1111/j.1349-7006.2010.01785.x. [Epub ahead of print]

Abstract

The Karunagapally cohort in Kerala, India was established in the 1990s. The years in the 277 men aged 30-84 present study examined oral cancer risk among 66 cohort, using Poisson regression analysis of grouped data, stratified on attained age, calendar time, education, and family income. By the end of 2005, 160 oral cancer cases were identified by the Karunagapally Cancer Registry. Tobacco chewing increased oral cancer risk (P<0.001). Particularly increased was the risk of cancers of the gum and mouth (relative risk 2.8-7.9), which increased with higher = 4.7; 95% confidence interval [CI] = [RR] daily frequencies (P< 0.001) and longer duration (P <0.001) of tobacco chewing. Alcohol drinking was not significantly related to oral cancer risk regardless of tobacco chewing. Bidi smoking significantly increased oral cancer 1.4-4.9) only among men without tobacco chewing habits. = 2.6; 95%CI = risk (RR The risk increased with higher daily consumption (P<0.001), longer duration 0.007). In = 0.001), and younger age at start of bidi smoking (P = (P location-specific analysis, bidi smoking was significantly associated with 1.1-12.1), and its risk = 3.6; 95%CI = cancer of the gum and mouth (RR 0.013) and = significantly increased with larger daily consumption of bidis (P 0.044). Tongue cancer risk was = younger age at the start of smoking (P years or longer, and significantly increased among men who smoked bidis for 30 years old or younger. The present study is the men started bidi smoking at 18 first cohort study showing that tobacco chewing increases cancers of the gum and mouth among men keeping chewing tobacco in the cheek, and that bidi smoking strongly increased oral cancer risk among men without a tobacco chewing habit. (Cancer Sci, doi: 10.1111/j.1349-7006.2010.01785.x, 2010).

Annexure 53

International Journal of Epidemiology 2000;29:609–614

Tobacco habits and risk of lung, oropharyngeal and oral cavity cancer: a population-based case-control study in Bhopal, India

Rajesh P Dikshit and Shiela Kanhere

Background Tobacco habits in India are unique and vary in different regions. Few studies, and none from central India, have reported on type of tobacco used and risk of the most common cancer types in India. We conducted a population-based case-control study to evaluate the risk of tobacco particularly *bidi* smoking and tobacco *quid* chewing on the most common cancer sites among males in Bhopal.

Methods In all, 163 lung, 247 oropharyngeal and 148 oral cavity cancer cases from the Population-Based Cancer Registry records and 260 controls randomly selected from a tobacco survey conducted in the Bhopal population formed the study population.

Results A significant risk of *bidi* and cigarette smoking with a dose-response relationship was observed for lung and oropharyngeal cancer. Tobacco *quid* chewing showed no risk for lung, marginally increased risk for oropharyngeal and about a sixfold increased risk for oral cavity cancer. Population-attributable risk per cent (PARP) was observed to be 82.7% and 71.6% for smokers for the development of lung and oropharyngeal cancer, while the same was found to be 66.1% for tobacco chewers for the development of oral cavity cancer.

Conclusions These data provide strong evidence that smoking *bidi* is even more hazardous than cigarette smoking in the development of lung and oropharyngeal cancer. An intervention study to prevent the use of tobacco will be useful in this population as it also underwent gas exposure due to a chemical accident in 1984.

Keywords *Bidi* smoking, tobacco *quid* chewing, lung cancer, oropharynx cancer, oral cavity cancer

Accepted 10 January 2000

Lung, oropharyngeal and oral cavity cancer are the most common cancer sites observed by Indian registries.[1] These cancer sites are causally related to the use of tobacco in different forms.[2] In India, the use of tobacco is common in the form of chewing and smoking of *bidis* and cigarettes.[3]

Two studies are available from India on the role of *bidi* smoking in the development of lung cancer.[4,5] A few studies, mainly from West Maharashtra and South India, have reported the risk of oropharyngeal and oral cavity cancer and smoking and oral use of tobacco,[6,7,8] but no study has been reported from central India.

In the present study three cancer sites (lung, oropharynx and oral cavity) were investigated using a common protocol and data from the Bhopal Cancer Registry. The risk of tobacco use, particularly *bidi* smoking and chewing, was estimated for these three sites. A study on tobacco use in this population is particularly important as it suffered exposure to methyl-isocyanate gas due to a chemical accident in 1984 and thus is different from other parts of the world.

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Materials and Methods

The present study examines data for the three most common cancer sites in males (lung, oropharynx and oral cavity), collected by the Bhopal Population-Based Cancer Registry during the years 1986–1992.

The cancer cases were coded by four-digit International Classification of Diseases for Oncology (ICD-O) code.[9] The cancer sites included under oropharynx were posterior third of tongue (141.0 and 141.6), soft palate (145.3), uvula (145.4), oropharynx (146.0–146.9), nasopharynx (147.0–147.9), and hypopharynx (148.0–149.0). The cancer sites included under oral cavity were lip (140.0–140.9), anterior two-thirds of tongue

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(141.1–141.5), gingivum (143.0–143.9), floor of mouth (144.0–144.9), cheek mucosa (145.0–145.2), hard-palate and retromolar area (145.5–145.9). A total of 260 controls were randomly sampled from a total of about 2500 males surveyed for tobacco habits in the Bhopal population. This tobacco survey was based on random samples from the voter list of the Bhopal municipal corporation area. The survey was conducted by the Bhopal cancer registry during 1989–1992. The controls were not matched for age with the cases, however, they were age-stratified and then randomly selected to follow the age distribution of cases.

The cases and controls were interviewed according to a pre-coded questionnaire. The subjects were asked about identification particulars, socioeconomic parameters, tobacco habits, and clinical history. The interview was conducted by three qualified social workers of the Cancer Registry staff. The cases for which detailed information about smoking or chewing history were not available were excluded from the study. Cases registered from death certificates were excluded. Similarly, the tongue not otherwise specified cases (141.9) were not included in the analysis. After exclusion, a total of 163 lung, 247 oropharyngeal and 148 oral cavity cancer cases were available for the analysis.

The data collected were compiled and quality checks were carried out. Age-adjusted odds ratio (OR) and 95% CI for the sites under study according to religion, educational status, smoking and chewing habits were estimated using unconditional multiple logistic regression models. The models were compared using the differences in deviance and in degrees of freedom. The result of variable of interest with and without confounding variable was tabulated. The effect of interaction between variable of interest and confounder were also obtained to understand the validity of adjustment. The dummy variable and linear dose-response model was compared for testing the extent to which the linear trend adequately explains the variation between the dose level.[10] The population attributable risk and attributable risk of individuals exposed to exposure of interest were also estimated. For model fitting, the statistical program GLIM was used.[11]

Results

Table 1 presents the distribution of socio-demographic, smoking and chewing habits for lung, oropharyngeal and oral cavity cancer cases and controls. Most of the cases and controls were Hindu. Of the controls, 51.5% never had formal education, while 53.4% of lung, 64% of oropharyngeal and 70.9% of oral cavity cancer cases had never attended the school. The habit of smoking and tobacco chewing was more common among cases than the controls.

Religion and educational status did not appear to increase the risk of lung, oropharyngeal and oral cavity cancer after controlling for smoking and chewing habits (Table 2). As shown in Table 2, tobacco smokers showed increased risk for lung and oropharyngeal cancer but marginally increased risk for oral cavity cancer. Tobacco chewing showed about a sixfold increase in risk for oral cavity, marginally increased risk for cancer of the

Table 1 Distribution of socio-demographical, smoking and chewing variables studied among lung, oropharyngeal and oral cavity cancer cases and controls

Variable	Cancer sites						Controls	
	Lung		Oropharynx		Oral cavity			
	No.	%	No.	%	No.	%	No.	%
Religion								
Hindu	104	63.8	174	70.4	107	72.3	201	77.3
Muslim	56	34.4	73	29.6	40	27.0	57	21.9
Others	3	1.8	–	–	1	0.7	2	0.8
Education								
Ever had schooling	76	46.6	89	36.0	43	29.1	126	48.5
Never had schooling	87	53.4	158	64.0	105	70.9	134	51.5
Smoking								
Smokers[a]	146	89.6	209	84.6	72	48.6	114	43.8
Bidi smokers only	100	68.5	167	79.9	50	69.4	81	71.1
Cigarette smokers only	15	10.3	21	10.0	6	8.3	20	17.5
Bidi and cigarette smokers	31	21.2	21	10.0	16	22.2	13	11.4
Non-smokers	17	10.4	38	15.4	76	51.4	146	56.2
Chewing								
Chewers[b]	56	34.4	108	43.7	120	81.1	120	46.2
Without tobacco	4	7.1	4	3.7	4	3 3	12	10.0
With tobacco	52	92.9	104	96.3	116	96.7	108	90.0
Non-chewers	107	65.6	139	56.3	28	18.9	140	53.8
Smoking + tobacco chewing	45	27.6	81	33.0	49	33.0	43	16.5
No tobacco habits	10	6.1	15	6 1	9	6.0	81	31.2

[a] Smokers with tobacco chewing habits included.

[b] Chewers with smoking habits included.

Table 2 Risk of lung, oropharyngeal and oral cavity cancer by religion, education, smoking and chewing habits

Variable	Cancer sites					
	Lung		Oropharyngeal		Oral cavity	
	OR[a] (95% CI)	OR[b,c] (95% CI)	OR[a] (95% CI)	OR[b,c] (95% CI)	OR[a] (95% CI)	OR[b,c] (95% CI)
Religion						
Hindu and others	1.0	1.0	1.0	1.0	1.0	1.0
Muslims	1.8 (1.2–2.9)	1.0[b] (0.6–1.7)	1.5 (0.9–2.2)	1.1[b] (0.7–1.8)	1.4 (0.9–2.2)	1.2[c] (0.7–2.0)
Education status						
Never had schooling	1.0	1.0	1.0	1.0	1.0	1.0
Ever had schooling	1.1 (0.7–1.6)	0.7[b] (0.4–1.1)	1.7 (1.2–2.4)	1.4[b] (0.9–2.0)	2.4 (1.5–3.7)	1.5[c] (0.9–2.5)
Smoking status						
No	1.0	1.0	1.0	1.0	1.0	1.0
Yes	12.3 (6.9–22.0)	12.1[c] (6.7–21.6)	7.1 (4.6–10.7)	7.3[c] (4.7–11.2)	1.3 (0.8–1.9)	1.5[c] (0.9–2.4)
Tobacco *quid* chewing						
No	1.0	1.0	1.0	1.0	1.0	1.0
Yes	0.6 (0.4–0.9)	0.7[b] (0.4–1.2)	1.1 (0.7–1.5)	1.2[b] (0.8–1.8)	5.5 (3.4–8.9)	5.8[b] (3.6–9.5)
Chewing without tobacco						
No	–	–	–	–	1.0	1.0
Yes	–	–	–	–	1.9 (1.0–3.4)	1.7[b] (0.9–3.3)

[a] Odds ratios adjusted for age.

[b] Odds ratios adjusted for age and smoking.

[c] Odds ratios adjusted for age and tobacco *quid* chewing.

Table 3 Risk of lung and oropharyngeal cancer by type, and number of *bidi*/cigarette smoked per day

Type of smoking	Lung			Oropharynx		
	No.	OR[a,b]	95% CI	No.	OR[a,b]	95% CI
***Bidi* smoking[a]**						
Never	32	1.0	–	59	1.0	–
1–10	33	3.0	1.4–6.5	63	4.1	2.4–7.0
11–20	56	16.1	8.0–32.4	84	11.4	6.5–19.9
>20	42	33.2	13.9–79.2	41	17.0	7.7–37.6
Departure from linear trend[c]	χ_2^2 = 2.16 (NS)			χ_2^2 = 3.82 (NS)		
Cigarette smoking[b]						
Never	117	1.0		205	1.0	
1–10	14	1.5	0.3–6.7	15	1.5	0.5–4.4
11–20	21	11.1	3.4–35.9	18	5.7	2.2–15.0
>20	11	26.8	6.0–120.2	9	11.4	2.7–48.8
Departure from linear trend[c]	χ_2^2 = 1.78 (NS)			χ_2^2 = 0.82 (NS)		

[a] Odds ratios adjusted for age and cigarette smoking.

[b] Odds ratios adjusted for age and *bidi*-smoking.

[c] By comparing the dummy variable and linear dose-response model.

NS = Not significant at 5% level.

oropharynx and no increase in risk for lung cancer in comparison to non-tobacco chewers. There were only 16 subjects who had a history of chewing regularly without using tobacco. The estimates for relative risk, based on small numbers, showed increased risk for oral cavity cancer in comparison to non-chewers even after controlling for smoking habits.

Table 3 illustrates the risk of lung and oropharyngeal cancer according to the number of *bidi* and cigarettes smoked per day. The risk estimates for oral cavity cancer could not be estimated separately for *bidi* and cigarette smoking, as there were only six cigarette smokers among the oral cavity cancer cases. The risk of lung and oropharyngeal cancer increased with number of *bidi* as well as cigarettes smoked. This relationship seemed to be linear as observed departure from linear trend was not statistically significant at the 5% level.

The multiplicative interaction between *bidi* and cigarette smoking was significant at the 5% level: the risk of *bidi* and cigarette smoking combined was observed to be 24.1 and 6.2 for

lung and oropharyngeal cancer, respectively, in comparison to non-smokers of *bidi* and cigarettes. The risk of developing lung cancer (11.6/7.7 = 1.5) and oropharyngeal cancer (7.9/4.1 = 1.9) was higher for *bidi* smokers in comparison to cigarette smokers (Table 4).

As shown in Table 5, the risk of lung and oropharyngeal cancer increased approximately more than four and three times, respectively, within three levels of grouping done for duration of smoking of *bidi*/cigarettes. The risk of getting oral cavity cancer was 4.3 for those who had smoked for >30 years compared to non-smokers. The risk of >500 cumulative years of tobacco smoked compared to non-smokers was 67.6 for lung cancer, 23.0 for oropharyngeal cancer and 6.0 for oral cavity cancer. The lung cancer risk according to histological types among smokers compared to non-smokers shows that the risk is higher for squamous cell carcinoma. The OR estimates for small cell and oat cell carcinoma were based on small numbers and no convergence was obtained for this type. The risk among smokers by histological types was not estimated for oropharyngeal and oral cavity cancer as only one case of adenocarcinoma was reported for oropharyngeal cancer while for the oral cavity only squamous cell carcinomas were reported during the study period.

Table 6 presents the risk of oropharyngeal and oral cavity cancer according to number and duration of chewing tobacco *quid* compared to non-tobacco chewers. The same was not estimated for lung cancer as chewing tobacco *quid* was not observed to increase the risk of lung cancer. A linear dose-response relationship was observed between number of times tobacco *quid* were chewed per day and the risk of development of oral cavity cancer. The risk of oropharyngeal cancer was close to unity ≤10 tobacco *quid* chewed per day but it was 3.6 for tobacco *quid* chewed >10 times per day in comparison to non-chewers of tobacco. The risk for oral cavity cancer increased about five times with increase in duration from 20 years to >30 years of chewing tobacco. A risk of 3.1 was observed for oropharyngeal cancer among tobacco *quid* chewers for >30 years. The trend was not linear for both the sites.

Table 7 presents the joint effect of smoking and tobacco chewing on risk of oral cavity cancer. The multiplicative interaction although not significant at the 5% level, was almost significant at the 10% level ($\chi_2^2 = 4.04$; $P \approx 0.10$). Tobacco *quid* chewing and *bidi* and/or cigarette smoking had a risk of 16.3 in

Table 4 Estimates of odds ratio (OR) for lung and oropharyngeal cancer among smokers of both *bidi* and cigarettes compared ton non-smokers of both. Adjusted for age[a]

	Cigarette smoking			
	No		Yes	
Cancer site	OR	95% CI	OR	95% CI
Lung				
Bidi smoking				
No	1.0	–	7.7	3.2–18.4
Yes	11.6	6.4–21.3	24.1	10.4–56.1
Oropharynx				
Bidi smoking				
No	1.0	–	4.1	2.0–8.4
Yes	7.9	5.1–12.4	6.2	2.8–13.4

[a] The multiplicative interaction between *bidi* and cigarette smokers, significant at 5% level.

Table 5 Risk of lung, oropharyngeal and oral cavity cancer by duration, cumulative years of smoking and histological types for smokers compared to non-smokers

	Cancer sites								
	Lung			Oropharynx			Oral cavity		
Variable	No.	OR[a]	95% CI	No.	OR[a]	95% CI	No.	OR[b]	95% CI
Duration of smoking (years)									
1–20	15	2.5	1.1–5.6	36	2.7	1.5–4.8	20	0.9	0.4–1.6
21–30	50	12.0	5.9–24.0	83	6.9	4.1–11.4	26	1.4	0.8–2.6
>30	81	52.0	24.0–112.8	90	18.6	10.0–34.5	26	4.3	2.0–9.1
Departure from linear trend[c]	$\chi_2^2 = 1.13$ (NS)			$\chi_2^2 = 0.02$ (NS)			$\chi_2^2 = 5.51$ (NS)		
Cumulative years of smoking[d]									
1–250	10	1.8	0.7–4.1	32	2.1	1.2–3.7	20	0.7	0.4–1.3
250–500	38	8.5	4.3–17.0	89	8.2	4.9–13.7	30	1.9	1.0–3.5
>500	98	67.6	31.2–146.3	88	23.0	11.9–4.0	22	6.0	2.6–13.7
Departure from linear trend[c]	$\chi_2^2 = 7.46$			$\chi_2^2 = 1.29$ (NS)			$\chi_2^2 = 9.4$		
Histological type				Not estimable[e]			Not estimable[e]		
Squamous cell carcinoma	75	26.2	9.5–72.2						
Adenocarcinoma and large cell carcinoma	19	3.9	1.2–8.6						
Small cell and oat cell carcinoma	6	5.2	0.6–44.7						

[a] Odds ratios adjusted for age.

[b] Odds ratios adjusted for age and tobacco *quid* chewing.

[c] By comparing the dummy variable and linear dose-response model.

[d] Number of *bidis*/cigarettes smoked • duration of smoking.

[e] See text.

NS = Not significant at 5% level.

Table 6 Risk of oropharyngeal and oral cavity cancer according to number (per day) and duration (in years) of chewing tobacco quids. Adjusted for age and smoking, reference category non-tobacco chewers

	Cancer site					
	Oropharynx			Oral cavity		
Variable	No.	OR[a]	95% CI	No.	OR[a]	95% CI
Amount of tobacco *quid* chewed per day						
1–5	29	0.5	0.3–0.9	19	2.0	1.0–3.8
6–10	43	1.6	0.9–2.8	47	6.7	3.7–12.1
>10	32	3.6	1.7–7.4	15	13.9	7.1–27.2
Departure from linear trend[b]			$\chi_2^2 = 12.87$			$\chi_2^2 = 0.89$ (NS)
Duration (in years) of chewing tobacco *quids*						
1–20	17	0.4	0.2–1.0	12	1.1	0.5–2.4
21–30	31	1.5	0.6–2.1	32	5.5	2.9–10.6
>30	56	3.1	1.6–5.7	72	23.9	12.0–47.3
Departure from linear trend			$\chi_2^2 = 13.76$			$\chi_2^2 = 7.33$

[a] Odds ratios adjusted for age and smoking.

[b] By comparing the dummy variable and linear dose-response model.

NS = Not significant at 5% level

Table 7 Joint effects of smoking and tobacco *quid* chewing on risk of oral cavity cancer

	Tobacco chewing					
	No			Yes		
Tobacco smoking per day	OR[a]	(No.)	95% CI	OR[a]	(No.)	95% CI
Nil	1.0	(76)	–	10.6	(9)	4.8–23.5
1–10	1.0	(24)	0.2–4.1	8.4	(3)	3.3–21.0
10+	4.9	(48)	2.0–12.1	16.3	(20)	6.7–43.3

[a] Odds ratios adjusted for age.

comparison to non-smokers and non-chewers of tobacco for developing oral cavity cancer.

Discussion

The motivation for examining the carcinogenic effects of tobacco smoking and chewing in this population was that smoking habits differ in India and in this region from other parts of the world. The habit of *bidi* smoking and *'zarda'*, a form of tobacco chewing, is peculiar to this region. Case ascertainment in the present study is based on Cancer Registry data and thus entailed high-quality diagnostic confirmation. The controls were randomly selected from a tobacco survey conducted in the same population. Although the controls were not selected concurrently with the cases, it seems unlikely that this will alter the risk estimates as the period of survey (1989–1992) was almost same as the recruitment of cases (1986–1992) for the study. Further, no anti-tobacco activities were organized during the study period to alter the prevalence of tobacco habits in this population.

Religion and educational status were not observed to be risk factors in the present study. A study of the association of religion and smoking habits with lung cancer likewise did not observe any excess risk for different religion.[5] Both *bidis* and cigarettes were found to be independently associated with increased risk of lung and oropharynx cancer. Two previous studies on the risk of lung cancer among *bidi* smokers have shown conflicting results. Notani and Sanghavi,[4] taking hospital controls, found a relative risk of 2.6, while Jussawalla and Jain,[5] taking community controls, found a relative risk of 19.3 in comparison to non-smokers. Similar to the present study increased risk for oropharyngeal cancer among *bidi* smokers was observed in a previous study.[6]

The observed OR for *bidi* and cigarette smoking combined (OR = 24.1 for lung and OR = 6.2 for oropharynx) in comparison to non-smokers of both was much lower than expected, indicating that either mode of action is not multiplicative or those smoking both *bidis* and cigarettes are light smokers of each. The risk estimates further revealed that smoking *bidi* is even more hazardous than cigarette smoking in the development of lung and oropharyngeal cancer (Table 4).

The Indian *bidi* contains only a small amount of tobacco dust rolled in a dried leaf of tendu (*Diospyrous malanoxylon*) or Temburni tree (*Diospyrous ebenum*).[12] In comparison to US cigarettes, the mainstream smoke of *bidi* contains a much higher concentration of several toxic agents such as hydrogen cyanide, carbon monoxide, ammonia, other volatile phenols, and carcinogenic hydrocarbons such as benz(a)anthracene and benzopyrene. *Bidi* also delivers more nicotine than Indian cigarettes. The nitrosonornicotine (NNN) and 4(methyl-nitrosoamino)-1-(3-pyridol) (NNK) level of *bidi* tobacco ranged from 6.2 to 12 μg/g compared with 1.3 to 58.0 μg/g in cigarette tobacco.[13] Further, *bidi* smokers were found to take almost five puffs per minute compared to the cigarette smokers who smoked two puffs per minute.[12] Thus, higher yields of tobacco-specific nitrosamines (TSNA) and higher puffing frequency among *bidi* smokers

suggest that the finding of the present study, that the risk for development of lung and oropharyngeal cancer is higher among *bidi* smokers, is biologically plausible. The effect of smoking differed according to cell type of lung cancer. The risk was highest for squamous cell carcinoma. While the risk of smoking was lowest for developing adenocarcinoma, it was still high (OR = 3.9). These results are consistent with the result of other workers.[14,15]

Chewing tobacco contains a high level of TSNA.[13] Of these, for NNK and its reduction product 4-(methyal(nitrosoamino)-1-1(3-pyridyl)-1-butanol) (NNAL) the major target organ is the lung, especially the peripheral part of the lung. This is independent of the route of admission, whether these procarcinogens are applied topically to the skin, taken orally or by intraperitoneal injection.[16,17] These experimental studies suggest that tobacco chewing may also enhance the risk of lung cancer. The present study, however, did not observe any increased risk of tobacco chewing for lung cancer. The increased risk for oral cavity cancer among tobacco chewers is in accordance to that observed by other workers.[7,8,18] These risk estimates in the present study could not be adjusted for the use of alcohol as history of alcohol use was not taken in the Cancer Registry proforma. However, this does not seem to alter the risk of tobacco chewing to a great extent. In India the prevalence of alcohol consumption particularly relative to tobacco chewing is low. Studies from India have not observed excess risk for oral cancer among alcohol users.[7,8] The interaction model presented in Table 7 gave an indication that the mode of action of tobacco *quid* chewing and smoking may not be multiplicative. It further indicated a decline in risk of chewing of tobacco with increased amount of tobacco smoked, this may be because heavy smokers chew less than light smokers.

In India cross-sectional surveys have shown that the percentage of people who chew betel *quid* without tobacco is small. In the present study also, based on small numbers, elevated risk was observed for oral cavity cancer among chewers not using tobacco, a finding similar to another study from south India.[8]

Tobacco consumption has decreased in many developed countries while in most developing countries it is still increasing. This may largely be due to the fact that relatively fewer studies have been reported from developing countries, including India, on the risk of cancer at different cancer sites due to the use of various forms of tobacco.[19] In the present study it was estimated that the population attributable risk per cent (PARP) for smoking was quite high for lung (82.7%) and oropharyngeal cancer (71.6%). Similarly, the PARP was found to be 66.1% for tobacco chewers for development of oral cavity cancer. The attributable risk among smokers was observed to be 92% and 85% for lung and oropharyngeal cancer, respectively. The attributable risk for those who chewed tobacco was 84.4% for development of oral cavity cancer. This suggests that the high percentage of lung, oropharyngeal and oral cavity cancers in Bhopal could be prevented if tobacco habits were not started. Intervention studies encouraging quitting tobacco use have much relevance in Bhopal as in this population lungs are already damaged to some extent due to exposure to methyl isocynate gas as a result of the chemical disaster in December 1984. Even if gas exposure proves to be carcinogenic in future, by preventing the use of tobacco, a large number of cancer cases could be prevented.

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Annexure 5:

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INDEPENDENT AND COMBINED EFFECTS OF TOBACCO SMOKING, CHEWING AND ALCOHOL DRINKING ON THE RISK OF ORAL, PHARYNGEAL AND ESOPHAGEAL CANCERS IN INDIAN MEN

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Oral, pharyngeal and esophageal cancers are 3 of the 5 most common cancer sites in Indian men. To assess the effect of different patterns of smoking, chewing and alcohol drinking in the development of the above 3 neoplasms and to determine the interaction among these habits, we conducted a case-control study in Chennai and Trivandrum, South India. The cases included 1,563 oral, 636 pharyngeal and 566 esophageal male cancer patients who were compared with 1,711 male disease controls from the 2 centers as well as 1,927 male healthy hospital visitors from Chennai. We observed a significant dose-response relationship for duration and amount of consumption of the 3 habits with the development of the 3 neoplasms. Tobacco chewing emerged as the strongest risk factor for oral cancer, with the highest odds ratio (OR) for chewing products containing tobacco of 5.05 [95% confidence internal (CI) 4.26–5.97]. The strongest risk factor for pharyngeal and esophageal cancers was tobacco smoking, with ORs of 4.00 (95% CI 3.07–5.22) and 2.83 (95% CI 2.18–3.66) in current smokers, respectively. An independent increase in risk was observed for each habit in the absence of the other 2. For example, the OR of oral cancers for alcohol drinking in never smokers and never chewers was 2.56 (95% CI 1.42–4.64) and that of esophageal cancers was 3.41 (95% CI 1.46–7.99). Furthermore, significant decreases in risks for all 3 cancer sites were observed in subjects who quit smoking even among those who had quit smoking 2–4 years before the interview.

Oral, pharyngeal and esophageal cancer are 3 of the 5 most common cancer sites in males, as reported by the population-based cancer registries in Chennai and Trivandrum, and the age-standardized incidence rates of these neoplasms are among the highest in the world.[1] Based on studies conducted in India and elsewhere, it has been established that oral, pharyngeal and esophageal cancers are causally related to the use of tobacco and alcohol.[2–17] Tobacco is most commonly smoked in India in the form of cigarettes and bidis. A bidi is a smoking stick 4–8 cm in length with 0.25–0.50g of coarse ground tobacco, made by rolling a dried piece of *temburni* leaf into a conical shape and securing it with a thread. Less common forms of smoking are cheroot, which is similar to the Western-type cigar, and chutta, which is a coarsely prepared cheroot, often smoked in reverse.[18] Most studies from Southern India assessed the effect of cigarette and bidi smoking in the development of oral, pharyngeal and esophageal cancers, although the role of other smoking habits was not assessed.[5–14] A number of studies have shown an association between tobacco chewing and oral, pharyngeal and esophageal cancers.[5–16] Betal quid chewing without tobacco is common in South India, although the evidence for the role of chewing products without tobacco in the development of cancer is limited.[4] Similarly, there is also no evidence for the role of various types of alcohol traditionally consumed in Southern India in the development of oral, pharyngeal and esophageal cancers. The types of alcohol consumed frequently include *arrack* (spirit containing 40–50% ethanol), country liquor (locally brewed spirit containing about 40% ethanol) and *toddy* (fermented sap from palm trees containing about 5% ethanol).[2,5]

The objective of this study was to investigate the association with patterns of tobacco smoking, chewing and alcohol drinking in the development of oral, pharyngeal and esophageal cancers in Southern India and to assess interactions between the three habits.

MATERIAL AND METHODS

This study was conducted during 1993 and 1999 at the Cancer Institute in Chennai, Tamilnadu and the Regional Cancer Center in Trivandrum, Kerala. The cases were 1,563 oral, 636 pharyngeal and 566 esophageal male cancer patients. The sites were coded by the Ninth Revision of International Classification of Diseases (ICD-9).[19] The oral cancer sites included were lip (ICD 140), tongue (ICD 141) and mouth (ICD 143–5). The pharyngeal cancer sites were oropharynx (ICD 146), hypopharynx (ICD 148) and pharynx unspecified (ICD 149). The ICD code for esophagus was 150. Male patients with non-tobacco-related cancers (ICD 152–154, 156, 158, 170, 171, 173, 175, 185, 187, 190) reported during the same study period from the same centers were selected as disease controls. All cases and cancer controls were histologically confirmed. In addition to 1,711 cancer controls from the two centers, 1,927 male healthy hospital visitors were also selected from Chennai as controls. All subjects were interviewed by trained social investigators. The subjects were questioned about demographic and socioeconomic parameters, clinical history, tobacco and alcohol habits, diet and occupational exposures.

Ever-smokers, chewers and drinkers were defined as those who smoked, chewed or consumed alcohol at least once a day for a minimum period of 6 months. Former smokers were defined as those who had stopped smoking 2 or more years before the interview. For the calculation of pack-years, the amount of tobacco in grams was estimated as 1 per cigarette, 0.5 per bidi and 2 per cigar, cheroot and chutta.[3,14] For the calculation of total lifetime consumption of ethanol, the percentage of ethanol was estimated as 0.40 for spirits (whisky, gin, rum, brandy, arrack and country liquor), 0.03 for beer and 0.05 for toddy.[2,5]

Odds ratios (ORs) and 95% confidence intervals (CIs) for the sites under study were estimated according to smoking, chewing and alcohol habits using unconditional multiple logistic regression models.[20] Interactions between the effects of the 3 habits were also

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assessed. All ORs were adjusted for age, center and level of education. ORs corresponding to 1 habit were obtained after adjusting for the other 2 habits, and the joint effects of 2 habits were obtained after adjusting for the third habit.

RESULTS

The two centers contributed 1,563 oral cancer cases, 636 pharyngeal cancer cases and 566 esophageal cancer cases and 3,638 controls. There were some disparities between the case and control groups regarding the distribution of age and level of education (Table I). Table II shows the risks of oral, pharyngeal and esophageal cancers associated with smoking, chewing and alcohol drinking habit. Current smokers showed about a 2-fold increased risk for oral cancer, about a 4-fold increased risk for pharyngeal cancer and around a 3-fold increased risk for esophageal cancer compared with never-smokers. Former smokers showed a significantly increased risk for esophageal cancer but not for oral and pharyngeal cancers. An increased risk for oral cancers of over 2-fold and a 60% increased risk for esophageal cancers were observed among chewers without tobacco, whereas among chewers with tobacco, the increase in risk was 5-fold (95% CI 4.26–5.97) for oral cancers and about 2-fold for pharyngeal (95% CI 1.43–2.33) and esophageal cancers (95% CI 1.62–2.63). A two-fold increased risk was observed among ever-drinkers for all 3 sites (Table II).

Chewers with and without tobacco showed higher risks for cancer of the mouth [OR 6.95 (95% CI 5.72–8.46) and OR 2.60 (95% CI 1.82–3.73) for chewers with and without tobacco, respectively] than for cancer of the tongue, whereas smokers and alcohol drinkers showed higher risks for cancer of the oropharynx [OR 5.46 (95% CI 3.46–8.61) and OR 2.51 (95% CI 1.85–3.40) for current smokers and alcohol users, respectively] than for cancer of the hypopharynx (Table III).

A significant dose-response relationship was observed between the duration of smoking and oral, pharyngeal and esophageal cancers up to the 40 years of smoking, after which no increase in the risk was observed (Table IV). Similarly, a significant dose-response relationship was also observed between the average daily amount of tobacco and all 3 sites of cancer up to 20 g of tobacco per day, after which no further increase was observed. All types of tobacco smokers showed a statistically significant increased risk for pharyngeal and esophageal cancers. For oral cancers, all types of smoking except cigarette smoking showed statistically significant increased risk. Cigar or cheroot smokers showed the highest increased risk for oral cancers, whereas bidi smokers showed the highest risk for pharyngeal and esophageal cancers. Decreased risk for all 3 sites were observed in former smokers compared with current smokers (Table IV).

Table V shows the risks of oral, pharyngeal and esophageal cancers associated with duration of chewing, average daily amount, cumulative chewing years and quitting. This analysis was not performed separately for chewers without and with tobacco because there were only 34 cases of pharyngeal cancers and 33 cases of esophageal cancers who used chewing without tobacco. A significant dose-response relationship was observed between the duration of chewing and all three sites of cancer up to 40 years of chewing, after which no further increase in the risk was observed for oral and esophageal cancers. A significant dose-response relationship was also observed between the average daily amount and all 3 sites of cancer and between the cumulative years of chewing and all 3 sites of cancer. The increase in risk for oral cancers was 12-fold (95% CI 8.93–15.96) and 13-fold (95% CI 8.49–20.89) for the highest categories of average daily amount and cumulative exposure to chewing, respectively (Table V). Quitting chewing only showed a decrease of risk for all 3 cancers after 10 years or more.

A significant dose-response relationship was observed for duration of drinking and average daily amount of ethanol consumption with oral, pharyngeal and esophageal cancers (Table VI). Among all types of alcohol analyzed, arrack drinkers showed the highest risk for oral, pharyngeal and esophageal cancers, the increase of risk being about 7-fold (95% CI 5.11–10.12), 4-fold (95% CI 2.49–6.16) and 4.5-fold (95% CI 2.90–7.29), respectively. The consumption of western-type spirits (gin, rum, whisky or brandy) did not show a significant increase of risk for any of the three sites (Table VI).

Table VII shows the joint effects of smoking, drinking and chewing habits. It can be observed that both smoking and chewing with tobacco induced a significant increase of risk for oral, pharyngeal and esophageal cancer even for subjects who were never exposed to other habits. Chewing without tobacco and also drinking induced a significant increase of risk for oral and esophageal cancer for subjects never exposed to other habits. The role of drinking in the development of pharyngeal cancer for subjects never exposed to other habits could not be assessed because there were no pharyngeal cancer cases in this category. The joint effect of the three habits in the development of oral, pharyngeal and esophageal cancer appeared to be greater than additive, although less than multiplicative, inducing the highest increase of risk for pharyngeal and esophageal cancer. For oral cancer, a multiplicative interaction between drinking and chewing with tobacco was observed, inducing a 24-fold increase of risk.

Likelihood ratio test statistics for interactions among smoking, drinking and chewing habits were calculated by treating each of the habits as a dichotomous variable (Table VIII). Likelihood ratio tests were statistically significant ($p < 0.05$) for all combinations of the 3 habits except for the interaction between chewing and drinking for oral cavity and pharyngeal cancers, and between drinking and smoking for esophageal cancer. The tested models

TABLE I – DISTRIBUTION OF ORAL, PHARYNGEAL AND ESOPHAGEAL CANCER CASES AND CONTROLS BY CENTER, AGE AND LEVEL OF EDUCATION

	Oral		Pharynx		Esophagus		Controls	
	No.	%	No.	%	No.	%	No.	%
Center								
Chennai	656	42.0	283	44.5	261	46.1	2,747	75.5
Trivandrum	907	58.0	353	55.5	305	53.8	891	24.4
Age (yr)								
25–34	44	2.82	26	4.09	8	1.41	694	19.08
35–44	184	11.77	63	9.91	58	10.25	854	23.47
45–54	461	29.49	188	29.56	136	24.03	888	24.41
55–64	615	39.35	263	41.35	248	43.82	842	23.14
65–74	218	13.95	84	13.21	106	18.73	303	8.33
≥75	41	2.62	12	1.89	10	1.77	57	1.57
Level of education								
None	287	18.36	113	17.77	66	11.66	442	12.15
Less than 5th year	462	29.56	172	27.04	175	30.92	493	13.55
5th < high school	588	23.77	272	42.77	248	43.82	1,886	76.23
High school	175	11.20	64	10.06	57	10.07	693	19.05
College/graduation	51	3.26	15	2.36	20	3.53	124	3.41

TABLE II – ODDS RATIOS OF ORAL, PHARYNGEAL AND ESOPHAGEAL CANCER FOR SMOKING, CHEWING AND ALCOHOL DRINKING

Site	Control	Cases	OR[1]	95% CI	OR[2]	95% CI
Oral cavity						
Smoking						
Never[3]	1,799	424	1.00	—	1.00	—
Former	444	185	1.76	1.45–2.16	0.83	0.65–1.06
Current	1,395	954	2.90	2.54–3.32	1.91	1.61–2.26
Chewing						
Never[3]	3,079	711	1.00	—	1.00	—
Without tobacco	181	88	2.11	1.61–2.75	2.19	1.63–2.95
With tobacco	374	757	8.77	7.56–10.17	5.05	4.26–5.97
Alcohol drinking						
Never[3]	2,919	780	1.00	—	1.00	—
Ever	719	783	4.08	3.58–4.63	1.98	1.68–2.33
Pharynx						
Smoking						
Never[3]	1,799	87	1.00	—	1.00	—
Former	444	57	2.65	1.87–3.77	1.23	0.84–1.79
Current	1,395	492	7.29	5.75–9.26	4.00	3.07–5.22
Chewing						
Never[3]	3,079	424	1.00	—	1.00	—
Without tobacco	181	34	1.36	0.93–1.99	1.37	0.89–2.10
With tobacco	374	178	3.46	2.81–4.24	1.83	1.43–2.33
Alcohol drinking						
Never[3]	2,919	297	1.00	—		
Ever	719	339	4.63	3.89–5.52	2.07	1.67–2.56
Esophagus						
Smoking						
Never[3]	1,799	107	1.00	—	1.00	—
Former	444	86	3.26	2.41–4.41	1.58	1.14–2.20
Current	1,395	373	4.50	3.59–5.64	2.83	2.18–3.66
Chewing						
Never[3]	3,079	371	1.00	—	1.00	—
Without tobacco	181	33	1.51	1.03–2.23	1.60	1.05–2.45
With tobacco	374	160	3.55	2.87–4.40	2.06	1.62–2.63
Alcohol drinking						
Never[3]	2,919	304	1.00	—	1.00	—
Ever	719	262	3.50	2.91–4.21	1.70	1.36–2.13

[1]Crude odds ratio (OR).–[2]OR adjusted for age, center, education level, two other habits.–[3]Reference category.

TABLE III – ODDS RATIOS OF SPECIFIC ORAL AND PHARYNGEAL CANCER SITES FOR SMOKING, CHEWING AND ALCOHOL DRINKING[1]

	Site (ICD code)							
	Tongue (140)		Mouth (141–143)		Oropharynx (146)		Hypopharynx (148)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Smoking								
Never[3]	1.00	—	1.00	—	1.00	—	1.00	—
Former	0.95	0.69–1.32	0.73	0.54–0.99	1.14	0.60–2.17	1.48	0.93–2.35
Current	1.92	1.52–2.43	1.79	1.45–2.22	5.46	3.46–8.61	3.73	2.66–5.24
Chewing								
Never[3]	1.00	—	1.00	—	1.00	—	1.00	—
Without tobacco	1.71	1.13–2.59	2.60	1.82–3.73	1.45	0.77–2.74	1.34	0.78–2.30
With tobacco	2.74	2.18–3.43	6.95	5.72–8.46	1.74	1.25–2.43	1.98	1.46–2.68
Alcohol drinking								
Never[3]	1.00	—	1.00	—	1.00	—	1.00	—
Ever	1.92	1.54–2.39	2.06	1.69–2.50	2.51	1.85–3.40	1.78	1.35–2.34

[1]Odds ratio (OR) adjusted for age, center, education level, two other habits.–[3]Reference category.

were adjusted for age, center, and education level and the third habit for 2-way interactions.

DISCUSSION

In summary, the 3 habits analyzed were all significant risk factors for all 3 cancer sites. The study confirmed the previous findings that identified chewing as the strongest risk factor for oral cancer,[5–8,16] in particular for chewing products containing tobacco. Chewing products without tobacco was also an independent risk factor for cancers of the oral cavity and esophagus, whereas the evidence concerning pharyngeal cancers was suggestive but not conclusive. For the latter cancer, smoking emerged as the strongest risk factor.

Chewing without tobacco induced a higher risk of esophageal cancer than chewing with tobacco.[12,13,17] This may be explained by swallowing the liquid extract produced by chewing (chewers without tobacco) as opposed to spitting it out (chewers with tobacco).[12] Another reason may be that the ORs were not adjusted for smoking and alcohol habits.[12,13,17] The evidence concerning carcinogenicity of betel quid without tobacco was evaluated in 1985 as inadequate in the relevant IARC monograph on tobacco habits other than smoking.[4] However, since that period, the potential mechanisms of carcinogenicity of betel quid without tobacco have been further elucidated. One of the major components of betel quid is the areca nut. *In vitro* evidence has shown that areca nut alkaloid arecoline can give rise to at least four N-nitrosamines.

TABLE IV – ODDS RATIOS FOR ORAL, PHARYNGEAL AND ESOPHAGEAL CANCER FOR DURATION AND AMOUNT OF SMOKING, TYPE OF TOBACCO PRODUCT AND TIME SINCE QUITTING SMOKING[1]

	Controls	Oral			Pharynx			Esophagus		
		Cases	OR	95% CI	Cases	OR	95% CI	Cases	OR	95% CI
Never smokers	1,799	424	1.00	—	87	1.00	—	107	1.00	—
Duration of smoking (yr)[2]										
<20	723	188	1.21	0.95–1.52	66	1.73	1.21–2.47	59	1.61	1.12–2.31
20–29	474	276	1.69	1.36–2.11	122	2.85	2.06–3.93	104	2.47	1.79–3.40
30–39	384	382	1.91	1.53–2.38	192	4.55	3.33–6.20	148	2.90	2.13–3.94
≥40	258	293	1.60	1.25–2.06	169	4.68	3.30–6.64	148	2.88	2.06–4.02
p for linear trend										
Average daily amount of tobacco (g)[2]										
<9	1,132	631	1.41	1.18–1.69	263	2.62	1.98–3.46	232	2.12	1.62–2.78
10–19	534	376	1.82	1.47–2.24	222	4.17	3.10–5.62	172	2.92	2.17–3.92
≥20	162	131	1.99	1.47–2.68	63	3.76	2.53–5.60	53	2.72	1.81–4.10
p for linear trend										
Type of tobacco[2]										
Cigarette only	789	207	0.99	0.79–1.23	85	1.79	1.29–2.50	97	1.83	1.34–2.50
Bidi only	548	474	2.15	1.75–2.63	248	4.68	3.50–6.27	186	3.28	2.45–4.39
Cigarette and bidi only	357	366	1.49	1.18–1.88	184	3.57	2.55–4.98	155	2.72	1.95–3.79
Chutta only	83	43	2.28	1.50–3.45	17	3.22	1.85–5.78	8	1.20	0.55–2.61
Cigar/cheroot only	18	32	4.72	2.41–9.25	7	4.28	1.63–11.20	8	3.17	1.24–8.09
Other combinations	27	16	1.56	0.75–3.25	7	2.97	1.19–7.42	4	1.39	0.45–4.23
Time since quitting smoking (yr)[3]										
Current smokers	1,395	954	1.00	—	492	1.00	—	373	1.00	—
2–4	148	65	0.49	0.34–0.71	24	0.42	0.23–0.67	28	0.59	0.38–0.93
5–9	97	46	0.46	0.30–0.70	13	0.30	0.16–0.55	23	0.63	0.38–1.06
10–14	89	25	0.26	0.15–0.44	9	0.21	0.01–0.43	15	0.45	0.24–0.81
≥15	99	49	0.51	0.34–0.76	10	0.24	0.12–0.48	19	0.53	0.31–0.90

[1]Odds ratio (OR) adjusted for age, center, education level, alcohol consumption and chewing.–[2]Reference category: new smokers.–[3]Reference category: current smokers.

