MISCELLANEOUS

Health effects associated with smokeless tobacco: a systematic review

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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 the following outcomes (all cause mortality, oral and pharyngeal cancers, other cancers, cardiovascular diseases, dental diseases, pregnancy outcomes, surgical outcomes). Data extraction covered control of confounding, selection of cases and controls, sample size, clear definitions and measurements of the health outcome, and ST use. Selection, extraction and quality assessments were carried out by one or two independent reviewers.
Results: A narrative review was carried out. Many of the studies lacked sufficient power to estimate precise risks, mainly due to the small number of ST users. Studies were often not designed to investigate ST use, and many also had major methodological limitations including poor control for cigarette smoking and imprecise measurements of exposure. Studies in India showed a substantial risk of oral or oropharyngeal cancers associated with chewing betel quid and tobacco. Studies from other regions and of other cancer types were not consistent. Few studies have adequately considered the non-cancer health effects of ST use.
Conclusions: Chewing betel quid and tobacco is associated with a substantial risk of oral cancers in India. Most recent studies from the US and Scandinavia are not statistically significant, but moderate positive associations cannot be ruled out due to lack of power. Further rigorous studies with adequate sample sizes are required, especially for cardiovascular disease.

Smokeless tobacco (ST) is tobacco consumed orally, not smoked. It has been in use for as long as other forms of tobacco consumption and its use has increased.[1] The main types of ST in Western countries are chewing tobacco and oral snuff. Chewing tobacco is predominantly used in the USA and snuff (snus) in Sweden. In developing countries, tobacco is mostly chewed with other ingredients. Chewing is practised in different ways: the main ingredients are usually areca nut (betel), betel leaf, lime and tobacco. Other types exist worldwide.[2 3]

Major reviews in the mid 1980s concluded that ST use has substantial negative health implications. A US Surgeon General report in 1986 concluded that "the use of snuff can cause cancer in humans" and "the excess risk of cancer of the cheek and gum may reach nearly 50-fold among long term snuff users".[4] ST use can be addictive, leading to oral leukoplakias (oral mucosal lesions), gingival recession, and may play a contributory role in the development of cardiovascular disease, peripheral vascular disease, hypertension, peptic ulcers, and fetal morbidity and mortality".[4] An IARC monograph in 1984 similarly concluded that snuff use causes cancer.[5] Nevertheless, the negative health effects of ST use have been questioned. ST is not homogeneous[1]; there are significant differences in composition and production. Levels of the most powerful carcinogens—tobacco-specific N-nitrosamines (TSNAs)—vary widely in different ST products[6] and recent production trends may have reduced these levels.[7 8]

The ecological analyses available to date from Western countries have been inconclusive. Sweden has a low rate of oral and pharyngeal cancers despite high ST use. The US states with highest ST use (West Virginia) do not have high rates of oral cancers.[9] In Asia, the majority of ST studies have been carried out in India where both the habits and the negative outcomes (mainly oral cancers) are most prevalent, and strong dose dependent associations have been found.[10–13] Tobacco here is generally used with other substances such as areca nut and lime, which may themselves be associated with oral disease.[14–16]

Although reductions in cigarette smoking have been achieved in many developed countries, these falls have begun to level off.[17] Further reductions may be difficult to attain,[18] despite a myriad of effective cessation products. Success rates regarding long term smoking abstinence are disappointing, with less than 50% of smokers quitting permanently.[19 20] Persuading resistant smokers to reduce[21] or to switch to less harmful products[22–24] could benefit public health.[23 25] Tilashalski *et al*[23] estimated that, if all US smokers switched to ST use, 12 000 cases of oral cancer would occur each year, representing only 5% of all tobacco smoking related lung cancers and 50% of the oral cancers now attributed to cigarette smoking.[22 23] This is controversial as the precise health effects of ST use are uncertain and are not necessarily limited to oral cancers.[26] The health benefits of switching to supposedly "less harmful" smoked tobacco forms (such as cigars, pipes, low yield or light cigarettes) have been disappointing.[20 25] Others argue that the development of new improved smoking cessation pharmacotherapies is preferable.[26]

This review has been carried out in an attempt to quantify the major health effects associated with ST use and to critically appraise the studies performed. Significant numbers of new studies have been published since the major reviews of the mid 1980s and early 1990s, and types of ST have changed. Many literature reviews have been published, mostly confined to a single health effect such as oral cancer,[27–29] cancer,[30–32] or

periodontal disease.[33–35] None appears to be "systematic" in its approach and all lack a search strategy or inclusion criteria.

METHODS

The objectives of the review were to (1) identify and describe epidemiological studies; (2) provide narrative and tabular summaries of results; and (3) interpret results including the potential impact on the population.

Criteria for considering studies for review

Types of studies

Analytical epidemiological studies were reviewed, provided they included users of a form of ST and a group who used no tobacco products or smoked cigarettes only. Small studies (total sample size <500) were excluded as they may be subject to publication bias and are more likely to be published if they are "positive",[36 37] while larger studies are likely to be published regardless of their finding and may provide more power. Excluded studies are listed in the appropriate tables of excluded studies for each health outcome. All the studies meeting the inclusion criteria are described in detail in appendix 1 (available on the *Thorax* website, http://thoraxjnl.com/supplemental; other appendices are available from the authors on request).

Types of outcome measures

Studies reporting one or more of the following health outcomes were included: oral/pharyngeal cancers, other cancers, all cause mortality, vascular diseases, dental health, complications of pregnancy, and surgery. Ideally, outcomes should be clearly defined according to International Classification of Disease system (ICD). The author's statement that the study considered one of these outcomes was accepted. Excluding studies with no clearly defined outcomes may bias against older studies. Studies reporting on one or more "intermediate" outcomes such as blood pressure or lipid levels,[38 39] or oral lesions such as leukoplakia were excluded.

Search strategy for identification of primary studies

A comprehensive search strategy was developed which included electronic databases, websites, and contact with experts. A small number of non-English language studies were identified but were not included (see appendix 2).

Relevant studies were identified by searching several electronic databases from inception (appendix 3). Databases searched include Medline, Embase, CINAHL, and Dissertation Abstracts. Both key words and MeSH headings were used. Websites (WHO, ASH UK, ASH US, NIH, CDC) were also searched using the key term "smokeless tobacco". Contact was sought from experts including those in the tobacco industry (appendix 4) and supplemented by cross checking reference lists of articles (appendix 5).

The form of electronic searching for the databases (Medline, Embase, CINAHL) was: (ST or synonyms) and (epidemiological studies or synonyms). The search strategy for study types was adapted from previous reviews.[40 41] The strategy was piloted in Medline and cross checked against possible terms for ST use.[42] We checked that the omission of brand names (such as Skoal, Hawken, etc) did not affect the number of potentially relevant hits.

The electronic searches identified 2889 records and a further 34 were obtained from checking references, giving a total of 2923 relevant hits although these included some duplicates. The websites also obtained many "hits" (appendix 4).

The downloaded records were imported to Reference Manager and the titles, keywords, and abstracts were scanned by at least one reviewer. A conservative approach was used—that is, all records were checked unless sufficient details were available to decide that the study was definitely not relevant. The first 1557 articles downloaded (from Medline) were also screened independently by a second reviewer. Articles identified in this way (n=317) were scrutinised and/or a copy obtained to consider eligibility further. A total of 189 possibly relevant articles were identified. Ideally, two reviewers should independently assess each study for inclusion and extract data. The first 41 papers assessed for inclusion by the co-reviewer were independently considered by the first reviewer. Agreement was good (90.2%, kappa=0.74), and disagreements were resolved by discussion (fig 1).

An inclusion criteria form and data extraction form was developed[41] (appendix 6) and pilot tested on four articles. Once initially identified, one of two reviewers extracted data from all the articles to be included.

Unlike randomised controlled trials, there are no generally accepted lists of appropriate quality criteria for observational studies.[43 44] Rather than using scoring methods, specific aspects of quality such as control of confounding, selection of cases and controls, sample size, clear definitions of the outcome of interest and ST use, evidence of a dose-response relationship between ST use and outcomes are described for each study. Both reviewers independently classified each study as either methodologically adequate or flawed (coded as A or F under "Comments", appendix 1). Agreement was high (kappa=0.76). Flawed studies were those which either (1) contained <10 cases among ST users, or (2) did not control for the most "critical" confounders (age, sex, and use of other tobacco products), or (3) did not state what form of ST was used or did not perform separate analyses for each type of ST.

All studies meeting the inclusion criteria are listed in appendix 1, but only those achieving these quality criteria and published after 1980 are described in this paper. These are cross referenced to the tables in appendix 1 (ID number).

RESULTS

Studies excluded are listed alphabetically by first author under the categories of "oral and oropharyngeal cancers", "other cancers", "cardiovascular diseases", "all-cause mortality", "dental diseases", "pregnancy outcomes", "surgical outcomes", and "miscellaneous" (appendix 7).

The results for each study included in the review are presented in a series of tables (appendix 1). The health outcomes are listed in the same order as above. Separate tables are prepared by region (US, Scandinavia, Asia, other) for each outcome and are then listed by study type (cohort study, case-control study, cross-sectional study). Within these subsections the studies are listed in date order.

Oral and pharyngeal cancers

US case-control studies

One study from a Veterans Hospital in New Jersey found no increased risk of oral cancer among users of either snuff or chewing tobacco, and no trend in risk according to the duration of chewing (ID8).[45] This study included many ST users although it was mainly concerned with smoking and alcohol consumption. Sites included were not clearly defined and the case series was incomplete. Although important confounders were analysed, the reference categories for both tobacco smoking and alcohol consumption were "minimal users", including smokers of 1–5 cigarettes per day. This is likely to underestimate the risk associated with ST use.