TABLE V – ODDS RATIOS OF ORAL, PHARYNGEAL AND ESOPHAGEAL CANCER FOR DURATION, LEVEL AND CUMULATIVE CHEWING[1]

	Controls	Oral cavity			Pharynx			Esophagus		
		Cases	OR	95% CI	Cases	OR	95% CI	Cases	OR	95% CI
Never chewing	3,079	711	1.00	—	424	1.00	—	371	1.00	—
Duration of chewing (yr)[2]										
0–19	286	250	3.11	2.51–3.86	67	1.23	0.89–1.71	71	1.78	1.30–2.45
20–39	209	432	5.31	4.32–6.52	101	1.97	1.46–2.67	84	2.05	1.50–2.80
≥40	64	170	5.19	3.70–7.29	44	2.60	1.60–4.20	40	2.26	1.42–3.62
p for linear trend										
Average daily amount (no. of quids)[2]										
1–3	343	279	2.06	1.68–2.53	101	1.21	0.91–1.61	81	1.19	0.88–1.60
4–5	135	273	6.02	4.70–7.72	55	1.89	1.29–2.76	51	2.18	1.48–3.19
>5	800	300	11.94	8.93–15.96	56	4.22	2.71–6.56	63	6.07	4.03–9.14
p for linear trend										
Cumulative exposure to chewing										
<1000	158	354	3.78	2.95–4.84	101	1.36	0.97–1.90	69	0.94	0.66–1.34
>1000	26	211	13.32	8.49–20.89	31	1.97	1.05–3.68	23	1.72	0.90–3.27
p for linear trend										
Time since quitting chewing (yr)[3]										
Current chewers	460	640	1.00	—	171	1.00	—	160	1.00	—
2–4	41	93	1.15	0.75–1.77	15	0.81	0.40–1.66	12	0.51	0.24–1.09
5–9	20	59	1.60	0.92–2.81	10	1.23	0.51–3.01	8	0.90	0.36–2.26
10–14	19	30	0.71	0.37–1.35	6	0.45	0.15–1.33	8	0.61	0.24–1.58
≥15	19	30	0.67	0.36–1.26	10	0.57	0.24–1.39	7	0.43	0.17–1.12

[1]Odds ratio (OR) adjusted for age, center, education level, alcohol consumption and smoking.–[2]Reference category: new chewers.–[3]Reference category: current chewers.

Two of these N-nitrosamines are carcinogens.[21–23] Genotoxic and cytotoxic effects of areca nut extract and arecoline on various kinds of cells and cell growth-inhibiting effects on gingival keratinocytes, oral fibroblasts and oral mucosa cells have been demonstrated by a number of studies.[24–28] Prostaglandins, which are inflammatory mediators, are considered to be important for tumor initiation, promotion and metastasis.[29] Areca nut ingredients have also been suggested to be critical in the pathogenesis of oral cancer via their stimulatory effects on prostaglandins and cyclooxygenase-2.[30] Roles for the p53 gene, certain protooncogenes and genetic polymorphisms in the carcinogenesis of oral cancer in betel quid chewers have also been proposed.[31–34]

The higher risk for oral, pharyngeal and esophageal cancers among bidi smokers observed in the present study was consistent with results of previous studies,[5–7,10–14] except for the study of oral cancer in Bangalore,[8] which was based on small number of bidi smokers. Reverse smoking of chutta has previously been associated with high rates of palatal cancer[18] but not with significant risk for pharyngeal and esophageal cancers.[35] In this study, information on whether chutta was smoked in reverse or in the ordinary manner was not available. Also, the role of chutta smoking in the development of palatal cancer could not be assessed because the fourth digit of the ICD code was not available. Nevertheless, in this study chutta smoking was a significant risk factor for cancers of the oral cavity and pharynx.

TABLE VI – ODDS RATIOS OF ORAL, PHARYNGEAL AND ESOPHAGEAL CANCER FOR DURATION OF ALCOHOL DRINKING, LEVEL AND TYPE[1]

	Controls	Oral cavity			Pharynx			Esophagus		
		Cases	OR	95% CI	Cases	OR	95% CI	Cases	OR	95% CI
Never drinkers	2,919	780	1.00	—	297	1.00	—	304	1.00	—
Duration of chewing (years)[2]										
<20	428	280	1.79	1.44–2.21	89	1.36	1.01–1.83	69	1.21	0.88–1.67
20–29	181	245	2.06	1.62–2.62	119	2.46	1.83–3.30	82	1.69	1.23–2.34
30–39	85	185	2.20	1.62–3.00	97	2.95	2.06–4.21	91	2.80	1.95–4.01
≥40	25	73	2.51	1.51–4.16	34	3.06	1.72–5.45	20	1.88	0.98–3.59
p for linear trend										
Average daily amount of ethanol (ml)[2]										
<20	371	213	1.23	0.98–1.54	70	1.09	0.80–1.49	70	1.13	0.83–1.55
20–50	178	256	2.40	1.87–3.06	106	2.34	1.71–3.21	80	1.83	1.31–2.55
>50	167	308	2.98	2.34–3.80	162	3.60	2.70–4.82	110	2.53	1.85–3.46
p for linear trend										
Type of beverage										
Arrack only	66	131	7.19	5.11–10.12	39	3.91	2.49–6.16	37	4.60	2.90–7.29
Country liquor only	114	233	1.73	1.30–2.32	111	2.53	1.78–3.60	68	1.46	0.99–2.14
Spirits only	262	101	1.04	0.78–1.38	46	1.14	0.79–1.65	39	0.97	0.65–1.44
Cliq/arrac + spirits only	41	50	2.12	1.33–3.40	23	2.42	1.37–4.26	26	2.67	1.53–4.66
Cliq/arrac + spirits + toddy only	93	176	1.80	1.32–2.46	90	2.89	2.00–4.17	67	2.00	1.35–2.95

[1]Odds ratios (OR) adjusted for age, center, education level, alcohol consumption and smoking. A total of 92 cases of oral cavity cancer, 30 cases of pharynx cancer, 25 cases of esophagus cancer and 143 controls consumed other combinations of beverages and were excluded form this analysis.–[2]Reference category: new chewers or drinkers.

TABLE VII – ODDS RATIOS OF ORAL, PHARYNGEAL AND ESOPHAGEAL CANCER FOR COMBINATION OF SMOKING, CHEWING AND ALCOHOL DRINKING[1]

Smoke	Chewing	Alcohol	Controls	Oral cavity			Pharynx			Esophagus		
				Cases	OR	95% CI	Cases	OR	95% CI	Cases	OR	95% CI
No	No	No	1,471	122	1.00	—	50	1.00	—	45	1.00	—
No	Yes-T–	No	83	24	3.39	2.04–5.66	5	1.60	0.61–4.17	9	3.30	1.53–7.13
No	Yes-T+	No	127	159	9.27	6.79–12.66	25	3.73	2.20–6.31	35	5.74	3.50–9.42
Yes	No	No	1,084	268	2.45	1.94–3.10	175	3.54	2.54–4.94	155	3.57	2.51–5.06
No	No	Yes	75	16	2.56	1.42–4.64	0	—	—	7	3.41	1.46–7.99
Yes	Yes-T–	No	49	25	4.80	2.79–8.27	10	4.89	2.29–10.43	10	4.82	2.23–10.44
Yes	Yes-T+	No	102	161	8.53	6.13–11.89	32	4.55	2.74–7.56	48	7.22	4.47–11.64
No	Yes-T–	Yes	15	6/	4.36	1.55–12.30	0	—	—	0	—	—
No	Yes-T+	Yes	26	95	24.28	14.87–39.65	7	4.28	1.72–10.62	10	6.71	2.94–15.32
Yes	No	Yes	449	287	4.81	3.74–6.19	199	8.41	5.94–11.90	164	7.33	5.06–10.62
Yes	Yes-T–	Yes	34	33	8.10	4.68–14.02	19	10.75	5.53–20.90	14	9.12	4.35–19.12
Yes	Yes-T+	Yes	119	342	16.34	12.13–22.00	114	13.44	8.90–20.29	67	8.65	5.50–13.62

[1]Odds ratios (ORs) adjusted for age, center and education level. T+, with tobacco, T−, without tobacco.– [2]Reference category.

TABLE VIII – LIKELIHOOD RATIO TEST FOR INTERACTION MODELS BETWEEN DRINKING, SMOKING AND CHEWING HABITS, AND ORAL, PHARYNGEAL AND ESOPHAGEAL CANCER

	Oral cavity			Pharynx			Esophagus		
	χ^2	*p*	d.f.	χ^2	*p*	d.f.	χ^2	*p*	d.f.
Drinking and smoking	5.14	0.02	1	5.63	0.02	1	0.24	0.62	1
Chewing and drinking	2.12	0.15	1	0.29	0.59	1	12.66	0.00	1
Chewing and smoking	30.18	0.00	1	6.05	0.01	1	17.97	0.00	1
Chewing and smoking and drinking	32.48	0.00	2	19.59	0.00	2	25.03	0.00	2

Quitting smoking conveyed a significant decrease in risk compared with current smokers for all 3 cancer sites, even for those who had stopped smoking 2–4 years before the interview, and was confirmed when we excluded chewers and drinkers from the analysis. No dose-response effect was observed with time since quitting smoking, and it could be hypothesized that smoking contributes to late-stage carcinogenesis in the development of oral, pharyngeal and esophageal cancer. Alcohol was an independent risk factor for all 3 cancer sites. Of the different types of alcohol analyzed, arrack exerted the strongest carcinogenic effect.

The evidence for interactions among the 3 habits from previous studies is inconsistent.[5–7,12–17] This inconsistency might be attributed to the fact that previous studies did not control for alcohol consumption, which is an independent risk factor for the 3 cancer sites and therefore could be a strong confounder. Apart from not assessing alcohol consumption, the limitation of previous studies was a too small sample size for assessing interactions. In our study, the number of cases and controls was large enough to assess all 2-way and 3-way interactions. When assessing interaction between 2 habits, the third habit was controlled for. Only 2 previous studies from this region assessed the joint effects of combination of alcohol with other habits.[14,15] One study, restricted to oral cancer, identified a multiplicative interaction between chewing and drinking, as well as chewing and poor oral hygiene.[14] The second study showed multiplicative interaction between alcohol consumption and smoking and alcohol consumption and chewing in the development of all 3 cancer sites, but the analysis was confined to only one age group.

Although our study has several limitations inherent to case-control studies, the advantages include a large sample size, a large heterogeneity of distribution of exposures, a detailed assessment of

lifestyle habits and internal consistency of the results in both centers and for both groups of controls. From the public health point of view, the important finding of our study is a significant decrease of risk for oral, pharyngeal and esophageal cancers for subjects who had stopped smoking, which was already apparent after 2 years. Another important finding is the role of chewing without tobacco in the development of oral and esophageal cancers. In India this habit is not considered dangerous and is often indulged in by women and children. Finally, due to the well-established role of lifestyle factors in the development of oral, pharyngeal and esophageal cancers, they should be considered an important cause of avoidable morbidity and mortality in India, and their prevention should be an important target of public health initiatives.

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Annexe 55

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ORAL CANCER IN SOUTHERN INDIA: THE INFLUENCE OF SMOKING, DRINKING, PAAN-CHEWING AND ORAL HYGIENE

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Between 1996 and 1999 we carried out a case-control study in 3 areas in Southern India (Bangalore, Madras and Trivandrum) including 591 incident cases of cancer of the oral cavity (282 women) and 582 hospital controls (290 women), frequency-matched with cases by age and gender. Odds ratios (ORs) and 95% confidence intervals (CIs) were obtained from unconditional multiple logistic regressions and adjusted for age, gender, center, education, chewing habit and (men only) smoking and drinking habits. Low educational attainment, occupation as a farmer or manual worker and various indicators of poor oral hygiene were associated with significantly increased risk. An OR of 2.5 (95% CI 1.4–4.4) was found in men for smoking ≥ 20 bidi or equivalents *versus* 0/day. The OR for alcohol drinking was 2.2 (95% CI 1.4–3.3). The OR for paan chewing was more elevated among women (OR 42; 95% CI 24–76) than among men (OR 5.1; 95% CI 3.4–7.8). A similar OR was found among chewers of paan with (OR 6.1 in men and 46 in women) and without tobacco (OR 4.2 in men and 16.4 in women). Among men, 35% of oral cancer is attributable to the combination of smoking and alcohol drinking and 49% to pan-tobacco chewing. Among women, chewing and poor oral hygiene explained 95% of oral cancer.

Key words: *oral cancer; tobacco; paan chewing; alcohol; oral hygiene*

Cancer of the oral cavity and pharynx is the first and third commonest cancer in Indian men and women, respectively.[1] Whereas in most areas at high risk for cancer of the oral cavity other than India (*e.g.*, central and Eastern Europe, South America), the ratios between male and female incidence rates range between 3 and 10, in India the male-to-female ratio is approximately 1 (*e.g.*, Madras) or lower than 0.5 (Bangalore).[2] Such very high incidence rates in Indian women reflect the persistent importance in India of paan chewing, a habit that is equally common in the 2 genders.[3] Paan generally includes calcium hydroxide, areca nut (from the *Areca catechu* tree) and betel leaf (from the *Piper betle* vine). Tobacco and/or various spices are commonly added.[4] Paan represents a cheap pharmacologically addicting stimulant, principally used by members of low social classes in South Asia. Fewer efforts have been made in Asia to discourage paan chewing than tobacco smoking,[5] and only recently have links been established between paan and oral cancer that cannot be explained by the presence of tobacco.[3,6]

Annual per capita consumption of cigarettes in India was maximal in the 1970s and 1980s and declined by approximately 40% in the early 1990s.[7] Two nation-wide surveys[8,9] showed a somewhat lower prevalence of tobacco use in any form in 1993–1994 (23% in urban and 34% in rural areas in men and 4% and 9%, respectively, in women) than in 1987–1988 (26% and 35% in men and 6% and 11% in women, respectively). It is estimated that 150 million males and 34 million females used tobacco in India in 1996.[8,9]

Relatively few case-control studies have recently addressed the impact of paan chewing and smoking on oral cancer in India,[10–12] and information on women and on risk factors other than smoking or chewing is scanty.[12]

The present case-control study was conducted in 3 areas of Southern India in order to evaluate the relative importance of smoking, alcohol drinking and paan chewing, with or without tobacco, on cancer of the oral cavity in men and women and the modifying effect, if any, of various indicators of oral hygiene. Our study is part of an international study on oral cancer coordinated by the International Agency for Research on Cancer and carried out also in Italy,[13] Cuba,[14] Spain, Northern Ireland, Poland, Canada, Sudan and Australia, whose major aim is to evaluate the role of human papillomavirus (HPV).[15] In fact, many case-series and a few case-control studies have raised the possibility that HPV may be causally associated with a subset of head and neck cancer, most notably tonsillar carcinoma.[15]

MATERIAL AND METHODS

Between July 1996 and May 1999 the incident cases of cancer of the oral cavity were identified in 3 Indian centers: Bangalore, Madras and Trivandrum, Southern India. Among identified cases, 20 were too sick to be interviewed. A total of 309 male cases (median age 56; range 22–85 years) and 282 female cases (median age 58; range 18–87 years) were thus enrolled (Table I). Twenty-nine cases (24 males) of oropharynx cancer were also interviewed but were not included in the analysis. The distribution by cancer stage among men was as follows: stage 1, 16%; stage 2, 18%; stage 3, 28%; and stage 4, 38%. Among women, it was as follows: stage 1, 8%; stage 2, 14%; stage 3, 38%; and stage 4, 40%. All cases had their interview and oral examination before any cancer treatment.

Control subjects were frequency-matched with cases by center, quinquennium of age and gender. They were all identified and interviewed in the same hospital where cases were found. In Madras and Bangalore, control subjects were identified among relatives and friends who were attending patients admitted for cancer other than oral cancer to, respectively, the Madras Cancer Institute or the Kidwai Memorial Institute of Oncology. In Trivandrum, control subjects were chosen among outpatients who attended the clinics of the Medical College Hospital or of the

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TABLE I – DISTRIBUTION AND ODDS RATIOS (OR) AND CORRESPONDING 95% CONFIDENCE INTERVALS (CI) FOR CANCER OF THE ORAL CAVITY BY SELECTED CHARACTERISTICS AND GENDER (591 CASES AND 582 CONTROLS, INDIA, 1996–1999)[1]

	Men			Women		
	Cases	Controls	OR[2] (95% CI)	Cases	Controls	OR[2] (95% CI)
Age (yr)						
<55	126	136		109	159	
55–64	103	92		98	77	
≥65	80	64		75	54	
Education (years)						
≥7[3]	101	163	1	13	112	1
1–6	138	88	1.89 (1.24–2.88)	45	72	1.09 (0.44–2.69)
0	70	41	2.06 (1.21–3.49)	222	104	5.52 (2.36–12.90)
χ_1^2 for trend			9.83; $p = 0.002$			20.12; $p < 0.001$
Number of siblings						
<3[3]	50	54	1	87	73	1
3–4	58	56	1.32 (0.72–2.43)	62	54	0.98 (0.45–2.11)
≥5	55	75	0.84 (0.46–1.55)	58	94	0.97 (0.46–2.01)
χ_1^2 for trend			0.47; $p = 0.49$			0.04; $p = 0.85$
Religion						
Hindu or buddhist[3]	199	193	1	120	120	1
Christian	27	21	1.88 (0.90–3.91)	10	14	0.86 (0.22–3.37)
Muslim	25	16	1.30 (0.60–2.83)	20	18	1.14 (0.38–3.39)
Occupation						
Clerical[3]	44	89	1	13	23	1
Industrial workers	89	82	2.19 (1.26–3.78)	108	103	2.29 (0.80–6.58)
Farmers	153	90	2.76 (1.62–4.70)	57	21	2.18 (0.62–7.66)
Others	23	29	1.69 (0.77–3.70)	102	140	1.50 (0.51–4.42)
Smoking habit						
Never[3]	86	127	1	274	285	1
Ever	223	165	1.77 (1.17–2.69)	8	5	3.18 (0.58–17.46)
Drinking habit						
Never[3]	137	232	1	273	285	1
Ever	172	90	2.18 (1.43–3.33)	6	5	0.31 (0.07–1.40)

[1]Distribution: some strata do not add up to the total because of missing values.–[2]Estimates from unconditional regression equations, including terms for age, center, education and chewing habits and (men only) smoking and drinking habits.–[3]Reference category.

Regional Cancer Center but were found to be free from malignant diseases. In all 3 centers, over 90% of eligible controls accepted participation in the study. Overall, the control group included 292 men (median age 55; range 20–76 years) and 290 women (median age 52; range 18–80 years) (Table I).

Cases and controls were interviewed by social workers. The section of smoking habits included questions of smoking status (never, ex-smoker or current smokers), daily number of cigarettes, cigars or bidi smoked, age at starting and duration of the habit. Bidi is a local cigarette made by wrapping less than 0.5 g of coarse tobacco dust in a dry temburni (*Diospyros melanoxylon*) leaf. When estimating risk associated with tobacco smoking, 1 bidi was considered equivalent to 1 cigarette or ¼ of a cigar. The consumption of the commonest alcoholic beverages was also investigated. The alcoholic beverages used are mainly a locally fermented and distilled sap from palm trees called "toddy" (approximately 4% ethanol) and another locally brewed liquor called "arrack" (approximately 40% ethanol). Taking into account the different ethanol concentration, 1 drink corresponded to approximately 40 ml of hard liquor (arrack included), 450 ml of beer and toddy, and 150 ml of wine, equivalent to 15 g of ethanol. In Bangalore, a simplified questionnaire was used for drinking habits, and study subjects could be classified as ever/never drinkers only.

The habit of paan chewing was investigated by considering the chewing status (never, ex-chewer or current chewer) before cancer onset, different kinds of products (*i.e.*, paan with or without tobacco), number of paan consumed per day, age at starting and duration of the habit. Paan chewing involved the addition of locally cured dried tobacco leaves and/or stem in most study subjects. Never-smokers, never-drinkers and never-chewers were individuals who had abstained respectively from smoking, alcoholic beverages and chewing, lifelong. Former smokers, former drinkers and former chewers had abstained respectively from any type of smoking, chewing or drinking for at least 12 months before cancer diagnosis or interview (for controls).

Indicators of oral hygiene were self-reported by means of 9 specific questions. The number of missing teeth that had not been replaced and the general oral condition, on the basis of presence of tartar, decayed teeth and mucosal irritation, were evaluated by the interviewer through inspection of the mouth. The questionnaire also included information on sociodemographic characteristics, prior occurrence of sexually transmitted diseases and other infections, family history of cancer and a dietary questionnaire.

The present project was reviewed and approved by the Ethical Committee of IARC and the local ethical and research committees.

Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were computed for the 3 centers together using unconditional multiple logistic regression models. Men and women were assessed separately. All models included terms for center, age quinquennium, educational years and chewing habit in addition to other variables as specified. Detailed evaluation of and adjustment for smoking and drinking habits was restricted to men, since very few women reported any consumption of cigarettes or alcoholic beverages (Table I). Attributable risk fractions were computed, separately for men and women, according to a method that implies knowledge of the risk estimates and of the joint distribution of risk factors among cases only, and is therefore applicable to hospital-based case-control studies.[16]

RESULTS

Oral cancer cases reported significantly fewer years of education than control subjects. The difference was more marked in women (OR for 0 *versus* ≥7 years of education 5.5) than men (OR 2.1). Industrial manual workers and farmers were at an approximately 2-fold increased risk compared with clerical workers in either gender. Housewives represented the majority of occupations in the "other" category. A direct association also emerged between cancer risk and spouse's education (OR for 0 *versus* ≥ 7 years of education 1.9; 95% CI 1.1–3.4 in men and 1.6; 95% CI 0.6–4.4 in

women, not shown). Number of siblings was unrelated to oral cancer risk in either gender, whereas Christian men, but not Christian women, were at a 1.9-fold greater risk than Hindus or Buddhists. Tobacco smoking was associated with oral cancer risk among men (OR 1.8) and women (OR 3.2), but less than 3% of female cases had ever smoked. Consumption of alcoholic beverages was associated with an OR of 2.2 among men, but no risk increase was detected among the few drinking women (2% of female cases).

Smoking and drinking habits in men only are considered in detail in Table II. Fifty-three percent of cases and 39% of controls were current smokers. The majority of them smoked bidi, alone or in combination with cigarettes or cigars (OR for ≥ 20 bidi or equivalent/day *versus* never smokers 2.5; 95% CI 1.4–4.4). Only 28 cases and 40 controls smoked cigarettes only (OR 1.1). Age at starting among current smokers was relatively late (median age starting at 20 years among both cases and controls), and it was not related to oral cancer risk. Quitting smoking was associated with a nonsignificant decline in risk compared with current smokers (OR for ≥ 10 years after quitting 0.7), but former smokers were few. Tobacco snuffing was rare (7% of male cases and 5% of controls) and not significantly associated with oral cancer risk (not shown).

Current drinkers of alcoholic beverages were 32% among male cases, and 19% among male controls (Table II). A significant trend of increase in oral cancer risk with increasing number of drinks per week was found (χ_2 = 6.0; p = 0.01). Toddy accounted for 38% of the alcohol consumption, whereas arrack and liquors such as whisky or gin represented 33 and 28%, respectively, of the total amount. Only 1% of alcohol intake came from wine and beer. Neither age at start drinking nor cessation of the habit were related to oral cancer risk.

Table III shows paan chewing habits in men and women separately. Among cases, 59% of men and 90% of women were ever-chewers (OR 5.1; 95% CI 3.4–7.8 and 42.4; 95% CI 23.8–75.6, respectively). Ninety-one percent of chewers, in both genders, reported the use of paan with tobacco (OR 6.1 in men and 45.9 in women). However, a significantly elevated risk was also found in the few subjects who reported chewing paan without tobacco (OR 4.2 in men and 16.4 in women). Among chewers of paan without tobacco, 9 male cases and 4 male controls, but no women, reported tobacco smoking. Median number of paan consumed per day was 5 in either female or male cases. A significant trend of increase in oral cancer risk by number of paan per day was seen in both genders. The OR for ≥10 paans per day was substantially greater in women (OR 112) than in men (OR 7.9). Women reported starting at an earlier age (median 20 years) than men (median 22 years), and early starting of chewing (<20 *versus* ≥ 25 years of age) was associated with a 5-fold elevated OR in women, but not in men. There were few former chewers. No clear decline of oral cancer risk was seen after chewing cessation in either gender.

TABLE II – ODDS RATIOS (OR) AND CORRESPONDING 95% CONFIDENCE INTERVALS (CI) FOR CANCER OF THE ORAL CAVITY IN MEN BY SMOKING AND DRINKING HABITS (309 CASES AND 292 CONTROLS, INDIA, 1996–99)[1]

	Cases	Controls	OR[2]	(95% CI)
Smoking habit				
Never smokers	86	127	1[3]	
Former smokers	59	50	1.38	(0.78–2.47)
Current smokers				
Cigarettes only	28	40	1.08	(0.56–2.09)
Cigars only	8	1	10.17	(1.12–92.18)
Bidi or equiv. (no./day)				
<20	55	33	2.04	(1.10–3.79)
≥20	73	41	2.50	(1.41–4.42)
Age started smoking (yr)[4]				
≥23	54	34	1[3]	
20–22	63	46	0.82	(0.42–1.61)
<20	47	35	0.84	(0.41–1.73)
χ^2_1 for trend			0.23; p = 0.63	
Years since quit smoking[4]				
Current smoker	164	115	1[3]	
<10	39	33	0.71	(0.37–1.34)
≥10	20	17	0.73	(0.32–1.68)
χ^2_1 for trend			1.07; p = 0.30	
Drinking habit[5]				
Abstainers	102	152	1[3]	
Former drinkers	65	34	1.78	(0.97–3.28)
Current drinkers (drinks/wk)[6]				
<3	29	18	2.17	(1.00–4.69)
3–13	22	13	2.14	(0.89–5.19)
≥14	29	12	1.97	(0.85–4.57)
χ^2_1 for trend			6.02; p = 0.01	
Age at start drinking[4,5] (yr)				
≥31	26	13	1[3]	
23–30	29	12	2.11	(0.69–6.48)
<23	25	18	0.67	(0.20–2.26)
χ^2_1 for trend			0.08; p = 0.78	
Years since quit drinking[4,5]				
Current drinkers	84	44	1[3]	
<10	49	27	0.94	(0.43–2.09)
≥10	16	7	0.62	(0.19–2.05)
χ^2_1 for trend			0.36; p = 0.55	

[1]Some strata do not add up to the total because of missing values.–[2]Estimates from unconditional regression equations, including terms for age, center, education, smoking, drinking and chewing habits.–[3]Reference category.–[4]Current smokers or drinkers only.–[5]Information not available for Bangalore.–[6]One drink corresponds to approximately 150 ml of wine, 450 ml of beer and 40 ml of liquor (*i.e.*, 15 g of ethanol).

TABLE III – ODDS RATIOS (OR) AND CORRESPONDING 95% CONFIDENCE INTERVALS (CI) FOR CANCER OF THE ORAL CAVITY BY PAAN CHEWING HABITS AND GENDER (591 CASES AND 582 CONTROLS, INDIA, 1996–99)[1]

	Men			Women		
	Cases	Controls	OR[2] (95% CI)	Cases	Controls	OR[2] (95% CI)
Chewing habit						
Never chewers[3]	127	232	1	29	251	1
Ever chewers	182	60	5.12 (3.38–7.76)	253	39	42.40 (23.78–75.59)
Type of paan						
With tobacco	139	37	6.10 (3.84–9.71)	222	31	45.89 (25.02–84.14)
Without tobacco	15	6	4.16 (1.46–11.83)	14	5	16.42 (4.77–56.48)
No. of paan/day						
Former chewers						
<5	28	11	4.24 (1.87–9.63)	17	6	20.24 (6.40–63.94)
≥5	31	9	5.77 (2.53–13.16)	31	3	60.42 (15.83–230.67)
Current chewers						
<5	40	18	3.06 (1.58–5.91)	51	13	22.10 (10.06–48.52)
5–9	46	12	8.15 (3.93–16.90)	101	13	58.58 (26.61–128.99)
≥10	34	7	7.91 (3.23–19.41)	51	3	112.41 (30.85–409.55)
χ^2_1 for trend			18.37; $p < 0.001$			71.21; $p < 0.001$
Age started chewing (yr)[4]						
≥25[3]	51	21	1	56	13	1
20–24	42	10	1.53 (0.56–4.18)	74	12	1.92 (0.69–5.34)
<20	27	6	1.54 (0.47–5.02)	73	4	5.43 (1.50–19.65)
			0.73; $p = 0.39$			6.86; $p = 0.01$
Years since quit chewing						
Current chewer[3]	120	37	1	203	29	1
<10	45	14	1.02 (0.45–2.29)	31	6	0.72 (0.23–2.21)
≥10	14	6	0.75 (0.23–2.52)	17	3	0.97 (0.23–4.11)
χ^2_1 for trend			0.50; $p = 0.48$			0.17; $p = 0.68$

[1]Some strata do not add up to the total because of missing values.–[2]Estimates from unconditional regression equations, including terms for age, center, education, chewing and (men only) smoking and drinking habits.–[3]Reference category.–[4]Current chewers only.

TABLE IV – ODDS RATIOS (OR) AND CORRESPONDING 95% CONFIDENCE INTERVALS (CI) FOR CANCER OF THE ORAL CAVITY BY INDICATORS OF ORAL HYGIENE AND DENTITION AND GENDER (591 CASES AND 582 CONTROLS, INDIA, 1996–99)[1]

	Men				Women			
	Cases	Controls	OR[2]	(95% CI)	Cases	Controls	OR[2]	(95% CI)
Self-reported:								
Tooth cleaning (times/day)								
≥2[3]	53	60	1		33	73	1	
≤1	254	232	0.96	(0.59–1.59)	244	217	3.39	(1.65–6.98)
Instrument used								
Tooth brush[3]	96	177	1		35	177	1	
Finger	183	103	1.75	(1.11–2.76)	236	109	3.40	(1.80–6.45)
Other	30	12	3.65	(1.50–8.84)	11	4	2.87	(0.54–15.40)
Wearing dentures								
No[3]	296	276	1		274	263	1	
Yes	11	16	0.86	(0.35–2.06)	4	26	0.26	(0.05–1.25)
Dental check-ups								
Never[3]	252	217	1		246	198	1	
Yes	52	72	0.89	(0.56–1.42)	31	88	0.41	(0.19–0.87)
Gum bleeding								
No[3]	199	238	1		124	198	1	
Yes	108	53	2.83	(1.71–4.68)	154	92	3.35	(1.82–6.15)
Interviewer-reported								
Missing teeth								
≤5[3]	161	235	1		114	229	1	
>5	145	56	3.89	(2.46–6.17)	164	60	7.61	(3.89–14.88)
General oral condition								
Good or average[3]	127	232	1		68	218	1	
Poor	177	58	4.90	(3.09–7.78)	209	72	5.99	(3.00–11.96)

[1]Some strata do not add up to the total because of missing values.–[2]Estimates from unconditional regression equations, including terms for age, center, education and (men only) smoking and drinking habits.–[3]Reference category.

To elucidate the difference between genders, the influence of paan chewing was examined separately in men who, like the vast majority of women in our study, never smoked or drank alcoholic beverages (63 cases and 110 controls, not shown). ORs were more elevated (OR for ≥ 5 *versus* 0 paan/day 18; 95% CI 6.2–53.8) than in the total male population but were still lower than among women. When the gender-specific ORs for paan chewing were examined in 3 separate strata of education, no difference was found between male (OR 5.2) and female (OR 3.7) chewers who reported 7 years of education or more.

Various indicators of oral hygiene and dentition are shown in Table IV according to gender. Female, but not male, cases reported that they cleaned their teeth less often than controls. For this purpose, the majority of study participants, most notably women,

TABLE V – ODDS RATIOS (OR) AND CORRESPONDING 95% CONFIDENCE INTERVALS (CI) OF ORAL CAVITY CANCER ACCORDING TO VARIOUS COMBINATIONS OF CHEWING AND SMOKING, DRINKING AND ORAL HYGIENE IN MEN (309 CASES AND 292 CONTROLS, INDIA, 1996–99)[1]

	Paan chewing					
	Never			Current chewers		
	Cases/controls	OR[2]	(95% CI)	Cases/controls	OR[2]	(95% CI)
Tobacco smoking						
Never smokers	25/106	1[3]		49/16	9.19	(4.38–19.28)
Current smokers (cig./day)						
1–19	33/55	1.78	(0.93–3.47)	35/10	8.86	(3.60–21.83)
≥20	48/35	3.69	(1.89–7.23)	22/8	6.69	(2.45–18.27)
Alcohol drinking						
Never drinker	64/174	1[3]		48/18	7.31	(3.79–14.10)
Current drinker	48/38	2.83	(1.58–5.09)	46/13	8.62	(4.12–18.06)
Toothbrush use						
Yes	42/152	1[3]		31/18	4.65	(2.27–9.54)
No	85/80	2.52	(1.49–4.24)	89/19	11.82	(6.15–22.74)

[1]Some strata do not add up to the total because of missing values.–[2]Estimates from unconditional regression equations, including terms for age, center, education, oral hygiene, chewing and smoking and drinking habits, as appropriate.–[3]Reference category.

TABLE VI – PERCENT OF CANCER OF THE ORAL CAVITY ATTRIBUTABLE TO SELECTED HABITS BY GENDER (591 CASES AND 582 CONTROLS, INDIA, 1996–99)

Factor	Attributable risk percentage (95% CI)[1]	
	Men	Women
Tobacco smoking	21 (−2–44)	—
Alcohol drinking	26 (13–39)	—
Smoking and drinking	35 (15–55)	—
Paan chewing	49 (40–57)	87 (83–92)
Paan chewing and smoking	68 (53–82)	—
Poor oral hygiene	32 (15–49)	64 (47–80)
Chewing and hygiene	50 (22–78)	95 (91–98)
All above	76 (65–86)	95 (91–98)

[1]Estimates from a multiple logistic regression model including terms for gender, age, center, education and the main effects of the factors above. Ranges are in parentheses.

reported using fingers (OR 1.8 in men and 3.4 in women) or other instruments (OR 3.7 in men and 2.9 in women), instead of a toothbrush. A few subjects reported using a soft wooden stick. Regular toothpaste was used by 25% of oral cancer cases and 60% of control subjects. Few cases and controls reported wearing dentures and having dental check-ups. Dental check-up seemed to be significantly protective in women (OR 0.4), but not in men. Conversely, gum bleeding (OR 2.8 and 3.4 in men and women, respectively), having 6 or more missing teeth (OR 3.9 in men and 7.6 in women) and interviewer-reported poor general oral condition (OR 4.9 in men and 6.0 in women) were associated with a significantly increased risk in both genders.

The combined effects of chewing with smoking, alcohol drinking and toothbrush use (as an indicator of oral hygiene) are shown in Table V, for men only. Men who smoked 20 bidi or equivalents per day or more and chewed paan had a 6.7-fold (95% CI 2.5–18.3) increased oral cancer risk. This OR is consistent with a significant negative interaction of smoking and chewing on a multiplicative scale ($\chi_2 = 7.27$; $p < 0.05$). Conversely, the combined effects of chewing and drinking (OR 8.6) and chewing and no use of a toothbrush (OR 11.8) show no significant departure from risk-product multiplicativity.

DISCUSSION

In our present case-control study, paan-tobacco chewing was confirmed to be the most important determinant of oral cancer in Southern India. The fraction of the disease attributable to this habit was 49% in men and over 87% in women (Table VI). Among women, tobacco smoking and alcohol drinking have a negligible influence, whereas among men, smoking and drinking accounted for 21 and 26% of oral cancer cases, respectively. A lack of oral hygiene, as indicated by no use of toothbrush, accounted for 32% of oral cancer in men and 64% in women. All together, the factors above seemed to explain 76% of oral cancer in males and 95% in females (Table VI).

The ORs we found for various levels of smoking and alcohol drinking among men are consistent with those shown before in India[10–12,17–20] and in Europe[13] and North America.[21] Bidi is confirmed to be at least equally harmful as regular cigarettes. Studies conducted in India have shown that bidis produce more carbon dioxide, nicotine, tar and alkaloids than regular cigarettes.[22,23] Furthermore, the filterless design of the bidi combined with low combustibility may contribute to higher toxin yields than with regular cigarettes.[22] It is, however, worth noting that most Indian men in our present study started smoking relatively late, at 20 years or older. Heavy alcohol intake was not common, and the corresponding attributable risk was well below the ones found elsewhere.[21,24] For the combination of drinking and smoking in men, the attributable risk was approximately 80% in the United States and Europe and Latin America[14,21,24] *versus* 35% in our present study (Table VI).

Our present ORs for paan chewing in men are similar to those reported by Nandakumar *et al.*[10] and Sankaranarayanan *et al.*.[11] In the latter study, the fraction of oral cancer attributable to chewing (73%) in Trivandrum in the mid-1980s was greater than in our present investigation, whereas the smoking-attributable fraction was lower (19%, bidi only). In agreement with our findings concerning different types of paan, a study from Pakistan[5] showed an OR of 12.5 for paan-tobacco chewing and of 5.2 for chewing paan without tobacco. Interestingly, areca nut, 1 of the main ingredients of paan, is considered the strongest risk factor for oral submucous fibrosis, a precancerous condition very common in India.[6,25] Thus, our findings, albeit based on relatively few exposed subjects, contribute to the evaluation of carcinogenicity of paan without tobacco, which was still deemed to be inadequate in an IARC monograph.[3]

Women showed substantially higher ORs at any level of paan chewing than men. This difference was found consistently in the 3 participating centers after allowance for town or village of living, in different age groups and when the comparison between men and women was restricted to men who had never smoked or drunk alcoholic beverages. The only 2 Indian studies in which the 2 genders were analyzed separately also showed more elevated ORs in women than men,[10,19] although the difference was less marked than in our present study. In a large cross-sectional study on 927 cases of oral leukoplakia and 47,772 controls, interviewed in the framework of an oral cancer screening trial in the Trivandrum district, tobacco chewers showed an OR of 3.4 (95% CI 2.8–4.1) among men, but 37.7 (95% CI 24.2–58.7) among women.[26] A

greater susceptibility to the oral damage of pan-tobacco chewing in females is thus possible, as has been reported already for alcohol drinking.[26,27] It is also worth noting that women reported starting chewing on average 2 years earlier than men.

The percentage of ever chewers among female controls in our present study (13%), however, was lower than expected. In the aforementioned oral cancer screening trial, for instance, 22% of 65,792 women 35 years or older were pan-tobacco chewers.[28] More than half of control women were chewers in previous case-control studies in Trivandrum[28] and Bangalore.[10] It is conceivable that the poorest, illiterate women, among whom chewing is commonest, do go to the hospital for advanced oral cancer (stage 3 and 4 in 80% of female cases in our present study), but they seldom attend as outpatients for less severe diseases or go to hospital in order to visit relatives and friends. Such scope for selection bias among female hospital controls should be taken into account in future planning of case-control studies in poor countries.

A gender-related difference was also found in respect to risk related to years of education and, to some extent, oral hygiene, on which our present study provides the first data in an Indian population. The great majority of study participants cleaned their teeth once per day or less, did not use a toothbrush and never had dental check-ups. The number of individuals missing more than 5 teeth or wearing a denture was, however, substantially lower than in studies done with the same protocol in Italy[13] and Cuba.[14] Among indicators of dental care, the use of a toothbrush, gum bleeding and number of missing teeth were associated with oral cancer risk after adjustment for smoking, drinking and chewing habits. These findings are in agreement with those from the Americas,[14,29] China[30] and Europe.[13,31] As in Talamini *et al.*[13] the strongest association emerged for general oral conditions reported by trained interviewers who performed oral inspection. Since inspection was performed before cancer treatment, however, interviewers could not be blinded about case-control status, and results must be interpreted cautiously.

In conclusion, our present study offers an up-to-date picture of major causes of oral cancer in Southern India. Traditional methods for mouth cleaning, such as the use of finger or wooden sticks, seem less effective than the use of a toothbrush. Paan chewing represents the most important cause of oral cancer in men and, most notably, in women. Among men, however, 35% of cases are attributable to the combination of smoking and alcohol drinking. Aggressive campaigns aimed at eliminating paan chewing are thus warranted, in addition to continued efforts to prevent the spread of tobacco smoking. Types of paan that do not include tobacco (*e.g.*, some types of paan-masala) should not be marketed as safe alternatives to paan-tobacco chewing.

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Systematic review of the relation between smokeless tobacco and cancer in Europe and North America

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Abstract

Background: Interest is rising in smokeless tobacco as a safer alternative to smoking, but published reviews on smokeless tobacco and cancer are limited. We review North American and European studies and compare effects of smokeless tobacco and smoking.

Methods: We obtained papers from MEDLINE searches, published reviews and secondary references describing epidemiological cohort and case-control studies relating any form of cancer to smokeless tobacco use. For each study, details were abstracted on design, smokeless tobacco exposure, cancers studied, analysis methods and adjustment for smoking and other factors. For each cancer, relative risks or odds ratios with 95% confidence intervals were tabulated. Overall, and also for USA and Scandinavia separately, meta-analyses were conducted using all available estimates, smoking-adjusted estimates, or estimates for never smokers. For seven cancers, smoking-attributable deaths in US men in 2005 were compared with deaths attributable to introducing smokeless tobacco into a population of never-smoking men.

Results: Eighty-nine studies were identified; 62 US and 18 Scandinavian. Forty-six (52%) controlled for smoking. Random-effects meta-analysis estimates for most sites showed little association. Smoking-adjusted estimates were only significant for oropharyngeal cancer (1.36, CI 1.04–1.77, n = 19) and prostate cancer (1.29, 1.07–1.55, n = 4). The oropharyngeal association disappeared for estimates published since 1990 (1.00, 0.83–1.20, n = 14), for Scandinavia (0.97, 0.68–1.37, n = 7), and for alcohol-adjusted estimates (1.07, 0.84–1.37, n = 10). Any effect of current US products or Scandinavian snuff seems very limited. The prostate cancer data are inadequate for a clear conclusion.

Some meta-analyses suggest a possible effect for oesophagus, pancreas, larynx and kidney cancer, but other cancers show no effect of smokeless tobacco. Any possible effects are not evident in Scandinavia. Of 142,205 smoking-related male US cancer deaths in 2005, 104,737 are smoking-attributable. Smokeless tobacco-attributable deaths would be 1,102 (1.1%) if as many used smokeless tobacco as had smoked, and 2,081 (2.0%) if everyone used smokeless tobacco.

Conclusion: An increased risk of oropharyngeal cancer is evident most clearly for past smokeless tobacco use in the USA, but not for Scandinavian snuff. Effects of smokeless tobacco use on other cancers are not clearly demonstrated. Risk from modern products is much less than for smoking.

Background

Over the last 10 years, interest in smokeless tobacco (ST) as a possible safer alternative to smoking has risen. Although a number of recent reviews have considered the evidence relating ST to cancer, some have not included meta-analyses [1-3], and others have only provided quantitative summaries for specific sites: oropharyngeal cancer [4], pancreatic cancer [5], or oropharyngeal, oesophageal, pancreatic and lung cancer [6]. No formal comparisons have been conducted with the well-known effects of smoking [7,8].

The review described in this paper is restricted to studies in Western populations. In practice this predominantly means studies in the USA and Sweden, the only North American and European countries where the two major types of ST – chewing tobacco and snuff – are commonly used [2]. Although ST is also widely used in developing countries, particularly parts of Central and South-East Asia, the tobacco is often used in combination with other products, such as betel nut quid, slaked lime, areca nut and even snail shells [1,2,9]. This review also does not consider the limited data on nicotine chewing gum.

Our first objective is to carry out a comprehensive review of the available epidemiological evidence in Western countries relating ST to cancer, including meta-analyses for as many cancer types as the data justify. In meeting this objective, we take proper account of the potential confounding role of smoking by distinguishing effect estimates which are unadjusted for smoking and those which take smoking into account (either by adjustment in analyses based on the whole population of smokers and non-smokers combined or by restricting analysis to lifelong never smokers). Our second objective is to provide a quantitative indication of the relative effects of ST and cigarette smoking.

Methods

Study identification and selection

All reports had to satisfy the following inclusion criteria: published in a peer reviewed journal or the results publicly available, epidemiological study in humans, of cohort or case-control design, study location specified, any form of cancer as the outcome, and chewing tobacco, oral snuff or unspecified ST as the exposure. They also had to fall outside the exclusion criteria: conducted in an Asian or African population, no control group, or inappropriate design (case report, qualitative study or review/meta-analysis). Relevant papers were sought from a MEDLINE search conducted in May 2008 of "cancer" AND ("smokeless tobacco" OR "chewing tobacco" OR "snuff" OR "snus"), supplemented by citations in recent reviews [1-6,10] and in the papers obtained.

Data extraction

Reports were grouped by study, and for each study details were abstracted (see Tables 1 and 2 [11-114]) relating to the design, period, location, controls used and size, the exposure (method of assessment, type of ST, exposure doses and durations considered), the outcome (cancer sites studied) and issues relating to analysis (type of effect measure, analysis methods, extent of adjustment for smoking and other factors, and availability of dose-response data). The extent of adjustment for smoking for a study was categorised into five groups: A. *no information* – effect estimates are provided but no details are given of any adjustments made; B. *no adjustment* – effect estimates are available for the whole population, but smoking is not taken into account; C. *never smokers* – the only effect estimates available are for never smokers; D. *some adjustment* – effect estimates adjusted for smoking are available, but the adjustment is relatively simple, using two or three level broad groupings (for example, ever/never smoked, current/non-current smoker, current/former/never smoker), and takes no account of daily amount smoked or duration of smoking; and E. *more adjustment* – effect estimates are available that take into account daily amount smoked, duration of smoking and/or their product (pack-years). Studies were categorised under D or E if smoking-adjusted effect estimates are available, regardless of whether some results for never smokers are also presented. The method used to adjust for smoking is not always clear. Studies where the authors merely report that they 'adjusted for cigarette smoking' are included in category D.

Based on the availability of relevant data, 13 cancer groupings (oropharyngeal, oesophagus, stomach, pancreas, other digestive, larynx and nasal, lung, prostate, bladder, kidney, haematopoietic and lymphoid, other and all), were selected, with results for each grouping tabulated in a standard way, with details given of the source, exposure to ST, smoking group, sex, number of cases and adjustment factors for each effect estimate or indication of association (see tables dealing with individual effects estimates, below). For each study the intent is to extract the relative risk (RR) or odds ratio (OR) adjusted for the most factors, relevant to current, former or ever exposure to chewing tobacco, snuff or overall/undefined ST. Where relevant results for a study are reported in more than one paper, those based on the greatest number of cases are used.

Results are included, where available, for the whole population and for never smokers, and for sexes separately. RR or OR estimates based on zero exposed cases (or controls) are not included as providing too little information and because a valid confidence interval (CI) cannot be calculated. Suitable estimates of effect (RR or OR) and precision (CI) provided by the authors are used if possible, estimates otherwise being calculated from available data

Table 1: Cohort studies of smokeless tobacco and cancer

Study	Country	Follow-up period	Baseline population	Exposure[a]	Reference[b]	Cancers studied (cases)[c]
Lutheran Brotherhood cohort[d]	USA	1966 to 1986	17,633 white men aged 35+ years	ST	Hsing *et al.* 1990 [11]	Prostate (149)
US Veterans cohort[e]	USA	1954/57 to 1980	248,046 US veterans aged 31–84 years, over 99.5% men	ST	Kneller *et al.* 1991 [12] Zheng *et al.* 1993 [13] Hsing *et al.* 1991 [15]	Stomach (75) Pancreas (57) Prostate (4,607)
					Heineman *et al.* 1992 [16] Zahm *et al.* 1992 [17]	Multiple myeloma (582)[f] Soft tissue sarcoma (119), pharynx (55), buccal cavity (74)
Iowa cohort	USA	1986/89 to 1995	1,572 men aged 40+ years, controls in a case-control study	ST	Heineman *et al.* 1995 [18] Putnam *et al.* 2000 [20]	Colon (3,812), rectum (1,100) Prostate (101)[f]
NHANES I follow-up cohort[g]	USA	1971/75 to 2002	14,407 adults aged 25–74 years[h]	ST	Accort *et al.* 2002 [21]	All, lung[i]
CPS-I[j]	USA	1959 to 1972	77,407 never smoking men aged 30+ years from 25 states	ST	Accort *et al.* 2005 [22] Henley *et al.* 2005 [23]	All, lung, breast, digestive, oral, prostate[f, i] All (2,332), oral (13), digestive (913), lung (134), genitourinary (559)
CPS-II[k]	USA	1982 to 2000	114,809 never smoking men aged 30+ years nationwide	ST[l]	Henley *et al.* 2005 [23]	All (6,140), oral (46), digestive (1,999), lung (400), genitourinary (1,709), haematopoietic (923)
Norway cohorts[l,m]	Norway	1982 to 1996 1966 to 2001	467,788 men aged 30+ years nationwide 10,136 men from two cohorts, a sample of the 1960 census and relatives of Norwegian migrants to the USA	ST Snuff	Chao *et al.* 2002 [24] Boffetta *et al.* 2005 [26]	Stomach (996) Oral (34), oesophagus (27), stomach (217), pancreas (105), lung (343), kidney (88), bladder (239)[n]
Swedish construction workers	Sweden	1974 to 1985	135,036 men	Snuff	Bolinder *et al.* 1994 [28]	All (1,269), lung (204)
		1971 to 2000	337,311 men		Odenbro *et al.* 2005 [29]	Cutaneous squamous cell carcinoma (756)[f]
		1971 to 2000	335,612 adults, over 99.3% men		Fernberg *et al.* 2006 [30]	Malignant lymphoma (1,514)[f]
		1971 to 2004	336,381 men		Fernberg *et al.* 2007 [31]	Leukaemia (372), multiple myeloma (520)[f]
		1978 to 2004	279,897 men		Luo *et al.* 2007 [32]	Oral (248), lung (2,198), pancreas (448)[f]
		1971 to 2004	339,802 men		Odenbro *et al.* 2007 [33]	Melanoma (1,639)[o]
		1971 to 2004	336,381 men		Zendehdel *et al.* 2008 [34]	Stomach (1,385), oesophagus (366)[f]
Uppsala County cohort	Sweden	1973/74 to 2002	9,976 men	Snuff	Roosaar *et al.* 2008 [35]	All (1,572), smoking-related (493), oral (34)[p]

[a]Only exposures for which results are available are shown.
[b]Main references. Other references supplying limited data are indicated in footnotes.
[c]Numbers of cases are totals for the sexes specified. Numbers of cases exposed to ST are shown in the tables presenting results by site. Cases are deaths, unless indicated. Oral is used as an abbreviation for oropharynx.
[d]Some limited additional results for the Lutheran Brotherhood cohort, based on follow-up to 1981, were reported earlier for cancers of the prostate, pancreas and oesophagus in IARC Monograph 37 in 1985 [14].
[e]Some limited additional results for the US Veterans cohort, based on follow-up from 1954 to 1969 were presented earlier for a range of cancers in an abstract by Winn *et al.* in 1982 [19].
[f]Cancers listed are incident cases.
[g]NHANES I = First National Health and Nutrition Examination Survey.
[h]Data on ST use were only collected in 3,847 subjects at baseline in 1971–1975, but were collected for all subjects in follow-up surveys in 1982–1984. 6,805 subjects were considered in the mortality analyses [21] and 7,779 in the incidence analyses [22].
[i]Numbers of cases not given.
[j]CPS-I = Cancer Prevention Study I.
[k]CPS-II = Cancer Prevention Study II. Some additional results for lung cancer, based on mortality to 2002, comparing 111,952 men who quit cigarette smoking with 4,443 who switched to ST, were presented by Henley *et al.* in 2007 [25].
[l]Results for chewing and snuff are also given for all cancers and lung cancers.
[m]Some limited additional results, based on follow-up to 1978, were reported by Hench *et al.* in 1983 [27] for pancreatic cancer incidence and in IARC Monograph 37 in 1985 [14] for cancers of the buccal cavity/pharynx, oesophagus, pancreas and prostate.
[n]Cancers listed include incident cases.
[o]Includes cutaneous malignant melanoma, melanoma in situ and intraocular malignant melanoma.
[p]Numbers are incident cases. An analysis of overall cancer based on 1,574 deaths was also conducted.
ST = smokeless tobacco.

Table 2: Case-control studies of smokeless tobacco and cancer

Study	Country	Study period[a]	Controls[a]	Sex[b]	Exposures studied[c]	Cancers studied (cases)[d]
Broders 1920 [37]	USA	NA	Hospital	M+F	Chew, snuff, ST	Oral (537)
Doll and Hill 1952 [38]	UK	1948–1952	Hospital	M	Chew, snuff	Lung (1,209)
Moore *et al.* 1953 [39]	USA	1951–1952	Hospital	M	ST	Oral (112), face (93)
Wynder *et al.* 1957 [40]	Sweden	1952–1955	Hospital	M	Chew	Oral (166), oesophagus (39), larynx (60)
Wynder and Bross 1957 [41]	USA	NA	Hospital	M	Chew	Oral (543)
Peacock *et al.* 1960 [42]	USA	1952–1958	Hospital	M+F	ST	Oral (45)
Lockwood 1961 [43]	Denmark	1942–1956	Population	M+F	ST	Bladder (282)
Wynder and Bross 1961 [44]	USA	1956–1959	Hospital	M	Chew	Oesophagus (150)
Vogler *et al.* 1962 [36]	USA	1956–1957	Hospital	M+F	Chew, snuff	Oral (228)
Vincent and Marchetta 1963 [45]	USA	NA	Hospital	M	Snuff	Oral (66), larynx (23)
Wynder *et al.* 1963 [46]	USA	1957–1960	Hospital	M	Chew, snuff, ST	Bladder (300)
Bennington and Laubscher 1968 [47]	USA	1951–1956	Hospital	M	Chew	Kidney (88)
Dunham *et al.* 1968 [48]	USA	1958–1964	Hospital	M+F	ST	Bladder (493)
Martinez 1969 [49]	Puerto Rico	1966	Hospital, population	M+F	Chew	Oral (221), oesophagus (179)
Keller 1970 [50]	USA	1958–1962	Hospital	M	ST	Oral (314)
Cole *et al.* 1971 [51]	USA	1967–1968	Population	M+F	Chew, snuff	Bladder (470)
Bjelke *et al.* 1974 [52]	USA	NA	NA	NA	Chew	Colorectal (373), oesophagus (52), stomach (83)
Armstrong *et al.* 1976 [53]	Norway	NA	NA	NA	Chew	Colorectal (278), stomach (228)
Browne *et al.* 1977 [54]	UK	1972–1974	Hospital	M	ST	Kidney (96)
Williams and Horm 1977 [55]	UK	1957–1971	Population	M+F	Chew	Oral (75)
Wynder and Stellman 1977 [56]	USA	1969–1971	Hospital	M+F	ST	Many types (7,518)[e]
	USA	1969–1975	Hospital	M	Chew, snuff, ST	Oral (593), bladder (589), larynx (387), lung (1,051), oesophagus (183)
Engzell *et al.* 1978 [57]	Sweden	1961–1971	Population	M	Snuff	Nose (36)
Howe *et al.* 1980 [58]	Canada	1974–1976	Population	M	Chew	Bladder (480)
Westbrook *et al.* 1980 [59]	USA	1955–1975	Hospital	F	Snuff	Oral (55)
Pottern *et al.* 1981 [60]	USA	1975–1977	Decedent	M	Chew, snuff	Oesophagus (120)
Winn *et al.* 1981 [61]	USA	1975–1978	Hospital	F	Snuff	Oral (255)
Mommsen and Aagaard 1983 [62]	Denmark	1977–1980	Population	M	Chew	Bladder (165)
Wynder *et al.* 1983 [63]	USA	1977–1980	Hospital	M	Chew, snuff, ST	Oral (414)
Brinton *et al.* 1984 [64]	USA	1970–1980	Hospital, decedent	M+F	Chew, snuff, ST	Nose (160)
McLaughlin *et al.* 1984 [65]	USA	1974–1979	Population	M	Chew, snuff, ST	Kidney (313)
Hartge *et al.* 1985 [66]	USA	1977–1978	Population	M	Chew, snuff, ST	Bladder (2,240)
Weinberg *et al.* 1985 [67]	USA	1978–1980	Decedent, population	M	Chew	Stomach (178)
Goodman *et al.* 1986 [68]	USA	1977–1983	Hospital	M+F	Chew	Kidney (267)
Kabat *et al.* 1986 [69]	USA	1976–1983	Hospital	F	Snuff	Bladder (152)
Stockwell and Lyman 1986 [70]	USA	1982	Population	M+F	ST	Oral (1,462), nose (92), larynx (161)
Young *et al.* 1986 [71]	USA	4 yr period	Hospital	M+F	ST	Oral (317), larynx (179)
Lindquist *et al.* 1987 [72]	Sweden	1980–1983	Population	M	Snuff	Leukaemia (76)
Asal *et al.* 1988 [73]	USA	1981–1984	Hospital, population	M	Snuff	Kidney (209)
Blot *et al.* 1988 [74]	USA	1984–1985	Population	M+F	ST	Oral (1,114)
Falk *et al.* 1988 [75]	USA	1979–1983	Hospital	M+F	Chew, snuff	Pancreas (363)
Morris Brown *et al.* 1988 [76]	USA	1982–1984	Population	M	ST	Oesophagus (207)
Slattery *et al.* 1988 [77]	USA	1977–1983	Population	M	Chew, snuff, ST	Bladder (332)
Spitz *et al.* 1988 [78]	USA	1985–1987	Hospital	M+F	Chew, snuff, ST	Oral (185)[f]
Burch *et al.* 1989 [79]	Canada	1979–1982	Population	M	Chew, snuff	Bladder (627)
Franco *et al.* 1989 [80]	Brazil	1986–1988	Hospital	M+F	ST	Oral (232)
Zahm *et al.* 1989 [81]	USA	1976–1982	Population	M	ST	Soft tissue sarcoma (133)
Farrow *et al.* 1990 [82]	USA	1982–1986	Population	M	Chew	Pancreas (148)
Blomqvist *et al.* 1991 [83]	Sweden	NA	Hospital	M+F	Snuff	Oral (61)
Ghadirian *et al.* 1991 [84]	Canada	1984–1988	Population	M+F	Chew	Pancreas (179)
Maden *et al.* 1992 [85]	USA	1985–1989	Population	M	ST	Oral (131)
Marshall *et al.* 1992 [86]	USA	1975–1983	Population	M+F	Chew	Oral (290)
Morris Brown *et al.* 1992 [87]	USA	1981–984	Population	M	ST	Leukaemia (578)
Morris Brown *et al.* 1992 [88]	USA	1981–1984	Population	M	ST	Non-Hodgkin's lymphoma (622)

Table 2: Case-control studies of smokeless tobacco and cancer *(Continued)*

Sterling *et al.* 1992 [89]	USA	1986	Population	M+F	Snuff, ST	All cancer (459,792), oral (6,976), all digestive (109,514)
Mashberg *et al.* 1993 [90]	USA	1972–1989	Hospital	M	Chew, snuff, ST	Oral (359)
Perry *et al.* 1993[g]	USA	About 1992	Hospital	M+F	ST	Oral (133)
Spitz *et al.* 1993 [92]	USA	1987–1991	Hospital	M+F	Chew	Oral (108)[f]
Chow *et al.* 1994 [93]	Sweden	1985–1997	Population	M	Chew	Bile duct (49)
Hansson *et al.* 1994 [94]	Sweden	1989–1992	Population	M+F	Chew, snuff	Stomach (338)
Hardell *et al.* 1994 [95]	USA	1974–1978	Population	M	Snuff	Non-Hodgkin's lymphoma (105)
Hayes *et al.* 1994 [96]	USA	1986–1989	Population	M	Chew, snuff, ST	Prostate (981)
Kabat *et al.* 1994 [97]	Denmark	1977–1990	Hospital	M+F	Chew, snuff	Oral (1,560)
Bundgaard *et al.* 1995 [98]	5 countries[h]	1986–1990	Population	M+F	Chew	Oral (161)
McLaughlin *et al.* 1995 [99]	USA	1989–1991	Population	M+F	ST	Kidney (1,732)
Muscat *et al.* 1995 [100]	USA	1977–1993	Hospital	M	Chew	Kidney (543)
Muscat *et al.* 1997 [101]	Sweden	1985–1993	Hospital	M	Chew, snuff	Pancreas (290)
Lewin *et al.* 1998 [102]		1980–1989	Population	M	Snuff	Oral (266), larynx (157), oesophagus (122)
Muscat and Wynder 1998 [103]	USA	1977–1980	Hospital	M+F	Chew, ST	Oral (128)
Schildt *et al.* 1998 [104]	Sweden	1980–1989	Population	M+F	Chew, snuff, ST	Oral (410)
Schwartz *et al.* 1998 [105]	USA	1990–1995	Population	M	ST	Oral (165)
Yuan *et al.* 1998 [106]	USA	1986–1994	Population	M+F	ST	Kidney (1,204)
Ye *et al.* 1999 [107]	Sweden	1989–1995	Population	M+F	Chew, snuff	Stomach (514)
Lagergren *et al.* 2000 [108]	Sweden	1995–1997	Population	M+F	Snuff	Oesophagus (189), stomach (429)
Zheng *et al.* 2001 [109]	USA	NA	Population	M+F	Chew, snuff	Brain (375)
Schroeder *et al.* 2002 [110]	USA	1980–1982	Population	M	Chew, snuff, ST	Non-Hodgkin's lymphoma (182)
Alguacil and Silverman 2004 [111]	USA	1986–1989	Population	M+F	ST	Pancreas (526)
Bracci and Holly 2005 [112]	USA	1988–1993	Population	M	ST	Non-Hodgkin's lymphoma (725)
Rosenquist *et al.* 2005 [113]	Sweden	2000–2004	Population	M+F	Snuff	Oral (132)
Hassan *et al.* 2007 [114]	USA	2000–2006	Hospital	M+F	Chew, snuff, ST	Pancreas (808)

[a]NA = not available.
[b]M = male, F = female, M+F = both sexes. Studies of both sexes with results reported only for males are shown as M.
[c]Only exposures for which results are available are shown.
[d]Oral (oropharyngeal) is defined as in Weitkunat et al. 2007 [4] to include any of the following sites: buccal mucosa, floor of mouth, gingival, gum/palate, lip, oral cavity/mouth, pharynx/alveolus, tongue, tonsils, salivary glands and oral unspecified. This reference also shows the actual sites included for most of the studies included here. For other cancers, more precise definitions of site or histology are given, where relevant, in the tables presenting the findings. Numbers of cases are totals for the sexes specified. Numbers of cases exposed to ST are shown in the tables presenting results by site.
[e]Results were presented for the following 'known tobacco-related' sites: oral (298 cases), oesophagus (72), larynx (119), lung (931) and bladder (306), with comparisons made with all other 'non-related' sites. Results were also presented for various non-related sites: stomach (266), small intestine (19), colon (722), rectum (339), liver (45), gall bladder/bile duct (81), pancreas (224) breast (1,177), cervix (266), uterus (38), ovary (180), vulva (31), prostate (531), male genitalia (53), kidney (126), connective tissue (84), melanoma (99), nervous system (136), thyroid gland (94), lymphosarcoma (121), Hodgkin's disease (84), other lymphomas (33), multiple myeloma (86), leukaemia (172) and other or unknown primaries (385), with comparisons made with all other non-related sites combined.
[f]Includes larynx cancer.
[g]"Attributable oral cancer risk due to smokeless tobacco use based on a case-control study at Sinai Hospital in Detroit"; Perry et al., unpublished. Cited by Gross et al. 1995 [91].
[h]Australia, Denmark, Germany, Sweden and USA.
ST = smokeless tobacco.

presented in the source publication, based on methods [115-118] summarised elsewhere [4]. Where an effect estimate cannot be calculated, statements made by the authors are summarised into terms such as 'no association' or 'no significant association'. Data are summarised for all types of cancer, except those relating to subdivision by type within site (for example, adenocarcinoma or squamous cell carcinoma of the lung, or t(14; 18)-positive and -negative non-Hodgkin's lymphoma or those relating to combined 'other' groups of cancers, which typically vary in definition from study to study).

Data presentation

Study-specific results for the different types of cancer are presented in an essentially identical format, with a standard set of information included for each effect estimate included. Points to note about the entries in the various columns are discussed below.

Source

For the case-control studies, the source reference is shown. For the cohort studies, the source reference is also shown, but the study is also identified by name.

smoking. The *smoking-adjusted* analyses only include estimates that are for the whole population and adjusted for smoking or are for never smokers. The *never smokers* analyses are restricted to estimates for never smokers. For oropharyngeal cancer, where more estimates are available, some additional meta-analysis results are shown, based on estimates that are smoking and alcohol adjusted, and on estimates published since 1990.

To avoid double-counting multiple non-independent estimates from the same study, estimates from each study are selected for inclusion in the meta-analyses using order of preference lists for ST exposure (ever use/unspecified use/current use/former use), then smoking status (any – based on the combined population of smokers and non-smokers/never smokers), and then ST type (ST/snuff/chew), with each list being in order of most to least preferred. At each step we retain those estimates highest up the list, discarding any estimate lower in the preference order. If the procedure ends up with separate estimates for males and for females, both are included in the analysis. In one study [36], the results available are for males for chewing and for females for snuff (see Table 3). Although the procedure, strictly applied, selects only the snuff estimate, it was decided to include both in the relevant meta-analyses.

The presentation of the meta-analyses shows the number of estimates combined; the identification numbers of these estimates (so that they can be related to the preceding table of individual effect estimates); the combined random-effects estimate, with its 95% CI [116], the chi-squared and *P* value of homogeneity [119] and the I^2 statistic [120]. The meta-analyses conducted also include a test for publication bias [121] where five or more estimates are combined. Findings significant at $P < 0.1$ are indicated.

Forest plots are also included for most of the cancers. These are generally based on the smoking-adjusted analyses, with the estimates split by region and shown with cohort data first, then case-control, presented in order of publication year.

Sensitivity analysis

For each estimate included, the value of Q^2 is calculated by $w(x - \bar{x})^2$, where w is the inverse-variance weight, x is the logarithm of the effect size and $\bar{x}$ its mean. Q^2 is the contribution of the estimate to the heterogeneity chi-squared statistic [116]. Where there is significant ($P < 0.05$) heterogeneity of estimates, sensitivity to potentially outlying estimates is tested by removing that with the largest Q^2 value and rerunning the analyses. This process is continued until there is no longer significant heterogeneity.

Sensitivity to the criterion for including estimates based on ST exposure is also tested by rerunning the meta-analyses with the preference list for ST exposure changed from ever use/unspecified use/current use/former use to current use/ever use/unspecified use/former use.

Meta-regression analysis

For oropharyngeal cancer, fixed-effects regression analysis is used to investigate how the estimates selected for the first set of meta-analyses vary by region (USA; Scandinavia; other), period × study type (cohort; case-control published before 1990; case-control published after 1990), sex (male; female; combined), ST exposure (ever or unspecified use; current use), smoking (any, adjusted for smoking; any, unadjusted for smoking; never) and alcohol adjustment (yes; no). For those other cancers where more than five estimates are available and where there was evidence of significant ($P < 0.05$) heterogeneity, the meta-regression analyses use a more limited variable list: region, sex, and smoking as above, and also study type (cohort; case-control).

Regression analyses are only conducted based on the overall data and smoking-adjusted data. The analyses successively introduce the most significant factor into the model, stopping when no further factor significant at $P < 0.05$ can be added. Significance is estimated by treating the ratio of the deviance per degree of freedom (d.f.) explained by the factor to the residual deviance per d.f. as an F statistic. For oropharyngeal cancer some additional analyses investigate the drop in deviance resulting from introducing each factor individually, and others are conducted having excluded 'outlying' observations with a very high Q^2 value.

Estimating deaths attributable to smoking

RRs for current and former cigarette smokers (compared with never cigarette smokers) for men aged 35+ for seven major cancers caused by smoking (lip/oral cavity/pharynx, oesophagus, pancreas, larynx, lung, bladder, kidney/other urinary organs) were obtained from the American Cancer Society Cancer Prevention Study II (CPS-II) [122]. Numbers of deaths for these seven cancers occurring in US men aged 35+ in 2005 were obtained from WHO [123]. Estimates of the proportion of current and former cigarette smokers in US men aged 35+ in 2005 were obtained from the National Health Interview Survey [124].

Defining D_i as the number of deaths for cancer i (i = 1,..., 7), R_{ci} and R_{fi} as the RRs for current and former cigarette smokers for cancer i, and p_c and p_f as the proportions of current and former cigarette smokers in the population, the estimated number of deaths, D_i^*, that would have occurred

Table 3: Oropharyngeal cancer; individual effect (relative risk/odds ratio) estimates

Source[a]	ST use				RR/OR			
	Type[b]	Exposure[c]	Smoking	Sex	Id.	Cases[d]	Estimate (95%CI)	Adjustment factors[e]
Cohort studies								
US Veterans: Zahm *et al.* 1992 [17]	ST	Ever	Any	M[f]	1	129	4.11 (2.90–5.84)[g]	age, time
CPS-I: Henley *et al.* 2005 [23]	ST	Current	Never	M	2	4	2.02 (0.53–7.74)	age, afc, asp, bmi, diet, edu, exer, occ, race
CPS-II: Henley *et al.* 2005 [23]	ST	Current	Never	M	3	1	0.90 (0.12–6.71)	age, alc, asp, bmi, diet, edu, exer, occ, race
Norway Cohorts: Boffetta *et al.* 2005 [26]	Snuff	Current	Any	M	4	6	1.13 (0.45–2.83)	age, smok
		Former			5	3	1.04 (0.31–3.50)	
		Ever			6	9	1.10 (0.50–2.41)	
Swedish construction workers: Luo *et al.* 2007 [32]	Snuff	Ever	Any	M	7	NA	0.70 (0.50–0.90)	age, bmi, smok
		Current	Never		8	9	0.90 (0.40–1.80)	age, bmi
		Former			9	1	0.70 (0.10–5.00)	
		Ever			10	10	0.80 (0.40–1.70)	
Uppsala County: Roosaar *et al.* 2008 [35]	Snuff	Ever	Any	M	11	11	3.10 (1.50–6.60)	age, alc, res, smok, time
			Never		12	5	2.30 (0.70–8.30)	age, alc, res, time
Case-control studies								
Broders 1920 [37]	Chew	Use	Any	M+F	13	128	2.05 (1.48–2.83)[g]	smok
	Snuff				14	2	1.76 (0.12–26.52)[g]	none
	ST				15	130	2.05 (1.48–2.83)[g]	
Moore *et al.* 1953 [39]	ST	Use	Any	M	16	65	3.00 (1.37–6.54)[g]	none
Wynder *et al.* 1957 [40]	Chew	Ever	Any	M	17	NA	no association[h]	none
Wynder and Bross 1957 [41]	Chew	Ever	Any	M	18	91	2.00 (1.16–3.47)[g]	smok
Peacock *et al.* 1960 [42]	ST	Use	Any	M	19	14	3.06 (1.08–8.63)[g]	age, ins
				F	20	11	2.00 (0.66–6.01)[g]	
Vogler *et al.* 1962 [36]	Chew	Ever	Any	M	21	46	7.38 (4.31–12.62)[g]	none
	Snuff			F	22	54	38.28 (21.49–68.15)[g]	
Vincent and Marchetta 1963 [45]	Snuff	Use	Any	M	23	12	4.22 (1.41–12.63)[g]	none
Martinez *et al.* 1969 [49]	Chew	Use	Any	M	24	4	2.29 (0.62–8.48)[g]	none
				F	25	1	0.34 (0.04–2.79)[g]	
Keller 1970 [50]	ST	Use	Any	M	26	11	3.63 (1.02–12.95)[g]	smok
			Never		27	4	3.04 (0.62–14.99)[g]	
Browne *et al.* 1977 [54]	Chew	Use	Any	M+F	28	7	0.67 (0.27–1.66)[g]	none
Williams and Horm 1977 [55]	ST	Ever	Any	M	29	16	0.91 (0.53–1.56)[g]	none
				F	30	2	1.54 (0.37–6.42)[g]	
Wynder and Stellman 1977 [56]	Chew	Ever	Any	M	31	10	0.62 (0.32–1.21)[g]	none
	Snuff				32	61	1.15 (0.85–1.55)[g]	
	ST				33	71	1.02 (0.78–1.34)[i]	
Westbrook *et al.* 1980 [59]	Snuff	Ever	Any	F	34	50	540.00 (60.97–4782.82)[g]	none
Winn *et al.* 1981 [61]	Snuff	Ever	Any	F	35	107	2.67 (1.83–3.90)[g]	race, smok
Wynder *et al.* 1983 [63]	Chew	Ever	Any	M	36	37	1.00 (0.62–1.61)[g]	none
	Snuff				37	12	0.42 (0.11–1.65)[g]	
	ST				38	49	0.90 (0.57–1.41)[i]	
Stockwell and Lyman 1986 [70]	ST	Ever	Any	M+F	39	11	2.02 (1.01–4.02)[g]	none
Young *et al.* 1986 [71]	ST	Ever	Any	M	40	NA	no association	none
Blot *et al.* 1988 [74]	ST	Ever	Any	M	41	46	0.85 (0.57–1.26)[g]	none
				F	42	11	3.44 (1.09–10.91)[g]	
			Never	F	43	6	6.20 (1.90–19.80)	age, race, res, resp
Spitz *et al.* 1988 [78]	Chew	Ever	Any	M+F	44	23	1.00 (0.54–1.85)[g]	none
	Snuff				45	9	3.40 (1.00–10.90)	
	ST				46	25	1.05 (0.57–1.91)[g]	
Franco *et al.* 1989 [80]	ST	Use	Any	M+F	47	9	1.40 (0.59–3.33)[g]	none
Blomqvist *et al.* 1991 [83]	Snuff	Ever	Never	M+F	48	2	0.67 (0.08–5.75)[g]	none
Maden *et al.* 1992 [85]	ST	Ever	Any	M	49	19	4.50 (1.50–14.30)	age
Marshall *et al.* 1992 [86]	Chew	Use	Any	M	50	NA	no significant association	none
Sterling *et al.* 1992 [89]	ST	Ever	Any	M+F	51	28[g]	1.04 (0.41–2.68)[g]	age, alc, occ, race, sex, smok
	Snuff	Ever	Any	M+F	52	NA	2.42 (1.28–4.59)	age, race, sex
Mashberg *et al.* 1993 [90]	Chew	Ever	Any	M[f]	53	NA	1.00 (0.70–1.40)	age, alc, race, smok
	Snuff				54	NA	0.80 (0.40–1.90)	
	ST				55	52	0.96 (0.70–1.33)[i]	

Table 3: Oropharyngeal cancer; individual effect (relative risk/odds ratio) estimates *(Continued)*

Perry *et al.* 1993[j]	ST	Use	Any	M+F	56	10	1.43 (0.64–3.21)[g]	age, alc, occ, race, sex, smok
Spitz *et al.* 1993 [92]	Chew	Use	Any	M+F	57	NA	1.20 (not significant)	none
Kabat *et al.* 1994 [97]	Chew	Ever	Any	M	58	67	1.11 (0.81–1.53)[g]	smok
	Snuff	Ever	Never	M+F	59	4	4.79 (1.19–19.30)[g]	none
Bundgaard *et al.* 1995 [98]	Chew	Ever	Any	M+F	60	8	1.44 (0.59–3.51)[g]	none
Lewin *et al.* 1998 [102]	Snuff	Current	Any	M	61	18	0.84 (0.47–1.50)[g]	age, alc, res, smok
		Former			62	22	1.28 (0.70–2.35)[g]	
		Ever			63	40	0.98 (0.63–1.50)[g]	
Muscat *et al.* 1998 [103]	Chew	Ever	Any	M+F	64	3	0.89 (0.18–4.49)[g]	none
	ST				65	4	1.19 (0.26–5.45)[i]	
Schildt *et al.* 1998 [104]	Chew	Use	Any	M+F	66	5	0.60 (0.20–2.00)	age, sex, res
	Snuff	Current			67[j]	39	0.70 (0.40–1.10)	
		Former			68	28	1.50 (0.80–2.90)	
		Ever			69	67	0.80 (0.50–1.30)	age, alc, sex, smok, res
		Current	Never		70	19	0.70 (0.40–1.20)	age, sex, res
		Former			71	9	1.80 (0.90–3.50)	
		Ever			72	28	1.01 (0.64–1.57)[g]	
	ST	Ever	Any		73	72	0.87 (0.61–1.25)[i]	none
Schwartz *et al.* 1998 [105]	ST	Ever	Any	M	74	NA	1.00 (0.40–2.30)	age, alc, smok
Rosenquist *et al.* 2005 [113]	Snuff	Current	Any	M+F	75	13	1.10 (0.50–2.50)	alc, smok
		Former			76	7	0.30 (0.10–0.90)	
		Ever			77	20	0.70 (0.30–1.30)	

[a]Fuller details of the studies are given in Tables 1 and 2.
[b]ST implies smokeless tobacco unspecified, or combined snuff use or chewing.
[c]Ever, former and current ST use were compared with never ST. Use indicates timing not given and comparison is with non use.
[d]'Id.' is the RR/OR identification number used in Table 4, and 'Cases' is the number of cases in ST users as defined. NA = not available.
[e]Abbreviations used: alc = alcohol, asp = aspirin, bmi = body mass index, edu = education, exer = exercise, ins = insurance status, occ = occupation, res = area of residence, resp = respondent, smok = smoking.
[f]The population included < 0.5% females.
[g]RR/OR and/or 95% CI estimated from data provided in the source.
[h]The average ridit duration of chewing did not differ significantly from the controls for any type of oral cancer.
[i]RR/OR and/or 95% CI estimated from data provided in the source assuming that no one both chewed and used snuff.
[j]"Attributable oral cancer risk due to smokeless tobacco use based on a case-control study at Sinai Hospital in Detroit", Perry et al., unpublished. Cited by Gross et al. 1995 [91].
CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

had the whole population the risk of never smokers, is then estimated by:

$$D_i^* = D_i / (1 + p_c(R_{ci} - 1) + p_f(R_{fi} - 1))$$

The number of deaths avoided from these seven cancers, had the whole population the risk of never smokers (that is, the deaths attributable to smoking) is then estimated by:

$$E = \sum_{i=1}^{7} (D_i - D_i^*)$$

Estimating deaths attributable to ST in a population of never smokers

Let us further define R_{si} as the estimated relative risk from ST for cancer i based on the meta-analyses using smoking-adjusted effect estimates. Where R_{si} is estimated to be less than 1, it is taken to be 1 for the purposes of calculating deaths attributable to ST.

For a population of never smokers, the number of deaths from cancer i that would have occurred had the same proportion of men used ST as had ever smoked is then estimated by:

$$D_i^{**} = D_i^*(1 + (p_c + p_f)(R_{si} - 1))$$

The increase in overall deaths from these seven cancers is then given by:

$$I_1 = \sum_{i=1}^{7} (D_i^{**} - D_i^*)$$

I_1 can then be compared with E as an indicator of the relative effects of ST and smoking.

Also for a population of never smokers, the number of deaths from cancer i that would have occurred had all the men used ST, is estimated by:

$$D_i^{***} = D_i^* R_{si}$$

The increase, compared with E, is then calculated by:

$$I_2 = \sum_{i=1}^{7} (D_i^{****} - D_i^{*})$$

Results

The MEDLINE search identified 690 publications. Two hundred and thirty-eight were rejected as describing studies conducted in Asia or Africa or relating to products typically used there, 96 as not describing epidemiological studies, 112 as not relating to cancer and 163 as being reviews, letters or comments not providing primary data. Seventeen were rejected as having an inappropriate study design and three as not providing relevant results. This left 61 apparently relevant publications. Taking into account also citations in recent reviews [1-6,10], and eliminating publications that referred to studies more recently or completely covered in other publications, a total of 104 publications were considered. Twenty-five related to nine cohort studies, and 79 to 80 case-control studies. Fuller details of the search are given in Figure 1, whilst the studies and publications considered are presented in the following two sections.

Cohort studies

Results relating ST use to mortality or incidence have been reported for nine cohort studies, with results provided by multiple publications for some studies. Six studies have been conducted in the USA and are based on the Lutheran Brotherhood cohort [11-14], the US Veterans cohort [15-19], the Iowa cohort [20], the First National Health and Nutrition Examination Survey (NHANES I) Follow-up cohort [21,22], and the American Cancer Society Cancer Prevention Study I (CPS-I) [23] and Study II (CPS-II) [23-25]. One study was based on two Norway cohorts [14,26,27] while the remaining two were conducted in Sweden; one based on construction workers [28-34], and the other on a cohort in Uppsala County [35]. Fuller details of these studies are given in Table 1. A number of these studies (US Veterans, CPS-I, CPS-II, Swedish Construction Workers) are extremely large, involving at least 100,000 subjects, though the number of ST users is less than this,

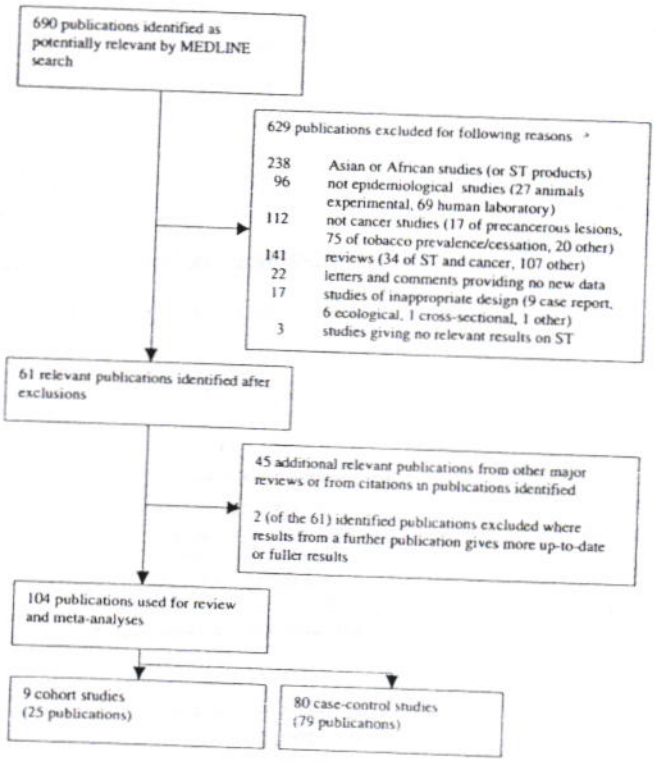

Figure 1

Flow chart for search strategy for review of literature on smokeless tobacco and cancer. The flow chart shows the number of publications identified by the MEDLINE search, and the number excluded by reason. The number of additional publications identified from reviews and secondary references is also indicated, as is the total number of publications considered in the review and meta-analysis, subdivided by study type.

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Table 4: Oropharyngeal cancer; meta-analysis results

Type of ST (region)[a]	Adjustments/ restrictions[b]	Number of estimates (RR/OR ids)[c]	Random-effects RR/OR (95% CI)	Heterogeneity χ^2	I^2	$P(\chi^2)$
Any	Overall data	n = 41 (1, 2, 3, 6, 7, 11, 15, 16, 18, 19, 20, 21, 22, 23, 24, 25, 26, 28, 29, 30, 33, 34, 35, 38, 39, 41, 42, 46, 47, 48, 49, 51, 55, 56, 58, 60, 63, 65, 73, 74, 77)	1.79 (1.36–2.36)	335.6	88.1	< 0.001
	Smoking-adjusted	n = 19 (2, 3, 6, 7, 11, 13, 18, 26, 35, 43, 48, 51, 55, 56, 58, 63, 69, 74, 77)	1.36 (1.04–1.77)	69.5	74.1	< 0.001
	Smoking and alcohol adjusted	n = 10 (2, 3, 11, 51, 55, 56, 63, 69, 74, 77)	1.07 (0.84–1.37)	12.5	28.0	0.186
	Never smokers	n = 9 (2, 3, 10, 12, 27, 43, 48, 59, 72)	1.72 (1.01–2.94)	15.9	49.7	0.044
	Never smokers – alcohol adjusted	n = 3 (2, 3, 12)	1.87 (0.82–4.27)	0.6	0.0	0.731
Any (USA)[d]	Overall data	n = 31 (1, 2, 3, 15, 16, 18, 19, 20, 21, 22, 23, 24, 25, 26, 29, 30, 33, 34, 35, 38, 39, 41, 42, 46, 49, 51, 55, 56, 58, 65, 74)	2.16 (1.55–3.02)	275.8	89.1	< 0.001
	Smoking-adjusted	n = 12 (2, 3, 13, 18, 26, 35, 43, 51, 55, 56, 58, 74)	1.65 (1.22–2.25)	33.6	67.3	< 0.001
	Smoking and alcohol adjusted	n = 6 (2, 3, 51, 55, 56, 74)	1.04 (0.80–1.35)	1.8	0.0	0.875
	Never smokers	n = 5 (2, 3, 27, 43, 59)	3.33 (1.76–6.32)	3.5	0.0	0.476
	Never smokers – alcohol adjusted	n = 2 (2, 3)	1.58 (0.52–4.81)	0.4	0.0	0.512
Snuff (Scandinavia)	Overall data	n = 7 (6, 7, 11, 48, 63, 69, 77)	0.97 (0.68–1.37)	14.5	58.8	0.024
	Smoking-adjusted	n = 7 (6, 7, 11, 48, 63, 69, 77)	0.97 (0.68–1.37)	14.5	58.8	0.024
	Smoking and alcohol adjusted	n = 4 (11, 63, 69, 77)	1.10 (0.64–1.90)	10.7	71.9	0.014
	Never smokers	n = 4 (10, 12, 48, 72)	1.01 (0.71–1.45)	2.2	0.0	0.524
	Never smokers – alcohol adjusted	n = 1 (12)	2.30 (0.67–7.92)	–	–	–
Published since 1990	Overall data	n = 18 (1, 2, 3, 6, 7, 11, 48, 49, 51, 55, 56, 58, 60, 63, 65, 73, 74, 77)	1.28 (0.94–1.76)	81.7	79.2	< 0.001
	Smoking-adjusted	n = 14 (2, 3, 6, 7, 11, 48, 51, 55, 56, 58, 63, 69, 74, 77)	1.00 (0.83–1.20)	18.5	29.8	0.139
	Smoking and alcohol adjusted	n = 10 (2, 3, 11, 51, 55, 56, 63, 69, 74, 77)	1.07 (0.84–1.37)	12.5	28.0	0.186
	Never smokers	n = 7 (2, 3, 10, 12, 48, 59, 72)	1.24 (0.80–1.90)	7.5	20.1	0.277
	Never smokers – alcohol adjusted	n = 3 (2, 3, 12)	1.87 (0.82–4.27)	0.6	0.0	0.731

[a]For each study/sex, the RR/OR for ST from Table 3 was included if available, otherwise that for chewing tobacco or snuff was used.
[b]Smoking-adjusted includes estimates for smokers and non-smokers combined, adjusted for smoking if available, and estimates for never smokers otherwise.
[c]The actual estimates included are identified by their RR/OR identification numbers as given in Table 3.
[d]Includes estimates 24 and 25 from a study in Puerto Rico [49].
CI = confidence interval; ST = smokeless tobacco; OR = odds ratio, RR = relative risk.

into the current analysis. The overall data show an association with any ST use (1.79, 1.36–2.36) that, though highly significant, is based on an extremely heterogeneous set of estimates ($P < 0.001$). Limiting consideration to smoking-adjusted data, the estimate reduces substantially, to 1.36 (1.04–1.77, $n = 19$), though it is still significant, and marked heterogeneity remains ($P < 0.001$). Further limiting attention to estimates adjusted for both smoking and alcohol, the two major risk factors for oropharyngeal cancer [7,8], eliminates both heterogeneity and excess risk (1.07, 0.84–1.37, $n = 10$). A significant relationship is seen in never smokers (1.72, 1.01–2.94, $n = 9$), though the estimates are heterogeneous ($P = 0.044$), and generally based on a very small number of oropharyngeal cancer cases that used ST.

When the analyses are restricted to US studies, the pattern is similar to that for the overall data, with the effect estimates reduced when attention is limited to those that are smoking-adjusted, and close to 1.0 when estimates that are adjusted both for smoking and alcohol are considered. The effect estimate for never smokers is significantly increased (3.33, 1.76–6.32), based on five small studies, in total involving 19 ST-exposed oropharyngeal cancer cases.

No real evidence of a relationship with snuff use is seen in studies conducted in Scandinavia, where seven estimates, all adjusted for smoking, and four additionally adjusted for alcohol, give a combined estimate of 0.97 (0.68–1.37). However some heterogeneity should be noted, a high RR of 3.1 (1.5–6.6) in the Uppsala County study [35] conflicting with six other estimates ranging from 0.67 to 1.10.

Many of the higher estimates seen in Table 4 come from older studies which often did not adjust for smoking. If attention is limited to studies published since 1990, which generally did adjust, no association is seen. Indeed, the combined estimate from the 14 smoking-adjusted studies published since 1990 is 1.00 (0.83–1.20), and shows no significant heterogeneity.