Another large population based study using cancer registry data in Florida found a strong association between ST use and cancers of the mouth and gum (for example, odds ratio (OR) 11.2, 95% CI 4.1 to 30.7), salivary glands, and larynx. This study was unable to control for use of alcohol (ID10) and the number of ST users was small.[46]

In the late 1970s a key study was carried out among women with oral and pharyngeal cancers in North Carolina which found strong associations with ST use (ID13).[47] The OR for

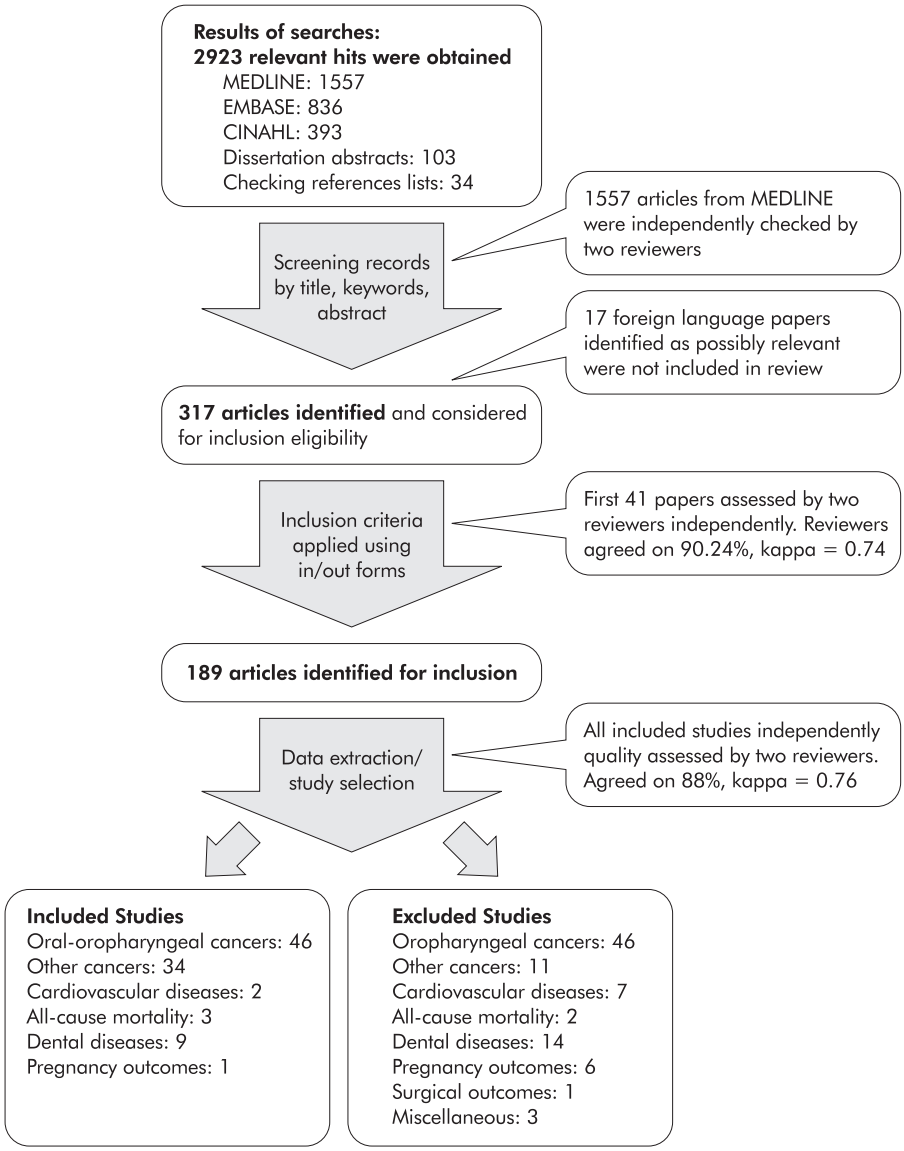

Figure 1 Flow chart of search strategy for review of literature on smokeless tobacco.

snuff dipping was 4.2 (95% CI 2.6 to 6.7) among white women for cancers of the gum and buccal mucosa. Significant dose-response relationships were observed—for example, an OR of 47.5 (95% CI 9.1 to 249.5) for those who had used snuff for 50 years or more. This study was well designed with clear definitions of the sites included, selection of controls, and important confounders considered. A high proportion of interviews were carried out with "next of kin" among cases (51%) compared with controls (21%). This study remains the strongest evidence for an association of ST use with oral cancers in the US, although it is limited to women and was carried out many years ago.

Scandinavian case-control studies

Swedish studies are easier to interpret than those in the US as only moist oral snuff is used. Scandinavian studies are also facilitated by the excellent population based statistical information available. However, there may be important differences between different snuff brands.

In south Sweden and Stockholm a recent study of men with oesophageal and oral cancers found a raised risk for ex-snuff users compared with never users of tobacco (ID19).[48] The risks were higher for ex-users than for current users, suggesting possible selection bias. The OR for current users was 3.3 (95% CI 0.8 to 12.0) and for ex-users was 10.5 (95% CI 1.4 to 117.8). This study lacked power as the number of never users of tobacco was small. Control of confounding was mostly limited to age and region, and cases were interviewed in hospital while population based controls were interviewed at home, suggesting possible recall biases.

Similar results were found from an earlier study in northern Sweden of cancers of the oral cavity (ID20).[49] The most common tumour was lip with an OR of 1.8 (95% CI 0.9 to 3.7) for ex-snuff users but close to unity for current users. This study is methodologically strong, with high response rates and clear definitions of sites included and snuff use. A large proportion of the cases had died, so responses were obtained from relatives. Furthermore, the number of snuff users was relatively small.

Asian studies

Asian studies are less equivocal in their interpretation than those from Scandinavia and the US. Both oral cancers and ST use are many times more prevalent, particularly in India. Some studies have been able to collect substantial trend data including frequency and years of use, and age at starting.[11 50]

However, the use of ST is different, with tobacco being chewed mainly with other ingredients which may be carcinogenic. The duration and amount used daily may also be higher, as traditionally Indians commence chewing when young and chew regularly, possibly to stave off hunger.[51] These studies provide strong evidence that the oral use of tobacco can be carcinogenic.

Cancer registry data from Bhopal showed a sixfold increased risk for cancer of the oral cavity (OR 5.8, 95% CI 2.6 to 9.5) after adjusting for age and smoking (ID24).[52] Chewing for over 30 years was associated with an OR of 23.9 (95% CI 12.0 to 47.3) for oral cancer. The attributable risk of cancer of the oral cavity for tobacco chewers was estimated at 84.4%. Outcomes were clearly defined in this study but the response rates were unclear and alcohol consumption was not controlled for. Information on ST use among cases was obtained from a separate survey in Bhopal which could bias risk estimates.

This is supported by two studies of men with tongue and oral cancer from Bombay (ID25, ID26).[53 54] Statistically significant ORs were found for cancers of the anterior two thirds of the tongue after multivariate analysis (OR 1.7, 95% CI 1.2 to 2.6) and for the whole oral cavity combined (OR 2.6, 95% CI 2.1 to 3.4), but not for the posterior third of the tongue (OR 0.9, 95% CI 0.6 to 1.2). Trends for all oral cancers were found with increasing daily frequency of use and duration of use in years—for example, crude OR 1.3 (95% CI 0.9 to 1.8) for 1–10 years of use and 3.9 (95% CI 2.5 to 5.8) for 31+ years of use. This study was well designed with clear definitions of outcomes and good control of potential confounders.

Three further studies considering dose-response relationships for different cancer locations were carried out in Kerala, India in 1983–4 (ID28–30).[11 12 55] These were methodologically sound and the sites included were clearly described. Control of confounding was good (alcohol consumption, duration of bidi smoking, snuff use).[55] Strong significant associations and dose-response relationships were observed for cancers of the gingiva, tongue and floor of mouth, and oral cavity.[12 55] For example, for cancers of the buccal and labial mucosa the OR for men associated with chewing ⩽10 times per day was 6.9 (95% CI 2.8 to 16.8), while those who chewed >41 times per day had an OR of 37.8 (95% CI 19.5 to 73.1), adjusted for age and religion.[12]

One prospective cohort study was carried out among villages in India (ID23).[56] The sample size was large with frequent follow up, allowing for changes in tobacco habits over time. Oral cancer (and oral lesions) occurred almost solely among those who practised tobacco habits in some form, and was always preceded by some type of precancerous lesion.[57] Indeed, malignant transformation of leukoplakia was not observed in those who smoked but did not chew tobacco; the rate of malignant transformation per 1000 persons per year was estimated as 9.7 in those who chewed, 5.0 in those with mixed tobacco habits, and zero in those who smoked only or had no habits (only six cases of leukoplakia had no tobacco habit).[58] Despite the large sample size and fairly long follow up period (10 years), only 23 new cases of oral cancer were observed.

Other regions

Strong associations between "toombak" use and squamous cell carcinoma of the lip, buccal cavity, and floor of mouth were found in a case-control study in Sudan (ID41).[59] The OR was 7.3 (95% CI 4.3 to 12.4) compared with hospital controls and 3.9 (95% CI 2.9 to 5.3) compared with population controls. The ORs for squamous cell carcinoma of the tongue, palate, and maxillary sinus were not statistically significant. All neoplasms were found at sites of preference for placement of toombak quid. Toombak is manufactured using a different tobacco species (*N rustica*) mixed with sodium bicarbonate. This study had clearly defined outcomes and reasonable control of confounding.