While the choice of 1990 as the cut-point was not defined *a priori*, the change in estimates about that time is very clear. As shown in Figure 2, smoking-adjusted estimates for case-control studies published between 1920 and 1988 are consistently high (overall 2.38, 95% CI 1.87–3.04), while estimates for case-control studies published between 1991 and 2005 show no association at all (0.98, 0.83–1.16). There is no evidence of heterogeneity within either period ($P = 0.34$ for pre-1990 and $P = 0.93$ for post-1990) and a highly significant ($P < 0.001$) difference between estimates in the two periods. Smoking-adjusted estimates for the cohort studies which, though published between 2005 and 2008, generally cover a long follow-up period extending from before 1990, give an intermediate result (1.32, 0.65–2.68).

The findings are very similar to those in an earlier review [4]. That review provides additional meta-analyses of the slightly smaller data set, further investigating variation by type of ST, sex, study design, study location and study period. It also provides full details of the various types of cancer that have been considered in the source papers.

The evidence presented suggests that snuff as used in Scandinavia has no effect on oropharyngeal cancer risk. Products used in the past in the USA may have increased the risk but any effect that exists now seems likely to be quite small.

Oesophageal cancer

Table 5 summarises the data from four cohort and 10 case-control studies. For five of these studies effect estimates with CI are not available, one of these [52] reporting a 'synergistic effect of tobacco chewing and alcohol', another [19] presenting a RR of 2.28, but not whether it was significant, and the others [14,40,60] showing no significant relationship. Of the remaining nine studies, six provide smoking-adjusted estimates, three of which are also adjusted for alcohol. Though estimates are generally somewhat above 1.0 in these nine studies, they are rarely significant, exceptions being the estimate of 1.92 (1.00–3.68) for snuff in never smokers in the Swedish Construction Workers study [34] and that for chewing of 2.39 (1.23–4.64) in the Wynder and Bross case-control study [44].

The meta-analyses (see Table 6 and Figure 3) show some indication of an association, though this is not always statistically significant. Based on all available smoking-adjusted data, the combined estimate for any ST use is 1.13 (0.95–1.36, $n = 7$), somewhat lower than when there is no restriction to smoking-adjusted data (1.25, 1.03–1.51, $n = 10$). The corresponding analyses show no real indication of an effect for snuff in Scandinavia, but are more suggestive for the USA. Even here, the smoking-adjusted estimate is not significant (1.89, 0.84–4.25), though this is based on only three small studies, involving a total of 11 cases using ST. The estimates based on all the available smoking-adjusted data include an any smoking RR of 1.00 (0.79–1.27) from the study with the largest weight, the Swedish Construction Workers study [34], this RR being derived by combining the findings for adenocarcinoma and squamous cell carcinoma. The meta-analyses for never smokers give a higher combined estimate of 1.91 (1.15–3.17, $n = 4$) for any ST use, mainly because they use a higher (combined adeno/squamous) estimate of 1.92 (1.00–3.68) for the Swedish Construction Workers study [34].

Overall, the data must be regarded as providing suggestive evidence of a possible weak relationship between ST use and oesophageal cancer.

Stomach cancer

Table 7 presents results from 12 studies, eight of which provide a total of 17 estimates which could be used in meta-analyses. Although the Swedish construction workers study [34] shows a significant increase in risk of stomach cancer associated with snuff use for never smokers (RR 1.33, 95% CI 1.03–1.72), no other significant associations are reported, and the meta-analyses conducted (see Table 8 and Figure 4) are all non-significant. Based on smoking-adjusted estimates from eight studies, the combined RR estimate is 1.03 (95% CI 0.88–1.20). Four studies did not provide

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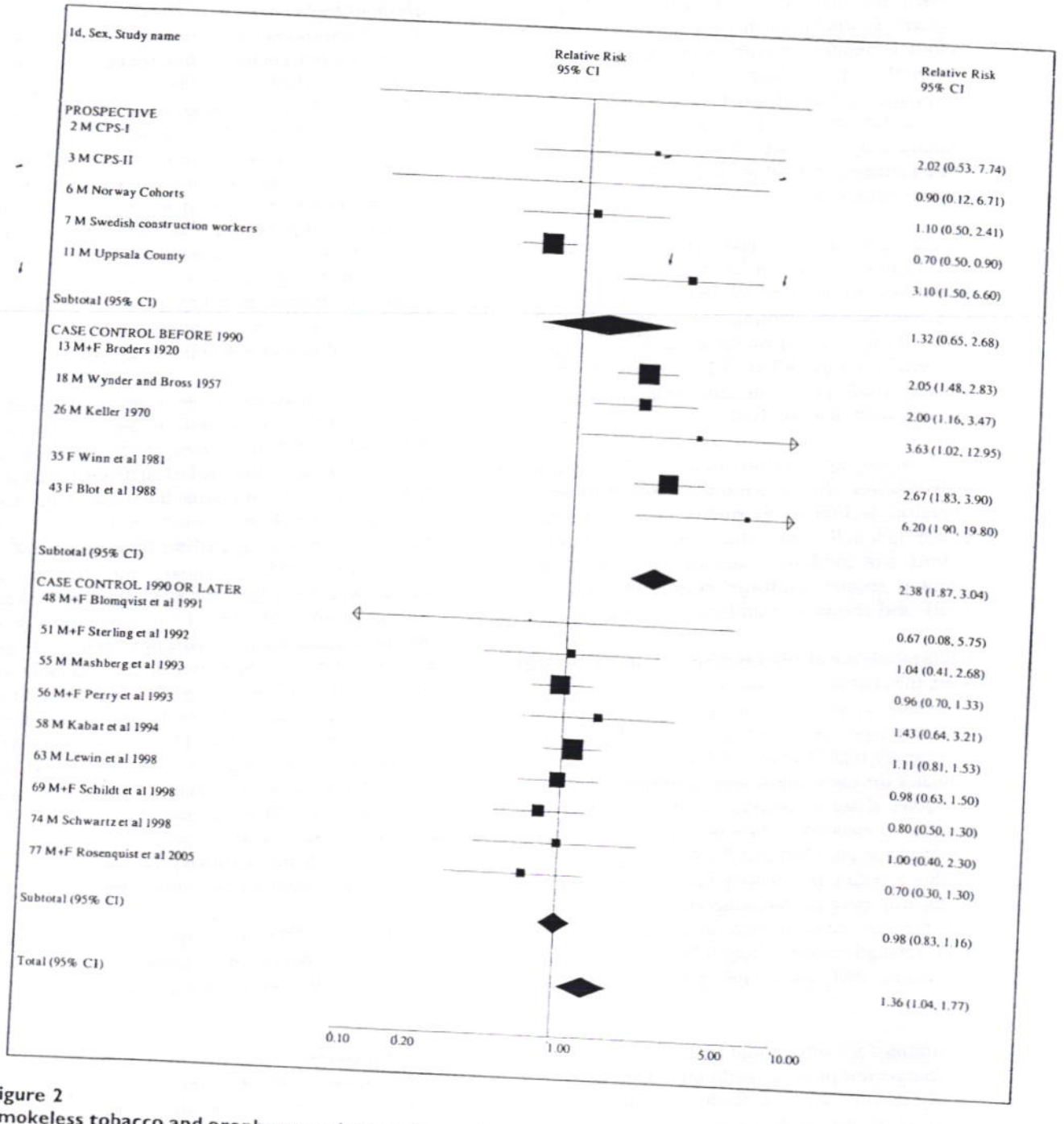

Figure 2

Smokeless tobacco and oropharyngeal cancer by study type and period of publication (smoking-adjusted data). The 19 individual smoking-adjusted relative risk (RR) and 95% confidence interval (CI) estimates separated by study type, and for case-control studies by period of publication, are shown numerically and also graphically on a logarithmic scale. They are sorted in order of year of publication. In the graphical representation individual RR estimates are indicated by a solid square, with the area of the square proportional to the weight (inverse-variance) of the estimate. Also shown are the combined estimates, for the subgroups and overall, derived by random-effects meta-analysis. These are represented by a diamond of standard height, with the width indicating the 95% CI. See Table 3 for further details relating to the estimates, and Table 4 for fuller details of the meta-analyses.

Table 5: Oesophageal cancer; individual effect (relative risk/odds ratio) estimates

Source[a]	ST use				RR/OR			
	Type[b]	Exposure[c]	Smoking	Sex[d]	Id.	Cases[e]	Estimate (95%CI)[d]	Adjustment factors[f]
Cohort studies								
Lutheran Brotherhood: IARC Monograph 37 1985 [14]	ST	Ever	Any	M	1	NA	2.6 (not significant)	age, res
US Veterans: Winn *et al.* 1982 [19]	ST	Ever	Never	M[g]	2	1	2.28 (NA)	age
Norway cohorts: Boffetta *et al.* 2005 [26]	Snuff	Current	Any	M	3	4	1.06 (0.35–3.23)	age, smok
		Former		M	4	5	1.90 (0.69–5.27)	
		Ever		M	5	9	1.40 (0.61–3.24)	
Swedish construction workers: Zendehdel *et al.* 2008 [34]	Snuff	Ever	Any	M	6	77	1.00 (0.79–1.27)[h]	age, bmi, smok
			Never		7	11	1.92 (1.00–3.68)[i]	age, bmi
Case-control studies								
Wynder *et al.* 1957 [40]	Chew	Ever	Any	M	8	NA	no association[j]	none
Wynder and Bross 1961 [44]	Chew	Ever	Any	M	9	21	2.39 (1.23–4.64)[k]	none
Martinez *et al.* 1969 [49]	Chew	Use	Never	M	10	3	1.18 (0.28–4.90)[k]	none
				F	11	7	2.69 (0.92–7.87)[k]	
Bjelke *et al.* 1974 USA [52]	Chew	Use	NA	NA	12	NA	association[l]	NA
Williams and Horm 1977 [55]	ST	Ever	Any	M	13	2	0.55 (0.13–2.31)	none
Wynder and Stellman 1977 [56]	Chew	Ever	Any	M	14	20	1.23 (0.76–1.99)[k]	none
	Snuff				15	8	1.65 (0.78–3.49)[k]	
	ST				16	28	1.35 (0.89–2.06)[m]	
Pottern *et al.* 1981 [60]	Chew	Ever	Any	M	17	4	no association[n]	none
	Snuff				18	2	no association[n]	
Morris Brown *et al.* 1988 [76]	ST	Ever	Never	M	19	1	1.20 (0.10–13.30)	alc, incm
Lewin *et al.* 1998 [102]	Snuff	Current	Any	M	20	10	1.10 (0.50–2.40)	age, alc, res, smok
		Former			21	9	1.30 (0.60–3.10)	
		Ever			22	19	1.20 (0.70–2.20)	
Lagergren *et al.* 2000 [108]	Snuff	Ever	Any	M+F	23	68	1.31 (0.89–1.92)[k]	age, alc, bmi, diet, edu, exer, rflx, sex, smok

[a]Fuller details of the studies are given in Tables 1 and 2.
[b]ST implies smokeless tobacco unspecified, or combined snuff use or chewing.
[c]Ever, former and current ST use were compared with never ST. Use indicates timing not given and comparison is with non-use.
[d]NA = not available.
[e]'Id.' is the RR/OR identification number used in Table 6, and 'Cases' is the number of cases in ST users as defined. NA = not available.
[f]Abbreviations used: alc = alcohol, bmi = body mass index, edu = education, exer = exercise, incm = incidence or mortality, res = area of residence, rflx = reflux symptoms, smok = smoking, NA = not available.
[g]The population included < 0.5% females.
[h]RRs for adenocarcinoma (1.0, 95% CI 0.6–1.5) and squamous cell carcinoma (1.0, 0.8–1.4) combined.
[i]RRs for adenocarcinoma (0.2, 95% CI 0.0–1.9) and squamous cell carcinoma (3.5, 1.6–7.6) combined.
[j]The average ridit duration of chewing was non-significantly lower in the oesophageal cancer cases.
[k]RR/OR and/or 95% CI estimated from data provided in the source.
[l]The abstract noted a "synergistic effect of tobacco chewing and alcohol".
[m]RR/OR and/or 95% CI estimated from data provided in the source assuming that no one both chewed and used snuff.
[n]The authors noted the percentage of ever users was "slightly higher" in the controls than in the cases for chewing but not for snuff.
CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

detailed data. No association with stomach cancer was reported by Weinberg *et al.* [67] or for the US data considered by Bjelke [52]. However, Bjelke did report an "Association ... with tobacco chewing" for the Norwegian data, and a standardised mortality ratio of 1.51 was given for the US Veterans' Study [19], but not whether this was statistically significant.

The combined evidence does not indicate an effect of ST use on the risk of stomach cancer.

Pancreatic cancer

Table 9 presents results from four cohort and seven case-control studies. For four of the studies effect estimates that can be included in meta-analyses are not available; two [75,84] of these studies merely reported finding no association, one [19] reported an elevated RR of 1.65 with no CI, and another [82] a reduced RR of 0.80, also with no CI. Of the other seven studies, significant increases have been reported in two. The Norway cohorts study [26] reports an increase in ever users of snuff in a

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Table 8: Stomach cancer; meta-analysis results

Type of ST (region)[a]	Adjustments/restrictions[b]	Number of estimates (RR/OR ids)[c]	Random-effects RR/OR (95% CI)	Heterogeneity		
				χ^2	I^2	$P(\chi^2)$
Any	Overall data	9 (1, 6, 9, 10, 14, 15, 17, 19, 21)	1.03 (0.90–1.19)	10.5	24.0	0.230
	Smoking-adjusted	8 (1, 6, 9, 10, 14, 17, 19, 21)	1.03 (0.88–1.20)	10.3	31.9	0.173
	Never smokers	4 (2, 6, 11, 20)	1.27 (0.75–2.13)	7.0	57.2	0.072
Any (USA)	Overall data	4 (1, 6, 14, 15)	1.41 (0.95–2.10)	0.1	0.0	0.988
	Smoking-adjusted	3 (1, 6, 14)	1.41 (0.93–2.12)	0.1	0.0	0.942
	Never smokers	2 (2, 6)	1.96 (0.82–4.70)	1.6	38.2	0.203
Snuff (Scandinavia)	Overall data	5 (9, 10, 17, 19, 21)	0.98 (0.82–1.17)	8.1	50.4	0.089
	Smoking-adjusted	5 (9, 10, 17, 19, 21)	0.98 (0.82–1.17)	8.1	50.4	0.089
	Never smokers	2 (11, 20)	0.90 (0.35–2.30)	4.2	76.4	0.040

[a]For each study/sex, the RR/OR for ST from Table 7 was included if available, otherwise that for chewing tobacco or snuff was used.
[b]Smoking-adjusted includes estimates for smokers and non-smokers combined, adjusted for smoking if available, and estimates for never smokers otherwise.
[c]The actual estimates included are identified by their RR/OR identification numbers as given in Table 7.
CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

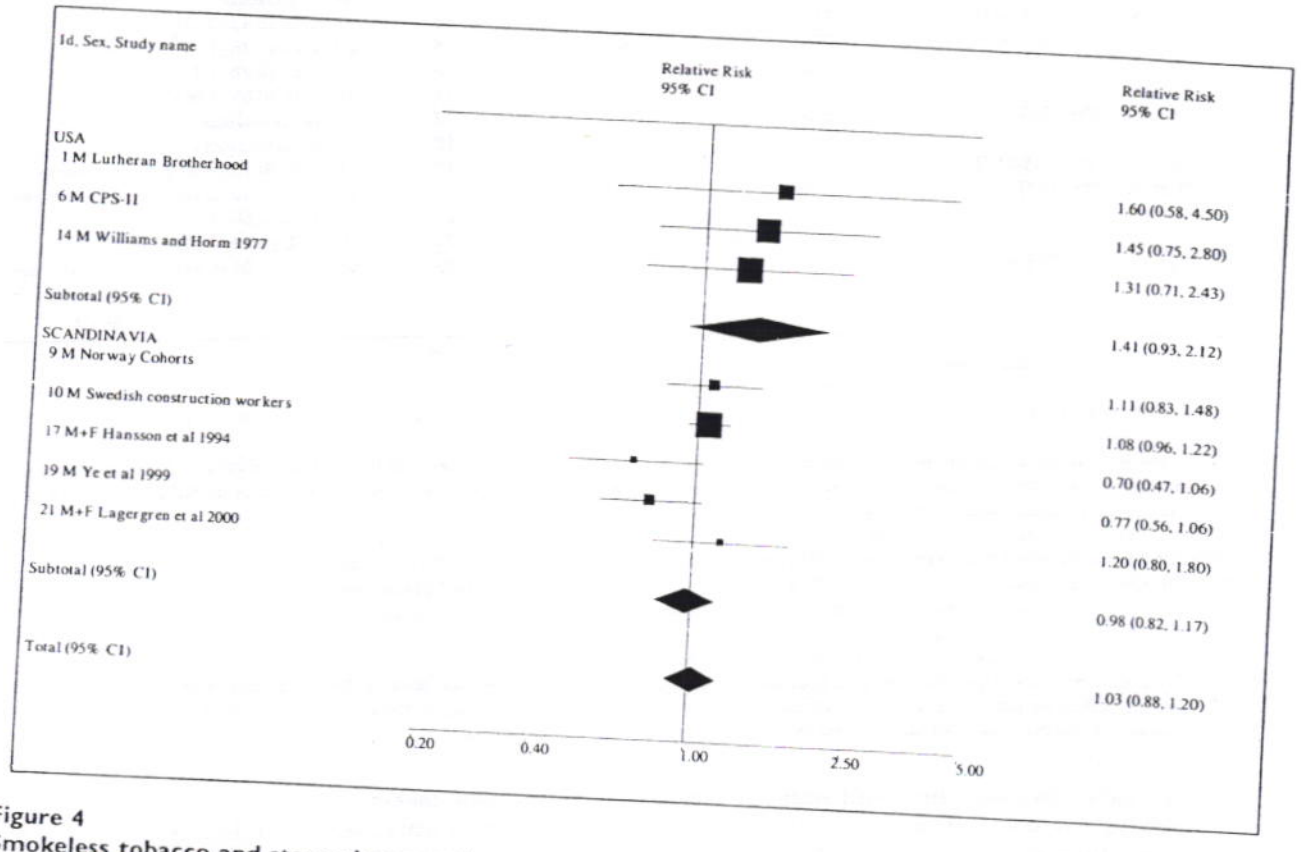

Figure 4

Smokeless tobacco and stomach cancer by region (smoking-adjusted data). The eight individual smoking-adjusted relative risk (RR) and 95% confidence interval (CI) estimates, separated by region, are shown numerically and also graphically on a logarithmic scale. They are sorted in order of year of publication within study type (cohort, case-control). In the graphical representation individual RR estimates are indicated by a solid square, with the area of the square proportional to the weight (inverse-variance) of the estimate. Also shown are the combined estimates, for the subgroups and overall, derived by random-effects meta-analysis. These are represented by a diamond of standard height, with the width indicating the 95% CI. See Table 7 for further details relating to the estimates, and Table 8 for fuller details of the meta-analyses.

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Table 9: Pancreatic cancer; individual effect (relative risk/odds ratio) estimates

Source[a]	ST use		Smoking	Sex	RR/OR			
	Type[b]	Exposure[c]			Id.	Cases[d]	Estimate (95%CI)[e]	Adjustment factors[f]
Cohort studies								
Lutheran Brotherhood: Zheng *et al.* 1993 [13]	ST	Ever	Any	M	1	16	1.70 (0.90–3.10)	age, alc, smok
US Veterans: Winn *et al.* 1982 [19]	ST	Ever	Never	M[g]	2	NA	1.65 (NA)	age
Norway cohorts: Boffetta *et al.* 2005 [26]	Snuff	Current	Any	M	3	27	1.60 (1.00–2.55)	age, smok
		Former			4	18	1.80 (1.04–3.09)	
		Ever			5	45	1.67 (1.12–2.50)	
		Ever	Never		6	3	0.85 (0.24–3.07)	age
Swedish construction workers: Luo *et al.* 2007 [32]	Snuff	Ever	Any	M	7	NA	0.90 (0.70–1.20)	age, bmi, smok
		Current	Never		8	18	2.10 (1.20–3.60)	age, bmi
		Former			9	2	1.40 (0.40–5.90)	
		Ever			10	20	2.00 (1.20–3.30)	
Case-control studies								
Williams and Horm 1977[55]	ST	Ever	Any	M	11	3	0.29 (0.09–0.92)[h]	age, race, smok
Falk *et al.* 1988 [75]	Chew	Use	Any	M+F	12	NA	no association	none
	Snuff				13	NA	no association	
Farrow and Davis 1990 [82]	Chew	Ever	Any	M	14	NA	0.80 (NA)	edu, race
Ghadirian *et al.* 1991[84]	Chew	Use	Any	M+F	15	NA	no association	none
Muscat *et al.* 1997 [101]	Chew	Ever	Never[i]	M	16	6	2.82 (0.85–9.39)[j]	none
	Snuff		Any		17	2	1.32 (0.22–7.93)	
Alguacil and Silverman 2004 [111]	ST	Ever	Never[k]	M+F	18	5	1.10 (0.40–3.10)	age, race, res, sex, smok[k]
Hassan *et al.* 2007 [114]	Chew	Ever	Any	M+F	19	34	0.70 (0.40–1.10)	age, alc, diab, edu, mar, race, res, sex, smok
			Never		20	10	0.60 (0.30–1.40)	age, alc, diab, edu, mar, race, res, sex
	Snuff	Ever	Any		21	18	0.60 (0.30–1.10)	age, alc, diab, edu, mar, race, res, sex, smok
			Never		22	4	0.50 (0.10–1.50)	age, alc, diab, edu, mar, race, res, sex
	ST	Ever	Any		23	52	0.65 (0.43–0.97)[l]	age, alc, diab, edu, mar, race, res, sex, smok
			Never		24	14	0.57 (0.29–1.11)[l]	age, alc, diab, edu, mar, race, res, sex

[a]Fuller details of the studies are given in Tables 1 and 2.
[b]ST implies smokeless tobacco unspecified, or combined snuff use or chewing.
[c]Ever, former and current ST use were compared with never ST. Use indicates timing not given and comparison is with non use.
[d]'Id.' is the RR/OR identification number used in Table 10, and 'Cases' is the number of cases in ST users as defined. NA = not available.
[e]NA = not available.
[f]Abbreviations used: alc = alcohol consumption, bmi = body mass index, diab = diabetes, edu = education, mar = marital status, res = area of residence, smok = smoking.
[g]The population included < 0.5% females.
[h]RR/OR and/or 95% CI estimated from data provided in the source.
[i]Includes long-term (10+ years) quitters.
[j]Personal communication from Dr Muscat. The estimate given in the source of 3.60 (1.00–12.80) is for noncurrent smokers.
[k]Estimates are for never cigarette smokers with adjustment for other tobacco use.
[l]RR/OR and/or 95% CI estimated from data provided in the source assuming that no one both chewed and used snuff.
CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

cohort and five case-control, with one or two studies providing data for colon cancer, rectal cancer, colorectal cancer, small intestine cancer, liver cancer, gall bladder and bile duct cancer. These data, which are insufficient for meta-analysis, include two statistically significant effect estimates: an RR of 1.9 (1.2–3.1) for rectal cancer and ST use from the US Veterans study [18] and a remarkably high OR from the case-control study of Chow *et al.* [93] of 18.0 (1.4–227.7) for bile duct cancer and chewing tobacco, based on only three exposed cases.

There are rather more data for the combined category of all cancers of the digestive system. Of the four studies providing data, all conducted in the USA, NHANES I

Table 10: Pancreatic cancer; meta-analysis results

Type of ST (region)[a]	Adjustments/restrictions[b]	Number of estimates (RR/OR ids)[c]	Random-effects RR/OR (95% CI)	Heterogeneity		
				χ^2	I^2	$P(\chi^2)$
Any	Overall data	7 (1, 5, 7, 11, 17, 18, 23)	1.00 (0.68–1.47)	18.5	67.5	0.005
	Smoking-adjusted	7 (1, 5, 7, 11, 16, 18, 23)	1.07 (0.71–1.60)	21.2	71.7	0.002
	Never smokers	5 (6, 10, 16, 18, 24)	1.23 (0.66–2.31)	10.7	62.7	0.030
Any (USA)	Overall data	5 (1, 11, 17, 18, 23)	0.86 (0.47–1.57)	10.2	61.0	0.037
	Smoking-adjusted	5 (1, 11, 16, 18, 23)	0.99 (0.51–1.91)	13.8	71.0	0.008
	Never smokers	3 (16, 18, 24)	1.09 (0.44–2.67)	5.4	63.0	0.067
Snuff (Scandinavia)	Overall data	2 (5, 7)	1.20 (0.66–2.20)	6.3	84.1	0.012
	Smoking-adjusted	2 (5, 7)	1.20 (0.66–2.20)	6.3	84.1	0.012
	Never smokers	2 (6, 10)	1.61 (0.77–3.34)	1.5	33.2	0.221

[a]For each study/sex, the RR/OR for ST from Table 9 was included if available, otherwise that for chewing tobacco or snuff was used.
[b]Smoking-adjusted includes estimates for smokers and non-smokers combined, adjusted for smoking if available, and estimates for never smokers otherwise.
[c]The actual estimates included are identified by their RR/OR identification numbers as given in Table 9.
CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

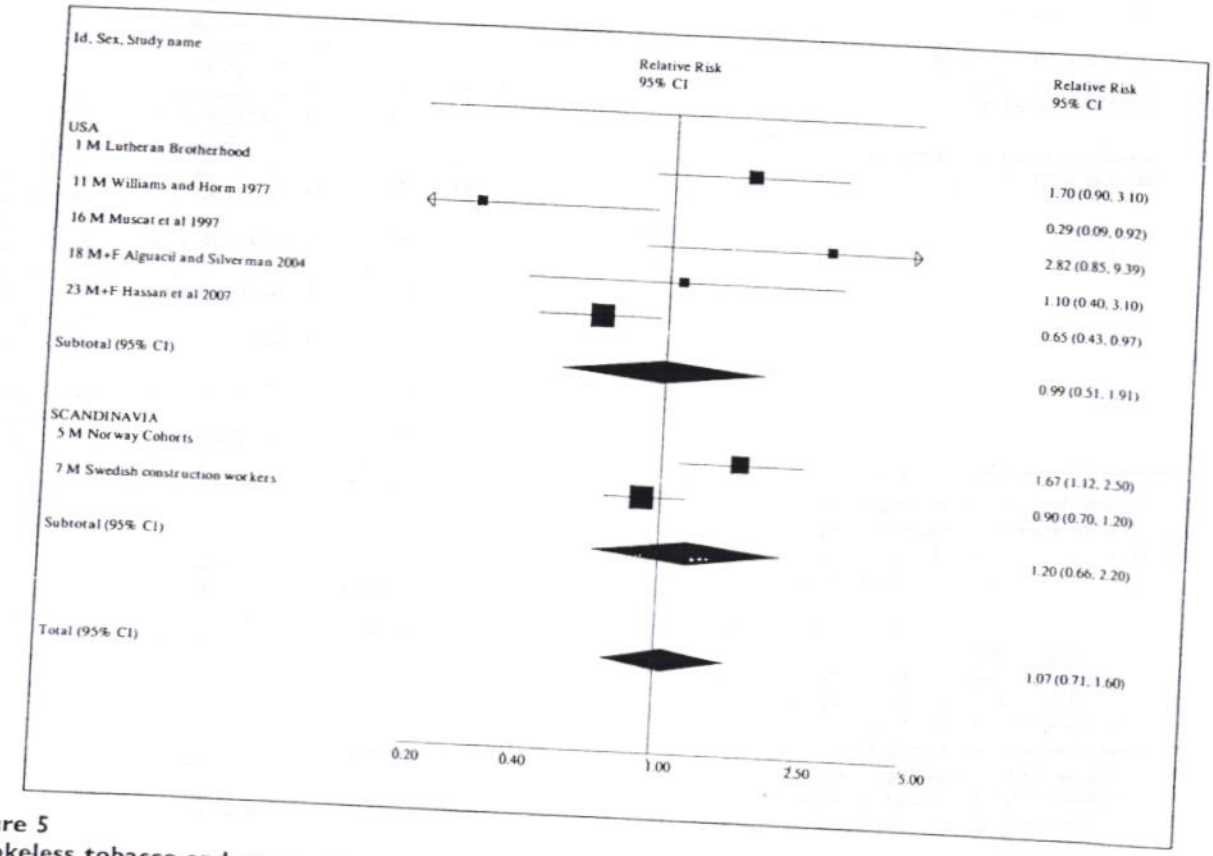

Figure 5

Smokeless tobacco and pancreatic cancer by region (smoking-adjusted data). The seven individual smoking-adjusted relative risk (RR) and 95% confidence interval (CI) estimates, separated by region, are shown numerically and also graphically on a logarithmic scale. They are sorted in order of year of publication within study type (cohort, case-control). In the graphical representation individual RR estimates are indicated by a solid square, with the area of the square proportional to the weight (inverse-variance) of the estimate. Also shown are the combined estimates, for the subgroups and overall, derived by random-effects meta-analysis. These are represented by a diamond of standard height, with the width indicating the 95% CI. See Table 9 for further details relating to the estimates, and Table 10 for fuller details of the meta-analyses.

Table 11: Other cancers of the digestive system; individual effect (relative risk/odds ratio) estimates

Source[a]	ST use				RR/OR			
	Type[b]	Exposure[c]	Smoking	Sex[d]	Id.	Cases[e]	Estimate (95%CI)[d]	Adjustment factors[f]
Cohort studies								
US Veterans: Heineman *et al.* 1995 [18]								
- colon cancer	ST	Ever	Never	M[g]	1	39	1.20 (0.90–1.70)[h]	age, sed, ses, time, yriv
- rectal cancer			Never		2	17	1.90 (1.20–3.10)[h]	
US Veterans: Winn *et al.* 1982 [19]								
- liver cancer	ST	Ever	Never	M[g]	3	NA	2.81 (NA)	age
NHANES I: Accortt *et al.* 2005 [22]								
- digestive cancer	ST	Ever	Never	M	4	13	0.80 (0.40–1.80)	age, pov, race
				F	5	4	0.80 (0.30–2.40)	
CPS-I: Henley *et al.* 2005 [23]								
- digestive cancer	ST	Current	Never	M	6	153	1.26 (1.05–1.52)	age, alc, asp, bmi, diet, edu, exer, occ, race
CPS-II: Henley *et al.* 2005 [23]								
- digestive cancer	ST	Current	Never	M	7	48	1.04 (0.77–1.38)	age, alc, asp, bmi, diet, edu, exer, occ, race
		Former			8	19	0.99 (0.63–1.57)	
		Ever			9	67	1.03 (0.80–1.31)[h]	
Case-control studies								
Bjelke 1974 [52] USA								
- colorectal cancer	Chew	Use	Any	NA	10	NA	No association	NA
Bjelke 1974 [52] Norway								
- colorectal cancer	Chew	Use	Any	NA	11	NA	No association	NA
Williams and Horm 1977 [55]								
- small intestine cancer	ST	Ever	Any	M	12	2	3.11 (0.65–14.8)[h]	age, race, smok
- colon cancer	ST	Ever	Any	M	13	30	1.36 (0.90–2.07)[h]	age, race, smok
				F	14	7	1.28 (0.58–2.87)[h]	
- rectal cancer	ST	Ever	Any	M	15	13	0.75 (0.42–1.35)[h]	age, race, smok
				F	16	2	0.87 (0.21–3.62)[h]	
- liver cancer	ST	Ever	Any	M	17	1	0.58 (0.08–4.39)[h]	none
- gall bladder cancer	ST	Ever	Any	M	18	1	0.41 (0.05–3.04)[h]	none
Sterling *et al.* 1992 [89]								
- digestive cancer	ST	Ever	Any	M+F	19	555	0.40 (0.24–0.69)[h]	age, alc, occ, race, sex, smok
Chow *et al.* 1994 [93]								
- bile duct cancer[i]	Chew	Use	Any	M	20	3	18.0 (1.40–227.70)	NA

[a]Fuller details of the studies are given in Tables 1 and 2.
[b]ST implies smokeless tobacco unspecified, or combined snuff use or chewing.
[c]Ever, former and current ST use were compared with never ST. Use indicates timing not given and comparison is with non use.
[d]NA = not available.
[e]'Id.' is the RR/OR identification number used in Table 12, and 'Cases' is the number of cases in ST users as defined. NA = not available.
[f]Abbreviations used: alc = alcohol, asp = aspirin, bmi = body mass index, edu = education, exer = exercise, occ = occupation, pov = poverty, sed = sedentary lifestyle, ses = socioeconomic status, smok = smoking, yriv = year of interview, NA = not available.
[g]The population included < 0.5% females.
[h]RR/OR and/or 95% CI estimated from data provided in the source.
[i]Results are for cancer of ampulla of Vater; extrahepatic bile duct cancers were also studied, but results were not given for chewing.
CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

[22] and CPS-II [23] show no relationship, CPS-I [23] a weak, but significant, positive relationship, and the case-control study of Sterling *et al.* [89] a significant negative relationship. Overall, the combined estimate (see Table 12 and Figure 6), all based on smoking-adjusted data, is 0.86 (0.59–1.25, $n = 5$), with significant evidence of heterogeneity ($P = 0.002$). The analysis for never smokers removes the case-control study and eliminates the heterogeneity. However the combined estimate of 1.14 (0.99–1.33, $n = 4$) remains non-significant.

More data are needed before any conclusion can be drawn for these cancers.

Table 12: Overall digestive cancer; meta-analysis results

Type of ST (region)[a]	Adjustments/restrictions[b]	Number of estimates (RR/OR ids)[c]	Random-effects RR/OR (95% CI)	Heterogeneity χ^2	I^2	$P(\chi^2)$
Any (USA)[d]	Overall data	5 (4, 5, 6, 9, 19)	0.86 (0.59–1.25)	17.3	76.9	0.002
	Smoking-adjusted	5 (4, 5, 6, 9, 19)	0.86 (0.59–1.25)	17.3	76.9	0.002
	Never smokers	4 (4, 5, 6, 9)	1.14 (0.99–1.33)	3.1	2.1	0.382

[a]For each study/sex, the RR/OR for ST from Table 11 was included if available, otherwise that for chewing tobacco or snuff was used.
[b]Smoking-adjusted includes estimates for smokers and non-smokers combined, adjusted for smoking if available, and estimates for never smokers otherwise.
[c]The actual estimates included are identified by their RR/OR identification numbers as given in Table 11.
[d]All the available data for overall digestive cancer are from US studies.
CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

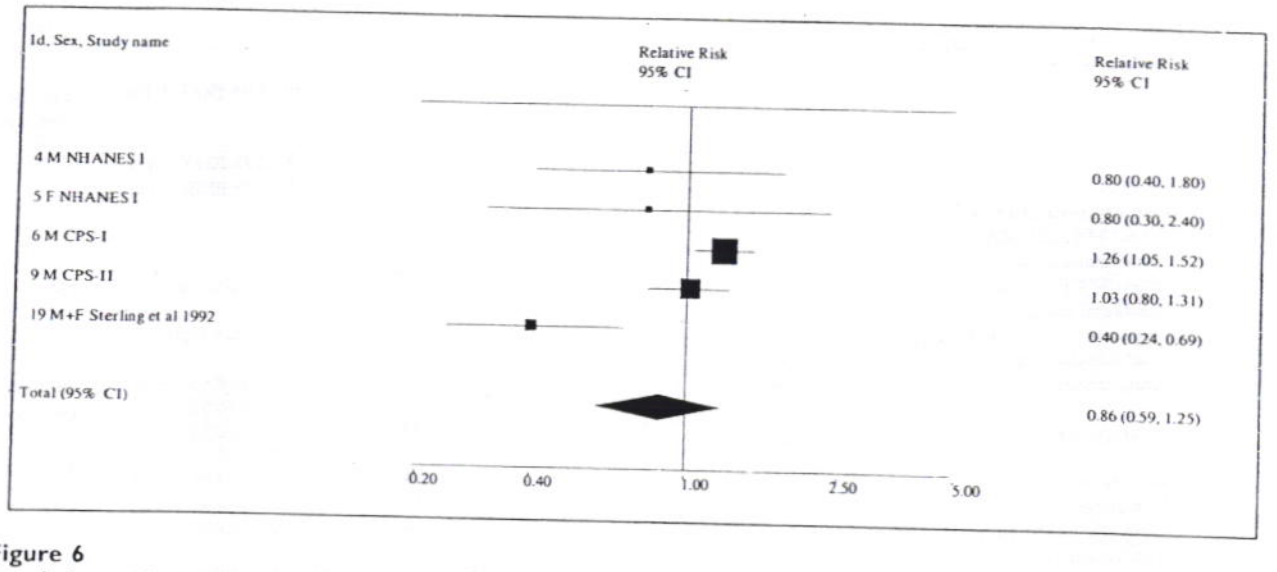

Figure 6
Smokeless tobacco and overall digestive cancer (USA smoking-adjusted data). The five individual relative risk (RR) and 95% confidence interval (CI) estimates, all smoking-adjusted and for the USA, are shown numerically and also graphically on a logarithmic scale. They are sorted in order of year of publication within study type (cohort, case-control). In the graphical representation individual RR estimates are indicated by a solid square, with the area of the square proportional to the weight (inverse-variance) of the estimate. Also shown is the combined estimate, derived by random-effects meta-analysis. This is represented by a diamond of standard height, with the width indicating the 95% CI. See Table 11 for further details relating to the estimates, and Table 12 for fuller details of the meta-analysis.

Larynx and nasal cancer

The data shown in Table 13 are quite limited. The evidence for nasal cancer is based on only three studies, none reporting a significant association with ST use. Seven studies investigated the relationship of ST to larynx cancer, two providing no effect estimates and merely reporting a lack of association. Control for confounding variables is very limited, with only two studies providing estimates adjusted for smoking, only one adjusting for alcohol and no study presenting any results for never smokers. The only study to adjust for smoking and alcohol [102], which shows no relationship of snuff to risk of larynx cancer, is the only study conducted in Scandinavia. Two US studies [55,56] report a significant relationship, however, and, as shown in Table 14 (see also Figure 7), an association is seen in the overall data (1.43, 1.08–1.89, $n = 5$).

Given the independent role of smoking and alcohol in larynx cancer [7,8], and the lack of association in the one study that has adjusted for both these factors [102], any independent association of ST use with larynx cancer risk has not been established. More data are needed before any conclusion can be drawn on the role of ST in larynx and nasal cancers.

Table 13: Larynx and nasal cancer; individual effect (relative risk/odds ratio) estimates

Source[a]	ST use				RR/OR			
	Type[b]	Exposure[c]	Smoking	Sex	Id.	Cases[d]	Estimate (95%CI)	Adjustment factors[e]
Case-control studies								
Wynder *et al.* 1957 [40]								
- larynx cancer	Chew	Ever	Any	M	1	NA	no association[f]	none
Vincent and Marchetta 1963 [45]								
- larynx cancer	Snuff	Use	Any	M	2	5	1.81 (0.33–9.97)	none
Williams and Horm 1977 [55]								
- larynx cancer	ST	Ever	Any	M	3	16	2.01 (1.15–3.51)[g]	age, race, smok
Wynder and Stellman 1977 [56]								
- larynx cancer	Chew	Ever	Any	M	4	46	1.35 (0.96–1.89)[g]	none
	Snuff				5	15	1.46 (0.82–2.57)[g]	none
	ST				6	61	1.40 (1.04–1.89)[h]	none
Engzell *et al.* 1978 [57]								
- nasal cancer	Snuff	Use	Any	M	7	NA	no association	none
Brinton *et al.* 1984 [64]								
- nasal cancer	Chew	Use	Any	M+F	8	15	0.74 (0.40–1.50)	sex
	Snuff				9	23	1.47 (0.80–2.80)	
	ST				10	38	1.08 (0.68–1.70)[h]	none
Stockwell and Lyman 1986 [70]								
- nasal cancer	ST	Ever	Any	M+F	11	1	2.93 (0.40–21.66)[g]	none
- larynx cancer	ST	Ever	Any	M+F	12	6	2.02 (0.84–4.86)[g]	none
Young *et al.* 1986 [71]								
- larynx cancer	ST	Ever	Any	M	13	NA	no association	none
Lewin *et al.* 1998 [102]								
- larynx cancer	Snuff	Current	Any	M	14	15	1.00 (0.50–1.90)	age, alc, res, smok
		Former			15	9	0.80 (0.40–1.70)	
		Ever			16	24	0.90 (0.50–1.50)	

[a]Fuller details of the studies are given in Tables 1 and 2.
[b]ST implies smokeless tobacco unspecified, or combined snuff use or chewing.
[c]Ever, former and current ST use were compared with never ST. Use indicates timing not given and comparison is with non use.
[d]'Id.' is the RR/OR identification number used in Table 14, and 'Cases' is the number of cases in ST users as defined. NA = not available.
[e]Abbreviations used: alc = alcohol, res = area of residence, smok = smoking.
[f]The average ridit duration of chewing was non-significantly lower in the larynx cancer cases.
[g]RR/OR and/or 95% CI estimated from data provided in the source.
[h]RR/OR and/or 95% CI estimated from data provided in the source assuming that no one both chewed and used snuff.
CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

Lung cancer

Table 15 summarises data from six cohort and three case-control studies. The case-control studies provide only estimates for smokers and non-smokers combined, and only one of these is adjusted for smoking. The cohort studies all provide estimates for never smokers, with two also giving smoking-adjusted results for the overall population. The meta-analyses (see Table 16 and Figure 8) show no evidence that ST use increases risk of lung cancer, with the combined estimate for smoking-adjusted data 0.99 (95% CI 0.71–1.37). However, there is considerable heterogeneity ($P < 0.001$), the major contributors to this being the high RR of 6.80 (1.60–28.5) in never smokers in NHANES I [22], the significant increase of 1.77 (1.14–2.74) from CPS-II [23], and the low RR of 0.70 (0.60–0.70) for the Swedish construction workers study [32]. While the combined estimate for never smokers for any ST use is greater than 1.0 (1.34, 0.80–2.23, $n = 5$), it is not statistically significant.

While the data have unexplained heterogeneity, they do not provide any clear indication of a relationship of lung cancer to ST use.