Other cancers

US case-control studies

A number of different cancer sites were identified including the urinary tract (bladder, kidney), stomach, and lung. Cigarette smoking was usually included as a variable but ST use was not the main focus of any of the studies, and most had few ST users.[60–63] ST use was not usually clearly defined and no information on possible dose-response relationships was provided in any study. No significant association was found between ST use and cancer outcomes in most studies. Among studies meeting the quality threshold, no statistically significant relationship between ST use and bladder cancer was found (ID60).[60] One estimated a raised OR of borderline significance for chewing tobacco and renal cell cancer among men (OR 4.0, 95% CI 1.1 to 14.2) (ID61).[63]

Scandinavian prospective cohort study

Cancer mortality was not significantly higher in snuff users in Sweden; relative risk (RR) 1.2 (95% CI 0.8 to 1.9) in subjects aged 35–54 years and 1.0 (95% CI 0.8 to 1.3) in those aged 55–65 years (ID85).[64]

Scandinavian case-control studies

Lagergren *et al*[65] analysed patients with adenocarcinoma of the oesophagus or gastric cardia and oesophageal squamous cell carcinoma (ID70). Many potential confounders were considered including age, sex, education, cigarette smoking, alcohol consumption, dietary intakes of fruit and vegetables and energy intake, BMI, reflux symptoms, and physical activity. Snuff users had an OR of 1.2 (95% CI 0.7 to 2.0) for oesophageal adenocarcinoma compared with never users. No trends were found for years or intensity of use. The results were similar for those with adenocarcinoma of the gastric cardia (OR 1.2, 95% CI 0.8 to 1.8). For cases of oesophageal squamous cell carcinoma the adjusted OR was 1.4 (95% CI 0.9 to 2.3). Hansson *et al*[66] found no statistically significant relationship and no dose-response trends for any of the three types of gastric cancer (ID71).

Asian case-control studies

Six studies considered other cancer outcomes. Unlike US studies, most of these had sufficient numbers of ST users among both cases and controls and were designed specifically to consider the association between cancer and ST use.[67 68]

Oesophageal cancer

One study from Assam (ID74) found raised OR for chewing tobacco associated with oesophageal cancer. This was consistent among users of different betel types, chewing tobacco alone, and in both men and women—for example, chewing tobacco alone was associated with an OR of 4.9 (95% CI 2.8 to 11.6) in men.[69] Significant dose-response relationships were observed for all the variables considered (frequency of chewing per day, duration of chewing in years and starting age). The OR associated with chewing for >20 years was 10.6 (95% CI 5.6 to 17.3) in men and 7.2 (95% CI 2.6 to 14.2) in women, compared with 1.8 (95% CI 0.09 to 7.1) and 1.2 (95% CI 0.07 to 5.2) in men and women, respectively, who had chewed for <10 years.

Further studies of oesophageal cancer have been equivocal (ID76). In Bangalore, India[70] similar risks were associated with chewing paan with tobacco (OR 2.9, 95% CI 1.5 to 5.4) and chewing paan only (OR 2.8, 95% CI 1.5 to 5.2) after multivariate analyses. The risk was highest for the lower third of the oesophagus (OR 6.6, 95% CI 2.1 to 21.2) and was not statistically significant for other parts of the oesophagus. The number of tobacco chewers was not high (79 cases, 96 controls) and some risks were imprecisely estimated. Although important confounders were considered, the response rates were low (62.5%). Another study from Kerala, India found no

association between chewing betel and tobacco and oesophageal cancer (ID79).[13]

Larynx and lung

Little association was found between chewing betel and tobacco and cancer of the larynx (ID80)[50] or the lung (ID75).[52]

Penile

In one study the adjusted OR for chewing tobacco was 4.0 (95% CI 2.7 to 6.1) and for snuff use the OR was 4.2 (95% CI 1.6 to 11.3) (ID 77).[67] The OR of chewing tobacco use for <10 years was 1.7 (95% CI 0.9 to 3.3) compared with 3.6 (95% CI 2.5 to 5.3) for >10 years of use.

All cause mortality

Asian prospective cohort studies

The age adjusted RR of tobacco chewing for all cause mortality over a 10 year follow up period (reference group "no habit") was 1.2 and 1.3 for men and women, respectively (statistically significant for women) (ID83).[71] For those with mixed habits (smoking and pan together) the RR was statistically significant for men only (1.4 compared with 1.7 for women (CI not presented)). Similar results were found for other analyses from different parts of India (ID82, 84).[56 72]

Other

A prospective cohort study of cardiovascular disease mortality (ID85) estimated a RR of all cause mortality of 1.9 (95% CI 1.6 to 2.4) in those aged 35–54 years and 1.2 (95% CI 1.0 to 1.3) in those aged 55–65.[64]

Cardiovascular disease

Scandinavian prospective cohort study

A study of ST use and cardiovascular disease (CVD) was carried out in Swedish construction workers (n=135 036) (ID85).[64] Snuff use was defined as current and exclusive use—that is, users were never smokers. Among those aged 35–54 years the RR for ischaemic heart disease (IHD) was 2.0 (95% CI 1.49 to 2.9), for stroke 1.9 (95% CI 0.6 to 5.7), and for all CVD deaths 2.1 (95% CI 1.5 to 2.9). However, the associations were smaller and not all were statistically significant in those aged 55–64 (IHD 1.2, 95% CI 1.0 to 1.5; stroke 1.2, 95% CI 0.7 to 1.8; CVD 1.1, 95% CI 1.0 to 1.4). This was explained as "a healthy worker effect".

Scandinavian case-control studies

The MONICA (Monitoring Outcomes in Cardiovascular Disease) Sweden Project contributed two studies (ID86, 87),[73 74] both of which found that snuff dippers had no increased risk of myocardial infarction (MI) compared with non-tobacco users. In the second study, more detailed information about ST (present use, previous use, amount, type of preparation, age of onset) was obtained from MI patients or next of kin. The OR for all and fatal MI remained non-significant after adjustments for various potential confounders.

Dental disease

Dental diseases are defined here to include both dental caries (tooth decay) and periodontal disease. Numerous studies have examined the relationship between cigarette smoking and dental diseases,[28 33] but only a small number of cross sectional surveys of ST use and dental diseases have been undertaken.[75] These are hard to interpret as the time relationship between ST use and dental disease is uncertain (previous exposure to ST use may be more relevant than exposure at the time of the study). Furthermore, many are in young people who may not have accumulated sufficient exposure to ST.

Dental caries

A recent analysis of adults from the NHANES (National Health and Examination Study) III study in the US suggested that chewing tobacco may be a risk factor in the development of root surface caries and possibly coronal caries (ID89).[76] This large study used clearly defined caries indices, trained examiners, and found significantly raised ORs for decayed root surfaces among users of chewing tobacco (OR 3.24, 95% CI 2.0 to 4.4) compared with users of snuff, cigarettes only, cigars and pipes. Importantly, the decayed or filled root surfaces tended to match the side of the mouth on which the ST was used, although this did not reach statistical significance. Experimental evidence also suggests that chewing tobacco may be cariogenic due to its sugar content.[77]

A study among baseball players in Phoenix did not find any differences in dental caries between ST users and non-users, but the majority of ST users were snuff dippers (n=304) rather than users of chewing tobacco (n=89) (ID91).[78] A further survey of adolescent boys in Atlanta (ID92) found a raised risk of caries in boys who used ST and also had gingivitis, significantly higher than in non-users without gingivitis ($p<0.001$).[79]

Higher levels of caries were observed in snuff dippers than in non-tobacco users among teenagers in Gothenburg (ID94).[80] Controlling for cigarette smoking, a dose-response relationship was also shown between caries and the number of years of snuff use.

Periodontal diseases

Several US studies have examined the relationship between ST use and periodontal diseases. A study in Phoenix (ID91) was equivocal. No significant differences were found in gingival bleeding, pocket depth, or recession in at least one site of 12 teeth examined between ST users and non-users, but attachment loss of 4 mm or more was more common in snuff users both with (32.0%) and without (33.6%) oral lesions than in non-users (27.4%), $p<0.05$.[78] A further study of adolescent boys in Atlanta (ID92) found associations between ST use and gingival recession, but not with gingivitis.[79] The risk of gingival recession was only raised among ST users who also had gingivitis, but many important potential confounders such as diet and oral hygiene were not considered.

Adverse outcomes of pregnancy

Numerous studies have shown a strong association between cigarette smoking and adverse pregnancy outcomes, particularly low birth weight,[81] but relatively few have considered the relationship of these variables with ST use.[82 83] Generalisability of these studies elsewhere may be problematic, not simply because of differences in ST types but also in access to health care, nutritional status, cigarette smoking, and alcohol consumption.

The only study included in the review was of women in Delhi who delivered single infants in 1971–2 (ID98).[82] The stillbirth rate was increased among tobacco chewers (crude OR 3.0, 1.3 to 6.7). Birth weights were presented for chewers and non-chewers by maternal weight, gestation, and social class. Overall, there was a reduction in birth weight of about 100–200 g in each stratum in chewers compared with non-chewers, and this was mainly attributed to the greater proportion of chewers who delivered at 36 weeks or earlier. Other potentially important confounders were not considered, although smoking was "rare" in this population.

Impact of ST use on the population

Most of the studies included in the review are hospital based case-control studies, so it is not possible to estimate the incidence rate and excess risk among ST users. From those studies which met the quality criteria, an estimate has been made of the population impact of ST use. The population attributable risk (PAR) is a measure of the proportion of the disease

Table 1 Estimated number of deaths from oral cancer attributable to ST use in the US, Sweden, and India

Study	OR (95% CI)	PAR (95% CI)	No (95% CI) of deaths attributable to ST use
US			
Mashberg *et al*[45] (ID8)	0.8 (0.4 to 1.9)	0 (0 to 0.5)	0 (0 to 145)
Stockwell and Lyman[46] (ID10)	11.2 (4.1 to 30.7)	28% (10.5 to 53)	1224 (461 to 2324)
Winn *et al*[47] (ID13)	4.2 (2.6 to 6.7)	1.9% (0.9 to 3.3)	30 (15 to 54)
Sweden			
Lewin *et al*[48] (ID19) (men only)	3.3 (0.8 to 12.0)	32% (0 to 69)	28 (0 to 61)
Schildt *et al*[49] (ID20) (men only)	0.7 (0.4 to 1.1)	0 (0 to 2)	0 (0 to 2)
India			
Diskshit and Kanhere[52] (ID24)	5.8 (3.6 to 9.5)	51% (36 to 65)	23768 (16838 to 30152)
Rao *et al*[54] (ID26)	2.6 (2.0 to 3.4)	27% (19 to 34)	12270 (8818 to 15903)
Sankaranarayan *et al*[12] (ID28)	6.9 (2.8 to 16.8)	56% (28 to 78)	26138 (13283 to 35942)

OR=odds ratio; PAR=population attributable risk.
Estimated prevalence of ST use in US: 3.8% in 1995, 0.6% in women[98]; annual deaths from oral cavity cancers 2765 in men, 1618 in women.[99]
Estimated prevalence of ST use in Sweden: 20% of men, 2% of women[7 100]; annual deaths from oral cavity cancers 88 in men, 65 in women.[101] Estimated prevalence of ST use in India: 22% in men and women[102]; annual deaths from oral cavity cancers 29 054 in men, 17 222 in women.[99]

Table 2 Number of deaths from ischaemic heart disease (IHD) attributable to use of smokeless tobacco (ST) in Sweden

Study	OR (95% CI)	PAR (95% CI)	No (95% CI) of deaths attributable to ST use
Bolinder *et al*[64] (ID85)	RR at age 35–54 2.0 (1.5 to 2.9)	17% (9 to 28) at age 35–54	1886 (1010 to 3116) in men aged 35–54
	RR at age 55–65 1.2 (1.0 to 1.5)	4% (0 to 10) at age 55–65	
Huhtasaari *et al*[73] (ID86)	0.9 (0.6 to 1.3)	0% (0 to 5)	0 (0 to 620)
Huhtasaari *et al*[74] (ID87)	1.0 (0.6 to 1.6)	0% (0 to 7)	0 (0 to 858)

OR=odds ratio; PAR=population attributable risk.
Estimated Swedish prevalence of ST use, 20% in men, 2% in women.[7 100] Approximately 11 316 deaths from IHD in men.[101]

that could theoretically be prevented in the population if the use of ST was eradicated.

Table 1 estimates PAR fractions for oral cancers in each region and table 2 estimates PAR fractions for cardiovascular disease in Sweden. Where possible, PAR values for men and women were calculated separately. For other cancers it was considered that there were too few high quality studies. PARs are estimated using the formula:

PAR = [prevalence × (relative risk – 1)]/[prevalence × (relative risk – 1)] + 1

It is assumed that the OR for each study is a reasonable estimate of RR. The possible maximum and minimum estimates from each study represent the upper and lower 95% CI for the OR (appendix 1). The final column links the PAR to deaths from oral cancer to estimate the number of deaths due to ST.

Between 0 and 1000 or more oral cancer deaths in the US may be attributable to ST use each year; for Sweden this is lower (between 0 and 60) but in India it is very high with over 10 000 deaths from oral cancer possibly attributable to ST use alone. This clearly reflects the large population of India compared with the US or Sweden, as well as higher mortality rates. Table 2 highlights the importance of the relationship between ST use and CVD; the Swedish cohort study by Bolinder *et al*[64] suggests that, in the "worse case", up to 3000 fatal heart attacks in men (27% of annual number of deaths from heart disease in men) could be attributed to snus use but, in the "best case", this may scarcely be above zero.

These tables should be interpreted with extreme caution as the 95% CI and range of possible estimates are often quite wide. Although these studies met our "minimum" quality criteria, some still have many limitations. The estimates may not be fully adjusted for possible interactions with cigarette smoking and should be considered extremely "crude". As case-control studies they may be subject to a number of other biases. Many of the studies do not agree, hence estimates ranging from zero to high numbers of US deaths attributable to ST use are equally plausible. They highlight the uncertainty in the literature, particularly for CVD.

DISCUSSION

Limitations

Inadequate descriptions of ST use

The epidemiological evidence surrounding the health outcomes of ST use is not easily interpretable. Most of the US studies were not designed to consider this, have severe power limitations, and cannot estimate even a rough risk. A detailed description of ST use is often not available, sometimes the only variable is "ST use, ever or never". Assumptions then have to be made about the types of ST being used. Dose-response relationships provide strong evidence of causality and were especially important in early studies investigating the relationship between cigarette smoking and lung cancer or CVD.[84] Few studies have reported detailed analyses of important variables such as frequency or years of use.

ST types are highly variable between and within regions. It is unclear whether results can be generalised elsewhere, although consistent findings of risks associated with oral tobacco in any form are a cause for concern. The types of ST in use have changed considerably over the past few decades, resulting in substantial reductions in the levels of carcinogens. Manufacturers in the US and Sweden report continuing research to reduce these levels. In India the use of locally produced tobaccos has been partially replaced by commercially produced "pan masala". Future STs may therefore differ from those in use today. Some years must elapse for the health impacts of the newer types to be established.

Validation of ST use

Few studies attempted to validate ST use, biochemical validation being reported in just two cross sectional studies among baseball players in the US. Some studies of cigarette smoking have suggested that self-reporting is reasonably accurate when compared with biochemical markers of tobacco inhalation,[85] but research has found that self-reporting is less accurate for patients diagnosed with CVD,[86] and this may also apply to other diseases. Validation of daily or weekly usage

may be feasible by direct measurement, but only one study reported such an attempt.[87]

Control of confounding

Many studies reported very little control of confounding, frequently by matching and limited to age groups and sex. Cigarette smoking will be a critical confounder as most ST users also smoke, and this is a more powerful risk factor. The confounding effects cannot be fully controlled by simple analyses of cigarette smoking and require a detailed analysis of smoking history and habits including cigarettes smoked daily, years of smoking, brands used, and inhalation. Other important confounders have also been missed in many studies including alcohol, dietary factors, and socioeconomic status.

Observational data

Most studies were case-control, the only logical design where both the outcome of interest (cancer types such as oral cancers) and exposure (ST use) are rare. With any case-control study there are difficulties in choosing appropriate control series and recall biases may be hard to avoid. A few prospective cohort studies have reported on ST use but, outside India, these require extremely large sample sizes and long follow up periods. Significant loss to follow up may result and misclassification bias may become a significant problem. Some initially classified at baseline as non-ST users may commence use and, conversely, some ST users may give up or start using other tobacco products (particularly cigarettes). Only one prospective cohort study attempted to look at possible changes in exposure over time.

Main findings

Oral cavity cancers in India

There is a substantial risk of oral cancers associated with the types of ST used in India (chewing betel quid with tobacco). Studies from different regions with varying chewing practices have consistently found statistically significant and clinically important ORs associated with betel and tobacco chewing. Many also found clear trends with increased consumption—that is, dose-response relationships. It is likely that around 10 000 annual deaths from oral cancer in India can be attributed to ST use (table 1).

Oral and oropharyngeal cancers in the US

Recent studies have often found no association between ST use and oral or oropharyngeal cancers, and there is some suggestion that tobacco manufacturers may have reduced levels of carcinogenic TSNAs (Jaffe J, Star Scientific Inc, personal communication, 2002). However, the number of ST users is almost always small,[88–92] and these studies do not have sufficient statistical power to demonstrate an effect unless the risk is huge. A recent US study[88] reported that prior ST use was similar between cases and controls (OR 1.0, 95% CI 0.4 to 2.3), but only 19 cases and 28 controls used ST out of a total sample size of 284 cases and 477 controls. At least 373 cases and 634 controls would be required to have adequate power (80%) to detect a statistically significant (and clinically important) OR of 2.0 when the exposure (ST use) is this rare. This would increase to 1194 and 2030 cases and controls, respectively, to detect a more modest OR of 1.5. Most recent US studies have not been able to address this question.

Oral and oropharyngeal cancers in Scandinavia

The situation in Sweden is different from the US as ST use is much more common. Swedish snus also differs from US ST and tends to have lower levels of TSNAs, although US levels may also be decreasing. However, the incidence of these cancers is low and studies still tend to lack statistical power. Recent studies have not found significantly raised risks for current users, ever users, or ex-users of ST, but none are statistically significant and 95% confidence intervals are very wide. The risks are much higher for ex-users than for current users, which may suggest that early disease symptoms provoke some to quit. Although these findings are consistent with no effect, the studies do not have sufficient power to detect a moderately raised OR.

Dental diseases

Some studies have suggested a possible relationship between ST use and periodontal disease or dental caries, but there are relatively few cross sectional studies with many limitations. A recent study of US men found an increase in dental caries among chewers of tobacco, which may have added sugars.[76] One Swedish study also found an increase in dental caries among teenagers using oral snuff in Gothenburg.

Cardiovascular disease

In one prospective cohort study[64] an association was found between ST use and CVD mortality. The study population comprised construction workers, which raises questions about generalisability. No statistically significant associations were found in two population based case-control studies. More research is required, especially from other parts of the world with different ST habits. This is potentially critical as CVD is one of the most common causes of death in the world,[93 94] and even a small increase in risk could result in many deaths (table 2).[95 96]

Other cancer sites

No strong association was found between ST use and most other cancers, except for one Asian study of penile carcinoma.[67] The use of ST was found to be a risk factor for histologically verified pancreatic cancer in a Scandinavian study,[97] and there is some evidence that it may be a possible risk factor for oesophageal cancer.

What is required in the future?

Further studies with sufficient power and adequate control of confounding are required to elucidate the role of ST use. Studies would benefit from improved validation, trend information, and consideration of individual brands. More information is urgently required on the potential health effects of ST use other than cancer, particularly CVD.

A difficulty in many countries has been obtaining sufficient numbers of ST users to enable precise estimates of risk. Populations with high ST use (such as US baseball players) need to be identified and followed over time. One possibility is to set up a multicentre case-control study with centres in different regions such as the US, Sweden and other Scandinavian countries, India and other parts of Asia. There is some evidence that cigarette smokers have quit to become ST users, and some are promoting this as a method of "tobacco harm reduction". Long term follow up of populations of smokers who either quit tobacco use or become ST users should be established to compare the differences in a range of health outcomes between these two groups. Only further well designed epidemiological studies with adequate sample sizes will be able to resolve these controversies.

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Appendix 1 is available on the *Thorax* website (www.thoraxjnl.com/supplemental) and appendices 2–7 are available from the authors on request.