Not included in Table 15 are results from an analysis conducted by Henley *et al.* in 2007 [25] based on follow-up of the CPS-II cohort from 1982 to 2002. They report an increased risk of lung cancer (1.46, 1.24–1.73) in men who switched from cigarette smoking to ST compared with those who quit entirely, after adjusting for age, other demographic variables, as well as variables associated with smoking history. This analysis may be biased by reliance on tobacco use data recorded in 1982, and by residual confounding, with the paper reporting

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Table 14: Larynx and nasal cancer; meta-analysis results

Type of ST (region)[a]	Adjustments/restrictions[b]	Number of estimates (RR/OR ids)[c]	Random-effects RR/OR (95% CI)	Heterogeneity		
				χ^2	I^2	$P(\chi^2)$
Larynx cancer[d]						
Any	Overall data	5 (2, 3, 6, 12, 16)	1.43 (1.08–1.89)	4.8	17.4	0.304
	Smoking-adjusted	2 (3, 16)	1.34 (0.61–2.95)	4.0	75.3	0.044
Any (USA)	Overall data	4 (2, 3, 6, 12)	1.56 (1.21–2.00)	1.7	0.0	0.646
	Smoking-adjusted	1 (3)	2.01 (1.15–3.51)	–	–	–
Snuff (Scandinavia)	Overall data	1 (16)	0.90 (0.50–1.50)	–	–	–
	Smoking-adjusted	1 (16)	0.90 (0.50–1.50)	–	–	–
Nasal cancer[e]						
Any	Overall data	2 (10, 11)	1.14 (0.73–1.77)	0.9	0.0	0.339

[a]For each study/sex, the RR/OR for ST from Table 13 was included if available, otherwise that for chewing tobacco or snuff was used.
[b]Smoking-adjusted includes estimates for smokers and non-smokers combined, adjusted for smoking if available, and estimates for never smokers otherwise.
[c]The actual estimates included are identified by their RR/OR identification numbers as given in Table 13.
[d]For larynx cancer there are no data for never smokers.
[e]For nasal cancer the only data are from US studies and not smoking-adjusted.
CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

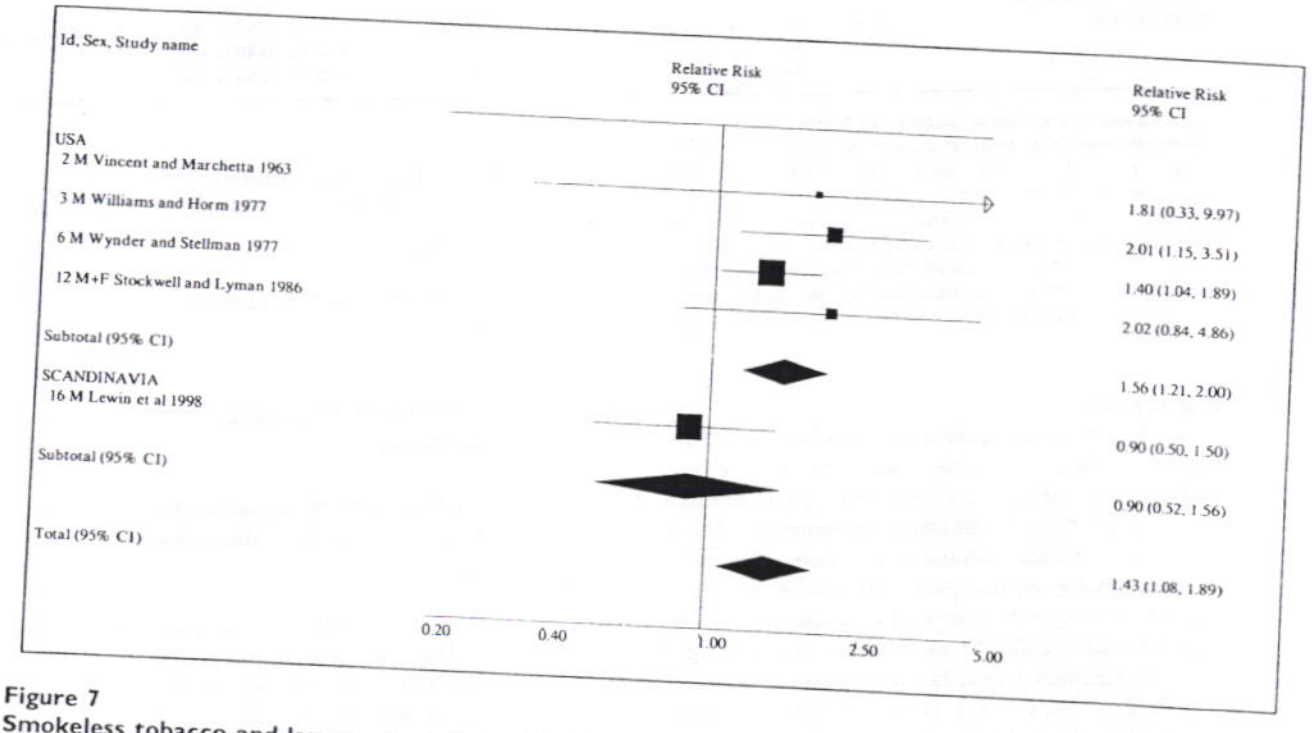

Figure 7

Smokeless tobacco and larynx cancer by region (overall data). The five individual relative risk (RR) and 95% confidence interval (CI) estimates, separated by region, are shown numerically and also graphically on a logarithmic scale. They are sorted in order of year of publication within study type (cohort, case-control). In the graphical representation individual RR estimates are indicated by a solid square, with the area of the square proportional to the weight (inverse-variance) of the estimate. Also shown are the combined estimates, for the subgroups and overall, derived by random-effects meta-analysis. These are represented by a diamond of standard height, with the width indicating the 95% CI. See Table 13 for further details relating to the estimates, and Table 14 for fuller details of the meta-analyses. Only estimates 3 and 16 are smoking adjusted.

Table 15: Lung cancer; individual effect (relative risk/odds ratio) estimates

Source[a]	ST use: Type[b]	ST use: Exposure[c]	Smoking	Sex	Id.	RR/OR: Cases[d]	RR/OR: Estimate (95%CI)[e]	Adjustment factors[f]
Cohort studies								
US Veterans: Winn *et al.* 1982 [19]	ST	Ever	Never	M[g]	1	NA	0.60 (NA)	age
NHANES I: Accortt *et al.* 2005 [22]	ST	Ever	Never	F	2	4	6.80 (1.60–28.5)	age, pov, race
CPS-I: Henley *et al.* 2005 [23]	ST	Current	Never	M	3	18	1.08 (0.64–1.83)	age, alc, asp, bmi, diet, edu, exer, occ, race
CPS-II: Henley *et al.* 2005 [23]	ST	Current	Never	M	4	18	2.00 (1.23–3.24)	age, alc, asp, bmi, diet, edu, exer, occ, race
	ST	Former			5	4	1.17 (0.43–3.14)	
	ST	Ever			6	22	1.77 (1.14–2.74)[h]	
	Chew only	Current			7	12	1.97 (1.10–3.54)	
	Snuff only				8	2	2.08 (0.51–8.46)	
Norway cohorts: Boffetta *et al.* 2005 [26]	Snuff	Current	Any	M	9	44	0.80 (0.58–1.11)	age, smok
		Former			10	28	0.80 (0.54–1.19)	
		Ever			11	72	0.80 (0.61–1.05)	
		Ever	Never		12	3	0.96 (0.26–3.56)	age
Swedish construction workers: Luo *et al.* 2007 [32]	Snuff	Ever	Any	M	13	NA	0.70 (0.60–0.70)	age, bmi, smok
		Current	Never		14	15	0.80 (0.40–1.30)	age, bmi
		Former			15	3	0.90 (0.30–3.00)	
		Ever			16	18	0.80 (0.50–1.30)	
Case-control studies								
Doll and Hill 1952 [38]	Chew	Ever	Any	M	17	40	0.61 (0.41–0.92)[h]	none
	Snuff				18	33	0.76 (0.48–1.21)[h]	
	ST				19	73	0.66 (0.41–0.90)[h]	
Williams and Horm 1977 [55]	ST	Ever	Any	M	20	36	0.69 (0.47–1.00)[h]	age, race, smok
				F	21	1	0.38 (0.05–2.80)[h]	none
Wynder and Stellman 1977 [56]	Chew	Ever	Any	M	22	117	1.26 (0.99–1.59)[h]	none
	Snuff				23	35	1.25 (0.83–1.89)[h]	
	ST				24	152	1.27 (1.03–1.57)[h]	

[a]Fuller details of the studies are given in Tables 1 and 2.
[b]ST implies smokeless tobacco unspecified, or combined snuff use or chewing.
[c]Ever, former and current ST use were compared with never ST. Use indicates timing not given and comparison is with non use.
[d]'Id.' is the RR/OR identification number used in Table 16, and 'Cases' is the number of cases in ST users as defined. NA = not available.
[e]NA = not available.
[f]Abbreviations used: alc = alcohol consumption, asp = aspirin, bmi = body mass index, edu = education, exer = exercise, occ = occupation, pov = poverty, smok = smoking.
[g]The population included < 0.5% females.
[h]RR/OR and/or 95% CI estimated from data provided in the source.
CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

marked differences between switchers and quitters in a range of characteristics, with adjustment substantially reducing the RR estimate from the age-adjusted estimate of 1.92 (1.63–3.26).

Prostate cancer

Table 17 presents data from five cohort and two case-control studies, all conducted in the USA. No significant association between ST and prostate cancer is evident in five studies, but significant increases are seen in the Lutheran Brotherhood Study [11] and, for current snuff users only, in the case-control study by Hayes *et al.* [96]. Based on the five studies which provide usable data, the overall estimate (see Table 18 and Figure 9) is 1.20 (95% CI 1.03–1.40).

Prostate cancer is not considered smoking related [7,8], and more information on its relationship with ST is needed before any clear conclusion can be drawn.

Table 16: Lung cancer; meta-analysis results

Type of ST (region)[a]	Adjustments/restrictions[b]	Number of estimates (RR/OR ids)[c]	Random-effects RR/OR (95% CI)	Heterogeneity χ^2	I^2	$P(\chi^2)$
Any	Overall data	9 (2, 3, 6, 11, 13, 19, 20, 21, 24)	0.96 (0.73–1.27)	53.2	85.0	< 0.001
	Smoking-adjusted	6 (2, 3, 6, 11, 13, 20)	0.99 (0.71–1.37)[d]	28.7	82.6	< 0.001
	Never smokers	5 (2, 3, 6, 12, 16)	1.34 (0.80–2.23)	11.5	65.3	0.021
Any (USA)	Overall data	6 (2, 3, 6, 20, 21, 24)	1.22 (0.82–1.83)	18.5	73.0	0.002
	Smoking-adjusted	4 (2, 3, 6, 20)	1.38 (0.72–2.64)	16.5	81.9	0.001
	Never smokers	3 (2, 3, 6)	1.79 (0.91–3.51)	6.2	67.8	0.045
Snuff (Scandinavia)	Overall data	2 (11, 13)	0.71 (0.66–0.76)	0.9	0.0	0.354
	Smoking-adjusted	2 (11, 13)	0.71 (0.66–0.76)	0.9	0.0	0.354
	Never smokers	2 (12, 16)	0.82 (0.52–1.28)	0.1	0.0	0.798

[a]For each study/sex, the RR/OR for ST from Table 15 was included if available, otherwise that for chewing tobacco or snuff was used.
[b]Smoking-adjusted includes estimates for smokers and non-smokers combined, adjusted for smoking if available, and estimates for never smokers otherwise.
[c]The actual estimates included are identified by their RR/OR identification numbers as given in Table 15.
[d]Test for publication bias $0.05 \leq P < 0.1$.
CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

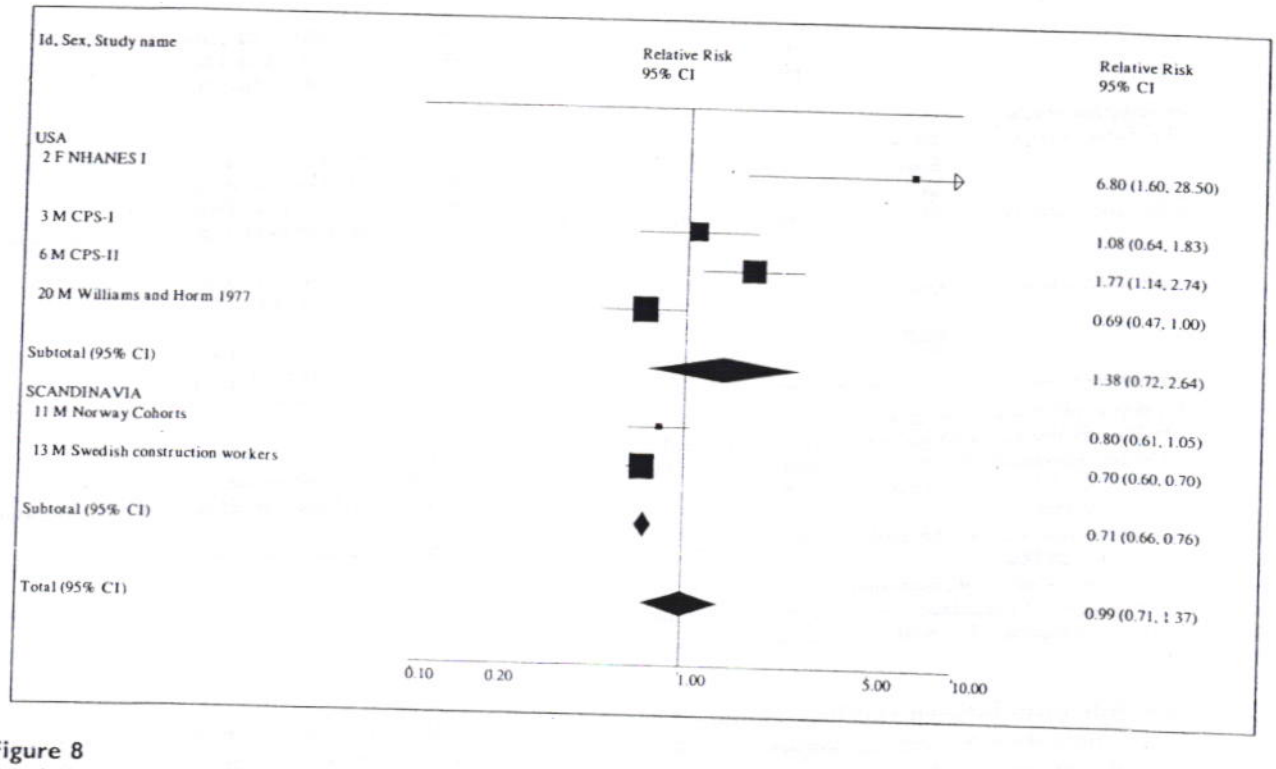

Figure 8
Smokeless tobacco and lung cancer by region (smoking-adjusted data). The six individual smoking-adjusted relative risk (RR) and 95% confidence interval (CI) estimates, separated by region, are shown numerically and also graphically on a logarithmic scale. They are sorted in order of year of publication within study type (cohort, case-control). In the graphical representation individual RR estimates are indicated by a solid square, with the area of the square proportional to the weight (inverse-variance) of the estimate. Also shown are the combined estimates, for the subgroups and overall, derived by random-effects meta-analysis. These are represented by a diamond of standard height, with the width indicating the 95% CI. See Table 15 for further details relating to the estimates, and Table 16 for fuller details of the meta-analyses.

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Table 17: Prostate cancer; individual effect (relative risk/odds ratio) estimates

Source[a]	ST use: Type[b]	ST use: Exposure[c]	Smoking	Id.	RR/OR: Cases[d]	RR/OR: Estimate (95%CI)	Adjustment factors[e]
Cohort studies							
Lutheran Brotherhood: Hsing *et al.* 1990 [11]	ST	Ever	Any	1	38	1.51 (1.03–2.19)[f]	age, smok
			Never	2	10	4.50 (2.10–9.70)	age
US Veterans: Hsing *et al.* 1991 [15]	ST	Ever	Never	3	48	1.17 (0.88–1.56)	age
Iowa cohort: Putnam *et al.* 2000 [20]	ST	Ever	Any	4	NA	no association	age
NHANES I: Accortt *et al.* 2005 [22]	ST	Ever	Never	5	19	1.20 (0.50–3.40)	age, pov, race
Norway cohorts: IARC Monograph 37 1985 [14]	ST	Use	Any	6	NA	no association	age, res, smok
Case-control studies							
Williams and Horm 1977 [55]	ST	Ever	Any	7	65	1.32 (0.94–1.84)[f]	age, race, smok
Hayes *et al.* 1994 [96]	Chew	Current	Any	8	14	0.56 (0.30–1.06)[f]	none
		Former		9	56	1.08 (0.75–1.55)[f]	
		Ever		10	70	0.91 (0.67–1.25)[f]	
	Snuff	Current	Any	11	10	6.74 (1.47–30.84)[f]	
		Former		12	10	0.79 (0.36–1.74)[f]	
		Ever		13	20	1.42 (0.75–2.67)[f]	
	ST	Current	Any	14	24	0.92 (0.54–1.58)[g]	
		Former		15	66	1.03 (0.74–1.43)[g]	
		Ever		16	90	1.00 (0.75–1.33)[g]	

[a]Fuller details of the studies are given in Tables 1 and 2.
[b]ST implies smokeless tobacco unspecified, or combined snuff use or chewing.
[c]Ever, former and current ST use were compared with never ST. Use indicates timing not given and comparison is with non use.
[d]'Id.' is the RR/OR identification number used in Table 18, and 'Cases' is the number of cases in ST users as defined. NA = not available.
[e]Abbreviations used: pov = poverty, res = area of residence, smok = smoking.
[f]RR/OR and/or 95% CI estimated from data provided in the source.
[g]RR/OR and/or 95% CI estimated from data provided in the source assuming that no one both chewed and used snuff.
CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

Table 18: Prostate cancer; meta-analysis results

Type of ST (region)[a]	Adjustments/restrictions[b]	Number of estimates (RR/OR ids)[c]	Random-effects RR/OR (95% CI)	Heterogeneity: χ^2	I^2	$P(\chi^2)$
Any[d]	Overall data	5 (1, 3, 5, 7, 16)	1.20 (1.03–1.40)	3.3	0.0	0.506
	Smoking-adjusted	4 (1, 3, 5, 7)	1.29 (1.07–1.55)	1.2	0.0	0.764
	Never smokers	3 (2, 3, 5)	1.81 (0.76–4.30)	10.5	81.0	0.005

[a]For each study/sex, the RR/OR for ST from Table 17 was included if available, otherwise that for chewing tobacco or snuff was used.
[b]Smoking-adjusted includes estimates for smokers and non-smokers combined, adjusted for smoking if available, and estimates for never smokers otherwise.
[c]The actual estimates included are identified by their RR/OR identification numbers as given in Table 17.
[d]All the available data for prostate cancer are from US studies.
CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

Bladder cancer

Table 19 summarises data from the Norway cohorts study [26] and from 12 case-control studies. None of the case-control studies were conducted after 1990, and with the exception of two studies in Denmark [43,62], all were carried out in the USA or Canada. The great majority of the estimates are non-significant, and based on 10 smoking-adjusted estimates the overall estimate (see Table 20 and Figure 10) is 0.95 (95% CI 0.71–1.29). However, there is significant heterogeneity due mainly to estimates 8, 12 and 22, which show a positive association, the last two of which are significant, and estimate 31 which shows a significant negative association.

Considered together, the data provide no real evidence of an association between ST and bladder cancer.

Kidney cancer

Table 21 summarises evidence from one cohort and nine case-control studies, none conducted in Sweden. The estimates are generally based on small numbers of cases

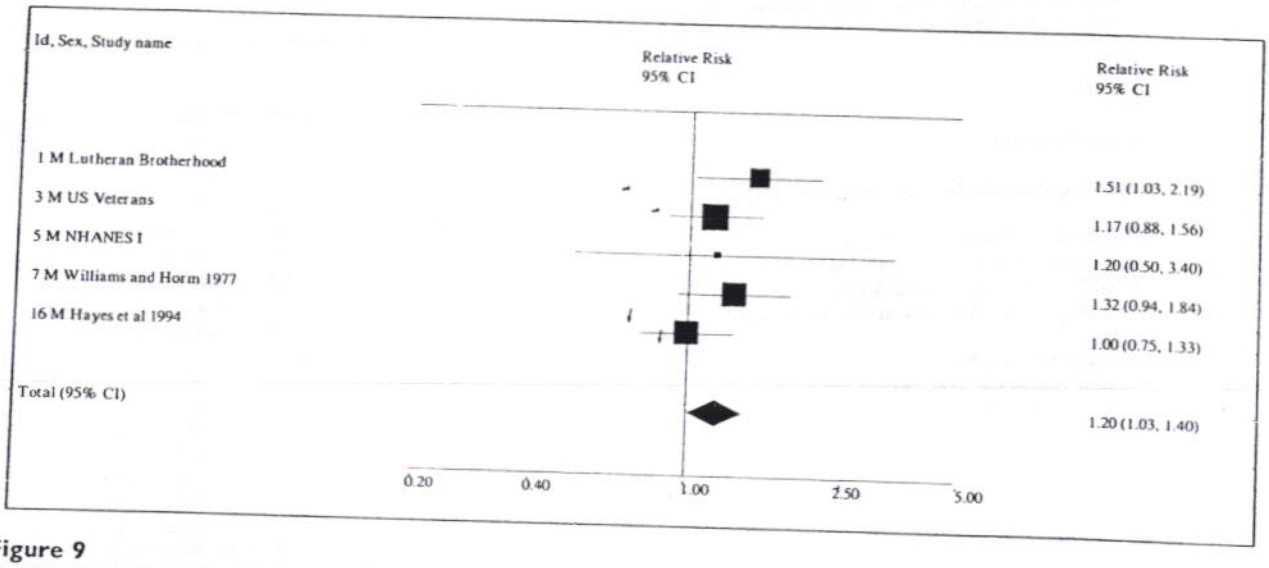

Figure 9

Smokeless tobacco and prostate cancer (USA overall data). The five individual relative risk (RR) and 95% confidence interval (CI) estimates, all for the USA, are shown numerically and also graphically on a logarithmic scale. They are sorted in order of year of publication within study type (cohort, case-control). In the graphical representation individual RR estimates are indicated by a solid square, with the area of the square proportional to the weight (inverse-variance) of the estimate. Also shown are the combined estimates, for the subgroups and overall, derived by random-effects meta-analysis. These are represented by a diamond of standard height, with the width indicating the 95% CI. See Table 17 for further details relating to the estimates, and Table 18 for fuller details of the meta-analyses.

using ST, and are variable, with four studies [47,68,73,100] providing a statistically significant OR estimate exceeding 3.0, and other studies (and other estimates from the four studies) showing notably smaller estimates, that are not significant. Most of the meta-analysis estimates shown in Table 22 (see also Figure 11) are elevated, with some evidence of heterogeneity, but none are statistically significant. Based on five smoking-adjusted estimates the overall estimate for any ST use is 1.09 (0.69–1.71).

While there is a suggestion of a possible relationship, more data are needed before any firm conclusions can be reached.

Haematopoietic and lymphoid cancer

Table 23 summarises evidence from three cohort and seven case-control studies for overall haematopoietic cancer and for specific types. The only report of a significant association is the OR of 4.0 (1.3–12.0) for non-Hodgkin's lymphoma in the case-control study of Bracci and Holly [112]. However, the combined evidence from the five studies (see Table 24 and Figure 12) for non-Hodgkin's lymphoma shows no significant relationship (1.20, 0.83–1.75), though there is significant heterogeneity ($P = 0.01$), due mainly to the Bracci and Holly estimate. The evidence for other endpoints – multiple myeloma, Hodgkin's disease, leukaemia, and overall haematopoietic cancer – is more limited, and does not suggest any relationship with ST use.

Other cancers

Table 25 summarises evidence from six cohort and four case-control studies relating to cancers of types not considered in Tables 3 to 24. Most of the results relate to specific cancer types, though some relate to broader groupings, such as genitourinary cancer and smoking-related cancer, which include cancer types considered earlier. Due to the variety of types, and the limited numbers of estimates relating to any one type, no meta-analyses were attempted. One of the studies [109] simply reported a lack of association (with glioma), and the remaining studies provided a total of 24 effect estimates with CI. Six of these are statistically significant. Zahm *et al.* [81] report an age-adjusted OR of 1.80 (95% CI 1.10–2.90) for soft tissue sarcoma based on a case-control study, though fail to confirm this later using data from the US Veterans Study [17]. The Williams and Horm study [55] provides a smoking-adjusted estimate of 4.18 (2.08–8.43) for cancer of the cervix, no other study giving relevant results. Moore *et al.* [39], in a study conducted in 1953, report a crude estimate of 2.41 (1.09–5.35) for cancer of the face, again an endpoint not considered by others. Roosaar *et al.* [35] report an increased risk of smoking-related cancer (1.6, 1.1–2.5) for never

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Table 19: Bladder cancer; individual effect (relative risk/odds ratio) estimates

Source[a]	ST use				RR/OR			
	Type[b]	Exposure[c]	Smoking	Sex	Id.	Cases[d]	Estimate (95%CI)	Adjustment factors[e]
Cohort studies								
Norway cohorts: Boffetta *et al.* 2005 [26]	Snuff	Current	Any	M	1	40	0.72 (0.52–1.06)	age, smok
		Former			2	30	0.98 (0.66–1.47)	
		Ever			3	69	0.83 (0.62–1.11)	
Case-control studies								
Lockwood 1961 [43]	ST	Current	Never	M	4	2	0.35 (0.07–1.77)[f]	none
Wynder *et al.* 1963 [46]	Chew	Ever	Any	M	5	33	1.42 (0.82–2.47)[f]	none
	Snuff				6	6	0.66 (0.23–1.88)[f]	
	ST				7	39	1.21 (0.74–1.98)[g]	
Dunham *et al.* 1968 [48]	ST	Ever	Never	M	8	4	2.57 (0.52–12.54)[f]	race
				F	9	3	0.58 (0.14–2.45)[f]	
Cole *et al.* 1971 [51]	Chew	Ever	Any	M	10	46	no association[h]	age
	Snuff				11	3	no association[i]	
Williams and Horm 1977 [55]	ST	Ever	Any	M	12	29	1.67 (1.09–2.55)[f]	age, race, smok
				F	13	1	0.82 (0.11–6.02)[f]	none
Wynder and Stellman 1977 [56]	Chew	Ever	Any	M	14	47	0.87 (0.63–1.21)[f]	none
	Snuff				15	11	0.69 (0.36–1.31)[f]	
	ST				16	58	0.82 (0.61–1.10)[g]	
Howe *et al.* 1980 [58]	Chew	Ever	Any	M	17	NA	0.90 (0.50–1.60)	age, smok
Mommsen and Aagaard 1983 [62]	Chew	Ever	Any	M	18	39	1.70 (1.00–2.90)	age, res
Hartge *et al.* 1985 [66]	Chew	Ever	Never[j]	M	19	40	1.02 (0.67–1.54)	age, race, res, smok[k]
	Snuff				20	11	0.77 (0.38–1.56)	
	ST				21	51	1.14 (0.80–1.61)[g]	none
Kabat *et al.* 1986 [69]	Snuff	Ever	Never	F	22	3	10.40 (1.07–101.46)	none
Slattery *et al.* 1988 [77]	Chew	Ever	Any	M	23	20	0.76 (0.42–1.39)	smok[k]
			Never		24	1	0.36 (0.05–2.82)[l]	none
	Snuff	Ever	Any		25	16	0.92 (0.47–1.82)	smok[k]
			Never		26	2	2.74 (0.45–16.69)[m]	none
	ST	Ever	Any		27	36	0.82 (0.52–1.29)[g]	smok[k]
			Never		28	3	0.86 (0.24–3.07)[g]	none
Burch *et al.* 1989 [79]	Chew	Ever	Any	M	29	26	0.60 (0.34–1.06)	age, res, smok
	Snuff				30	9	0.47 (0.21–1.07)	
	ST				31	35	0.54 (0.34–0.87)[g]	

[a]Fuller details of the studies are given in Tables 1 and 2.
[b]ST implies smokeless tobacco unspecified, or combined snuff use or chewing.
[c]Ever, former and current ST use were compared with never ST. Use indicates timing not given and comparison is with non use.
[d]'Id.' is the RR/OR identification number used in Table 20, and 'Cases' is the number of cases in ST users as defined. NA = not available.
[e]Abbreviations used: res = area of residence, smok = smoking.
[f]RR/OR and/or 95% CI estimated from data provided in the source.
[g]RR/OR and/or 95% CI estimated from data provided in the source assuming that no one both chewed and used snuff.
[h]Age-adjusted expected number of cases who chewed tobacco was given as 42.3 versus 46 observed.
[i]Age-adjusted expected number of cases who used snuff was given as 2.9 versus 3 observed.
[j]Estimates were for never cigarette smokers adjusted for other tobacco use.
[k]Adjusted for age started to smoke; results adjusted for smoking group, pack years or years stopped are similar.
[l]The source paper gave 2.78 (0.38–20.20) which is incorrect based on the numbers in the 2 × 2 table.
[m]The source paper gave 2.73 (0.48–15.57) which is incorrect based on the numbers in the 2 × 2 table.
CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

Table 20: Bladder cancer; meta-analysis results

Type of ST (region)[a]	Adjustments/restrictions[b]	Number of estimates (RR/OR ids)[c]	Random-effects RR/OR (95% CI)	Heterogeneity χ^2	I^2	$P(\chi^2)$
Any	Overall data	14 (3, 4, 7, 8, 9, 12, 13, 16, 17, 18, 21, 22, 27, 31)	1.00 (0.80–1.25)	28.7	54.7	0.007
	Smoking-adjusted	10 (3, 4, 8, 9, 12, 17, 21, 22, 27, 31)	0.95 (0.71–1.29)	22.3	59.6	0.008
	Never smokers	6 (4, 8, 9, 21, 22, 28)	1.10 (0.60–2.02)	7.7	35.1	0.173
Any (USA)	Overall data	9 (7, 8, 9, 12, 13, 16, 21, 22, 27)	1.11 (0.85–1.45)	14.8	45.9	0.064
	Smoking-adjusted	6 (8, 9, 12, 21, 22, 27)	1.24 (0.83–1.85)	10.4	52.1	0.064
	Never smokers	5 (8, 9, 21, 22, 28)	1.25 (0.69–2.26)	5.6	29.2	0.227
Snuff (Scandinavia)[d]	Overall data	1 (3)	0.83 (0.62–1.11)	–	–	–
	Smoking-adjusted	1 (3)	0.83 (0.62–1.11)	–	–	–

[a]For each study/sex, the RR/OR for ST from Table 19 was included if available, otherwise that for chewing tobacco or snuff was used.
[b]Smoking-adjusted includes estimates for smokers and non-smokers combined, adjusted for smoking if available, and estimates for never smokers otherwise.
[c]The actual estimates included are identified by their RR/OR identification numbers as given in Table 19.
[d]There are no data for never smokers for snuff in Scandinavia.
CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

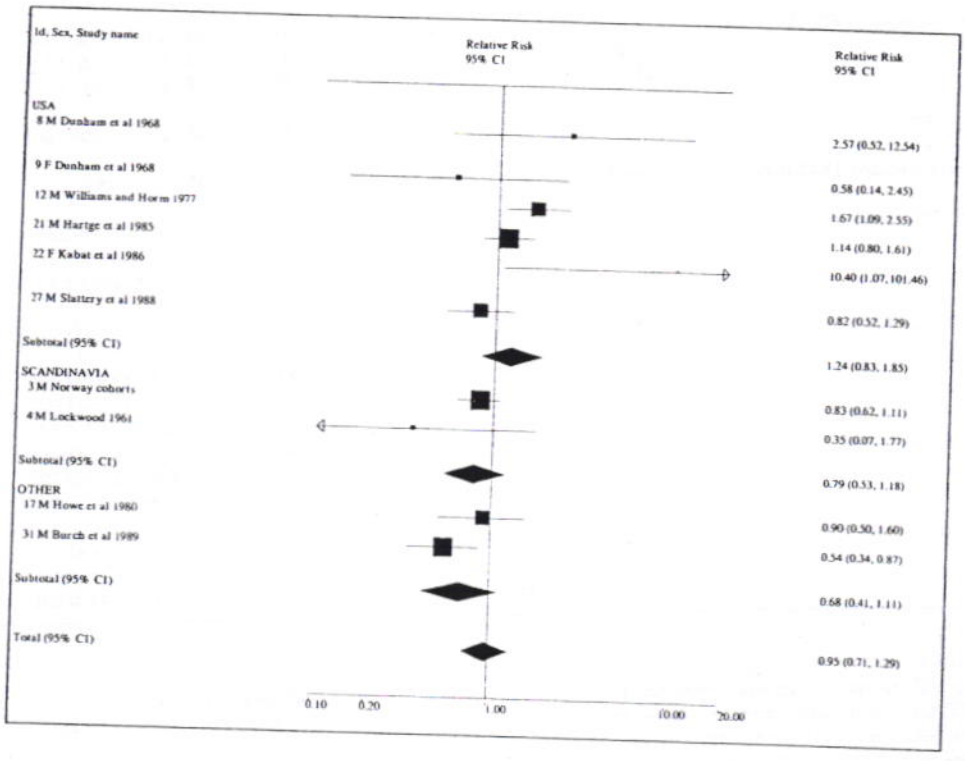

Figure 10

Smokeless tobacco and bladder cancer by region (smoking-adjusted data). The 10 individual smoking-adjusted relative risk (RR) and 95% confidence interval (CI) estimates, separated by region, are shown numerically and also graphically on a logarithmic scale. They are sorted in order of year of publication within study type (cohort, case-control). In the graphical representation individual RR estimates are indicated by a solid square, with the area of the square proportional to the weight (inverse-variance) of the estimate. Also shown are the combined estimates, for the subgroups and overall, derived by random-effects meta-analysis. These are represented by a diamond of standard height, with the width indicating the 95% CI. See Table 19 for further details relating to the estimates, and Table 20 for fuller details of the meta-analyses.

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Table 21: Kidney cancer; individual effect (relative risk/odds ratio) estimates

Source[a]	ST use				RR/OR			
	Type[b]	Exposure[c]	Smoking	Sex	Id.	Cases[d]	Estimate (95%CI)	Adjustment factors[e]
Cohort studies								
Norway cohorts: Boffetta *et al.* 2005 [26]	Snuff	Current	Any	M	1	9	0.47 (0.23–0.94)	age, smok
		Former			2	13	1.17 (0.63–2.16)	
		Ever			3	22	0.72 (0.44–1.18)	
Case-control studies								
Bennington and Laubscher 1968 [47]	Chew	Use	Any	M	4	5	1.22 (0.39–3.85)[f]	none
			Never		5	5	4.80 (1.18–19.59)[f]	age
Armstrong *et al.* 1976 [53]	ST	Current	Any	M	6	6	0.98 (0.30–3.15)[f]	none
		Former			7	6	0.73 (0.24–2.20)[f]	
		Ever			8	12	0.84 (0.37–1.92)[f]	
Williams and Horm 1977 [55]	ST	Ever	Any	M	9	3	0.59 (0.18–1.90)[f]	none
				F	10	1	1.26 (0.17–9.33)[f]	
McLaughlin *et al.* 1984 [65]	Chew	Use	Any	M	11	NA	0.40 (0.10–2.60)	age, smok
	Snuff				12	NA	1.70 (0.50–6.00)	
	ST				13	NA	1.00 (0.37–2.68)[g]	
Goodman *et al.* 1986 [68]	Chew	Ever	Any	M	14[h]	13	4.00 (1.13 – 14.17)	age, hosp, race, tadm
Asal *et al.* 1988 [73]	Snuff	Use	Any	M	15[i]	NA	3.60 (1.20–13.30)	age, hosp, race, tadm
					16[j]	NA	no association	age, race, tadm
McLaughlin *et al.* 1995 [99]	ST	Use	Never	M+F	17	11	1.30 (0.60–3.10)	age, bmi, res, sex
Muscat *et al.* 1995 [100]	Chew	Ever	Any	M	18	14	3.20 (1.10–8.70)	age, edu
Yuan *et al.* 1998 [106]	ST	Ever	Any	M+F	19	32	1.02 (0.56–1.85)	age, edu, smok

[a]Fuller details of the studies are given in Tables 1 and 2.
[b]ST implies smokeless tobacco unspecified, or combined snuff use or chewing.
[c]Ever, former and current ST use were compared with never ST. Use indicates timing not given and comparison is with non use.
[d]'Id.' is the RR/OR identification number used in Table 22, and 'Cases' is the number of cases in ST users as defined. NA = not available.
[e]Abbreviations used: bmi = body mass index, edu = education, hosp = hospital, res = residence, smok = smoking, tadm = time of admission.
[f]RR/OR and/or 95% CI estimated from data provided in the source.
[g]Estimated assuming ORs for chewing and snuff are independent.
[h]The authors also report the results of an analysis adjusting for the effects of the matching factors, body mass index, decaffeinated coffee use and continuous pack-years of cigarette smoking. The authors estimated an OR (95% CI) of 0.87 (0.15–5.14) for the effect of chewing among never smokers of cigarettes, and of 26.00 (4.41–153.00) for the joint effect of pack-years cigarette smoking and chewing tobacco use. These results could not readily be incorporated into the meta-analyses as no overall estimate for chewing tobacco use adjusted for cigarette smoking was available.
[i]Analysis uses hospital controls.
[j]Analysis uses population controls.
CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

Table 22: Kidney cancer; meta-analysis results

Type of ST (region)[a]	Adjustments/restrictions[b]	Number of estimates (RR/OR ids)[c]	Random-effects RR/OR (95% CI)	Heterogeneity		
				χ^2	I^2	$P(\chi^2)$
Any	Overall data	11 (3, 4, 8, 9, 10, 13, 14, 15, 17, 18, 19)	1.23 (0.86–1.76)[d]	16.5	39.2	0.087
	Smoking-adjusted	5 (3, 5, 13, 17, 19)	1.09 (0.69–1.71)[e]	6.9	41.9	0.142
	Never smokers	2 (5, 17)	2.19 (0.63–7.70)	2.5	59.6	0.116
Any (USA)	Overall data	8 (4, 9, 10, 13, 14, 15, 18, 19)	1.52 (0.94–2.46)	11.1	37.1	0.133
	Smoking-adjusted	3 (5, 13, 19)	1.41 (0.64–3.10)	4.2	51.8	0.125
	Never smokers	1 (5)	4.80 (1.18–19.56)	–	–	–
Snuff (Scandinavia)[f]	Overall data	1 (3)	0.72 (0.44–1.18)	–	–	–
	Smoking-adjusted	1 (3)	0.72 (0.44–1.18)	–	–	–

[a]For each study/sex, the RR/OR for ST from Table 21 was included if available, otherwise that for chewing tobacco or snuff was used.
[b]Smoking-adjusted includes estimates for smokers and non-smokers combined, adjusted for smoking if available, and estimates for never smokers otherwise.
[c]The actual estimates included are identified by their RR/OR identification numbers as given in Table 21.
[d]Test for publication bias $0.05 < P < 0.1$
[e]Test for publication bias $0.01 \leq P < 0.05$.
[f]There are no available data for never smokers using snuff in Scandinavia.
CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

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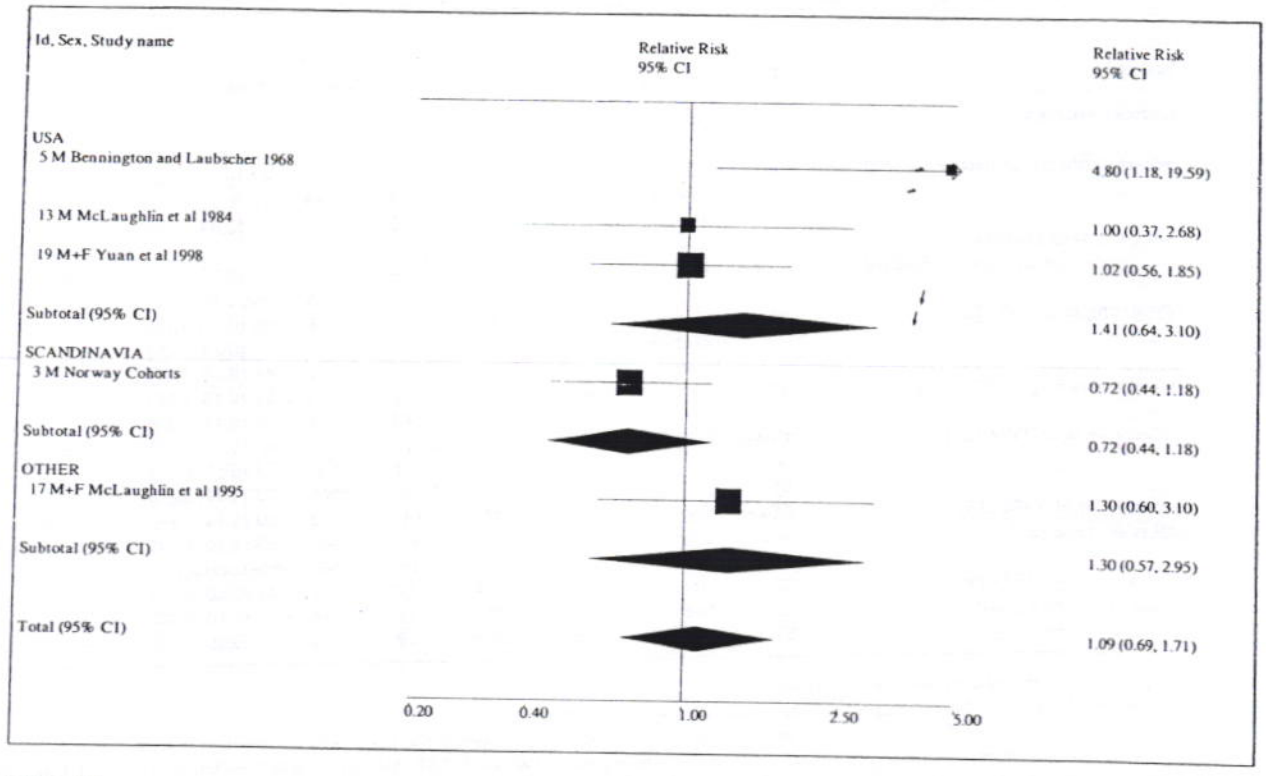

Figure 11

Smokeless tobacco and kidney cancer by region (smoking-adjusted data). The five individual smoking-adjusted relative risk (RR) and 95% confidence interval (CI) estimates, separated by region, are shown numerically and also graphically on a logarithmic scale. They are sorted in order of year of publication within study type (cohort, case-control). In the graphical representation individual RR estimates are indicated by a solid square, with the area of the square proportional to the weight (inverse-variance) of the estimate. Also shown are the combined estimates, for the subgroups and overall, derived by random-effects meta-analysis. These are represented by a diamond of standard height, with the width indicating the 95% CI. See Table 21 for further details relating to the estimates, and Table 22 for fuller details of the meta-analyses.

smokers, but not in a smoking-adjusted analysis for smoker and non-smokers combined (1.1, 0.8–1.4). Finally, based on the Swedish construction workers study, Odenbro *et al.* [29,33] report that snuff use is associated with a reduced smoking-adjusted risk of cutaneous squamous cell carcinoma (0.64, 0.44–0.95) and, in never smokers, with a reduced risk of melanoma (0.65, 0.52–0.82). These isolated reports need confirmation in other studies before any effect of ST can reliably be inferred. A study in Cherokee women [125,126] which shows no association of breast cancer with ever ST use, with an odds ratio adjusted for age at diagnosis estimated as 1.24 (0.26–6.02), is not considered in Table 25 as the study is of cross-sectional design. It contributes little to the evidence.

Overall cancer risk

As shown in Table 26, ST use has been related to overall cancer risk in five cohort studies and one case-control study. Two of the 12 estimates shown are smoking-adjusted estimates for smokers and non-smokers combined, one (estimate 10) showing no association at all (RR = 1.00) and the other (estimate 12, based on the case-control study [89]) a reduced OR of 0.64 (95% CI 0.53–0.78). The remaining 10 estimates, all from cohort studies, and all adjusted for age and various other potential confounders, are for never smokers. As shown in Table 27 and Figure 13, the combined estimate for all the smoking-adjusted data is not elevated (0.98, 0.84–1.15, $n = 7$). However, the combined estimate for never smokers, which excludes the low estimate from the case-control study, is a significant 1.10 (1.02–1.19, $n = 6$). The estimate for never smokers is similar for the US data (1.10, 1.01–1.20, $n = 4$) and the Scandinavian snuff data (1.10, 0.94–1.29, $n = 2$). The data are consistent with any excess risk of cancer in ST users being small.

Publication bias

There are 49 meta-analyses presented that combine five or more effect estimates. The test of publication bias [121]

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Table 23: Haematopoietic and lymphoid cancer; individual effect (relative risk/odds ratio) estimates

	ST use				RR/OR			
Source[a]	Type[b]	Exposure[c]	Smoking	Sex	Id.	Cases[d]	Estimate (95%CI)	Adjustment factors[e]
Cohort studies								
US veterans: Heinemann *et al.* 1992 [16]								
- multiple myeloma	ST	Use	Never	M[f]	1	6	1.00 (0.40–2.30)	age, time, yriv
CPS-II: Henley *et al.* 2005 [23]								
- any haematopoietic cancer	ST	Current	Never	M	2	19	0.95 (0.60–1.51)	age, alc, asp, bmi, diet, edu, exer, occ, race
		Former			3	9	1.16 (0.60–2.25)	
		Ever			4	28	1.01 (0.69–1.48)[g]	
Swedish construction workers: Fernberg *et al.* 2006 [30]								
- non-Hodgkin's lymphoma	Snuff	Ever	Never	M	5	66	0.77 (0.59–1.01)	age, bmi
- Hodgkin's disease	Snuff	Ever	Never	M	6	15	0.88 (0.49–1.58)	
Swedish construction workers: Fernberg *et al.* 2007 [31]								
- leukaemia	Snuff	Ever	Never	M	7	NA	no increased risk	age, bmi
- multiple myeloma	Snuff	Ever	Never	M	8	NA	no increased risk	age, bmi
Case-control studies								
Williams and Horm 1977 [55]								
- any haemopoietic cancer	ST	Ever	Any	M	9	13	0.63 (0.35–1.14)[g]	none
				F	10	3	1.01 (0.31–3.29)[g]	
Lindquist *et al.* 1987 [72]								
- leukaemia	Snuff	Ever	Any	M+F	11	18	0.94 (0.47–1.89)[h]	age, res, sex
Morris Brown *et al.* 1992 [87]								
- leukaemia	ST	Use	Never	M	12	24	1.80 (0.90–3.30)[i]	age, alc, res
Morris Brown *et al.* 1992 [88]								
- non-Hodgkin's lymphoma	ST	Use	Never	M	13	19	1.30 (0.70–2.50)[j]	age, res
- multiple myeloma	ST	Use	Never	M	14	5	1.90 (0.50–6.60)	age, res
Hardell *et al.* 1994 [95]								
- non-Hodgkin's lymphoma	Snuff	Use	Any	M	15	35	1.50 (0.90–2.50)	none
Schroeder *et al.* 2002 [110]								
- non-Hodgkin's lymphoma	Chew	Ever	Any	M	16	19	1.23 (0.80–1.88)[k]	age, res
	Snuff				17	19	0.93 (0.61–1.41)[k]	
	ST				18	38	1.06 (0.77–1.45)[l]	
Bracci and Holly 2005 [112]								
- non-Hodgkin's lymphoma	ST	Ever	Never	M	19	7	4.00 (1.30–12.00)	age, alc, edu

[a]Fuller details of the studies are given in Tables 1 and 2.
[b]ST implies smokeless tobacco unspecified, or combined snuff use or chewing.
[c]Ever, former and current ST use were compared with never ST. Use indicates timing not given and comparison is with non use.
[d]'Id.' is the RR/OR identification number used in Table 24, and 'Cases' is the number of cases in ST users as defined. NA = not available.
[e]Abbreviations used: alc = alcohol, asp = aspirin, bmi = body mass index, edu = education, exer = exercise, occ = occupation, smok = smoking, tadm = time of admission, yriv = year of interview.
[f]The population included < 0.5% females.
[g]Estimated from data on limited number of exposed cases for eight sub-types of haemopoietic cancer.
[h]RR/OR and/or 95% CI estimated from data provided in the source.
[i]Data for six subtypes of leukaemia were also provided, but none were statistically significant.
[j]Data for five subtypes of non-Hodgkin's lymphoma were also provided, but none were statistically significant.
[k]Estimated from data for t (14,18)-positive and t (14,18)-negative cases.
[l]Estimated from the results for chew and snuff, assuming that no one both chewed and used snuff.
CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

shows none to be significant at $P < 0.01$, and two significant at $P < 0.05$, similar to the numbers one would expect by chance. Both the significant cases (see Tables 22 and 24) arise due to a single high effect estimate, with the other estimates included in the analysis relatively close to 1.0.