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LUNG ALERT

Helical computed tomography (CT) is safe as the primary diagnostic test in suspected pulmonary embolism (PE)

▲ Van Strijen JL, de Monye W, Schiereck J, *et al*. Single-detector helical computed tomography as the primary diagnostic test in suspected pulmonary embolism: a multicenter clinical management study of 510 patients. *Ann Intern Med* 2003;**138**:307–14

Five hundred and ten patients with suspected PE underwent helical CT of the pulmonary arteries within 24 hours of presentation. If the CT scan was normal or inconclusive, lower limb ultrasonography was performed that day and on days 4 and 7. All patients were treated appropriately and followed up for 3 months.

Helical CT identified PE in 124 of 510 patients (24.3%). Of the 378 scans which did not show PE, 248 were normal while 130 identified an alternative diagnosis. Two of these 378 patients were found to have DVT on ultrasound that same day. The other 376 patients (who were not anticoagulated) had a 3 month thromboembolism rate of 0.8% (three of 376). If CT alone had been performed, the thromboembolism rate in those whose CT scan did not show PE would have been 1.3%. These rates are comparable to those after normal V/Q scans and normal pulmonary angiograms. Of the 246 patients who had a completely normal CT scan and normal ultrasound, only one had a confirmed PE over 3 months, giving this algorithm a false negative rate of 0.4% and a sensitivity of 99.6%.

Helical CT appears to be sufficient as the primary diagnostic tool for PE, becoming even more sensitive with ultrasonography. It also has the advantage of providing an alternative diagnosis for symptoms in 25% of patients. However, this study does not take into account the costs or hazards of CT scanning, nor does it incorporate such other tests as D-dimer estimation.

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APPENDIX 1 Tables of studies included

Oral and Pharyngeal cancers

US studies

Prospective cohorts

ID	Study and Type of ST	Subjects, Setting and years of recruitment	Sample size and No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
1	Zahm et al 1992[104] Chewing tobacco and oral snuff	US military veterans, ages 31-84, who held active US government life-insurance policies in 1953 and died by 1980. recruited 1954 - 1969	293,958 of whom 248,046 provided tobacco use histories on a questionnaire in either 1954 or 1957 No. of cases who used ST unclear among 43,451 P-Y of ST use	Frequent and infrequent ST use clearly defined. No information on any changes in ST use over time (23-26 years follow-up). Measurement of outcomes not described. Adjusted for age and calendar time - unclear whether other confounders controlled for.	Significant associations were found among ST users for cancers of buccal cavity (RR = 3.0, 95% CI, 2.0 to 4.5) and pharynx (RR = 8.7, 95% CI 4.1 to 18.3). For both these cancers, frequent users had higher risks than infrequent users (frequent users pharynx RR = 11.2, 95% CI, 5.0 to 25.0; infrequent users pharynx RR 4.5, 95% CI 1.7 to 11.7). RR were adjusted for age and calendar time.	Most veteran users of chewing tobacco or snuff also used other tobacco products. Higher risks found in ex-users than current users, and higher in those who started young, but risk did not increase with duration of use. Items left blank on questionnaire were coded as 'NO' which may underestimate risks. Quality: F

ID	Study and Type of ST	Subjects, Setting and years of recruitment	Sample size and No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
2	Bjelke and Schuman, 1982[105] Chewing tobacco and snuff	Cohorts of US and Norwegian men	16,930 US men and 12,945 Norwegian Men ST users: not stated	Abstract only – no information	Increases in risk of death for cancers of buccal cavity, pharynx, oesophagus (RR ranges from 2.6 to 3.1).	Abstract only – 95% CI not given[5] Quality: F
3	Winn et al. 1982[106] ST use (chewing tobacco and snuff)	16-year follow-up of US veterans	Approximately 300,000 ST Users: 951	Abstract only – no details	In the absence of smoking, ST related SMRs[1] for heart disease and for malignant neoplasms were approximately 100 (no deaths from oral or pharyngeal cancer were observed). SMRs were higher for cancer of digestive system (137), cancer of oesophagus (228), cancer of stomach (151), pancreas (165), and liver (281).	Abstract only - small numbers for some outcomes (only one death from cancer of oesophagus). Among chewers who were very light smokers, cancer risk was raised 8-fold for pharynx and 1.5 for oral cavity (but light smoking is not defined). Quality: F

[1] Standardised Mortality Ratios

Table 1.1.2 Case-control studies

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
4	Schwartz et al. 1998[88] ST use not described	Patients aged 18-65 with histologically confirmed squamous cell cancer (SCC) of oral cavity, identified through Cancer Surveillance System, part of NCI SEER[2] Program, Controls were residents of same regions and same age with no history of oral cancer, identified through random digit dialling. King Pierce and Snohomish counties, Washington State 1990-1995	284 cases, 477 controls 19 cases and 28 controls used ST	ST measurement not described Sites included clearly stated (tongue, gum, floor of mouth, other and unspecified parts of mouth, tonsils or oropharynx) but ICD codes not listed. All cases confirmed by histology. No control of confounding	Among men, prior ST use was similar between cases and controls (OR = 1.0, 95% CI, 0.4 to 2.3). Only 1 female (a control) used ST.	Main focus of study is sexual history, oral sex, and HPV infection, small numbers used ST and any effect was probably overwhelmed by the risk of cigarette smoking (a high proportion of cases were heavy smokers). Response rates were not high (63% of cases, 65% of controls) due to a combination of death and refusal. Quality: F

[2] National Cancer Institute, Surveillance, Epidemiology and End Results Program

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
5	Muscat et al. 1996[89] Oral snuff use and chewing tobacco	Patients with oral cancers attending hospitals in Chicago, Hines, Detroit, New York, Philadelphia Controls were patients admitted for conditions unrelated to tobacco use, matched by age, sex, race, date of admission. 1981-1990	1009 cases, 923 controls Snuff use – 11 cases, 11 controls. Chewing tobacco – 38 cases and 33 controls (none in women)	ST use not main focus of paper – no information on possible dose-response relationships. Oral cavity cancer – sites included clearly defined (ICD 9 141, 143-6, 148-9), confirmed histologically and newly diagnosed. Salivary gland (ICD 142) and nasopharynx. Does not state whether confounders controlled for.	Oral snuff use and chewing tobacco were unrelated to oral cancer risk	ICD 147 excluded. Response rates high (91% of cases, 97% of controls). Quality: F
6	Marshall et al 1992[91] Snuff and chewing tobacco	Patients with oral cavity cancers attending 20 major hospitals of 3 western New York counties of Erie, Niagara & Monroe Neighbourhood controls, matched on age, race and sex. 1975 – 1983	290 cases, 290 controls No. of ST users not stated	No description or defininition of ST use. Sites included stated (tongue, oropharynx, floor of mouth, pharynx or hypopharnyx), confirmed by pathology. Unclear whether confounders controlled for.	A risk is associated with chewing tobacco, but it was insignificant, with very few people exposed.	No information presented on numbers using ST (very few), and no information on possible dose-response relationships. High level of non-response (only 60% of cases included, 41% of controls contacted). Quality: F

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
7	Kabat et al 1994[90] Chewing tobacco, no further details	Patients with oral cancers, 8 cities in US, Hospital-based controls were patients with diseases not thought related to tobacco or alcohol 1977-1990	1560 cases and 2948 controls Among never-smoking males, 4 out of 82 cases were regular chewers compared with 10 out of 448 controls.	ST use was not main focus of study, use is not defined, no information on dose-response relationships. Sites included clearly defined and confirmed histologically Limited control for confounding	Among never-smokers, crude OR for oral and pharyngeal cancers in tobacco chewers versus non chewers: (OR = 2.25, 95% CI 0.69 to 7.34) for men (OR = 34.5, 95% CI 8.49 to 140.1) for women	Only a small number of cases and controls used chewing tobacco without concurrent smoking. Quality: F

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
8	Mashberg et al. 1993[45] Chewing tobacco and snuff	Patients admitted to Department of Veterans Affairs Medical Centre, New Jersey. Controls were patients without evidence of cancer or dysplasia of pharynx, larynx, lung or oesophagus. 1972 to 1983	359 cases 2280 controls 52 cases, 255 controls ever used chewing tobacco or snuff	No information on measurements of ST use Sites included not clearly defined (oral cavity and oropharynx), though all cases were incident and confirmed histologically. Important confounders were considered (including age, race, occupation, smoking and alcohol),	No increased risk of oral cancer found for use of snuff (OR 0.8, 95% CI 0.4 to 1.9) or chewing tobacco (OR 1.0, 95% CI 0.7 to 1.4). No trend in OR according to duration of tobacco chewing	Not a complete case series, states that "a large majority" of patients were examined. Limited to males only. Possible residual confounding for alcohol and tobacco smoking – referent category is "minimal smokers" which includes lifetime non-smokers, occasional smokers, smokers of 1-5 cigarette equivalent per day as there were too few non-smokers. Similar issues exist with control of alcohol consumption. Quality: A

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
9	Blot et al 1988[107] Chewing tobacco and snuff, no further details	Oral and pharyngeal cancers recorded in the Cancer Registry of Atlanta, Los Angeles, Santa Clara, and San Mateo, centres south of San Francisco-Oakland and state of New Jersey. 1984-1985	1114 cases, 1268 controls Males: 46 cases, 59 controls Females: 6 cases 4 controls	ST use is not defined, no information on dose-response relationships, Sites included clearly defined (ICD 9 141-149) excl 142 and 147 and confirmed pathologically. Limited control of confounding (adjusted for age, race, study location and respondent status)	Among females who were non-smokers, (crude OR= 6.2, 95% CI 1.9 to 19.8) Primarily snuff users, and all cases in oral cavity. No difference in proportion of ST users in male cases and controls (OR not given).	ST use was not main focus of study, small number of cases and controls used ST. Quality: F

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
10	Stockwell and Lyman, 1986[46] ST use not described.	All individuals with head and neck cancers first diagnosed among Florida residents in 1982. Controls were all state residents diagnosed with colon carcinoma, rectal carcinoma, cutaneous melanoma, or endocrine neoplasms during the same time period.	2,351 cases 8285 controls ST users: 18 cases and 31 controls	Types of ST used not defined clearly. Sites included clearly stated and patients identified using a population-based state-wide cancer registry. States that important confounders were considered (age, race, sex and tobacco use), but only the 'primary' tobacco product used was recorded. No information on quantity or duration of ST used.	Statistically significant adjusted ORs for cancer of mouth and gum (11.2, 95% CI 4.1 to 30.7), larynx (OR = 7.3, 95% CI = 2.9 to 18.3), and salivary gland (OR = 5.3, 95% CI 1.2 to 23.4). ORs for other sites were raised, but not statistically significant e.g. pharynx OR = 4.1, (95% CI = 0.9 to 18.0), nasopharynx OR = 5.3, (95% CI 0.7 to 41.6), nasal cavity/ paranasal sinuses OR = 3.3 (95% CI 0.4 to 25.9), tongue OR = 2.3 (95% CI 0.2 to 12.9). For mouth and gum, oropharynx, larynx and salivary glands, risks associated with ST use are greater than those observed among smokers of up to 20 cigarettes per day.	Data available for almost all cases and controls in the cancer registry, but the completeness of this source is uncertain. Number of ST users is relatively small, hence ORs are not precisely estimated. Quality: A

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
11	Young et al. 1986[92] Not stated	12 hospitals and 22 active physicians contributing to a computerised central database – the Wisconsin Head and Neck Cancer Network over an 18 month period (not specified). Two control series selected from the same cancer network (1) patients with cancer of head and neck sites not thought related to tobacco use (salivary gland, nasopharynx, paranasal sinus sites); (2) patients with cancer of larynx, a known smoking-related site	623 total cases, 202 oral cavity, 78 oropharynx, 37 hypopharyx, 127 with cancers not thought related to tobacco, 179 with cancer of larynx Approx. 16 males, 1 female had ever used ST	Measurement of exposure not described. Sites included not clearly described – oral cavity, oropharyngeal and hypopharyngeal. No control of confounding	No statistically significant difference between cancer sites on use of snuff or chewing tobacco	Control selection may dilute risk estimates (only includes those with other head and neck cancers or a known smoking related site). Response rates unclear, only small numbers used ST and any effect probably overwhelmed by cigarette smoking, which was very common (71% of males and 54% of females were current smokers). Quality: F

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
12	Wynder et al 1983[108] Chewing tobacco and snuff	Part of a large on-going study of tobacco related disease interviewed between 1977 and 1980	571 cases, 571 controls Males 37 cases and 37 controls chewed tobacco, 3 cases and 7 controls dipped snuff. Females – no chewing tobacco users, 2 cases used snuff.	No description or definition of ST use. Cases have histologically confirmed diagnosis of oral and pharyngeal cancer. Some control of confounding by matching (patients without tobacco-related disease on basis of age, sex, race, hospital and hospital status private, semiprivate, or ward).	No associations found in males. Two female cases reported using snuff for more than 30 years in contrast to no snuff users among female controls.	Part of larger study previously published (see Wynder and Stellman 1977 below). Main focus of study is mouthwash use, with little information on ST use and small numbers of users. Quality: F

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
13	Winn et al. 1981[47] Oral snuff and chewing tobacco, defined in paper	Female patients with oral and pharyngeal cancers identified by discharge diagnoses from 5 North Carolina Hospitals (n=156) and from death certificate diagnoses (n=99) Hospital controls excluding those with oral neoplasm and other pharyngeal diseases. Matched on age, source of ascertainment (hospital or death certificate), county of residence at time of hospital admission or usual residence at death 1976 to 1978	255 cases 502 controls ST users: 107 cases and 124 controls	ST use clearly described and defined. Sites included clearly stated – ICD 8 141, 143-146, 148-149. Control of confounding was good (age, education, religion, cigarette smoking, alcohol consumption, region of residence, source of ascertainment – death certificates or hospital, employment in various industries, urban or rural residence).	For snuff dipping, OR=4.2 (95% CI 2.6 to 6.7) among white women. Risk approached 50-fold for cancers of gum and buccal mucosa, significant dose-response relationship observed (e.g. OR = 47.5, 95% CI 9.1 to 249.5) for those who had been using snuff for 50 years or more compared with (OR=13.8, 95% CI, 1.9 to 98.0) for those who had used snuff for 1-24 years. Attributable risk % estimated at 31%. Risks were slightly lower among black women, who also consumed less snuff and had used snuff for a shorter duration compared with white women.	Response rates were good (91% of cases, 82% of controls). All were interviewed at home, but a much higher proportion of interviews were carried out with 'next of kin' among cases than controls (51% versus 21%). No information on risk in men. Quality: A

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
14	Williams and Horm, 1977[109] Chewing tobacco and snuff (cans or plugs per week * years of use)	Third National Cancer Survey – a random 10% sample of all incident cases in survey areas in the US 1969-72	7518 cases (controls are inter-case comparisons) Males, 132 cases, 169 controls Females 5 cases 53 controls	Some information and frequency and quantity of ST used. Sites clearly described (though not in this paper). Basic confounders (age, sex, race and cigarette smoking) are considered, but could not control for cigar / pipe smoking.	Use of chewing tobacco or snuff was positively associated with cancer of oral cavity (OR = 3.88 for 1-50 chewing years, OR = 6.65 for >50 chewing years in males. Larynx OR = 1.75 and 2.64 respectively.	Part of large national survey – should be representative. Controls are cancers from sites not thought related to tobacco or alcohol consumption in the TCNS – may dilute estimates of risk. Possible non-response bias – only 67% of sample interviewed. Quality: A

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
15	Wynder and Stellman, 1977[110] Chewing tobacco and oral snuff	Patients with cancer of lung, larynx, oesophagus or bladder from 20 hospitals in 8 American Cities – New York, Houston, Los Angeles, Birmingham, Miami, New Orleans. Controls from same hospitals but without tobacco-related disease. 1969-1975	3716 cases, and 3716 controls 291 cases, 233 controls had ever used chewing tobacco, 79 cases and 69 controls had ever used snuff	No defintion or description of ST use. Sites included clearly stated (lung cancer ICD 162, oral cavity 140-149, larynx 161, oesophagus 150, bladder 188) and histologically proven. Limited consideration of confounders (age, race and city), but states that smoking habits of users of chewing tobacco did not differ significantly from non-users of chewing tobacco in any cancer diagnosis category.	OR among snuff users ranged from 0.5 (Lung II cancer) to 1.7 (oesophagus) but none were statistically significant.	Insufficient cases to demonstrate increased risk due to chewing tobacco or snuff use alone, therefore use combined in analyses. Quality: F

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
16	Martinez, 1969[111] Chewing tobacco	All cases of malignancy of oesophagus, mouth and pharynx, in all hospitals and clinics in Puerto Rico in one year, 1968. Hospital controls (selected from same hospital or clinic, admitted immediately after patient and free from any of the carcinomas studied) and age-sex matched community controls using a pre-specified sampling frame.	400 cases, 179 oesophagus, 153 mouth, 68 pharynx, 1200 controls For those who chewed only and did not use other tobacco forms, 15 cases and 48 controls	No description or definition of chewing tobacco use. Sites included clearly stated (ICD codes 140-150) – 1955 classification. Includes only cancers histologically confirmed. Very limited control of confounding – by restricting analyses to those who chewed only and did not use other forms of tobacco.	Patients with cancer of the mouth did not often use chewing tobacco disproportionately (OR for all 3 sites was 1.53, 95% CI 0.76 to 3.05). For oesophagus, (OR= 1.94 95% CI 0.76 to 4.86), mouth (OR= 10.48 95% CI 1.63 to 84.68) pharynx (OR= 4.69, 95% CI 0.67 to 32.81).	Interviewers unaware of hypothesis of site of primary cancer. Few important confounders considered (age and sex by matching, other tobacco use by exclusion). Quality: A

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
17	Vogler et al 1962[112] Chewing tobacco (mainly among men), snuff dipping (mainly among women)	All new adult patients and new & old mouth cancer patients attending the Robert Winship Memorial Clinic, Atlanta. Jan 1956 to July 1957	333 with cancers of oral cavity and pharynx (group 1), 214 with other mouth diseases (group 2), 584 with cancers of sites other than mouth (group 3), pharynx and larynx, 500 with no cancers (group 4). Number of ST users: 110 in group 1, 58 in group 2, 230 in group 3, 166 in group 4.	No clear definition or descriptions of ST use. Sites included stated clearly (cancers of mouth, pharynx, larynx). No apparent control of confounders.	The proportion of ST users was generally higher among those in groups 1 and 2 than 3 and 4. Crude OR for women in group 1 versus groups 3 and 4 (OR= 3.69 95% CI, 2.37 to 5.75), and for males (OR= 1.45, 95% CI ,0.99 to 2.12). Dose-response relationships (chewing tobacco 7 hours or more) were generally not statistically significant, due to the small numbers involved.	Several control series were used (cancers of other sites and no cancers) and another series of patients with diseases of the mouth other than cancers (such as leukoplakia). Results were presented separately for urban and rural males and females. Number of chewers for males read off figure and therefore approximate. Quality: F

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
18	Wynder et al 1957[113] ST use not described	Oral cancers seen at Memorial Centre for Cancer and Allied Diseases, New York. Controls matched by age and religion from same clinic. Years of recruitment not stated	659 cases, 232 malignant controls, 207 benign controls. In males, 543 cases, 116 malignant controls, 91 benign controls In females, approx. 87 cases, 16 controls	ST use not described or defined Sites included stated (lip, floor of mouth, gum, buccal mucosa, tongue, palate, tonsil, pharynx), but selection details and response rates unclear. No further control of confounders (apart from matching).	There was a larger proportion of tobacco chewers among cases than in the control group (crude OR= 2.29, 95% CI 1.27 to 4.18) for all sites combined. However, all but one of the chewers also smoked, and all drank alcohol. No evidence of a dose-response relationship found. Crude ORs were highest for pharynx (OR=5.09, 95% CI 1.81 to 14.19), palate (OR = 3.34, 95% CI 1.24 to 8.9), lip (OR = 3.02, 95% CI, 1.32 to 6.9), buccal mucosa (OR = 2.97, 95% CI, 1.06 to 8.16), tongue (OR = 2.20, 95% CI, 1.1 to 4.44	Stated that in most cases interviewers were unaware of cancer diagnosis. Also states that only in cases of cancer of the gum and lip did the majority of cancers usually occur at the site at which the tobacco was usually held. Quality: F