Sensitivity analyses

Table 28 shows the effect on the smoking-adjusted analyses of successively removing those RR/OR estimates with the largest Q^2 values. Results are only shown for those cancers where significant ($P < 0.05$) heterogeneity was evident, and removal continues until no significant

Table 24: Non-Hodgkin's lymphoma; meta-analysis results

Type of ST (region)[a]	Adjustments/restrictions[b]	Number of estimates (RR/OR ids)[c]	Random-effects RR/OR (95% CI)	Heterogeneity χ^2	I^2	$P(\chi^2)$
Any	Overall data	5 (5, 13, 15, 18, 19)	1.20 (0.83–1.75)[d]	12.8	68.8	0.012
	Smoking-adjusted	3 (5, 13, 19)	1.35 (0.62–2.94)	9.5	78.9	0.009
	Never smokers	3 (5, 13, 19)	1.35 (0.62–2.94)	9.5	78.9	0.009
Any (USA)	Overall data	3 (13, 18, 19)	1.45 (0.81–2.59)	5.2	61.2	0.076
	Smoking-adjusted	2 (13, 19)	2.07 (0.70–6.13)	3.0	66.2	0.085
	Never smokers	2 (13, 19)	2.07 (0.70–6.13)	3.0	66.2	0.085
Snuff (Scandinavia)	Overall data	2 (5, 15)	1.04 (0.54–1.98)	5.1	80.5	0.024
	Smoking-adjusted	1 (5)	0.77 (0.59–1.01)	–	–	–
	Never smokers	1 (5)	0.77 (0.59–1.01)	–	–	–

[a]For each study/sex, the RR/OR for ST from Table 23 was included if available, otherwise that for chewing tobacco or snuff was used.
[b]Smoking-adjusted includes estimates for smokers and non-smokers combined, adjusted for smoking if available, and estimates for never smokers otherwise.
[c]The actual estimates included are identified by their RR/OR identification numbers as given in Table 23.
[d]Test for publication bias $0.01 \leq P < 0.05$.
CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

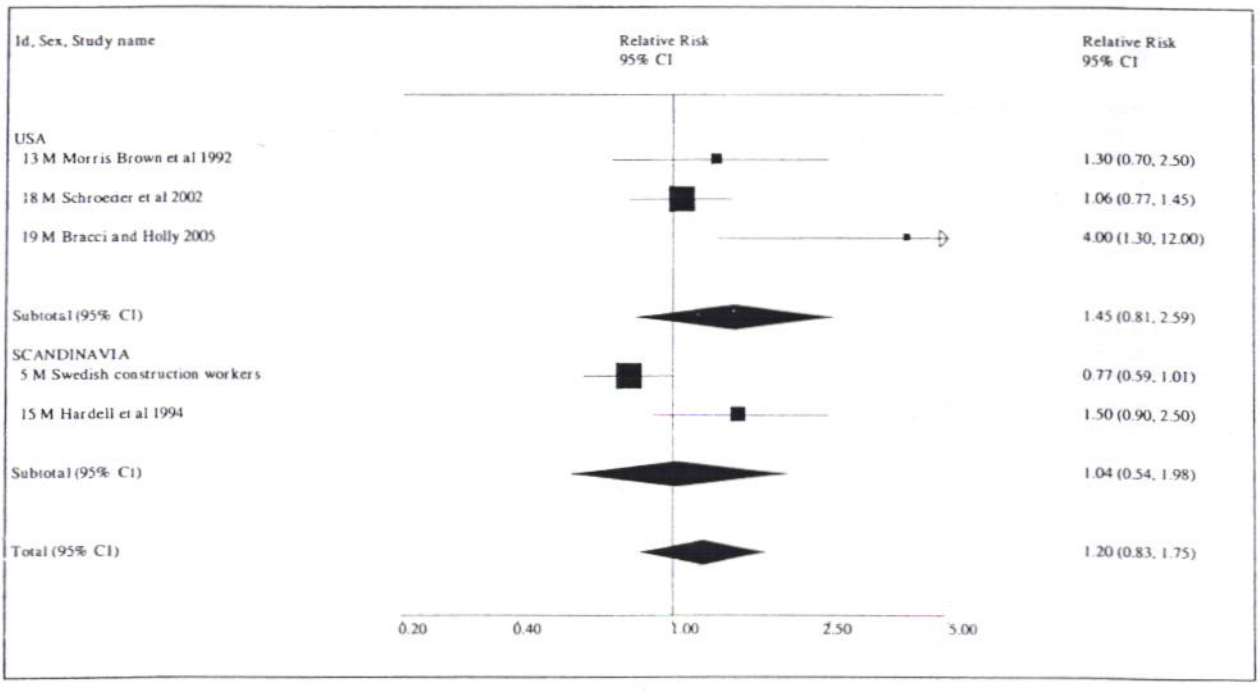

Figure 12
Smokeless tobacco and non-Hodgkin's lymphoma by region (overall data). The five individual relative risk (RR) and 95% confidence interval (CI) estimates, separated by region, are shown numerically and also graphically on a logarithmic scale. They are sorted in order of year of publication within study type (cohort, case-control). In the graphical representation individual RR estimates are indicated by a solid square, with the area of the square proportional to the weight (inverse-variance) of the estimate. Also shown are the combined estimates, for the subgroups and overall, derived by random-effects meta-analysis. These are represented by a diamond of standard height, with the width indicating the 95% CI. See Table 23 for further details relating to the estimates, and Table 24 for fuller details of the meta-analyses. Only estimates 5, 13 and 19 are smoking-adjusted.

Table 25: Other cancers; individual effect (relative risk/odds ratio) estimates

Source[a]	ST use				RR/OR			
	Type[b]	Exposure[c]	Smoking	Sex	Id.	Cases[d]	Estimate (95%CI)	Adjustment factors[e]
Cohort studies								
US Veterans: Zahm *et al.* 1992 [17]								
- soft tissue sarcoma	ST	Ever	Any	M[f]	1	21	0.85 (0.53–1.36)	age, smok, time
NHANES I: Accortt *et al.* 2005 [22]								
- breast cancer	ST	Ever	Never	F	2	5	1.80 (0.50–6.50)	age, pov, race
CPS-I: Henley *et al.* 2005 [23]								
- genitourinary cancer	ST	Current[f]	Never[f]	M	3	98	0.97 (0.77–1.22)	age, alc, asp, bmi, diet, edu, exer, occ, race
CPS-II: Henley *et al.* 2005 [23]								
- genitourinary cancer	ST	Current	Never	M	4	44	1.15 (0.85–1.56)	age, alc, asp, bmi, diet, edu, exer, occ, race
		Former			5	16	0.97 (0.59–1.59)	
		Ever			6	60	1.10 (0.84–1.42)[g]	
Swedish construction workers: Odenbro *et al.* 2005 [29]								
- cutaneous squamous cell carcinoma	Snuff	Ever	Any	M	7	29	0.64 (0.44–0.95)	age, smok
Swedish construction workers: Odenbro *et al.* 2007 [33]								
- melanoma[h]	Snuff	Ever	Never	M	8	96	0.65 (0.52–0.82)	age, bir, bmi
Uppsala County: Roosaar *et al.* 2008 [35]								
- smoking related cancer	Snuff	Ever	Any	M	9	71	1.10 (0.80–1.40)	age, alc, res, smok, time
			Never		10	39	1.60 (1.10–2.50)	age, alc, res, time
Case-control studies								
Moore *et al.* 1953 [39]								
- cancer of face	ST	Use	Any	M	11	49	2.41 (1.09–5.35)	none
Williams and Horm 1977 [55]								
- breast cancer	ST	Ever	Any	F	12	11	0.60 (0.31–1.17)[g]	age, smok
- cancer of male genitalia	ST	Ever	Any	M	13	2	0.47 (0.11–1.94)[g]	None
- cancer of cervix	ST	Ever	Any	F	14	10	4.18 (2.08–8.43)[g]	age, smok
- cancer of uterus	ST	Ever	Any	F	15	7	1.92 (0.86–4.28)[g]	age, smok
- cancer of ovary	ST	Ever	Any	F	16	2	0.77 (0.19–3.21)[g]	none
- cancer of vulva	ST	Ever	Any	F	17	1	2.06 (0.28–15.41)[g]	none
- connective tissue	ST	Ever	Any	M	18	1	0.26 (0.04–1.93)[g]	none
- melanoma	ST	Ever	Any	M	19	1	0.30 (0.04–2.18)[g]	none
- nervous system cancer	ST	Ever	Any	M	20	1	0.18 (0.02–1.32)[g]	none
				F	21	2	3.28 (0.77–13.99)[g]	
- thyroid cancer	ST	Ever	Any	M	22	1	0.36 (0.05–2.69)[g]	none
				F	23	1	0.73 (0.10–5.38)[g]	
Zahm *et al.* 1989 [81]								
- soft tissue sarcoma	ST	Ever	Any	M	24	28	1.80 (1.10–2.90)	Age
Zheng *et al.* 2001 [109]								
- brain cancer (glioma)	Chew	Use	Any	M+F	25	NA	no association	NA
	Snuff				26	NA	no association	

[a]Fuller details of the studies are given in Tables 1 and 2.
[b]ST implies smokeless tobacco unspecified, or combined snuff use or chewing.
[c]Ever, former and current ST use were compared with never ST. Use indicates timing not given and comparison is with non use.
[d]'Id.' is the RR/OR identification number, and 'Cases' is the number of cases in ST users as defined. NA = not available.
[e]Abbreviations used: alc = alcohol, asp = aspirin, bir = birth cohort, bmi = body mass index, edu = education, exer = exercise, occ = occupation, pov = poverty, res = area of residence, smok = smoking. NA = not available.
[f]The population included < 0.5% females.
[g]RR/OR and/or 95% CI estimated from data provided in the source.
[h]Including melanoma in situ
CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

Table 26: Overall cancer; individual effect (relative risk/odds ratio) estimates

	ST use					RR/OR		
Source[a]	Type[b]	Exposure[c]	Smoking	Sex	Id.	Cases[d]	Estimate (95%CI)[d]	Adjustment factors[e]
Cohort studies								
NHANES I: Accort *et al.* 2005 [22]	ST	Ever	Never	M	1	38	0.80 (0.40–1.60)	age, pov, race
				F	2	26	1.20 (0.70–2.10)	age, pov, race
CPS-I: Henley *et al.* 2005 [23]	ST	Current	Never	M	3	357	1.07 (0.95–1.20)	age, alc, asp, bmi, diet, edu, exer, occ, race
CPS-II: Henley *et al.* 2005 [23]	ST	Current	Never	M	4	162	1.19 (1.02–1.40)	age, alc, asp, bmi, diet, edu, exer, occ, race
	ST	Former			5	57	1.04 (0.80–1.36)	
	ST	Ever			6	219	1.15 (1.00–1.32)[f]	
	Chew only	Current			7	113	1.23 (1.02–1.49)	
	Snuff only	Current			8	14	0.93 (0.55–1.57)	
Swedish construction workers: Bolinder *et al.* 1994 [28]	Snuff	Current	Never	M	9	96	1.10 (0.90–1.40)	age, res
Uppsala County: Roosaar *et al.* 2008 [35]	Snuff	Ever	Any	M	10	237	1.00 (0.87–1.15)	age, alc, res, smok, time
			Never		11	138	1.10 (0.90–1.40)	age, alc, res, time
Case-control studies								
Sterling *et al.* 1992 [89]	ST	Ever	Any	M+F	12	2,498[g]	0.64 (0.53–0.78)[f]	age, alc, occ, race, sex, smok

[a]Fuller details of the studies are given in Tables 1 and 2.
[b]ST implies smokeless tobacco unspecified, or combined snuff use or chewing.
[c]Ever, former and current ST use were compared with never ST. Use indicates timing not given and comparison is with non use.
[d]'Id.' is the RR/OR identification number used in Table 27, and 'Cases' is the number of cases in ST users as defined.
[e]Abbreviations used: alc = alcohol, asp = aspirin, bmi = body mass index, edu = education, exer = exercise, occ = occupation, pov = poverty, res = area of residence, smok = smoking.
[f]RR/OR and/or 95% CI estimated from data provided in the source.
[g]Number of cases estimated from data provided in the source.
CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

Table 27: Overall cancer; meta-analysis results

				Heterogeneity		
Type of ST (region)[a]	Adjustments/restrictions[b]	Number of estimates (RR/OR ids)[c]	Random-effects RR/OR (95% CI)	χ^2	I^2	$P(\chi^2)$
Any	Overall data	7 (1, 2, 3, 6, 9, 10, 12)	0.98 (0.84–1.15)	27.1	77.9	< 0.001
	Smoking-adjusted	7 (1, 2, 3, 6, 9, 10, 12)	0.98 (0.84–1.15)	27.1	77.9	< 0.001
	Never smokers	6 (1, 2, 3, 6, 9, 11)	1.10 (1.02–1.19)	1.5	0.0	0.911
Any (USA)	Overall data	5 (1, 2, 3, 6, 12)	0.95 (0.74–1.22)	26.5	84.9	< 0.001
	Smoking-adjusted	5 (1, 2, 3, 6, 12)	0.95 (0.74–1.22)	26.5	84.9	< 0.001
	Never smokers	4 (1, 2, 3, 6)	1.10 (1.01–1.20)	1.5	0.0	0.679
Snuff (Scandinavia)	Overall data	2 (9, 10)	1.03 (0.91–1.16)	0.5	0.0	0.475
	Smoking-adjusted	2 (9, 10)	1.03 (0.91–1.16)	0.5	0.0	0.475
	Never smokers	2 (9, 11)	1.10 (0.94–1.29)	0.0	0.0	1.000

[a]For each study/sex, the RR/OR for ST from Table 26 was included if available, otherwise that for chewing tobacco or snuff was used.
[b]Smoking-adjusted includes estimates for smokers and non-smokers combined, adjusted for smoking if available, and estimates for never smokers otherwise.
[c]The actual estimates included are identified by their RR/OR identification numbers as given in Table 26.
CI = confidence interval; ST = smokeless tobacco; OR = odds ratio; RR = relative risk.

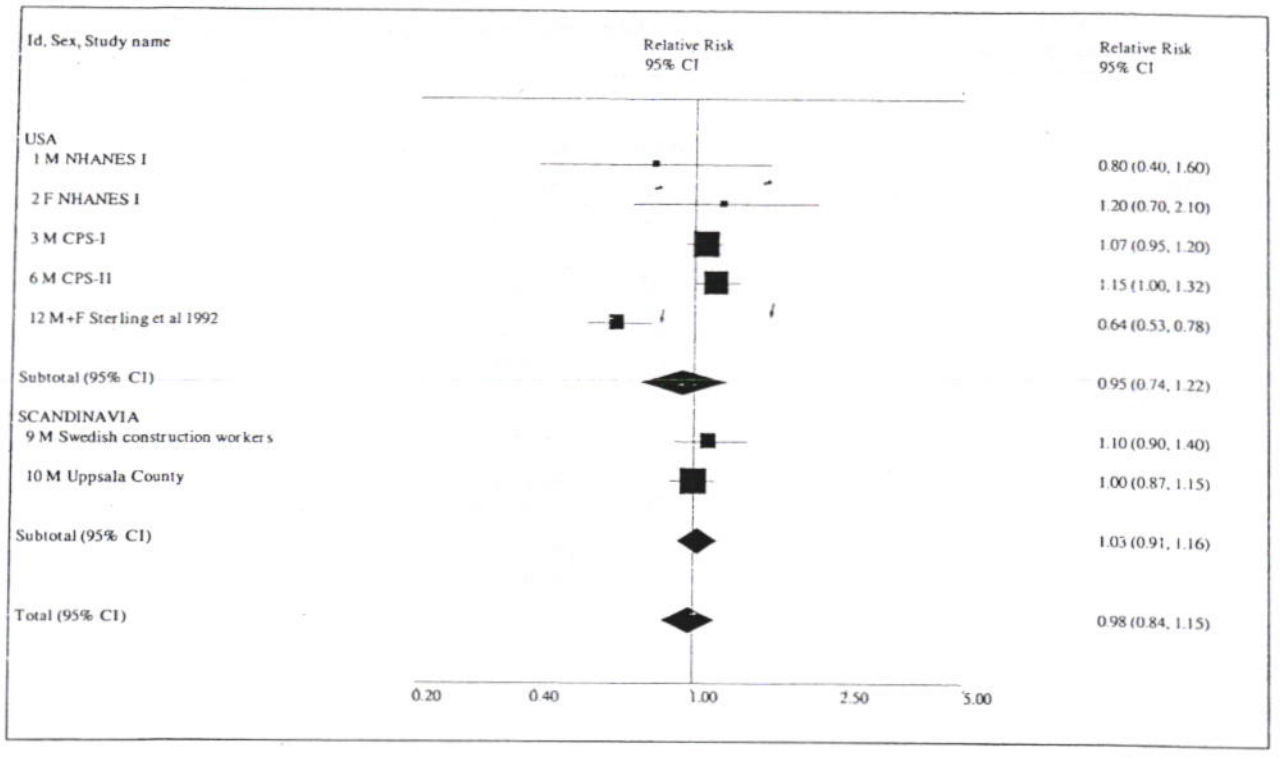

Figure 13

Smokeless tobacco and overall cancer by region (smoking-adjusted data). The seven individual smoking-adjusted relative risk (RR) and 95% confidence interval (CI) estimates, separated by region, are shown numerically and also graphically on a logarithmic scale. They are sorted in order of year of publication within study type (cohort, case-control). In the graphical representation individual RR estimates are indicated by a solid square, with the area of the square proportional to the weight (inverse-variance) of the estimate. Also shown are the combined estimates, for the subgroups and overall, derived by random-effects meta-analysis. These are represented by a diamond of standard height, with the width indicating the 95% CI. See Table 26 for further details relating to the estimates, and Table 27 for fuller details of the meta-analyses.

heterogeneity is seen. For pancreatic, lung and bladder cancer and for non-Hodgkin's lymphoma, only relatively high estimates are removed, and the random-effects estimate decreased, though only for lung cancer was the estimate now significantly below 1.0. For digestive cancer, the effect is to increase the estimate, but the significance is unchanged. For overall cancer, the effect is also to increase the estimate, here to marginal significance, 1.07 (1.00–1.15). For oropharyngeal cancer, the original substantial heterogeneity ($P < 0.001$) is seen to be due mainly to four estimates, three high and one low. The excess decreases from a significant 1.36 (1.04–1.77) to a non-significant 1.17 (0.95–1.45) after the removal of these estimates.

Similar analyses for the overall data (not shown) were also carried out. They also did not help to demonstrate any clear effect of ST on risk. For oropharyngeal cancer, where heterogeneity is very marked indeed, this is mainly due to estimates with atypically high values (see particularly Table 3 id. numbers 1, 15, 21, 22, 34 and 35).

Table 29 compares the smoking-adjusted meta-analysis estimates reported earlier with those recalculated preferring, where there was a choice, estimates for current ST use to those for ever use or unspecified ST use. The meta-analyses for the 12 cancers considered are based on a total of 83 effect estimates. In only 19 of these (23%) did the change in order of preference affect the estimate chosen. For 10 of these the estimate for current ST use is higher than that for ever or unspecified use, for eight it is lower, and for the other the two estimates are the same. The largest change is for pancreatic cancer in the Swedish construction workers study [32], where the selected RR value increases from 0.90 (0.70–1.20) in the original analysis to 2.10 (1.20–3.60) in the sensitivity analysis. However most of the changes, in either direction, are quite minor.

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Table 29: Further sensitivity analyses for smoking-adjusted data. Effect of preferring estimates for current smokeless tobacco use to those for ever or unspecified smokeless tobacco use

Cancer	Analysis[a]	N (nc)[b]	Random-effects RR/OR (95% CI)	Heterogeneity	
				χ^2	P
Oropharyngeal	Table 4	19	1.36 (1.04–1.77)	69.5	<-0.001
	Sensitivity	(5)	1.42 (1.10–1.84)	51.1	< 0.001
Oesophageal	Table 6	7	1.13 (0.95–1.36)	4.4	0.623
	Sensitivity	(2)	1.11 (0.92–1.34)	4.1	0.665
Stomach	Table 8	8	1.03 (0.88–1.20)	10.3	0.173
	Sensitivity	(2)	1.01 (0.86–1.19)	10.4	0.165
Pancreatic	Table 10	7	1.07 (0.71–1.60)	21.5	0.001
	Sensitivity	(2)	1.22 (0.75–2.01)	23.1	< 0.001
Overall digestive	Table 12	5	0.86 (0.59–1.25)	17.3	0.002
	Sensitivity	(1)	0.85 (0.57–1.27)	17.3	0.002
Larynx	Table 14	2	1.34 (0.61–2.95)	4.0	0.044
	Sensitivity	(1)	1.45 (0.73–2.88)	2.5	0.116
Lung	Table 16	6	0.99 (0.71–1.37)	28.7	< 0.001
	Sensitivity	(3)	1.11 (0.73–1.69)	20.6	< 0.001
Prostate	Table 18	4	1.29 (1.07–1.55)	1.2	0.764
	Sensitivity	(0)			
Bladder	Table 20	10	0.95 (0.71–1.29)	22.3	0.008
	Sensitivity	(1)	0.94 (0.68–1.29)	23.7	0.005
Kidney	Table 22	5	1.09 (0.69–1.71)	6.9	0.142
	Sensitivity	(1)	1.07 (0.60–1.91)	9.6	0.048
Non-Hodgkin's lymphoma	Table 24	3	1.35 (0.62–2.94)	9.5	0.009
	Sensitivity	(0)			
Overall	Table 27	7	0.98 (0.84–1.15)	27.1	< 0.001
	Sensitivity	(1)	0.99 (0.83–1.17)	27.9	< 0.001

[a]For each cancer the first line repeats the original results preferring ever or unspecified ST use shown in the Table indicated, while the second line presents the results of the sensitivity analysis preferring current ST use.

[b]N is the number of estimates included in the original and sensitivity analyses; nc is the number of changed estimates. For each cancer, the identification numbers for the estimates (shown in the Table indicated) included in the sensitivity analysis are shown below, with those not used in the original analysis in italic.

Oropharyngeal (Table 3): 2, 3, 4, 8, 11, 13, 18, 26, 35, 43, 48, 51, 55, 56, 58, 61, 70, 74, 75
Oesophageal (Table 5): 3, 6, 10, 11, 19, 20, 23
Stomach (Table 7): 1, 4, 7, 10, 14, 17, 19, 21
Pancreatic (Table 9): 1, 3, 8, 11, 16, 18, 23
Overall digestive (Table 11): 4, 5, 6, 7, 19
Larynx (Table 13): 3, 14
Lung (Table 15): 2, 3, 4, 9, 14, 20
Prostate (Table 17): 1, 3, 5, 7
Bladder (Table 19): 1, 4, 8, 9, 12, 17, 21, 22, 27, 31
Kidney (Table 21): 1, 5, 13, 17, 19
Non-Hodgkin's lymphoma (Table 23): 5, 13, 19
Overall cancer (Table 26): 1, 2, 3, 4, 9, 10, 12
CI = confidence interval; OR = odds ratio; RR = relative risk.

non-Hodgkin's lymphoma because of insufficient numbers of estimates; or for oesophageal, stomach and kidney cancer because of lack of heterogeneity. For pancreatic and bladder cancer, none of the factors investigated significantly (at $P < 0.05$) explained the heterogeneity. For overall cancer, study type was significant ($P = 0.001$), but this merely reflected the low estimate for the single case-control study, evident

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also in the sensitivity analysis shown in Table 28. For lung cancer, a tendency was noted for never-smoking estimates to be high, significant for both the smoking-adjusted data (P = 0.025) and the overall data (P = 0.029). This difference reflected the two high estimates already noted in the sensitivity analysis.

Summary of meta-analyses for ST use in Western populations

Table 30 brings together all the meta-analysis results for ST use in Western populations. Based on smoking-adjusted data, significant increases ($P < 0.05$) are seen for oropharyngeal cancer, though not based on studies published since 1990, and for prostate cancer, but not for any other cancer considered. For never smokers, significant increases are seen for oropharyngeal cancer (again not when based on studies published since 1990), for oesophageal cancer and also for overall cancer. Compared with the smoking-adjusted estimates, the estimates for never smokers tend to be more variable, due to smaller numbers of ST-exposed cases studied, though they consistently exceed 1.0.

Summary of meta-analyses for ST use in the USA

Table 31 similarly brings together the results for ST use in the USA. With the exception of oesophageal cancer in never smokers, significant increases seen in Table 28 are again significant here, with an increase additionally seen in the smoking-adjusted estimate for larynx cancer (although based on only a single study).

Summary of meta-analyses for snuff use in Scandinavia

As shown in Table 32, the meta-analyses of results provide overall effect estimates that, with one exception, are never significantly increased and generally are close to 1.00. The exception is for oesophageal cancer, where the marginally significant increased RR seen in relation to snuff use for never smokers (1.92, 1.00–3.68) derives solely from the Swedish Construction Workers study [34]. In that study, no increase was seen in smoking-adjusted analyses for the whole population (1.00, 0.79–1.27). Unlike the corresponding results for the USA, where meta-analysis estimates are predominantly greater than 1.0, the estimates for snuff as used in Scandinavia are as often below 1.0 as above 1.0. Generally, the results do not suggest that snuff as used in Scandinavia has any adverse effect on cancer risk.

Dose response data

Results relating the various cancers to dose of exposure to ST are only reported in a few studies and are not presented in detail here.

For oropharyngeal cancer, eight studies were identified that related risk to extent and/or duration of exposure. In seven of these studies, which all show no overall relationship of ST with risk in Table 3[32,55,89-91,104,113], no significant dose-response relationships are seen. It was only in one study [61], that did show a clear overall relationship, that a significant ($P < 0.001$) trend in risk with increasing duration of exposure is seen, though only for cancers of the gum and buccal mucosa, and not for other mouth and pharynx cancers.

For other cancer sites relatively few studies report dose-response data. In the CPS-II study [23] no trends with duration or frequency are seen for either total or lung cancer, while in the Swedish Construction Workers study no trend is seen for cutaneous squamous cell carcinoma with years of snuff dipping [29] or for oral cancer or lung cancer with daily amount of snuff consumed [32]. A significant trend ($P < 0.01$) is reported with daily amount of snuff consumed

Table 30: Summary of meta-analyses for smokeless tobacco use in Western populations

Cancer	Overall data		Smoking-adjusted data		Never smokers	
	n	RR/OR (95% CI)	*n*	RR/OR (95% CI)	*n*	RR/OR (95% CI)
Oropharyngeal (Table 4)	41	1.79 (1.36–2.36)	19	1.36 (1.04–1.77)	9	1.72 (1.01–2.94)
- (published since 1990)	18	1.28 (0.94–1.76)	14	1.00 (0.83–1.20)	7	1.24 (0.80–1.90)
Oesophageal (Table 6)	10	1.25 (1.03–1.51)	7	1.13 (0.95–1.36)	4	1.91 (1.15–3.17)
Stomach (Table 8)	9	1.03 (0.90–1.19)	8	1.03 (0.88–1.20)	4	1.27 (0.75–2.13)
Pancreatic (Table 10)	7	1.00 (0.68–1.47)	7	1.07 (0.71–1.60)	5	1.23 (0.66–2.31)
Any digestive (Table 12)	5	0.86 (0.59–1.25)	5	0.86 (0.59–1.25)	4	1.14 (0.99–1.33)
Larynx (Table 14)	5	1.43 (1.08–1.89)	2	1.34 (0.61–2.95)	0	-
Lung (Table 16)	9	0.96 (0.73–1.27)	6	0.99 (0.71–1.37)	5	1.34 (0.80–2.23)
Prostate (Table 18)	5	1.20 (1.03–1.40)	4	1.29 (1.07–1.55)	3	1.81 (0.76–4.30)
Bladder (Table 20)	14	1.00 (0.80–1.25)	10	0.95 (0.71–1.29)	6	1.10 (0.60–2.02)
Kidney (Table 22)	11	1.23 (0.86–1.76)	5	1.09 (0.69–1.71)	2	2.19 (0.63–7.70)
Non-Hodgkin's lymphoma (Table 24)	5	1.20 (0.83–1.75)	3	1.35 (0.62–2.95)	3	1.35 (0.62–2.95)
Overall cancer (Table 27)	7	0.98 (0.84–1.15)	7	0.98 (0.84–1.15)	6	1.10 (1.02–1.19)

n = number of estimates included in meta-analyses.
RR/OR = combined random-effects estimate based on RRs or ORs.
CI = confidence interval; OR = odds ratio; RR = relative risk.

than is ideal for a meta-analysis. Shortcomings include small numbers of cases, and in particular of cases exposed to ST, lack of histological confirmation, lack of division by cancer site, as well as an unclear description of inclusion and exclusion criteria, details of case and control selection, and methods of exposure assessment. Furthermore, details such as the type of ST used, and duration and frequency of use, are often not considered. The products used vary by country and over time, and increased risks seen in older studies for some cancers may not reflect the risks of more modern products, with reduced nitrosamine levels [128]. For most cancers, the number of effect estimates available is really too limited to allow a very detailed examination of variation in risk by such factors as type of product used, current or former use, country and sex. Though meta-regressions have been attempted for a number of cancers, they have not added materially to the interpretation, partly because of the limited amount of data for some cancers, and partly because of the number of apparently outlying estimates, notably for oropharyngeal cancer.

A major problem is that many of the studies fail to adjust for smoking and other important potential confounding variables. Although recent major reviews [7,8] consider that all the cancers considered in Table 30, with the exception of prostate cancer and non-Hodgkin's lymphoma, are caused by smoking, it is evident that a number of the studies do not provide estimates that are either for never smokers or for smokers and non-smokers combined with adjustment for smoking. Even where adjustment for smoking is carried out, this is often by a relatively simple approach, with no account taken of number of cigarettes smoked or duration of smoking. Smokers who also use ST may smoke fewer cigarettes a day than smokers who do not. Failure to adjust for smoking is particularly common for studies of oropharyngeal cancer, with many of the older studies not taking smoking into account at all when considering ST. The potential importance of this is illustrated by the overall estimate for oropharyngeal cancer being substantially reduced, from 1.79 to 1.36, when attention is restricted to smoking-adjusted data.

Adjustment for other risk factors is also important, as shown by the case of oropharyngeal cancer where the smoking-adjusted estimate of 1.36 (1.04–1.77, $n = 19$) can be compared with the estimate adjusted for smoking and alcohol of 1.07 (0.84–1.37, $n = 10$). Restricting attention to estimates adjusted for both factors also eliminated the highly significant ($P < 0.001$) heterogeneity seen in the smoking-adjusted data. Alcohol is also an important factor in the aetiology of oesophageal, larynx and liver cancer [8], but the number of ST effect estimates adjusted both for smoking and alcohol for these three cancers is very low indeed, respectively 2, 1 and 0. Other factors considered rarely, or not at all, include, for example, *Helicobacter pylori* infection for stomach cancer and diet for digestive cancer.

Another difficulty in interpreting the overall results is the variability of the findings. Heterogeneity significant at least at $P < 0.05$ is evident in the smoking-adjusted estimates for cancers of the oropharynx (though not in the more recent data), pancreas, larynx, lung and bladder, as well as for overall cancer and overall digestive cancer. As noted above, the evidence is too limited for most of the cancers to allow a proper investigation of the sources of this heterogeneity.

Based on the data analysed, there is little or no evidence of publication bias. However, it should be noted that the number of studies reporting results in a form that cannot be included in the meta-analyses is fairly high, representing up to about 30% for some cancers (see Tables 5, 7, 9, 13 and 17).

We are aware that the smoking-adjusted meta-analysis estimates we report for oropharyngeal cancer (1.36, 95% CI 1.04–1.77)), oesophageal cancer (1.13, 0.95–1.36), pancreatic cancer (1.07, 0.71–1.60) and lung cancer (0.99, 0.71–1.37) show much less evidence of a relationship with ST than do corresponding estimates recently reported in a review by Boffetta *et al.* [6] (oropharynx: 1.8, 1.1–2.9; oesophagus: 1.6, 1.1–2.3; pancreas: 1.6, 1.1–2.2; lung 1.2, 0.7–1.9). Reasons for this, based on a detailed analysis of this review, will be presented in a separate publication in BMC Cancer.

Comparison of the effects of smoking and ST use

In 2005 in US men aged 35 or over, there were a total of 142,205 deaths from seven cancers considered to be caused by smoking. Based on relative risks from CPS-II for current and former smoking [122] and estimates of the frequency of current and former smoking [124] for US men of this age group, we estimate that, had the population at risk the mortality rates of never smokers, the numbers would have reduced by 104,737, with the reduction in lung cancer deaths, 79,195, a major contributor. Any increase in risk resulting from the introduction of ST to a population of never smokers would be very much less than this. Even assuming that the smoking-adjusted meta-analysis estimates for the seven cancers all reflect a true effect of ST, the increase in deaths among a never-smoker population would be by 1,102 if 53% of the population used ST (the same proportion as had ever smoked) or by 2,081 if the whole population did. These increases represent, respectively, only 1.1% and 2.0% of the 104,737 deaths attributed to cigarette smoking.

There are a number of objections that can be made in respect of this comparison. These include the following:

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1. The RRs for current and former smoking are based on CPS-II, conducted in the 1980s, and may not reflect those appropriate for 2005, given *inter alia* changes in cigarettes that have occurred since then. However, CPS-II is widely used as a source of data for calculating deaths attributed to smoking (for example, [8,129]).

2. The RR estimates used for ST use are not specifically for the USA, or for males. However, 62 of the 89 studies considered in this review were conducted in the USA, and 41 of the 58 estimates used in the smoking-adjusted meta-analyses for the seven cancers are for males (with 12 for sexes combined and five for females).

3. The RR estimates used for ST are for any ST use, and do not separate current and former use, due to most studies not providing such data.

4. The calculations are limited to those seven cancers which the US Surgeon General, in his 1989 report [122] considered to be caused by smoking and for which RRs were provided for CPS-II. A more recent report [8] includes stomach cancer and leukaemia as caused by smoking. For stomach cancer, the meta-analyses in Table 6 showed virtually no association with ST use (1.03, 0.88–1.20, $n = 8$), while the more limited data for leukaemia also showed no clear evidence of a relationship.

5. It is theoretically possible that ST use might increase the risk of some cancers not increased by smoking. Here one should note the significant association for prostate cancer (1.29, 1.07–1.55).

6. The calculations do not take into account the fact that a proportion of US males aged 35+ already use ST. Given the relatively weak association between cancer and ST use, any attempt to do this would have had relatively little effect.

7. The calculations also do not take pipe and cigar smoking into account.

8. The approach used is somewhat simplistic, and a more realistic (but more complex) calculation might be to compare predicted cancer deaths over a long-term period in a population continuing to smoke as at present, with the predicted number in a population switching from cigarettes to ST.

Despite all these points, it is clear that any effect of ST on risk of cancer, if it exists at all, is quantitatively very much smaller than the known effects of smoking. This is in any case apparent from a simple comparison of the RRs for cigarette smoking and for ST use.

Conclusion

The available data relating to ST use have a number of weaknesses, including inadequate control for smoking in many, and limited data for never smokers. Nevertheless, it is possible to conduct meta-analyses based on smoking-adjusted estimates for a relatively wide range of cancers. These show no indication of an increased risk of cancer for snuff, as used in Scandinavia. The overall data for oropharyngeal cancer shows a significant increase in risk associated with ST use, but this is not evident for estimates adjusted for smoking and alcohol, or for studies published since 1990. Any effect of ST may relate mainly to products used in the past in the USA. A weak but significant association with prostate cancer, based on limited data from US studies, requires more confirmatory evidence. Reports of significant associations with pancreatic and oesophageal cancer in an earlier review [6] are not confirmed, and reasons for this will be discussed in a later publication. Risk from ST products as used in North America and Europe is clearly very much less than that from smoking, and is not evident at all in Scandinavia.

Abbreviations

CI: 95% confidence interval; CPS-I: American Cancer Society Cancer Prevention Study I; CPS-II: American Cancer Society Cancer Prevention Study II; d.f.: degrees of freedom; NHANES I: First National Health and Nutrition Examination Survey; OR: odds ratio; RR: relative risk; ST: smokeless tobacco.

Competing interests

PNL, founder of PN Lee Statistics and Computing Ltd., is an independent consultant in statistics and an advisor in the fields of epidemiology and toxicology to a number of tobacco, pharmaceutical and chemical companies. JH works for PN Lee Statistics and Computing Ltd.

Authors' contributions

PNL previously contributed to reviews of some of the data considered here [4,5,10]. He planned the study and carried out the literature search. PNL and JH jointly extracted the estimates and conducted the meta-analyses. The text and tables were drafted by PNL and checked by JH. Both authors read and approved the final manuscript.

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Annexe 57

Smokeless tobacco and cancer

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Use of smokeless tobacco products is common worldwide, with increasing consumption in many countries. Although epidemiological data from the USA and Asia show a raised risk of oral cancer (overall relative risk 2·6 [95% CI 1·3–5·2]), these are not confirmed in northern European studies (1·0 [0·7–1·3]). Risks of oesophageal cancer (1·6 [1·1–2·3]) and pancreatic cancer (1·6 [1·1–2·2]) have also increased, as shown in northern European studies. Results on lung cancer have been inconsistent, with northern European studies suggesting no excess risk. In India and Sudan, more than 50% of oral cancers are attributable to smokeless tobacco products used in those countries, as are about 4% of oral cancers in US men and 20% of oesophageal and pancreatic cancers in Swedish men. Smokeless tobacco products are a major source of carcinogenic nitrosamines; biomarkers of exposure have been developed to quantify exposure as a framework for a carcinogenesis model in people. Animal carcinogenicity studies strongly support clinical results. Cancer risk of smokeless tobacco users is probably lower than that of smokers, but higher than that of non-tobacco users.

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Introduction

Use of oral and nasal smokeless tobacco products has been common in many countries for centuries (figure 1). During most of the 20th century, use of these products has been common in India and other Asian countries, as well as in parts of Africa, but has declined in northern Europe and North America. However, during the past decades, an increase in use has been seen in the USA and some northern European countries, especially by young people.

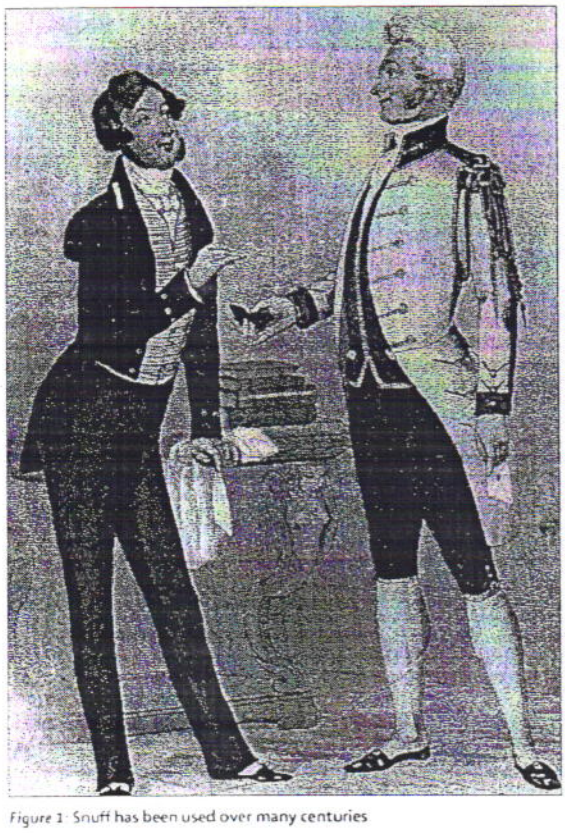
Products and patterns of use

Smokeless tobacco is consumed without burning the product, and can be used orally or nasally. Oral smokeless tobacco products are placed in the mouth, cheek, or lip, and are sucked (dipped) or chewed. Chewing tobacco can be classified as loose leaf (made from cigar leaf tobacco that is air-cured, sweetened, and loosely packed), plug (made from heavier grades of tobacco leaves harvested from the top of the plant, immersed in a mixture of licorice and sugar and pressed into a plug), or twist (air-cured or fire-cured burley tobacco leaves, flavoured and twisted in form of a rope). Snuff is a general term for finely cut or powdered, flavoured tobacco, which can be prepared as moist snuff (air-cured and fire-cured tobacco, flavoured and powdered into fine particles, containing 20–55% moisture by weight) and dry snuff (fire-cured, fermented tobacco powder that may contain aroma and flavour additives). Tobacco pastes or powders are also used orally and applied to the gums or teeth. Dry snuff can also be inhaled through the nasal passages.

Most smokeless tobacco products use *Nicotiana tabacum*, and sometimes *N rustica*. The major components of tobacco are alkaloids, with nicotine as the main compound (85–95% of total alkaloids). During product manufacturing, tobacco leaves, stems, and other ingredients are blended to achieve a specific nicotine content, pH, taste, flavour, and aroma. The pH strongly affects the concentration of bioavailable nicotine,[1] whereas the nitrite content affects nitrosamine concentrations in the product.[2]

Globally, a wide variety of different smokeless tobacco products are used, which can be used on their own, mixed with other products (such as slaked lime [khaini]), or as ingredients to other products (such as betel quid). These facts complicate the interpretation of epidemiological results, since study participants might have been exposed to products with variable amounts of carcinogens.

The frequency of smokeless tobacco use can vary substantially not only across countries, but also within countries by sex, age, ethnic origin, and socioeconomic



George Bernard/Science Photo Library

Figure 1: Snuff has been used over many centuries

characteristics. A detailed description of the different smokeless tobacco products worldwide and country-specific patterns of use is provided elsewhere.[3,4] Here, we describe major trends and patterns of use for the USA, Sweden, and India, where most epidemiological studies have been done and which have the highest frequency of use.

In the USA, chewing remained the dominant form of tobacco use until the expansion of the cigarette industry in 1918. After a decline in use, a resurgence in tobacco chewing (predominantly loose leaf) occurred in the 1970s, when new moist snuff products were developed and, accompanied with an aggressive marketing campaign, resulted in a three-times increase in snuff sales between 1980 and 2003.[5] In 2000, 4·4% of men and 0·3% of women in the USA were current users of smokeless tobacco products. Current use was more common in young men, non-Hispanic white people, people with a high-school diploma or a lower education, southern US states, and rural areas.[6]

The major form of smokeless tobacco used in Sweden is moist snuff (snus). In the 1950s and 1960s, use of moist snuff was decreasing and remained common only in older men. However, the development of new products and intensive advertisement and promotion led to a surge in use of moist snuff and consumption increased steadily from 393 g to 921 g per person between 1970 and 2002.[7] In 2004, 20% of men and 3% of women aged 16–75 years used moist snuff daily; the frequency of use was increased in young adults and in manual workers.[8]

In India, a large variety of commercial or home-made smokeless tobacco products exist. The use of chewing tobacco (often chewed with betel quid or other preparations including areca nut) is more common than the use of snuff; individuals applying smokeless tobacco products as dentifrice is also common. According to a 1998–99 survey,[9] 28% of adult men and 12% of women reported to chew tobacco. However, the prevalence could have been underestimated because of the use of household informants. The frequency of chewing tobacco varied greatly (8–60% in men, <1–61% in women) between states and was increased in rural, poor, and less educated groups. Use of smokeless tobacco in students aged 13–15 years varied between states from 3–56%.[10]

Smokeless tobacco products are also widely used in other countries in southeast Asia. Many other products are used in other regions and countries, including naswar in central Asia, zarda in western Asia, maraş in Turkey, toombak in Sudan, chimó in Venezuela, and iq'mik in Alaska.[4]

Carcinogens in smokeless tobacco

More than 30 carcinogens exist in smokeless tobacco, including volatile and tobacco-specific nitrosamines, nitrosamino acids, polycyclic aromatic hydrocarbons, aldehydes, metals.[4] Smokeless tobacco use entails the highest known non-occupational human exposure to carcinogenic nitrosamines, which is 100–1000 times greater than exposure in foods and beverages commonly containing nitrosamine carcinogens.[4] Every gram of commonly used smokeless tobacco contains 1–5 μg of the tobacco-specific nitrosamines 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N'-nitrosonornicotine (NNN), two recognised human carcinogens.[4,11] Furthermore, other carcinogenic tobacco-specific nitrosamines (eg, N'-nitrosoanabasine [NAB]) and nitrosamino acids (eg, 3-[methylnitrosamino] propionic acid) are found in these products.[4] The contamination of smokeless tobacco products, especially oral snuff, with NNK and NNN was first shown in the 1970s and although the concentrations of these compounds in some products have decreased, they are still moderately high in all products including Swedish snus.[12,13] The uptake of NNK and NNN by smokeless tobacco users has been clearly shown by the detection of their metabolites in urine. 20 years of smokeless tobacco use would expose users to an amount of NNK (75–150 mg, or about 1·5 mg/kg bodyweight) similar to that which has caused tumours in rats (1·8 mg/kg bodyweight), in addition to substantial exposure to NNN.[14]

Target tissues for cancer in smokeless tobacco users have shown some similarity with those seen in rats treated with NNK or NNN. Absolute consistency cannot be expected, since animals are treated with pure carcinogens in an experimental setting whereas people use product mixtures under many other environmental factors (eg, genetics, diet). Carcinogenicity in people affects the oral cavity, the oesophagus, the pancreas, and possibly the lung. A mixture of NNK and NNN swabbed in the rat oral cavity causes oral tumours,[15] and NNK and its metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) causes pancreatic tumours in rats when added to drinking water.[16] NNN added to the drinking water of rats has produced oesophageal tumours.[17] The lung is the main target tissue when NNK is added to the drinking water of rats.[17]

Cancer risk in human beings

Oral use—studies from Europe and North America

13 separate risk estimates have been made available from 11 studies examining the risk of oral cancer (oral and pharyngeal cancer in six studies) in users of smokeless tobacco products (table 1). Summary relative risk was 1·8 (95% CI 1·1–2·9), with evidence of heterogeneity in the results (table 2). When stratified by geographic region, the increased risk was restricted to the studies from the USA, whereas no increased risk was reported in the studies from Norway and Sweden (four risk estimates). Results were similar in studies including only non-smokers. Within geographic regions, no evidence of heterogeneity was reported in results between cohort and case-control studies. In the case-control study by Winn and colleagues,[18] in which US women were exposed

	Sex, study period	Study design	Exposure	Inclusion of smokers*	Exposure frequency	Cancer type (number of cases)	Relative risk (95% CI)	Comments	Ref
USA	Women, 1975-78	PCC	Snuff dipping	NS	White, 34·3%; black, 61·0%	Oral and pharyngeal cancer (132)	White, 4·2 (2·6–6·7); black, 1·5 (0·5–4·8)	Proxy interviews for many; mainly use of dry snuff with high nitrosamine concentrations	18
USA	Men/women, 1982	PCC	Smokeless tobacco use	SNS	0·4%	Oral cancer (755)	Tongue cancer, 2·3 (0·2–12·9); mouth cancer 11·2 (4·1–30·7)	Cancer controls; exposure data from hospital records	19
USA	Women, 1984–85	PCC	Smokeless tobacco use	NS	2·0%	Oral and pharyngeal cancer (50)	6·2 (1·9–19·8)	Mainly use of snuff	20
USA	Men, 1977–84	HCC	Smokeless tobacco use	NS	16·9%	Oesophageal cancer (4)	1·2 (0·1–13·3)	Proxy interview for many	21
USA	Men, 1972–83	HCC	Tobacco chewing	SNS	NA	Oral cancer (359)	1·0 (0·7–1·4)	Low response rate	22
USA	Men, 1966–86	Co	Smokeless tobacco use	SNS	NA	Pancreatic cancer (57)	1·7 (0·9–3·1)	–	23
USA	Men, 1970–90	HCC	Tobacco chewing	NS	2·2%	Oral and pharyngeal cancer (82)	2·3 (0·7–7·3)	Unadjusted relative risk	24
USA	Men, 1985–93	HCC	Tobacco chewing	NS	1·5%	Pancreatic cancer (146)	3·6 (1·0–12·8)	Low response rate	25
Sweden	Men, 1988–90	PCC	Oral snuff use	SNS	14·2%	Oral cancer (128); oesophageal cancer (123)	Oral cancer, 1·4 (0·8–2·4); oesophageal cancer, 1·2 (0·7–2·2)	–	26
Sweden	Men/women, 1980–89	PCC	Snuff use	SNS	20·3%	Oral cancer (410)	0·8 (0·5–1·3)	Proxy interview for most	27
Sweden	Men/women, 1995–97	PCC	Snuff use	SNS	15%	Oesophageal cancer (167)	1·4 (0·9–2·3)	Squamous-cell carcinoma	28
USA	Men/women, 1986–89	PCC	Smokeless tobacco use	NS	6·1%	Pancreatic cancer (130)	1·4 (0·5–3·6)	–	29
Norway	Men, 1966–2001	Co	Snus use	SNS	31·7%	Oral and pharyngeal cancer (34); oesophageal cancer (27); pancreatic cancer (85); lung cancer (343)	Oral and pharyngeal cancer, 1·1 (0·5–2·4); oesophageal cancer, 1·4 (0·6–3·2); pancreatic cancer, 1·7 (1·1–2·5); lung cancer, 0·8 (0·6–1·1)	–	30
USA	Men 1959–72	Co	Current spit tobacco use	NS	10%	Oral and pharyngeal cancer (13); lung cancer (134)	Oral and pharyngeal cancer, 2·0 (0·5–7·7); lung cancer, 1·1 (0·6–1·8)	–	31
USA	Men, 1982–2000	Co	Current spit tobacco use	NS	2·2%	Oral and pharyngeal cancer (46); lung cancer (396)	Oral and pharyngeal cancer, 0·9 (0·1–6·7); lung cancer 2·0 (1·2–3·2)	–	31
Sweden	Men, 1978–2004	Co	Snus use	NS	31%	Oral cancer (60); pancreatic cancer (83); lung cancer (154)	Oral cancer, 0·8 (0·4–1·7); pancreatic cancer, 2·0 (1·2–3·3); lung cancer, 0·8 (0·5–1·3)	–	32
USA	Men/women, 2000–06	HCC	Tobacco chewing	NS	4·8%	Pancreatic cancer (323)	0·6 (0·3–1·4)	Similar findings for use of snuff	33
Sweden	Men, 1971–2004	Co	Snus use	NS	29%	Oesophageal cancer (26)	3·5 (1·6–7·6)	Squamous-cell carcinoma	34

Co=cohort study. HCC=hospital-based case-control study. NA=not available. NS=non-smokers. PCC=population-based case-control study. SNS=smokers and non-smokers. *Relative risks that refer to both smokers and non-smokers are adjusted for tobacco smoking.

Table 1: Epidemiological studies of smokeless tobacco use and cancer risk of the oral cavity, oesophagus, pancreas, and lung in the USA and northern Europe

mainly to dry snuff with high nitrosamine concentrations, duration of smokeless tobacco use was strongly associated with risk of cancer of the gum and buccal mucosa; the association was weaker for cancer of other parts of the mouth and pharynx. Exclusion of that study resulted in a pooled relative risk of 2·6 (1·1–6·4, seven risk estimates). In a case-control study from Sweden,[26] a trend with the amount of smokeless tobacco was suggested.

With respect to oesophageal cancer, the summary relative risk was 1·6 (1·1–2·3), based on five studies (table 1) but with limited evidence of heterogeneity (table 2). Four of five studies were from northern Europe, thus limiting the possibility to explore differences in risk between regions. The increased risk was present both in cohort and case-control studies, and both in studies of non-smokers and smokers (data not shown). Results on duration or dose of smokeless tobacco use were reported in two studies,[26,28] both of which detected an increased risk in the category at highest exposure. Alcohol drinking did not seem to confound the association.

Results from six studies were available on the risk of pancreatic cancer (table 1). Summary relative risk was 1·6 (1·1–2·2), with limited evidence of heterogeneity (table 2). No clear increased risk was present in studies from the USA, whereas two cohort studies from Norway and Sweden reported a raised risk. In two studies,[29,32]

	Countries	Number of risk estimates	p*	Relative risk (95% CI)	p†
Oral cancer	Overall	13	<0·001	1·8 (1·1–2·9)	..
	USA	9	<0·001	2·6 (1·3–5·2)	..
	Nordic countries	4	0·4	1·0 (0·7–1·3)	0·01
Oesophageal cancer	Overall	5	0·3	1·6 (1·1–2·3)	..
	USA	1	..	1·2 (0·1–13)	..
	Nordic countries	4	0·08	1·6 (1·1–2·4)	0·8
Pancreatic cancer	Overall	6	0·08	1·6 (1·1–2·2)	..
	USA	4	0·3	1·4 (0·7–2·7)	..
	Nordic countries	2	0·6	1·8 (1·3–2·5)	0·5
Lung cancer	Overall	5	0·005	1·2 (0·7–1·9)	..
	USA	3	0·07	1·8 (0·9–3·5)	..
	Nordic countries	2	1·0	0·8 (0·6–1·0)	0·02

Nordic countries include Norway and Sweden. *Test of heterogeneity in individual studies. †Test of heterogeneity between geographical regions.

Table 2: Summary relative risk of selected cancers for ever use of smokeless tobacco in the USA and northern Europe

results were reported by duration or amount of smokeless tobacco exposure, consistently suggesting an association between risk and exposure.

Five cohort studies had available results on risk of lung cancer for use of smokeless tobacco (table 1). Heterogeneity in the results was reduced when studies were stratified by region; although the results of the three US studies indicated an increased risk, two studies from Norway and Sweden suggested a decreased risk (table 2).

Results are sparse on other tobacco smoking-related cancers, such as cancers of the larynx, bladder, and kidney, but none strongly indicates an increased risk for use of smokeless tobacco.[4] Furthermore, studies examining the risk of other neoplasms have mostly shown null results.[4]

In general, the available epidemiological studies indicate an increased risk of oral cancer for use of smokeless tobacco in the USA, whereas results of studies in the Nordic countries do not support such association. Available evidence for oesophageal and pancreatic cancer points to a causal association, mainly based on the studies from Nordic countries. Results on lung cancer risk are inconclusive, and data for other cancers are inadequate. Possible explanations for the heterogeneity of results by geographic area include the composition of the products used in the USA and northern Europe, the statistical power of the analyses based on few or imprecise risk estimates, and the variable presence of uncontrolled confounding or other sources of bias. Products historically consumed in the USA had, on average, higher nitrosamine content than those used in northern Europe, although the amount of nitrosamine (and other carcinogens) in the products used by the study participants in table 1 cannot be specified. In general, the precision of risk estimates is lower for the US studies than for the northern European studies, and is particularly low for oesophageal cancer. We addressed potential confounding by tobacco smoking by including only studies that controlled for confounding factors, and by repeating the meta-analysis on studies including only never smokers. Potential confounding by other risk factors (eg, alcohol drinking for oral and oesophageal cancer) was controlled for in most studies. Other sources of bias are difficult to rule out completely, but the general consistency of results between cohort and case-control studies is an argument against it.

Oral use—studies from Asia and Africa

Since the focus of this Review was on cancer risks of smokeless tobacco, we restricted the search to studies examining use of smokeless tobacco products without betel quid or areca nut. Betel quid without tobacco, as well as areca nut, the common ingredient of betel quid, have been classified as human carcinogens; they cause cancers of the oral cavity, pharynx, and oesophagus.[35]

Several case-control studies from India, Pakistan, and Sudan provide strong and consistent evidence of an increased risk of oral cancer (or oral and pharyngeal cancer) for use of smokeless tobacco (or tobacco plus lime) products, with relative risk as high as 10.[4] Another study[36] on naswar use from Pakistan reported an equally strong increase in risk for oral cancer after adjustment for tobacco smoking. Additional evidence comes from ecological studies showing positive correlations between use of smokeless tobacco products and increased oral cancer (eg, in Sudan, central Asia, and Saudi Arabia), as well as from case reports and case series from different regions worldwide, in which oral cancer cases reported high frequency of use of smokeless tobacco products.[4]

Data for other cancers are sparse. A study from India[37] reported a five-times increase in the risk of oesophageal cancer in non-smokers who chewed tobacco leaves; another multicentre study from India reported a raised risk of hypopharyngeal cancer (but not of laryngeal cancer) in non-smokers who used smokeless tobacco products.[38]

Nasal use

A case-control study from India reported an association between nasal snuff use and risk of cancer at different subsites of the oral cavity as well as the oesophagus, with relative risks from 2·4 to 4·0 and suggesting a dose-response relation.[39–42] A similar association was not detected for laryngeal cancer.[43] In a case-control study of lung cancer from Tunisia,[44] a two-times increase in relative risk was reported for ever use of inhaled snuff, after adjustment for tobacco smoking. These studies either were restricted to non-smokers or were adjusted for tobacco smoking and other potential confounders.

Switch from tobacco smoking to use of smokeless products

Henley and colleagues[45] compared men who switched from cigarette smoking to use of spit tobacco (switchers) with men who quit using tobacco entirely (quitters). Switchers had a higher mortality from cancer of the

oral cavity and pharynx than quitters (relative risk 2·6 [95% CI 1·2–5·8]). Compared with quitters, the relative risk of lung cancer was 1·5 (1·2–1·7) for all switchers, 1·3 (1·1–1·6) for switchers to chew only, 1·9 (1·2–2·5) for snuff only, and 2·0 (1·2–3·0) for chew and snuff combined. Compared with men who never used any tobacco product, the relative risk of lung cancer was 3·9 for quitters and 5·6 for switchers.

Health effects other than cancer

Many cross-sectional studies from the USA, India, Saudi Arabia, Uzbekistan, and Sudan reported a higher occurrence of oral soft tissue lesions in smokeless tobacco users than in non-users.[4] Most of the studies have accounted for tobacco smoking either by statistical adjustment or restriction to non-smokers. The lesions are described as leucoplakia, erythroplakia, snuff dipper's lesion, tobacco and lime user's lesion, verrucous hyperplasia, and submucosal deposits, and tend to be seen in the site of product application. Since these lesions are regarded as precursors of cancer, these findings support the carcinogenicity of smokeless tobacco products on the oral mucosa. Furthermore, a few studies have reported an increased occurrence of gingival recession, tooth wear, and dental caries in users of smokeless tobacco products.[4] Fewer studies on oral precancerous lesions are available from Nordic countries;[46,47] overall, an increased occurrence in snus users cannot be excluded.

Several studies have addressed the risk of cardiovascular diseases in users of smokeless tobacco products. Results generally indicate a small or non-existent increased risk of myocardial infarction and cerebrovascular diseases, with most relative risk estimates lower than 1·5.[4,48] No evidence has shown an increased risk of chronic obstructive pulmonary disease in users of smokeless tobacco products compared with non-users. A few studies have investigated a possible effect of smokeless tobacco on insulin resistance, glucose intolerance, and diabetes, although they have limitations and inconsistent results.[4]

Burden of smokeless tobacco-related cancer

The fraction attributable cancers (AF) is a measure of the burden of smokeless tobacco use on human cancer. It refers to the role of past exposure on current cancer burden, and, if exposure has changed (as has occurred in the composition of smokeless tobacco products used in North America and Europe), it cannot be applied to the effect of current exposure on future cancer. Attributable cancers can be estimated based on the relative risk due to the habit (RR) and the proportion of the exposed population (P), according to the formula:

$$AF = \frac{P \times (RR-1)}{[P \times (RR-1)+1]}$$

A global estimate of attributable cancers is complicated by heterogeneity in exposure circumstances and risk and by the limitations in available data on patterns of use. We therefore calculated the attributable cancers for selected countries, to provide an indication of the order of magnitude of the problem. We calculated the attributable cancers for oesophageal and pancreatic cancer in northern Europe and for oral cancer in Canada, USA, Sudan, India, and other southern and southeastern Asian countries (table 3). The proportion of oral cancer cases attributable to smokeless tobacco use was more than 50% in south and southeast Asia, resulting in more than 50 000 cases of oral cancer attributable to the habit in the eight countries considered, with 36 000 in India alone. This proportion was 68% in Sudanese men and 4·4% in US men, resulting in an estimated number of 627 and 948 cases per year, respectively. The number of oesophageal and pancreatic cancer cases attributable to smokeless tobacco use in northern Europe was small, because of the rarity of the diseases. In particular, 31 cases of oesophageal cancer and 62 cases of pancreatic cancer were attributable to smokeless tobacco use in Swedish men.

These figures are probably underestimated because data for occurrence of exposure refer to the present or the recent past, whereas the exposure relevant for carcinogenesis would have occurred further back in the past and was probably higher. Furthermore, cases of

	Sex	Relative risk	Proportion of population exposed to smokeless tobacco (%)	Cases attributable to smokeless tobacco use (%)	n
Oesophageal cancer					
Denmark	Men	1·6	3·5%[49]	2·1%	5
Norway	Men	1·6	6%[50]	3·5%	5
Sweden	Men	1·6	20%[8]	10·7%	31
Sweden	Women	1·6	1%[8]	0·6%	1
Pancreatic cancer					
Denmark	Men	1·8	3·5%[49]	2·7%	10
Norway	Men	1·8	6%[50]	4·6%	12
Sweden	Men	1·8	20%[8]	13·8%	62
Sweden	Women	1·8	1%[8]	0·8%	4
Oral cancer					
USA	Men	2·6	4·4%[51]	6·6%	948
Canada	Men	2·6	1%[52]	1·6%	24
Sudan	Men	7·3[53]	34%[54]	68·2%	627
Sudan	Women	7·3[53]	2·5%[54]	13·6%	79
India	Men	5·1[55]*	27%[56]†	52·5%	27 304
India	Women	5·1[55]*	26%[56]†	51·6%	8827
Other Asian countries‡	Men	5·1[55]*	25%[57]	50·6%	9568
Other Asian countries‡	Women	5·1[55]*	25%[57]	50·6%	6453

N=number of cases attributable to smokeless tobacco use in 2002 (total number of cancers derived from reference 58). *Other studies from India and other south Asian countries have provided similar risk estimates. † No stable risk estimates exist for non-smokers. ‡Other surveys from India have provided similar results. § †Bangladesh, Bhutan, Indonesia, Burma, Nepal, Pakistan, Sri Lanka.

Table 3: Proportion of oesophageal or oral cancer cases attributable to smokeless tobacco use in selected countries

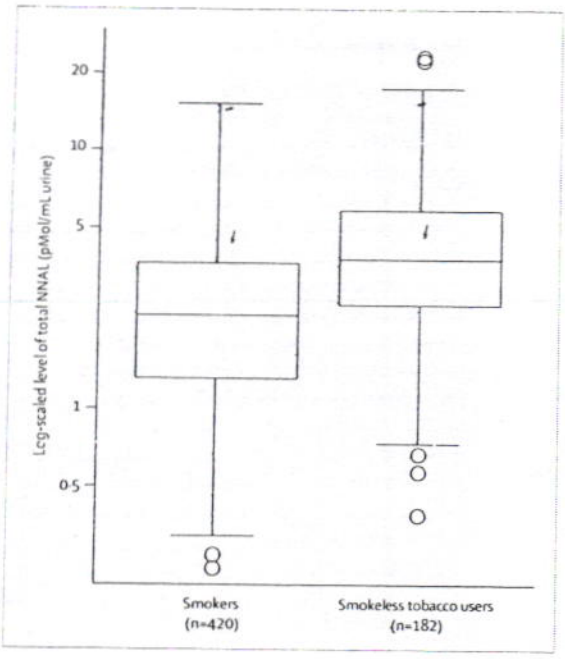


Figure 2: **Whisker plots of total NNAL in urine of smokers and smokeless tobacco users**
Summarised findings from reference 65.

pharyngeal cancer were not included in the calculation, despite the fact that an excess of this cancer was shown in several studies. Finally, the estimate excluded several populations in which smokeless tobacco is common, such as central and western Asian countries and Asian immigrants to Europe.

Biomarkers of carcinogen exposure in smokeless tobacco users

Biomarker studies clearly show the uptake and metabolism of tobacco carcinogens by smokeless tobacco users. These studies are crucial in linking smokeless tobacco use to cancer outcomes. Human beings and laboratory animals metabolise NNK into NNAL and NNK's glucuronides (NNAL-Glucs).[17] These compounds are excreted in the urine, and the total amount, known as total NNAL, is a practical and widely used biomarker of NNK exposure.[59]

The carcinogenic properties of NNAL are quite similar to those of NNK, whereas NNAL-Glucs are detoxification products.[17] The NNAL biomarker has been extensively used in studies of NNK exposure in smokers, smokeless tobacco users, and non-smokers exposed to involuntary tobacco smoke.[59] Advantages of this biomarker include its high reliability and specificity to tobacco products. Total NNAL in urine is not known to come from any source other than uptake of the tobacco-specific carcinogen NNK. Several small studies have clearly shown NNK uptake in smokeless tobacco users by measuring total urinary NNAL, including a study of Sudanese toombak users that recorded very high carcinogen exposures.[60–64] In a recent study,[65] total NNAL in the urine of larger groups of smokeless tobacco users and smokers was compared. Total NNAL was substantially higher in smokeless tobacco users than in smokers (figure 2). Similarly, concentrations of the nicotine metabolite cotinine were substantially higher in smokeless tobacco users than in smokers, consistent with previous studies.[66] Although differences in the pharmacokinetics of NNK and nicotine in smokeless tobacco users and smokers could complicate interpretation of these data, the results nevertheless show substantial uptake of the NNK in smokeless tobacco users, consistent with its amounts in smokeless tobacco products. However, cancer risk is higher in smokers than in smokeless tobacco users because, in addition to NNK, cigarette smoke contains many other carcinogens, tumour promoters, oxidants, and co-carcinogens, mostly derived from combustion.[67]

The tobacco-specific nitrosamines NNN, NAB, and NL-nitrosoanatabine (NAT) and their glucuronides have also been quantified in the urine of smokeless tobacco users, with generally higher concentrations than in smokers.[68] Total NNN could be a potentially useful biomarker of oesophageal carcinogen uptake in smokeless tobacco users. Tobacco-specific nitrosamines have also been quantified in the saliva of smokeless tobacco users.[4]

NNK and NNN are metabolically activated by cytochrome P450 enzymes resulting in the production of highly reactive pyridyloxobutyl (POB) diazonium ions and related species, which can react with DNA to form products that cause miscoding and mutations, initiating the carcinogenic process.[17,69] These POB species react with haemoglobin to produce adducts that can be quantified in human beings by mass spectrometry of released 4-hydroxy-1-(3-pyridyl)-1-butanone (HPB). The highest concentrations of HPB-releasing haemoglobin adducts have been reported in snuff-dippers, nasal snuff users, and toombak users.[64,70,71] These results have

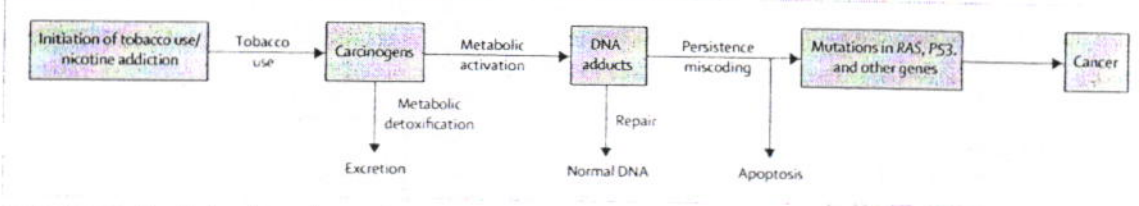


Figure 3: Conceptual model of smokeless tobacco carcinogenesis
Modified from reference 72.

shown that the metabolic activation of NNK and NNN, needed for carcinogenicity, occurs in smokeless tobacco users.

Mechanisms of carcinogenicity of smokeless tobacco

Figure 3 presents a conceptual framework for the carcinogenic mechanism by smokeless tobacco. People begin using these products generally at a young age, frequently because of effective marketing and peer pressure. These individuals become addicted to nicotine and cannot stop using the products. Nicotine is not a carcinogen, but as described above, every dip of smokeless tobacco contains more than 30 established carcinogens, with especially high amounts of the tobacco-specific nitrosamines NNK and NNN. These carcinogens are taken up, distributed, and metabolised in all smokeless tobacco users.

Few data exist about the levels of metabolic activation, detoxification, and DNA adduct formation in smokeless tobacco users,[4] compared with the substantial volume of information in smokers that is available. However, DNA adducts are probably formed in the oral tissue and other tissues of smokeless tobacco users; sister chromatid exchanges, chromosomal aberrations, and micronuclei—consequences of DNA adduct formation—have also been reported.[72] When DNA adducts persist unrepaired, by evading or overwhelming healthy cellular repair systems, the result can be miscoding, leading to permanent DNA mutations. If these mutations occur in crucial regions of specific genes, such as the *RAS* oncogene or the *P53* tumour suppressor gene, the result can be the loss of mechanisms of healthy cellular growth control, and ultimately the development of cancer. Many studies have demonstrated *RAS* and *P53* mutations in smokeless tobacco users.[73]

Although figure 3 represents a useful and supportable conceptual framework, there are certainly other factors participating in the carcinogenic mechanism of smokeless tobacco.[4] Oxidative stress and reactive oxygen species could have important roles, based on animal studies. Chronic local inflammation and irritation induced by smokeless tobacco and its constituents could have a tumour-promoting or co-carcinogenic effect. Upregulation of cyclo-oxygenase-2, involved in prostaglandin synthesis and inflammation, has been seen in animal studies on exposure to smokeless tobacco. Smokeless tobacco products have high amounts of sodium chloride, which could contribute to inflammation, tumour promotion, and co-carcinogenesis. Viruses have been shown to enhance the carcinogenicity of smokeless tobacco products in animal studies.[74]

Conclusion

We do not intend to address explicitly the use of smokeless tobacco to reduce the risk from tobacco smoking—eg, by promoting smokers to switch to smokeless products or by introducing these products in a population where the habit is not prevalent. Nevertheless, several conclusions can be reached based on the available data: use of smokeless tobacco products is widespread in many populations, but their health effects (especially with respect to cancer risk) need to be better characterised; such use results in exposure to carcinogens, notably nitrosamines; the risk of cancer depends on the type of product consumed, and the concentration of nitrosamines is the strongest factor to determine product-specific risk; the risk of cancer, especially that of oral and lung cancer, is probably lower in smokeless tobacco users in the USA and northern Europe than in smokers; and the risk of cancer is higher in smokeless tobacco users than in non-users of any form of tobacco. Available data for a possible benefit of switching from smoking to smokeless tobacco come from few studies and models from the USA and Sweden.[75] Comparative risk estimates depend on many assumptions, including the expected effect of the introduction of new smokeless products in populations where the habit has not been common.

Search strategy and selection criteria

We identified epidemiological studies of smokeless tobacco and cancer based on the IARC Monograph, which was prepared in October, 2004, and provides a very detailed review of the studies available at that time,[4] and by searching Medline, PubMed, and references from relevant articles for reports published in any language between October, 2004, and September, 2007, using the search terms "shus", "snuff", or "smokeless tobacco", and "cancer" or "neoplasm". Meeting abstracts and reports were excluded. We also included one manuscript that was in press in September, 2007. If several reports covered the same population, we used the most recent or comprehensive paper. A similar strategy was used in the 2004 IARC Monograph[4] to identify earlier publications. We did a quantitative review of epidemiological studies of smokeless tobacco use and risk of cancers of the oral cavity, oesophagus, pancreas, and lung. Results for other cancers were too sparse for a quantitative investigation. We included only studies restricted to non-smokers and studies that included smokers but were properly adjusted for the possible confounding effect of tobacco smoking.

Conflicts of interest

The authors declared no conflicts of interest.

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Smokeless tobacco and cancer

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Use of smokeless tobacco products is common worldwide, with increasing consumption in many countries. Although epidemiological data from the USA and Asia show a raised risk of oral cancer (overall relative risk 2·6 [95% CI 1·3–5·2]), these are not confirmed in northern European studies (1·0 [0·7–1·3]). Risks of oesophageal cancer (1·6 [1·1–2·3]) and pancreatic cancer (1·6 [1·1–2·2]) have also increased, as shown in northern European studies. Results on lung cancer have been inconsistent, with northern European studies suggesting no excess risk. In India and Sudan, more than 50% of oral cancers are attributable to smokeless tobacco products used in those countries, as are about 4% of oral cancers in US men and 20% of oesophageal and pancreatic cancers in Swedish men. Smokeless tobacco products are a major source of carcinogenic nitrosamines; biomarkers of exposure have been developed to quantify exposure as a framework for a carcinogenesis model in people. Animal carcinogenicity studies strongly support clinical results. Cancer risk of smokeless tobacco users is probably lower than that of smokers, but higher than that of non-tobacco users.

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Introduction

Use of oral and nasal smokeless tobacco products has been common in many countries for centuries (figure 1). During most of the 20th century, use of these products has been common in India and other Asian countries, as well as in parts of Africa, but has declined in northern Europe and North America. However, during the past decades, an increase in use has been seen in the USA and some northern European countries, especially by young people.

Products and patterns of use

Smokeless tobacco is consumed without burning the product, and can be used orally or nasally. Oral smokeless tobacco products are placed in the mouth, cheek, or lip, and are sucked (dipped) or chewed. Chewing tobacco can be classified as loose leaf (made from cigar leaf tobacco that is air-cured, sweetened, and loosely packed), plug (made from heavier grades of tobacco leaves harvested from the top of the plant, immersed in a mixture of licorice and sugar and pressed into a plug), or twist (air-cured or fire-cured burley tobacco leaves, flavoured and twisted in form of a rope). Snuff is a general term for finely cut or powdered, flavoured tobacco, which can be prepared as moist snuff (air-cured and fire-cured tobacco, flavoured and powdered into fine particles, containing 20–55% moisture by weight) and dry snuff (fire-cured, fermented tobacco powder that may contain aroma and flavour additives). Tobacco pastes or powders are also used orally and applied to the gums or teeth. Dry snuff can also be inhaled through the nasal passages.

Most smokeless tobacco products use *Nicotiana tabacum*, and sometimes *N rustica*. The major components of tobacco are alkaloids, with nicotine as the main compound (85–95% of total alkaloids). During product manufacturing, tobacco leaves, stems, and other ingredients are blended to achieve a specific nicotine content, pH, taste, flavour, and aroma. The pH strongly affects the concentration of bioavailable nicotine,[1] whereas the nitrite content affects nitrosamine concentrations in the product.[2]

Globally, a wide variety of different smokeless tobacco products are used, which can be used on their own, mixed with other products (such as slaked lime [khaini]), or as ingredients to other products (such as betel quid). These facts complicate the interpretation of epidemiological results, since study participants might have been exposed to products with variable amounts of carcinogens.

The frequency of smokeless tobacco use can vary substantially not only across countries, but also within countries by sex, age, ethnic origin, and socioeconomic

Figure 1: Snuff has been used over many centuries

characteristics. A detailed description of the different smokeless tobacco products worldwide and country-specific patterns of use is provided elsewhere.[3,4] Here, we describe major trends and patterns of use for the USA, Sweden, and India, where most epidemiological studies have been done and which have the highest frequency of use.

In the USA, chewing remained the dominant form of tobacco use until the expansion of the cigarette industry in 1918. After a decline in use, a resurgence in tobacco chewing (predominantly loose leaf) occurred in the 1970s, when new moist snuff products were developed and, accompanied with an aggressive marketing campaign, resulted in a three-times increase in snuff sales between 1980 and 2003.[5] In 2000, 4·4% of men and 0·3% of women in the USA were current users of smokeless tobacco products. Current use was more common in young men, non-Hispanic white people, people with a high-school diploma or a lower education, southern US states, and rural areas.[6]

The major form of smokeless tobacco used in Sweden is moist snuff (snus). In the 1950s and 1960s, use of moist snuff was decreasing and remained common only in older men. However, the development of new products and intensive advertisement and promotion led to a surge in use of moist snuff and consumption increased steadily from 393 g to 921 g per person between 1970 and 2002.[7] In 2004, 20% of men and 3% of women aged 16–75 years used moist snuff daily; the frequency of use was increased in young adults and in manual workers.[8]

In India, a large variety of commercial or home-made smokeless tobacco products exist. The use of chewing tobacco (often chewed with betel quid or other preparations including areca nut) is more common than the use of snuff; individuals applying smokeless tobacco products as dentifrice is also common. According to a 1998–99 survey,[9] 28% of adult men and 12% of women reported to chew tobacco. However, the prevalence could have been underestimated because of the use of household informants. The frequency of chewing tobacco varied greatly (8–60% in men, <1–61% in women) between states and was increased in rural, poor, and less educated groups. Use of smokeless tobacco in students aged 13–15 years varied between states from 3–56%.[10]

Smokeless tobacco products are also widely used in other countries in southeast Asia. Many other products are used in other regions and countries, including naswar in central Asia, zarda in western Asia, maraş in Turkey, toombak in Sudan, chimó in Venezuela, and iq'mik in Alaska.[4]

Carcinogens in smokeless tobacco

More than 30 carcinogens exist in smokeless tobacco, including volatile and tobacco-specific nitrosamines, nitrosamino acids, polycyclic aromatic hydrocarbons, aldehydes, metals.[4] Smokeless tobacco use entails the highest known non-occupational human exposure to carcinogenic nitrosamines, which is 100–1000 times greater than exposure in foods and beverages commonly containing nitrosamine carcinogens. Every gram of commonly used smokeless tobacco contains 1–5 µg of the tobacco-specific nitrosamines 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N'-nitrosonornicotine (NNN), two recognised human carcinogens.[4,11] Furthermore, other carcinogenic tobacco-specific nitrosamines (eg, N'-nitrosoanabasine [NAB]) and nitrosamino acids (eg, 3-[methylnitrosamino] propionic acid) are found in these products.[4] The contamination of smokeless tobacco products, especially oral snuff, with NNK and NNN was first shown in the 1970s and although the concentrations of these compounds in some products have decreased, they are still moderately high in all products including Swedish snus.[12,13] The uptake of NNK and NNN by smokeless tobacco users has been clearly shown by the detection of their metabolites in urine. 20 years of smokeless tobacco use would expose users to an amount of NNK (75–150 mg, or about 1·5 mg/kg bodyweight) similar to that which has caused tumours in rats (1·8 mg/kg bodyweight), in addition to substantial exposure to NNN.[14]

Target tissues for cancer in smokeless tobacco users have shown some similarity with those seen in rats treated with NNK or NNN. Absolute consistency cannot be expected, since animals are treated with pure carcinogens in an experimental setting whereas people use product mixtures under many other environmental factors (eg, genetics, diet). Carcinogenicity in people affects the oral cavity, the oesophagus, the pancreas, and possibly the lung. A mixture of NNK and NNN swabbed in the rat oral cavity causes oral tumours,[15] and NNK and its metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) causes pancreatic tumours in rats when added to drinking water.[16] NNN added to the drinking water of rats has produced oesophageal tumours.[17] The lung is the main target tissue when NNK is added to the drinking water of rats.[17]

Cancer risk in human beings

Oral use—studies from Europe and North America

13 separate risk estimates have been made available from 11 studies examining the risk of oral cancer (oral and pharyngeal cancer in six studies) in users of smokeless tobacco products (table 1). Summary relative risk was 1·8 (95% CI 1·1–2·9), with evidence of heterogeneity in the results (table 2). When stratified by geographic region, the increased risk was restricted to the studies from the USA, whereas no increased risk was reported in the studies from Norway and Sweden (four risk estimates). Results were similar in studies including only non-smokers. Within geographic regions, no evidence of heterogeneity was reported in results between cohort and case-control studies. In the case-control study by Winn and colleagues,[18] in which US women were exposed

	Sex, study period	Study design	Exposure	Inclusion of smokers*	Exposure frequency	Cancer type (number of cases)	Relative risk (95% CI)	Comments	Ref
USA	Women, 1975–78	PCC	Snuff dipping	NS	White, 34·3%; black, 61·0%	Oral and pharyngeal cancer (132)	White, 4·2 (2·6–6·7); black, 1·5 (0·5–4·8)	Proxy interviews for many; mainly use of dry snuff with high nitrosamine concentrations	18
USA	Men/women, 1982	PCC	Smokeless tobacco use	SNS	0·4%	Oral cancer (755)	Tongue cancer, 2·3 (0·2–12·9); mouth cancer 11·2 (4·1–30·7)	Cancer controls, exposure data from hospital records	19
USA	Women, 1984–85	PCC	Smokeless tobacco use	NS	2·0%	Oral and pharyngeal cancer (50)	6·2 (1·9–19·8)	Mainly use of snuff	20
USA	Men, 1977–84	HCC	Smokeless tobacco use	NS	16·9%	Oesophageal cancer (4)	1·2 (0·1–13·3)	Proxy interview for many	21
USA	Men, 1972–83	HCC	Tobacco chewing	SNS	NA	Oral cancer (359)	1·0 (0·7–1·4)	Low response rate	22
USA	Men, 1966–86	Co	Smokeless tobacco use	SNS	NA	Pancreatic cancer (57)	1·7 (0·9–3·1)	–	23
USA	Men, 1970–90	HCC	Tobacco chewing	NS	2·2%	Oral and pharyngeal cancer (82)	2·3 (0·7–7·3)	Unadjusted relative risk	24
USA	Men, 1985–93	HCC	Tobacco chewing	NS	1·5%	Pancreatic cancer (146)	3·6 (1·0–12·8)	Low response rate	25
Sweden	Men, 1988–90	PCC	Oral snuff use	SNS	14·2%	Oral cancer (128); oesophageal cancer (123)	Oral cancer, 1·4 (0·8–2·4); oesophageal cancer, 1·2 (0·7–2·2)	–	26
Sweden	Men/women, 1980–89	PCC	Snuff use	SNS	20·3%	Oral cancer (410)	0·8 (0·5–1·3)	Proxy interview for most	27
Sweden	Men/women, 1995–97	PCC	Snuff use	SNS	15%	Oesophageal cancer (167)	1·4 (0·9–2·3)	Squamous-cell carcinoma	28
USA	Men/women, 1986–89	PCC	Smokeless tobacco use	NS	6·1%	Pancreatic cancer (130)	1·4 (0·5–3·6)	–	29
Norway	Men, 1966–2001	Co	Snus use	SNS	31·7%	Oral and pharyngeal cancer (34); oesophageal cancer (27); pancreatic cancer (85); lung cancer (343)	Oral and pharyngeal cancer, 1·1 (0·5–2·4); oesophageal cancer, 1·4 (0·6–3·2); pancreatic cancer, 1·7 (1·1–2·5); lung cancer, 0·8 (0·6–1·1)	–	30
USA	Men 1959–72	Co	Current spit tobacco use	NS	10%	Oral and pharyngeal cancer (13); lung cancer (134)	Oral and pharyngeal cancer, 2·0 (0·5–7·7); lung cancer, 1·1 (0·6–1·8)	–	31
USA	Men, 1982–2000	Co	Current spit tobacco use	NS	2·2%	Oral and pharyngeal cancer (46); lung cancer (396)	Oral and pharyngeal cancer, 0·9 (0·1–6·7); lung cancer 2·0 (1·2–3·2)	–	31
Sweden	Men, 1978–2004	Co	Snus use	NS	31%	Oral cancer (60); pancreatic cancer (83); lung cancer (154)	Oral cancer, 0·8 (0·4–1·7); pancreatic cancer, 2·0 (1·2–3·3); lung cancer, 0·8 (0·5–1·3)	–	32
USA	Men/women, 2000–06	HCC	Tobacco chewing	NS	4·8%	Pancreatic cancer (323)	0·6 (0·3–1·4)	Similar findings for use of snuff	33
Sweden	Men, 1971–2004	Co	Snus use	NS	29%	Oesophageal cancer (26)	3·5 (1·6–7·6)	Squamous-cell carcinoma	34

Co=cohort study. HCC=hospital-based case-control study. NA=not available. NS=non-smokers. PCC=population-based case-control study. SNS=smokers and non-smokers. *Relative risks that refer to both smokers and non-smokers are adjusted for tobacco smoking.

Table 1: Epidemiological studies of smokeless tobacco use and cancer risk of the oral cavity, oesophagus, pancreas, and lung in the USA and northern Europe

mainly to dry snuff with high nitrosamine concentrations, duration of smokeless tobacco use was strongly associated with risk of cancer of the gum and buccal mucosa; the association was weaker for cancer of other parts of the mouth and pharynx. Exclusion of that study resulted in a pooled relative risk of 2·6 (1·1–6·4, seven risk estimates). In a case-control study from Sweden,[26] a trend with the amount of smokeless tobacco was suggested.

With respect to oesophageal cancer, the summary relative risk was 1·6 (1·1–2·3), based on five studies (table 1) but with limited evidence of heterogeneity (table 2). Four of five studies were from northern Europe, thus limiting the possibility to explore differences in risk between regions. The increased risk was present both in cohort and case-control studies, and both in studies of non-smokers and smokers (data not shown). Results on duration or dose of smokeless tobacco use were reported in two studies,[26,28] both of which detected an increased risk in the category at highest exposure. Alcohol drinking did not seem to confound the association.

Results from six studies were available on the risk of pancreatic cancer (table 1). Summary relative risk was 1·6 (1·1–2·2), with limited evidence of heterogeneity (table 2). No clear increased risk was present in studies from the USA, whereas two cohort studies from Norway and Sweden reported a raised risk. In two studies,[29,32]

	Countries	Number of risk estimates	p*	Relative risk (95% CI)	p†
Oral cancer	Overall	13	<0·001	1·8 (1·1–2·9)	..
	USA	9	<0·001	2·6 (1·3–5·2)	..
	Nordic countries	4	0·4	1·0 (0·7–1·3)	0·01
Oesophageal cancer	Overall	5	0·3	1·6 (1·1–2·3)	..
	USA	1	..	1·2 (0·1–13)	..
	Nordic countries	4	0·08	1·6 (1·1–2·4)	0·8
Pancreatic cancer	Overall	6	0·08	1·6 (1·1–2·2)	..
	USA	4	0·3	1·4 (0·7–2·7)	..
	Nordic countries	2	0·6	1·8 (1·3–2·5)	0·5
Lung cancer	Overall	5	0·005	1·2 (0·7–1·9)	..
	USA	3	0·07	1·8 (0·9–3·5)	..
	Nordic countries	2	1·0	0·8 (0·6–1·0)	0·02

Nordic countries include Norway and Sweden. *Test of heterogeneity in individual studies. †Test of heterogeneity between geographical regions.

Table 2: Summary relative risk of selected cancers for ever use of smokeless tobacco in the USA and northern Europe

results were reported by duration or amount of smokeless tobacco exposure, consistently suggesting an association between risk and exposure.

Five cohort studies had available results on risk of lung cancer for use of smokeless tobacco (table 1). Heterogeneity in the results was reduced when studies were stratified by region; although the results of the three US studies indicated an increased risk, two studies from Norway and Sweden suggested a decreased risk (table 2).

Results are sparse on other tobacco smoking-related cancers, such as cancers of the larynx, bladder, and kidney, but none strongly indicates an increased risk for use of smokeless tobacco.[4] Furthermore, studies examining the risk of other neoplasms have mostly shown null results.[4]

In general, the available epidemiological studies indicate an increased risk of oral cancer for use of smokeless tobacco in the USA, whereas results of studies in the Nordic countries do not support such association. Available evidence for oesophageal and pancreatic cancer points to a causal association, mainly based on the studies from Nordic countries. Results on lung cancer risk are inconclusive, and data for other cancers are inadequate. Possible explanations for the heterogeneity of results by geographic area include the composition of the products used in the USA and northern Europe, the statistical power of the analyses based on few or imprecise risk estimates, and the variable presence of uncontrolled confounding or other sources of bias. Products historically consumed in the USA had, on average, higher nitrosamine content than those used in northern Europe, although the amount of nitrosamine (and other carcinogens) in the products used by the study participants in table 1 cannot be specified. In general, the precision of risk estimates is lower for the US studies than for the northern European studies, and is particularly low for oesophageal cancer. We addressed potential confounding by tobacco smoking, by including only studies that controlled for confounding factors, and by repeating the meta-analysis on studies including only never smokers. Potential confounding by other risk factors (eg, alcohol drinking for oral and oesophageal cancer) was controlled for in most studies. Other sources of bias are difficult to rule out completely, but the general consistency of results between cohort and case-control studies is an argument against it.