Scandinavian Studies

Case-control studies

ID	Study Type of ST	Setting Years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings (relative risk)	Comments
19	Lewin et al 1998[48] Moist oral snuff, men who had ever regularly used 1 package (50g) per week defined as ever-users, men who used snuff 1 year prior to time of interview defined as current users.	Men living in and included in population registries of Stockholm county or southern health care region of Sweden. Cancers of oral cavity, oro- and hypo-pharynx, larynx and oesophagus. Population controls chosen from population registers every 6 months in study period, stratified by region and age 1988-1991	605 cases, 756 controls 91 cases, 106 controls used oral snuff	Oral snuff use clearly defined and described including trend information. Sites included clearly defined, unclear how cases were confirmed. Control of confounding limited to age and region (by matching), and cigarette smoking (by restricting some analyses to snuff users who had never smoked).	OR for current users compared with never tobacco users (OR= 3.3, 95% CI 0.8 to 12.0), ever-users (OR= 4.7, 95% CI 1.6 to 13.8), ex-users (OR=10.5, 95% CI, 1.4 to 117.8). With current smokers as reference category OR were not statistically significant. Age at starting, total no. of years of use, and total amount used in a lifetime had little or no impact on risk. High intensity of use (>50g/week) associated with moderately but not statistically significant higher risk for oral cavity cancer (OR = 1.7, 95% CI 0.8 to 3.9) and oesophageal cancer (OR = 1.9, 95% CI 0.8 to 3.0)	Restricted to men only. Response rates high (90% of cases, 85% of controls). Cases interviewed in hospital, controls at home. Referent category "never tobacco users" has low precision (9 cases, 10 controls) and other analyses use referent category of "current smokers", or "former smokers". Quality: A

ID	Study Type of ST	Setting Years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings (relative risk)	Comments
20	Schildt et al 1998[49] Moist oral snuff	All histologically verified SCC oral cancer cases diagnosed and reported to Cancer Registry in 4 most Northern counties of Sweden (Norbotten, Vasterbotten, Jamtland, and Vasternorrland). Population-based controls selected, matched on age, sex, county and year of death for dead cases 1980-1989	410 cases, 410 controls 67 cases, and 72 controls had used snuff 39 cases and 54 controls were active users, 28 cases and 18 controls were ex-snuff users	Use of oral snuff was clearly defined and some attempt made to estimate lifetime exposure. Sites included clearly defined (ICD-7 140, 141 143-5). Reported ORs matched on age, sex and county of residence. States that multivariate analyses (controlling for alcohol and smoking) made little difference.	OR for active snuff use was 0.7 (95% CI 0.4 to 1.1), for ex-users (OR= 1.5 95% CI 0.8 to 2.9). The most common tumour was lip, with OR= 1.8 95% CI 0.9 to 3.7 for ex-snuff users but close to unity for current users. Higher levels of consumption were not significantly associated with risk e.g. OR= 1.1 95% CI 0.5 to 2.0 for those consuming an estimated lifetime >156 kg, and (OR= 0.8, 95% CI 0.4 to 1.5) for < 156kg consumption.	All cases and controls sent mailed questionnaire and attempts made to disguise primary hypotheses. Response rates were high (86% after refusers and their counterparts excluded). A large proportion of cases had died (235 dead cases compared with 135 living cases) and information obtained from relatives. Number of oral snuff users is relatively small. Quality: A

ID	Study Type of ST	Setting Years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings (relative risk)	Comments
21	Bundgaard et al[114] 1994 Not stated	Oral cavity cancers, Aarhus University Hospital, Denmark Population-based controls selected randomly from Danish Central Population Register, matched on age and sex, 1986-1990	161 cases, 450 controls 8 cases 14 controls used chewing tobacco, no snuff users	Types of ST used not clearly described or defined, some information on weekly consumption, years at this consumption level, and years since quitting. Sites included clearly defined and confirmed histologically. Too few cases for multivariate analysis.	Very few participants reported current or previous consumption of chewing tobacco or snuff (crude OR = 1.64). A single patient had a carcinoma at precisely the site in the oral cavity where he had habitually put his chewing tobacco for the past 20 years.	Consecutively admitted incident patients, self-completed questionnaires used to avoid interviewer bias. Response rates high (96% for cases, 84% for controls). Quality: F
22	Wynder et al 1957[115] Chewing tobacco, Kentucky and Virginia Tobaccos, little else usually added	Patients with cancers of upper alimentary tract and respiratory tract attending Radiumhemmet, Stockholm Sweden. Controls were patients with other cancers and head and neck cancer other than SCC 1952 to 1955	472 cases, 271 controls Number of tobacco chewers not given (stated that no female patients chewed)	Limited description of ST use. Sites included quite clearly stated (though no ICD codes). Potential confounders not controlled for	Nearly half of patients with cancer of gum and buccal cavity had chewed for many years. In most cases, cancer appeared in the area in which the chewed tobacco was held.	Actual number of chewers among cases and controls is not given. Quality: F

Asian studies

Prospective cohorts

ID	Study Type of ST	Setting Years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings (relative risk)	Comments
23	Gupta et al 1980[57]; Mehta et al. 1981[58] Tobacco quid chewing No further details	Districts in Kerala, Gujarat, Andhra Pradesh, Bihar India 1966	30,525 No. ST users not stated 23,416 person-years of observation among tobacco chewers	Some details of tobacco use habits and changes over time. Outcomes (changes in lesions, type, locations, photographs, regression and recurrence rates) all clearly defined. Unable to consider other possible confounders other than tobacco habits and changes in these habits over time.	Oral cancer (and oral precancerous lesions) occurred almost solely among those who practiced tobacco habits in some form. Oral cancer was always preceeded by some type of precancerous lesion. The rate of malignant transformation for those with leukoplakia who chewed tobacco was 9.7 per 1000 per year, compared with zero for those who smoked and those who had no tobacco habit.	High response rates (ranged from 80% in early years to just under 70% in later years). Frequent follow-up (first follow-up 1969-70 then 8 annual surveys in Ernakulam, Gujarat and Bihar), allowed consideration of changes in tobacco chewing and smoking habits. Quality: A

Case-control studies

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
24	Dikshit and Kanhere 2000[52] Tobacco quid chewing, no further details	Bhopal Population-Based Cancer Registry, Bhopal, India 1986-1992	247 oropharyngeal cases, 148 oral cavity cases, 163 lung cases, 260 controls 52 among lung cases, 104 oropharynx cases, 116 oral cavity cases, 108 controls	No clear definitions of ST use, but detailed trend information reported. Sites included clearly defined using ICD-O codes, histologically confirmed. Controls for age, sex, education, religion and cigarette smoking (but does not specify how variables were measured or adjusted for). Stated that risk estimates could not be adjusted for alcohol use.	Tobacco chewing showed 6-fold increase (OR= 5.8, 95% CI 3.6 to 9.5), adjusted for age and smoking for oral cavity cancer - marginally increased risk for cancer of oropharynx (OR = 1.2, 95% CI 0.8 to 1.8), no increase for lung ca (OR= 0.7, 95% CI 0.4 to 1.2) compared with non-chewers. Linear dose-reponse relationship with amount chewed per day and duration of chewing in years for both oropharynx and oral cavity ca. For those chewing >10 pieces per day, OR 13.9, 95% CI 7.1 to 27.2), for oral cavity cancer and OR =3.6, (95% CI 1.7 to 7.4) for orophayngeal cancer. Chewing for over 30 years associated with (OR= 23.9, 95% CI 12.0 to 47.3) for oral cavity ca. Attributable risk for those who chewed tobacco estimated at 84.4% for development of oral cavity cancer.	Information on controls collected from a separate survey of 2500 males in Bhopal – based on a random sample of voter list of Bhopal cancer registry, 1989-1992. Response rates unclear – cases for which detailed information about smoking or chewing history was unavailable or cases registered from death certificates were excluded (unclear how many). Quality: A

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
25	Rao et al 1998[53] Betel chewing	Male tongue cancer patients seen at Tata Memorial Hospital, Bombay, India. Controls were male patients diagnosed as free from cancer, infectious disease and benign lesion at same hospital, unclear precisely how these were chosen. 1980-1984	637 cases 635 controls ST users: 229 cases, 233 controls	Some general information on composition of ST and dose-response information Sites included clearly defined (ICD 1410 BT and ICD 141-144 AT), all cases confirmed histologically. Many potential confounders considered (age, literacy, cigarette and bidi smoking, type of residence, alcohol consumption, vegetarian diet).	OR tobacco chewers compared with non-chewers (OR=1.81, 95% CI 1.21 to 2.73) for anterior tongue (AT), (OR=0.70, 95% CI 0.5 to 0.9) for base tongue (BT). Multivariate analysis OR = 1.74 (95% CI 1.17 to 2.57) for AT, 0.88 (95% CI 0.65 to 1.19) for BT. A statistically significant trend was found with increases in frequency and duration of tobacco use, but it is unclear whether this refers to chewing tobacco or smoking or both.	Information on dose-response collected, but not reported separately for tobacco chewers. Cases and controls were interviewed before clinical examination and investigators not aware of diagnosis. Not complete case series, unclear how many cases not included. Quality: A