Oral use—studies from Asia and Africa

Since the focus of this Review was on cancer risks of smokeless tobacco, we restricted the search to studies examining use of smokeless tobacco products without betel quid or areca nut. Betel quid without tobacco, as well as areca nut, the common ingredient of betel quid, have been classified as human carcinogens; they cause cancers of the oral cavity, pharynx, and oesophagus.[35]

Several case-control studies from India, Pakistan, and Sudan provide strong and consistent evidence of an increased risk of oral cancer (or oral and pharyngeal cancer) for use of smokeless tobacco (or tobacco plus lime) products, with relative risk as high as 10.[4] Another study[36] on naswar use from Pakistan reported an equally strong increase in risk for oral cancer after adjustment for tobacco smoking. Additional evidence comes from ecological studies showing positive correlations between use of smokeless tobacco products and increased oral cancer (eg, in Sudan, central Asia, and Saudi Arabia), as well as from case reports and case series from different regions worldwide, in which oral cancer cases reported high frequency of use of smokeless tobacco products.[4]

Data for other cancers are sparse. A study from India[37] reported a five-times increase in the risk of oesophageal cancer in non-smokers who chewed tobacco leaves; another multicentre study from India reported a raised risk of hypopharyngeal cancer (but not of laryngeal cancer) in non-smokers who used smokeless tobacco products.[38]

Nasal use

A case-control study from India reported an association between nasal snuff use and risk of cancer at different subsites of the oral cavity as well as the oesophagus, with relative risks from 2·4 to 4·0 and suggesting a dose-response relation.[39–42] A similar association was not detected for laryngeal cancer.[43] In a case-control study of lung cancer from Tunisia,[44] a two-times increase in relative risk was reported for ever use of inhaled snuff, after adjustment for tobacco smoking. These studies either were restricted to non-smokers or were adjusted for tobacco smoking and other potential confounders.

Switch from tobacco smoking to use of smokeless products

Henley and colleagues[45] compared men who switched from cigarette smoking to use of spit tobacco (switchers) with men who quit using tobacco entirely (quitters). Switchers had a higher mortality from cancer of the

oral cavity and pharynx than quitters (relative risk 2·6 [95% CI 1·2–5·8]). Compared with quitters, the relative risk of lung cancer was 1·5 (1·2–1·7) for all switchers, 1·3 (1·1–1·6) for switchers to chew only, 1·9 (1·2–2·5) for snuff only, and 2·0 (1·2–3·0) for chew and snuff combined. Compared with men who never used any tobacco product, the relative risk of lung cancer was 3·9 for quitters and 5·6 for switchers.

Health effects other than cancer

Many cross-sectional studies from the USA, India, Saudi Arabia, Uzbekistan, and Sudan reported a higher occurrence of oral soft tissue lesions in smokeless tobacco users than in non-users.[4] Most of the studies have accounted for tobacco smoking either by statistical adjustment or restriction to non-smokers. The lesions are described as leucoplakia, erythroplakia, snuff dipper's lesion, tobacco and lime user's lesion, verrucous hyperplasia, and submucosal deposits, and tend to be seen in the site of product application. Since these lesions are regarded as precursors of cancer, these findings support the carcinogenicity of smokeless tobacco products on the oral mucosa. Furthermore, a few studies have reported an increased occurrence of gingival recession, tooth wear, and dental caries in users of smokeless tobacco products.[4] Fewer studies on oral precancerous lesions are available from Nordic countries;[46,47] overall, an increased occurrence in snus users cannot be excluded.

Several studies have addressed the risk of cardiovascular diseases in users of smokeless tobacco products. Results generally indicate a small or non-existent increased risk of myocardial infarction and cerebrovascular diseases, with most relative risk estimates lower than 1·5.[4,48] No evidence has shown an increased risk of chronic obstructive pulmonary disease in users of smokeless tobacco products compared with non-users. A few studies have investigated a possible effect of smokeless tobacco on insulin resistance, glucose intolerance, and diabetes, although they have limitations and inconsistent results.[4]

Burden of smokeless tobacco-related cancer

The fraction attributable cancers (AF) is a measure of the burden of smokeless tobacco use on human cancer. It refers to the role of past exposure on current cancer burden, and, if exposure has changed (as has occurred in the composition of smokeless tobacco products used in North America and Europe), it cannot be applied to the effect of current exposure on future cancer. Attributable cancers can be estimated based on the relative risk due to the habit (RR) and the proportion of the exposed population (P), according to the formula:

$$AF = \frac{P \times (RR-1)}{[P \times (RR-1)+1]}$$

A global estimate of attributable cancers is complicated by heterogeneity in exposure circumstances and risk and by the limitations in available data on patterns of use. We therefore calculated the attributable cancers for selected countries, to provide an indication of the order of magnitude of the problem. We calculated the attributable cancers for oesophageal and pancreatic cancer in northern Europe and for oral cancer in Canada, USA, Sudan, India, and other southern and southeastern Asian countries (table 3). The proportion of oral cancer cases attributable to smokeless tobacco use was more than 50% in south and southeast Asia, resulting in more than 50 000 cases of oral cancer attributable to the habit in the eight countries considered, with 36 000 in India alone. This proportion was 68% in Sudanese men and 4·4% in US men, resulting in an estimated number of 627 and 948 cases per year, respectively. The number of oesophageal and pancreatic cancer cases attributable to smokeless tobacco use in northern Europe was small, because of the rarity of the diseases. In particular, 31 cases of oesophageal cancer and 62 cases of pancreatic cancer were attributable to smokeless tobacco use in Swedish men.

These figures are probably underestimated because data for occurrence of exposure refer to the present or the recent past, whereas the exposure relevant for carcinogenesis would have occurred further back in the past and was probably higher. Furthermore, cases of

	Sex	Relative risk	Proportion of population exposed to smokeless tobacco (%)	Cases attributable to smokeless tobacco use (%)	n
Oesophageal cancer					
Denmark	Men	1·6	3·5%[49]	2·1%	5
Norway	Men	1·6	6%[50]	3·5%	5
Sweden	Men	1·6	20%[8]	10·7%	31
Sweden	Women	1·6	1%[8]	0·6%	1
Pancreatic cancer					
Denmark	Men	1·8	3·5%[49]	2·7%	10
Norway	Men	1·8	6%[50]	4·6%	12
Sweden	Men	1·8	20%[8]	13·8%	62
Sweden	Women	1·8	1%[8]	0·8%	4
Oral cancer					
USA	Men	2·6	4·4%[51]	6·6%	948
Canada	Men	2·6	1%[52]	1·6%	24
Sudan	Men	7·3[53]	34%[54]	68·2%	627
Sudan	Women	7·3[53]	2·5%[54]	13·6%	79
India	Men	5·1[55]*	27%[56]†	52·5%	27 304
India	Women	5·1[55]*	26%[56]†	51·6%	8827
Other Asian countries‡	Men	5·1[55]*	25%[57]	50·6%	9568
Other Asian countries‡	Women	5·1[55]*	25%[57]	50·6%	6453

N=number of cases attributable to smokeless tobacco use in 2002 (total number of cancers derived from reference 58). *Other studies from India and other south Asian countries have provided similar risk estimates. †No stable risk estimates exist for non-smokers. ‡Other surveys from India have provided similar results. §Bangladesh, Bhutan, Indonesia, Burma, Nepal, Pakistan, Sri Lanka.

Table 3: Proportion of oesophageal or oral cancer cases attributable to smokeless tobacco use in selected countries

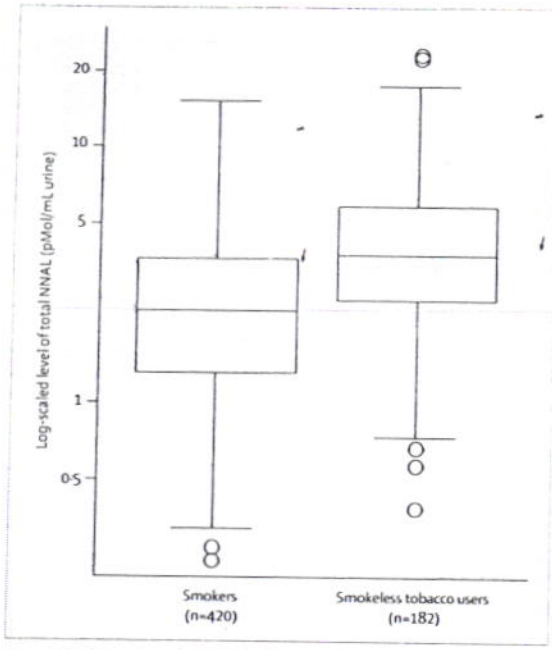

Figure 2: **Whisker plots of total NNAL in urine of smokers and smokeless tobacco users**
Summarised findings from reference 65.

pharyngeal cancer were not included in the calculation, despite the fact that an excess of this cancer was shown in several studies. Finally, the estimate excluded several populations in which smokeless tobacco is common, such as central and western Asian countries and Asian immigrants to Europe.

Biomarkers of carcinogen exposure in smokeless tobacco users

Biomarker studies clearly show the uptake and metabolism of tobacco carcinogens by smokeless tobacco users. These studies are crucial in linking smokeless tobacco use to cancer outcomes. Human beings and laboratory animals metabolise NNK into NNAL and NNK's glucuronides (NNAL-Glucs).[17] These compounds are excreted in the urine, and the total amount, known as total NNAL, is a practical and widely used biomarker of NNK exposure.[59]

The carcinogenic properties of NNAL are quite similar to those of NNK, whereas NNAL-Glucs are detoxification products.[17] The NNAL biomarker has been extensively used in studies of NNK exposure in smokers, smokeless tobacco users, and non-smokers exposed to involuntary tobacco smoke.[59] Advantages of this biomarker include its high reliability and specificity to tobacco products. Total NNAL in urine is not known to come from any source other than uptake of the tobacco-specific carcinogen NNK. Several small studies have clearly shown NNK uptake in smokeless tobacco users by measuring total urinary NNAL, including a study of Sudanese toombak users that recorded very high carcinogen exposures.[60-64] In a recent study,[65] total NNAL in the urine of larger groups of smokeless tobacco users and smokers was compared. Total NNAL was substantially higher in smokeless tobacco users than in smokers (figure 2). Similarly, concentrations of the nicotine metabolite cotinine were substantially higher in smokeless tobacco users than in smokers, consistent with previous studies.[66] Although differences in the pharmacokinetics of NNK and nicotine in smokeless tobacco users and smokers could complicate interpretation of these data, the results nevertheless show substantial uptake of the NNK in smokeless tobacco users, consistent with its amounts in smokeless tobacco products. However, cancer risk is higher in smokers than in smokeless tobacco users because, in addition to NNK, cigarette smoke contains many other carcinogens, tumour promoters, oxidants, and co-carcinogens, mostly derived from combustion.[67]

The tobacco-specific nitrosamines NNN, NAB, and NL-nitrosoanatabine (NAT) and their glucuronides have also been quantified in the urine of smokeless tobacco users, with generally higher concentrations than in smokers.[68] Total NNN could be a potentially useful biomarker of oesophageal carcinogen uptake in smokeless tobacco users. Tobacco-specific nitrosamines have also been quantified in the saliva of smokeless tobacco users.[4]

NNK and NNN are metabolically activated by cytochrome P450 enzymes resulting in the production of highly reactive pyridyloxobutyl (POB) diazonium ions and related species, which can react with DNA to form products that cause miscoding and mutations, initiating the carcinogenic process.[17,69] These POB species react with haemoglobin to produce adducts that can be quantified in human beings by mass spectrometry of released 4-hydroxy-1-(3-pyridyl)-1-butanone (HPB). The highest concentrations of HPB-releasing haemoglobin adducts have been reported in snuff-dippers, nasal snuff users, and toombak users.[64,70,71] These results have

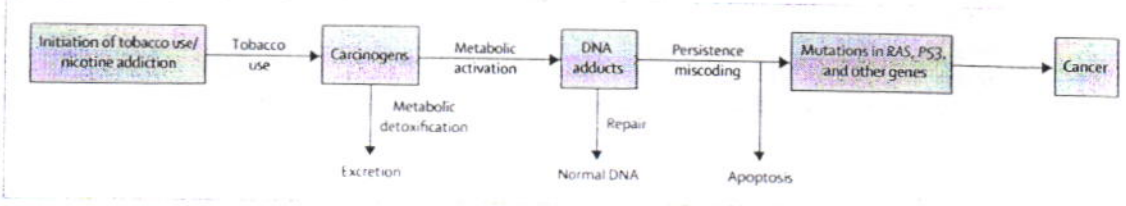

Figure 3: Conceptual model of smokeless tobacco carcinogenesis
Modified from reference 72

shown that the metabolic activation of NNK and NNN, needed for carcinogenicity, occurs in smokeless tobacco users.

Mechanisms of carcinogenicity of smokeless tobacco

Figure 3 presents a conceptual framework for the carcinogenic mechanism by smokeless tobacco. People begin using these products generally at a young age, frequently because of effective marketing and peer pressure. These individuals become addicted to nicotine and cannot stop using the products. Nicotine is not a carcinogen, but as described above, every dip of smokeless tobacco contains more than 30 established carcinogens, with especially high amounts of the tobacco-specific nitrosamines NNK and NNN. These carcinogens are taken up, distributed, and metabolised in all smokeless tobacco users.

Few data exist about the levels of metabolic activation, detoxification, and DNA adduct formation in smokeless tobacco users,[4] compared with the substantial volume of information in smokers that is available. However, DNA adducts are probably formed in the oral tissue and other tissues of smokeless tobacco users; sister chromatid exchanges, chromosomal aberrations, and micronuclei—consequences of DNA adduct formation—have also been reported.[72] When DNA adducts persist unrepaired, by evading or overwhelming healthy cellular repair systems, the result can be miscoding, leading to permanent DNA mutations. If these mutations occur in crucial regions of specific genes, such as the *RAS* oncogene or the *P53* tumour suppressor gene, the result can be the loss of mechanisms of healthy cellular growth control, and ultimately the development of cancer. Many studies have demonstrated *RAS* and *P53* mutations in smokeless tobacco users.[73]

Although figure 3 represents a useful and supportable conceptual framework, there are certainly other factors participating in the carcinogenic mechanism of smokeless tobacco.[4] Oxidative stress and reactive oxygen species could have important roles, based on animal studies. Chronic local inflammation and irritation induced by smokeless tobacco and its constituents could have a tumour-promoting or co-carcinogenic effect. Upregulation of cyclo-oxygenase-2, involved in prostaglandin synthesis and inflammation, has been seen in animal studies on exposure to smokeless tobacco. Smokeless tobacco products have high amounts of sodium chloride, which could contribute to inflammation, tumour promotion, and co-carcinogenesis. Viruses have been shown to enhance the carcinogenicity of smokeless tobacco products in animal studies.[74]

Conclusion

We do not intend to address explicitly the use of smokeless tobacco to reduce the risk from tobacco smoking—eg, by promoting smokers to switch to smokeless products or by introducing these products in a population where the habit is not prevalent. Nevertheless, several conclusions can be reached based on the available data: use of smokeless tobacco products is widespread in many populations, but their health effects (especially with respect to cancer risk) need to be better characterised; such use results in exposure to carcinogens, notably nitrosamines; the risk of cancer depends on the type of product consumed, and the concentration of nitrosamines is the strongest factor to determine product-specific risk; the risk of cancer, especially that of oral and lung cancer, is probably lower in smokeless tobacco users in the USA and northern Europe than in smokers; and the risk of cancer is higher in smokeless tobacco users than in non-users of any form of tobacco. Available data for a possible benefit of switching from smoking to smokeless tobacco come from few studies and models from the USA and Sweden.[75] Comparative risk estimates depend on many assumptions, including the expected effect of the introduction of new smokeless products in populations where the habit has not been common.

Search strategy and selection criteria

We identified epidemiological studies of smokeless tobacco and cancer based on the IARC Monograph, which was prepared in October, 2004, and provides a very detailed review of the studies available at that time,[4] and by searching Medline, PubMed, and references from relevant articles for reports published in any language between October, 2004, and September, 2007, using the search terms "snus", "snuff", or "smokeless tobacco", and "cancer" or "neoplasm". Meeting abstracts and reports were excluded. We also included one manuscript that was in press in September, 2007. If several reports covered the same population, we used the most recent or comprehensive paper. A similar strategy was used in the 2004 IARC Monograph[4] to identify earlier publications. We did a quantitative review of epidemiological studies of smokeless tobacco use and risk of cancers of the oral cavity, oesophagus, pancreas, and lung. Results for other cancers were too sparse for a quantitative investigation. We included only studies restricted to non-smokers and studies that included smokers but were properly adjusted for the possible confounding effect of tobacco smoking.

Conflicts of interest

The authors declared no conflicts of interest.

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Annexure 59

Int. J. Cancer: **122**, 1095–1099 (2008)

Risk of gastroesophageal cancer among smokers and users of Scandinavian moist snuff

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Although Scandinavian moist snuff ("snus"), no doubt, is a safer alternative to smoking, there is limited evidence against an association with gastroesophageal cancers. In a retrospective cohort study, we investigated esophageal and stomach cancer incidence among 336,381 male Swedish construction workers who provided information on tobacco smoking and snus habits within a health surveillance program between 1971 and 1993. Essentially complete follow-up through 2004 was accomplished through linkage to several nationwide registers. Multivariable Cox proportional hazards regression models estimated relative risks (RR) and 95% confidence intervals (CIs). Compared to never-users of any tobacco, smokers had increased risks for adenocarcinoma (RR = 2.3, 95% CI 1.4–3.7) and squamous cell carcinoma (RR = 5.2, 95% CI 3.1–8.6) of the esophagus, as well as cardia (RR = 2.1, 95% CI 1.5–3.0) and noncardia stomach (RR = 1.3, 95% CI 1.2–1.6) cancers. We also observed excess risks for esophageal squamous cell carcinoma (RR = 3.5, 95% CI 1.6–7.6) and noncardia stomach cancer (RR = 1.4, 95% CI 1.1–1.9) among snus users who had never smoked. Although confounding by unmeasured exposures, and some differential misclassification of smoking, might have inflated the associations, our study provides suggestive evidence for an independent carcinogenic effect of snus.

Key words: gastroesophageal cancer; tobacco smoking; snuff (snus) use; cohort; Sweden

Tobacco smoking is widely acknowledged as the main known cause of cancer-related death worldwide, estimated to be responsible for ~25% of all cancers in men and 4% in women.[1] Its relation to—among others—esophageal squamous cell carcinoma (ESCC) and adenocarcinoma (EAC) as well as stomach cancer is well established.[2] Snuff, particularly the moist Scandinavian variant (snus) with reduced levels of carcinogenic tobacco-specific nitrosamines (TSNAs), might help inveterate smokers stop or reduce their smoking habit. If acceptably safe, snus use might potentially be recommended to smokers in order to reduce risks for these cancers. Available investigations of snus use and risk of esophageal or stomach cancer are few but suggest an absence of risk elevation; only 1 study, published as an abstract,[3] found a statistically significant increased risk for esophageal cancer, while the other studies showed statistically nonsignificant relative risk estimates between 1.2 and 1.4 for esophageal cancer[4–6] and 0.9–1.1 for stomach cancer.[6,7] However, these studies generally had limited power and/or insufficient covariate information to rule out important positive or negative confounding by smoking intensity; there are good reasons for assuming that smokers smoke less if they also use smokeless tobacco.

We therefore studied the incidence of esophageal and stomach cancers in a large and highly exposed cohort of Swedish construction workers followed for up to 33 years from as far back as 1971. Snus exposure data were first analyzed without adjustment for smoking dose in order to evaluate the net effect of smoking and snus in combination (including the possible benefit conferred by a reduction in smoking dose). Then we tried to disentangle the independent effect of snus use by means of adjustment for smoking intensity. By virtue of the large sample size and the unprecedented exposure prevalence we could also investigate into these risks with reasonable statistical power in the stratum of never-smokers.

Subjects and methods

The cohort

The construction industry's Organization for Working Environment, Safety and Health, "Bygghälsan," offered preventive health check-ups to all blue- and white-collar workers in the Swedish building industry between 1969 and 1993. In all, 361,280 individuals had records of at least 1 visit between 1971 and 1993. Since less than 5% of the participants were women, we restricted our investigation to male workers (n = 343,822).

Exposure information

During 1971–75 each cohort member filled out a 200-item questionnaire that included detailed questions about smoking and snus use. During the visits answers were double-checked by attending staff. After a pause during 1976 through 1977, the collection of smoking and snus information was resumed in 1978 but on a new form filled out directly by the staff. All data were compiled in a computerized central register. The data quality has been reviewed previously and was deemed to be satisfactory.[8] Because repeat visits were variable in number and timing among the cohort members, to a large extent driven by self selection, we only used the exposure information recorded at the first registered visit, which also marked the entry into the cohort.

Follow-up

The national registration numbers (NRNs), unique personal identifiers assigned to all residents in Sweden, permitted follow-up through linkages to nationwide and essentially complete registers of cancer, causes of death, as well as to registers of the total population and migration. If a NRN could not be found in any of the latter 3 registers it was deemed to be erroneous and the record was excluded. The more than 98% complete cancer register,[9] established in 1958, has coded malignant neoplasms according to the 7th revision of International classification of diseases (ICD7) during the entire study period. The ICD7 code 150 (esophageal cancer) was broken down into EAC (code 096) and ESCC (code 146) using WHO/HS/CANC/24.1 histology codes,[10] and stomach cancer (ICD7 code 151) was subdivided into cardia (CSC) (151.1) and noncardia (N-CSC) (all other 151) cancer. Each cohort member contributed person–time from the date of first registered visit until the date of any diagnosis of cancer, death, emigration or December 31, 2004, whichever came first.

Statistical analysis

We computed the incidence of esophageal and stomach cancer by smoking and snus consumption categories, standardized to the

Anders Englund is now retired.
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TABLE I – CHARACTERISTICS OF THE MALE SWEDISH CONSTRUCTION WORKERS COHORT

Age at entry (years)	Number of men	Person-years of follow-up	No. of ever-smokers (%)	No. of snus users (%)	No. of never-smoking snus users (%)
≤20	37,622	774,582	11,583 (31)	13,523 (36)	9561 (25)
20–29	117,460	2,662,862	57,917 (49)	40,748 (35)	20,887 (18)
30–39	74,046	1,783,956	49,656 (67)	19,231 (26)	5201 (7)
40–49	49,959	1,151,843	34,578 (69)	9698 (19)	2087 (4)
50–59	41,762	847,497	29,280 (70)	8265 (20)	2063 (5)
≥60	15,532	254,886	10,476 (67)	3319 (21)	1133 (7)
Overall	336,381	7,475,628	193,490 (58)	94,784 (28)	40,932 (12)

distribution of person–time experienced by the entire construction workers cohort using 5-year age categories.[11] Cox proportional hazards regression models estimated relative risks (RRs) and corresponding 95% confidence intervals (CIs) using attained age (in years) as the time scale. All models were adjusted for body mass index (BMI) at entry, categorized into quartiles. Calendar year of entry into the cohort and residential place (northern, middle or southern Sweden) was also considered as a covariate but both proved to be redundant. Smoking status (never, current or previous), smoking dose (0, 1–9, 10–19 and ≥ 20 g of tobacco per day) and time since quitting (<5 years and ≥5 years), reported at entry into the cohort, were categorized prior to the analyses based on what was perceived as relevant in relation to factual consumption habits and biological effects. To create a summary variable for total tobacco smoking, a cigarette and a cigar were equated to 1 and 6 g of tobacco, respectively, while pipe smoking was already reported in grams per week. We evaluated trends by creating semicontinuous variables from medians of categories; in these analyses the never-users of any tobacco were omitted. We also analyzed the effect of different smoking habits separately, *i.e.* cigarette only, pipe only and cigar only. We restricted the analyses of smoking effects to never-users of snus.

To study effects of snus use, we first compared cancer risks among all users to those among all nonusers, with adjustments only for attained age and BMI. Although we cannot exclude the possibility that preexisting smoking dose could have been linked to the inclination to take up snus use, the analyses that were unadjusted for smoking were thought to accommodate the assumed dose-limiting effect of adding snus use to the smoking habit. Hence, the estimates were interpreted as the net effect of the combined habit. Next we tried to disentangle independent associations of snus use by additional adjustment for smoking. These unadjusted and adjusted analyses were then repeated in the substratum of ever-smokers at time of entry. This was because it was assumed that any positive net effect of snus use would be particularly evident among smokers. In addition to attained age and BMI, we adjusted for smoking status (current or previous at entry into the cohort), dose and type of smoking tobacco (cigarette only, cigar only, pipe only, pipe and cigarette and other combinations). Evaluation of the proportional hazards assumption with graphs of scaled Schoenfeld residuals[12] revealed that the assumption did not hold for the association of snus use with stomach and esophageal cancers. As the RRs were diverging at age 70, we further estimated RRs in two age strata using age of 70 as cut-point. To control more efficiently for smoking we estimated the RRs among never-smoking snus users in comparison to never-users of any tobacco and adjusted only for attained age and BMI. Stata statistical software (release 9.1) was used in all analyses. This study was approved by the Regional Ethics Committee of Karolinska Institutet.

Results

We removed 3,130 (0.9%) records because of invalid NRNs or inconsistencies found during record linkages. Moreover, we excluded 3,032 (0.8%) subjects due to missing information on BMI and—because we only considered first cancers—1,299 (0.3%) subjects with any cancer before entry into the cohort, leaving 336,381 workers for final analyses. They were followed for up to 33.5 years (mean 22.2) corresponding to 7,475,628 person-years under observation. The mean age at entry was 34.7 years. Table I shows characteristics of the cohort members by age categories. Overall, 58% of the workers were current or former smokers at time of entry. The prevalence of snus use was 28% overall but higher among young workers. We observed 130 cases of EAC, 236 ESCC, 276 CSC and 1109 N-CSC.

Smoking

Our observed associations between tobacco smoking and all 4 categories of esophagogastric cancer were in good accordance with the previous literature (Table II). With the possible exception of EAC, it appeared that pipe smoking was more strongly related to the risk of the studied cancers than were other types of smoking habits. We noted differential risk patterns for esophageal and stomach cancers after smoking cessation; while the risk of both major histological types of esophageal cancer fell to the unexposed level within 5 years of quitting, risks of CSC and N-CSC remained on increased and essentially unaltered levels even after 5–38 years.

Snus use and esophageal adenocarcinoma

In a model that included the entire cohort and where snus users were compared to nonusers of snus, regardless of smoking status and with adjustments only for attained age and BMI, we found no increased risk among snus users (Table III). The risk before the age of 70 years tended to be slightly below that among nonusers and slightly above this risk among those who were older. Additional adjustment for smoking dose had only trivial effects on our estimates. In a model restricted to ever-smokers and unadjusted for smoking variables, the relative risk among snus users overall was 1.0 but it was 0.6 (95% CI 0.3–1.1) among workers who had not yet attained age 70 and 2.3 (95% CI 1.1–4.6) above this age. Further adjustment for smoking variables tended to increase the RRs values somewhat overall and in age strata, but the pattern was otherwise similar. In a model restricted to never-smokers the adjusted relative risk based on 1 exposed case, tended to be markedly lower than in the reference group, but the confidence interval was large and included unity (RR = 0.2, 95% CI 0.0–1.9).

Snus use and esophageal squamous cell carcinoma

Models based on the entire cohort gave no indication of any overall increased or decreased risk for ESCC among snus users regardless of whether or not adjustments were made for smoking intensity (Table III). A restriction to smokers yielded a nonsignificant tendency toward decreased risk among snus users, relative to nonusers, but only before the age of 70 years. This risk reduction was attenuated after adjustments for smoking variables. However, we observed a significant 3.5-fold excess risk (95% CI 1.6–7.6) among isolated snus users relative to never-users of any tobacco. The excess was almost similar and statistically significant in both strata of attained age.

Snus use and stomach cancer

Snus use had no significant effect on the risk of CSC, irrespective of analytic approach (Table IV), but in the analyses that included the entire cohort it was associated with borderline significant 10% excesses of N-CSC risks, regardless of whether or not

TABLE II – SMOKING-ASSOCIATED RELATIVE RISKS (RR) AND 95% CONFIDENCE INTERVALS (CI) FOR ESOPHAGEAL AND STOMACH CANCERS AMONG MALE SWEDISH CONSTRUCTION WORKERS WHO WERE NEVER-USERS OF SNUS AT ENTRY INTO THE COHORT

Tobacco habit	Person-years	Esophageal cancer				Stomach cancer			
		Adenocarcinoma		Squamous cell carcinoma		Cardia		Noncardia	
		IR[1]	RR (95% CI)	IR[1]	RR (95% CI)	IR[1]	RR (95% CI)	IR[1]	RR (95% CI)
Never-users of any tobacco	2,241,175	1.0	Reference	0.8	Reference	2.1	Reference	11.7	Reference
Ever-smokers	3,179,735	2.2	2.3 (1.4–3.7)	4.4	5.2 (3.1–8.6)	4.5	2.1 (1.5–3.0)	16.0	1.3 (1.2–1.6)
Current smokers[2]	2,352,918	2.7	2.9 (1.8–4.8)	6.4	7.6 (4.5–12.7)	4.8	2.3 (1.6–3.3)	16.5	1.4 (1.2–1.6)
<10 g/day	1,073,818	1.7	1.8 (0.9–3.2)	6.2	6.9 (4.0–11.8)	4.3	2.1 (1.4–3.1)	15.8	1.3 (1.1–1.6)
10–19 g/day	821,973	3.4	3.8 (2.1–6.7)	5.4	6.3 (3.5–11.1)	5.0	2.4 (1.6–3.7)	17.7	1.4 (1.2–1.8)
≥20 g/day	457,127	4.4	4.7 (2.5–9.0)	8.6	11.2 (6.2–20.2)	5.6	3.0 (1.8–5.0)	15.9	1.4 (1.1–1.9)
p value for trend[3]			0.001		0.2		0.1		0.3
Previous smokers[4]	753,339	1.4	1.2 (0.6–2.4)	0.7	0.9 (0.4–2.0)	3.9	1.8 (1.2–2.7)	15.0	1.3 (1.1–1.5)
Smoke free <5 yr	330,898	2.2	2.1 (0.9–4.9)	0.8	1.0 (0.3–3.5)	4.1	1.9 (1.1–3.4)	14.1	1.2 (0.9–1.6)
Smoke free ≥ 5 yr	422,441	0.7	0.8 (0.3–1.8)	0.6	0.8 (0.3–2.1)	3.6	1.7 (1.1–2.6)	15.7	1.3 (1.1–1.6)
p value for trend[3]			0.1		0.8		0.7		0.6
Smoking product[5]									
Cigarette only	2,196,928	2.5	2.6 (1.5–4.3)	3.7	4.5 (2.6–7.8)	3.7	1.7 (1.2–2.5)	15.2	1.3 (1.1–1.5)
Pipe only	381,783	0.9	1.1 (0.5–2.4)	7.8	8.3 (4.8–14.5)	6.3	3.1 (2.1–4.7)	18.1	1.5 (1.2–1.8)
Cigar only	44,518	1.1	1.2 (0.2–9.3)	4.9	5.8 (1.9–17.4)	–	–	13.5	1.0 (0.5–1.8)

All relative risk estimates were adjusted for attained age and body mass index.
[1]IR, Incidence rate per 100,000 person-years, standardized to the age distribution of person-years among all workers using 5-year age categories.–[2]Observations with missing value for smoking intensity were excluded.–[3]The never-users of any tobacco were omitted in the trend analyses.–[4]Observations with missing value for time since cessation were excluded. Stratification was based on time prior to entry into the cohort.–[5]All smokers (both current and former smokers) were used when analyzing relative risks for different smoking products.

TABLE III – ASSOCIATION OF SNUS USE WITH ESOPHAGEAL CANCER BY HISTOLOGY AMONG MALE SWEDISH CONSTRUCTION WORKERS 1971–1993, FOLLOWED THROUGH 2004

Tobacco habit	Number of men	Person-years	Adenocarcinoma			Squamous cell carcinoma		
			Number of cases	IR[1]	Relative risk (95% CI)	Number of cases	IR[1]	Relative risk (95% CI)
In the entire Cohort								
Non-users of snus	241,597	5,420,909	103	1.8	Reference	186	3.1	Reference
Snus users, adjusted only for								
BMI and attained age	94,784	2,054,718	27	1.7	1.0 (0.6–1.5)	50	3.2	1.1 (0.8–1.5)
<70-years-old[2]	81,377	1,945,373	14	0.7	0.7 (0.4–1.2)	28	1.4	0.9 (0.6–1.4)
≥70-years-old	13,407	109,345	13	11.8	1.6 (0.8–3.0)	22	20.1	1.4 (0.8–2.2)
Snus users, additionally adjusted								
for smoking intensity	94,784	2,054,718	27	1.7	1.0 (0.6–1.5)	50	3.2	1.0 (0.8–1.4)
<70-years-old[2]	81,377	1,945,373	14	0.7	0.7 (0.4–1.3)	28	1.4	0.9 (0.6–1.3)
≥70-years-old	13,407	109,345	13	11.8	1.7 (0.9–3.3)	22	20.1	1.4 (0.8–2.2)
Among ever-smokers								
Non-users of snus	139,638	3,179,735	83	2.2	Reference	170	4.2	Reference
Snus users, adjusted only for								
BMI and attained age	53,852	1,250,860	26	2.2	1.0 (0.6–1.5)	40	3.5	0.8 (0.6–1.2)
<70-years-old[2]	43,792	1,172,133	13	1.1	0.6 (0.3–1.1)	23	2.0	0.7 (0.4–1.1)
≥70-years-old	10,060	78,727	13	16.5	2.3 (1.1–4.6)	17	22.0	1.1 (0.6–1.9)
Snus users, additionally adjusted								
for smoking variables	53,852	1,250,860	26	2.2	1.3 (0.8–2.0)	40	3.5	1.2 (0.8–1.7)
<70-years-old[2]	43,792	1,172,133	13	1.1	0.8 (0.4–1.5)	23	2.0	1.0 (0.6–1.6)
≥70-years-old	10,060	78,727	13	16.5	2.9 (1.4–6.0)	17	22.0	1.6 (0.9–2.8)
Among never-smokers[3]								
Never-users of any tobacco	101,959	2,241,175	20	1.0	Reference	16	0.8	Reference
Users of snus only	40,932	803,858	1	0.2	0.2 (0.0–1.9)	10	2.6	3.5 (1.6–7.6)
<70-years-old[2]	37,588	7,73,240	1	0.2	0.6 (0.1–5.0)	5	1.6	3.7 (1.2–11.4)
≥70-years-old	3,347	30,618	0	–	–	5	15.6	3.1 (1.0–9.4)

[1]Incidence rate per 100,000 person years, standardized to the age distribution of person-years among all workers using 5-year age categories.–[2]Since the observations were split by the attained age, each worker may contribute to both subcohorts, and thus the sum of the 2 subcohorts will exceed that in the main cohort.–[3]Relative risks were adjusted for attained age and body mass index.

adjustments were done for smoking dose. These excesses were confined to workers above age 70, among whom statistically significant 40–50% risk elevations were observed. Moreover, a significant 40% overall excess risk (RR = 1.4, 95% CI 1.1–1.9) for N-CSC emerged among snuff using never-smokers, relative to never-users of any tobacco.

Sensitivity analyses

Since we only used exposure information collected at entry into the cohort, there is a possibility that nonsmoking snus users, compared to nonusers of any tobacco, were more inclined to take up smoking in the follow-up period. With the reservation that cross-sectional data across successive repeat visits may be sensitive to selection bias, we analyzed such data among 60,833 workers who reported being never-users of any tobacco at entry (with at least 2 visits and an average 3.3 repeat visits) and 21,436 who said that they were never-smoking snus users (3.7 repeat visits). In the former and latter group, respectively, 4,080 (6.7%) and 2,828 (13.2%) had at least 1 repeat record that indicated current or previous smoking, confirming that differential misclassification of smoking status is indeed a valid concern.

TABLE IV – ASSOCIATION OF SNUS USE WITH STOMACH CANCER BY SUBSITE AMONG MALE SWEDISH CONSTRUCTION WORKERS 1971 TO 1993, FOLLOWED THROUGH 2004

Tobacco habit	Cardia			Noncardia		
	Number of cases	IR[1]	Relative risk (95% CI)	Number of cases	IR[1]	Relative risk (95% CI)
In the entire cohort						
Non-users of snus	218	3.7	Reference	856	14.5	Reference
Snus users, adjusted only for BMI and attained age	58	3.7	1.0 (0.7–1.3)	253	16.4	1.1 (1.0–1.3)
<70-years-old	31	1.6	0.8 (0.6–1.2)	128	6.6	0.9 (0.8–1.1)
≥70-years-old	27	24.7	1.3 (0.8–2.0)	125	114.3	1.4 (1.2–1.8)
Snus users, additionally adjusted for smoking intensity	58	3.7	1.0 (0.8–1.4)	253	16.4	1.1 (1.0–1.3)
<70-years-old	31	1.6	0.9 (0.6–1.3)	128	6.6	0.9 (0.7–1.1)
≥70-years-old	27	24.7	1.3 (0.8–1.9)	125	114.3	1.5 (1.2–1.8)
Among ever-smokers						
Non-users of snus	174	4.5	Reference	615	16.2	Reference
Snus users, adjusted only for BMI and attained age	50	4.3	0.9 (0.7–1.3)	185	16.2	1.0 (0.9–1.2)
<70-years-old	28	2.4	0.8 (0.5–1.2)	96	8.6	0.8 (0.7–1.0)
≥70-years-old	22	28	1.2 (0.8–2.0)	89	113.1	1.3 (1.0–1.7)
Snus users, additionally adjusted for smoking variables	50	4.3	1.1 (0.8–1.6)	185	16.2	1.0 (0.9–1.2)
<70-years-old	28	2.4	1.0 (0.7–1.6)	96	8.6	0.8 (0.7–1.1)
≥70-years-old	22	28	1.4 (0.8–2.2)	89	113.1	1.4 (1.1–1.8)
Among never-smokers[2]						
Never-users of any tobacco	44	2.1	Reference	242	11.7	Reference
Users of snus only	8	2.0	0.9 (0.4–2.0)	68	17.4	1.4 (1.1–1.9)
<70-years-old[2]	3	0.9	0.6 (0.2–2.1)	32	9.7	1.2 (0.8–1.8)
≥70-years-old	5	16.5	1.3 (0.5–3.4)	36	115.6	1.7 (1.2–2.5)

[1]Incidence rate per 100,000 person years, standardized to the age distribution of person-year among all workers using 5-year age categories.–[2]Relative risks were adjusted for attained age and body mass index.

In a sensitivity analysis, we extrapolated these proportions to the entire subcohorts of never-users of any tobacco and never-smoking snus users and assumed that workers with a positive smoking record at any point in time during follow-up were, in fact, smokers. Using the magnitude of smoking-disease associations shown in Tables II and III, we adjusted the observed associations between exclusive snus use and gastroesophageal cancers as proposed by Schneeweiss.[13] Taking the suspected misclassification into account, the relative risk for ESCC among never-smoking snus users would fall from 3.5 to 2.9 and, correspondingly, RRs for N-CSC would decrease from 1.4 to 1.37. We also estimated that at least 60% of the snus users would have to be smokers to shift a true null association with ESCC to the observed relative risk value, assuming no smoking misclassification among never-users of any tobacco. Moreover, not even 100% smoking prevalence among snus users would fully explain the observed association between exclusive snus use and noncardia stomach cancer.

Discussion

This large retrospective cohort study with long and essentially complete follow-up confirms the well-established link between smoking and all major types of gastroesophageal cancer. It also provides new data suggestive of snus-associated carcinogenic risks. Although effectively confined to septuagenarians or older, never-smoking snus users overall had a statistically significant 40% excess risk of N-CSC compared to never-users of any tobacco. Although our data indicated that some differential misclassification of smoking status may have occurred at entry or during follow-up, despite several reports suggesting that exclusive snus users rarely take up smoking,[14–17] this misclassification is an unlikely explanation for our finding. We found little evidence of any net protective effect of snus use through its presumed reduction of smoking dose—neither in the mixed population of smoking and nonsmoking workers, nor among workers who were reportedly ever-smokers at entry into the cohort. Never-smoking snus users, further, had a substantially increased risk of ESCC when compared to never-users of any tobacco, again not likely explained by differential misclassification of smoking status. There was a nonsignificant tendency for a lower risk of ESCC among smokers who also used snus, but the purported harm reduction by snus use[18–20] did not impress overall.

Generally, adjustments for smoking variables in analyses that also included smokers changed the unadjusted relative risk estimate surprisingly little. The main reason is that the proportions who reported being or having been smokers at entry were almost identical among users (56.8%) and nonusers (57.8%) of snus. Hence, based on the smoking information obtained at entry, the scope for confounding was limited to the observed variation among smokers in regard to smoking dose, smoking status (current or exsmoker) and type of smoking tobacco. If this information would not correctly reflect the relevant smoking exposure status, either because of erroneous reporting at entry or due to subsequent changes in habits (differential or nondifferential), residual confounding by smoking might be a concern.

We did, indeed, note certain weaknesses of the smoking information collected in 1971–75. Nonsmokers were not required to actively negate smoking. Instead, they were instructed to simply skip the smoking questions. All cohort members without answers to these questions were coded as nonusers. Thus, the never-smoker category may have contained some smokers, who skipped the smoking questions for other reasons than nonuse. As nonsmokers were instructed to move directly to the snus questions, where absence of any response was likewise coded as nonuse, it is conceivable that of all who skipped the smoking questions the proportion of negligent smokers who skipped it inadequately was greater when both sets of questions were skipped than when the snus questions were answered in the affirmative. Consequently, it was suspected that the reference category of never-smoking nonusers of snus may have contained more misclassified smokers than did the group classified as nonsmoking snus users. The sensitivity analysis using admittedly self-selected workers with 1 or several repeat visits did not support this suspicion, though.

None of the previous epidemiological studies on snus and esophageal cancer, 1 cohort study[6] and 2 population-based case-control studies,[4,5] has shown any significant excess risks, but the point estimates for the relative risk, multivariately adjusted for smoking dose, were above unity in all, ranging between 1.2[4] and 1.4.[5,6] Neither of the previous studies had sufficient power to analyze relative risk specifically for esophageal cancer in strata of

never-smokers. This was true also for the 2 studies that addressed the association between snus use and risk of stomach cancer.[6,7] These studies, 1 population-based case-control study[7] and 1 cohort study,[6] combined CSC and N-CSC, adjusted multivariately for smoking, and were both negative with RRs among ever-users, relative to never-users, of 0.9 and 1.1, respectively.

The observed departure from the proportional hazards assumption in our analyses pertaining to both esophageal and gastric cancer forced us to stratify our analyses by attained age (below and above age 70). This suggests effect modification by age. The RRs tended to be higher among workers who were older than 70, compared to those who were younger, consistent with a very long induction time. The oldest were also most exposed to snus from earlier parts of the 20th century. Such snus contained higher levels of carcinogenic TSNAs compared to the snus sold today.[21]

Some additional important caveats need to be highlighted. First, the analyses of some cancer sites in strata of never-smokers were based on small numbers (1, 10 and 8 snus-exposed cases of EAC, ESCC and CSC, respectively). Whereas the relative risk of ESCC among never-smoking snus users was statistically significant with a lower confidence limit of 1.6, chance could still have played a role, particularly since multiple significance testing was done in this study. Second, the lack of information about several confounding factors needs careful consideration. While alcohol is a candidate confounding factor for associations of tobacco use with ESCC and possibly also with CSC and unavailability of alcohol information is serious limitation, the weak or absent of association of alcohol use with N-CSC[22] makes such confounding unlikely. Since there is meager information about lifestyle differences between never-smokers who use snus and those who do not use snus, confounding from other unmeasured exposure cannot be confidently ruled out. The restriction to male construction workers—although a possible threat to the generalizability of our findings—allays concerns about confounding by gender, socioeconomic status and occupational exposures. Confounding by dietary factors remains a viable possibility, though.

Although some uncertainty remains regarding the causality and the strength of the association as well as the generalizability to other populations than Swedish men, we conclude that at present, Scandinavian snus cannot be considered to be without a carcinogenic risk.

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