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
26	Rao et al. 1994[54] Chewing paan with tobacco	Male oral cancer patients attending Tata Memorial hospital, Bombay, India. Controls selected from those diagnosed as free from cancer, infectious disease and benign lesions, but no other details provided. 1980-1984	713 cases, 635 controls ST users: 450 cases, 234 controls	Some general information on composition of ST and dose-response information Sites included clearly stated (cancers of lip, anterior 2/3 of tongue, upper and lower alveolus, floor of mouth, buccal mucosa and hard palate). Cancers of base of tongue (ICD 1410) and soft palate (ICD 1453) excluded. All cases histologically confirmed. Control of major confounders was good (age, literacy, bidi smoking, alcohol consumption, vegetarian diet, and residence).	Tobacco chewing was more frequent in cases (64.3%) than in controls (39.5%), adjusted OR= 2.64, (95% CI 2.07 to 3.38). No reduction in risk was shown for 'ex-chewers', even those who ceased over 1 year previously. Statistically significant trends were found with increasing daily frequency of use, and duration of use in years e.g. crude OR= 1.28 (95% CI 0.9 to 1.82) for 1-10 years use, OR=3.88, (95% CI 2.54 to 5.79) for 31+ years use. Also considers interaction of chewing with smoking and alcohol use (RR all 3 habits = 8.8).	Not complete case series – states that not all cases were diagnosed. Both cases and controls were interviewed prior to clinical examination. Some overlap with Rao et al. 1998 as anterior 2/3 of tongue included in both studies. Limited to males only. Quality: A

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
27	Nandakumar *et al.* 1990[116] Chewing betel leaf, areca nut and lime with or without tobacco	Patients registered with oral cancers at the Kidwai Memorial Institute of Oncology, Bangalore, India, 1982-94. Controls were those attending hospital for diagnosis of other ailments than cancer of the oral cavity, but found not to have any malignancy, matched for age, sex and area of residence.	348 cases, 348 controls Among males, 32 cases and 11 controls chewed tobacco. Among females, 205 cases and 59 controls.	Some information on frequency and duration of exposure to ST States sites included (lip, tongue, alveolus and mouth, though without ICD codes). Conditional logistic regression was carried out, but unclear which other risk factors were included.	Risk of oral cavity cancer associated with pan-tobacco chewing was significantly higher in both males (OR = 3.6, 95% CI 1.7 to 7.9) and females (OR =25.3, 95% CI 11.2 to 57.3). Significant trends were found with increasing number of years of chewing (e.g. OR = 15.95 95% CI 8.4 to 30.2) for chewing > 25 years compared with (OR = 1.7 95% CI 0.3 to 9.3) for 1-5 years of chewing), and number of times chewed per day.	Patients obtained from cancer registry at large regional centre, estimated that over 73% of resident cancer patients attend this hospital. Quality: F

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
28	Sankaranarayanan et al. 1990[12] Chewing betel, defined in paper	Patients registered with oral cancers at the Regional Cancer Centre Trivandrum, Kerala, India. For selection of controls see Sankaranarayanan et al. 1989[11]. 1983-1984	414 cases, 895 controls 203 cases, 181 controls, chewed betel quid. 6 cases and 7 controls inhaled nasal snuff	ST use defined in paper, and trend information available. Sites included clearly stated – buccal mucosa (ICD-O 145.0,145.1,145.6) and labial mucosa (ICD-O 140.3 & 140.4). Control of confounding good (adjusted for age, religion, bidi duration, alcohol and snuff use).	Strong, significant associations and dose-response relationships seen with frequency of chewing per day, and years of chewing in males and females (e.g. males chewing 10 or fewer times per day) OR = 6.9, 95% CI 2.83 to 16.81), chewing >45 times per day (OR = 37.75, 95% CI 19.49 to 73.12), adjusted for age and religion. Chewing for 40 years or more (OR = 29.02, 95% CI 14.2 to 59.28) compared with (OR=7.12, 95% CI 2.77 to 18.24) for 10 years or less after adjusting Risk for snuff use (OR = 2.28, 95% CI 0.74 to 7.03). Interactions were observed between pan-tobacco and bidi smoking when habits dichotomised as ever/never.	Also estimates risk associated with lifetime exposure (frequency * duration) for pan-tobacco and snuff use and risk associated with adoption after age 21. Very high risks associated with small number of occasional users, later excluded from all analyses. Quality: A

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
29	Sankaranarayanan et al. 1989[55] Chewing betel, defined in paper	Patients with carcinoma of gingiva at the Regional Cancer Centre and teaching hospitals of Medical College, Trivandrum, Kerala, India. For selection of controls see Sankaranarayanan et al. 1989[11]. 1983-84	187 cases, 895 controls 156 cases, 428 controls chewed pan-tobacco, 5 cases, 7 controls inhaled nasal snuff (all males)	Some description of types of ST use and dose-response relationships including an index of 'lifetime exposure'. Sites included clearly defined (ICD 143.0 and 143.1), Control of confounding was good (alcohol consumption, bidi smoking and duration in years, snuff use).	Pan-tobacco chewing is a major risk factor for gingival cancer, and daily frequency of chewing is a major predictor of risk (adjusted OR for chewing < 5 pieces / day (OR = 4.71, 95% CI 2.2 to 10.08) and OR > 10 pieces per day (OR= 13.25, 95% CI 6.28 to 27.88). Dose-response relationships also found for duration of chewing in years (e.g in males less than 10 years OR = 5.82, 95% CI 1.64 to 20.66), >41 years = (OR=32.06 95% CI 13.93 to 73.78). Risk was higher in occasional users than regular users for both males and females, though numbers were small. Attributable risk in male chewers for gingival cancer estimated at 54%. Risk associated with bidi smoking and tobacco chewing was only slightly higher than pan-tobacco alone. Adjusted OR snuff use = 3.9, (95% CI 1.19 to 12.7). Interaction observed between bidi smoking and pan-tobacco chewing.	Controls selected from patients who initially came to hospital to exclude malignancy in sites other than head and neck and from among those attending out-patients division of medical colleges with respiratory, intestinal and GU infections during 1983-84. Hospital records of cancer registry used, taken before diagnosis made. Occasional users excluded from main analyses, as daily frequency, age at starting habit, unknown. Quality: A

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
30	Sankaranarayanan et al. 1989[11]. Chewing betel, defined in paper	Patients with biopsy-proven SCC carcinoma of tongue and floor of mouth at the Regional Cancer Centre, Trivandrum, Kerala, India. Two controls for each case selected from 895 patients contemporaneously attending same hospital with non-malignant conditions at sites other than head and neck, with respiratory, intestinal and GU infections, matched for age, sex and religion. 1983-84	288 cases (188 tongue, 40 floor of mouth, 453 controls). 145 cases and 148 controls used pan-tobacco 8 cases and 6 controls (all males) inhaled nasal snuff	Some description of types of ST use and dose-response relationships including an index of 'lifetime exposure'. Sites included clearly stated (ICD-O 141.1, 141.2, 141.3, 141.4, for tongue), 144 floor of mouth, all confirmed by biopsy. Control of confounding good (age, sex, religion, cigarette and bidi smoking, alcohol consumption, and snuff inhalation).	Strong, significant associations and dose-response relationships seen with frequency of chewing per day, and years of chewing in males and females (e.g. males chewing< 5 times per day, OR = 4.0 (95% CI 2.15 to 7.46), 10+ per day, OR 5.52 (95% CI 2.85 to 10.67), 10 years or less of chewing, OR = 3.87 (95% CI 1.16 to 12.79), 41 years or more OR = 5.59 (95% CI 2.25 to 13.82). Also significant associations with 'lifetime exposure' e.g. for females with 70+ 'chewing years' (OR = 7.88, 95% CI 3.39 to 18.28), <70 chewing years (OR= 5.17, 95% CI 1.74 to 15.32). Interaction observed between bidi smoking and pan-tobacco chewing.	Unclear how controls were chosen. Information on dose-response relationships provided. Quality: A

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
31	Chattopadhyay 1989[117] Leaf of betel vine, lime, catechu, betel nut and tobacco	College and Hospital, Calcutta, India 1967-1987	732 cases, 1000 controls 558 cases and 146 controls chewed tobacco or dipped snuff 14 controls used chewing tobacco, no snuff users	Some description of types of ST used, no information on possible dose-response relationships. Sites included clearly stated and confirmed by biopsy. No further control of confounding, and many participants also smoked bidis or cigarettes.	Crude OR (not reported in paper) 18.8, (95% CI 14.6 to 24.1) Most cases involved lower jaw where contact of tobacco / paan quid would be maximised.	Study mostly retrospective (from 1967-85 and prospective only from 1986-87), some hospital records incomplete. Selection of controls unclear – those "not suffering from oral cancer or any precancerous lesion", matched on age and sex. Quality: F

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
32	Notani and Jayant, 1987[118] Chewing tobacco	Patients attending Tata Memorial Hospital with cancer of oral cavity, pharynx, oesophagus, larynx, Two control groups – hospital based (attended same hospital same time period, not diagnosed with cancer) & population controls, from electoral roles - comparable socio-economic group (OR based on hospital controls). 1976-1984	819 cases, (278 oral cavity; 225 pharynx, 236 oesophagus, 161 pharynx) 1211 controls No. of ST users not stated	No definition of ST use or information on possible dose-response relationships. Sites included clearly stated (ICD 141-145; 146, 148, 150 and 161). Control of confounding poor (age stratified only).	Age stratified relative OR for chewers versus non-chewers were: (OR=3.9, 95% CI 2.1 to 7.1) for oral cavity cancer, OR= 2.3, 95% CI 1.2 to 4.4) for pharynx, (OR=1.5, 95% CI 0.8 to 2.8) for oesophagus, (OR=1.6, 95% CI 0.6 to 5.1) for larynx.	Response rates are not mentioned, main focus of paper is diet and cancer - May underestimate risk as those who chewed or smoked less than twice a day were considered in the "no habit" group. Controls – all male members of one community (Hindus from state of Maharastra). Quality: F

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
33	Jussawalla, 1981[119] Chewing betel quid with or without tobacco	Patients attending Tata Memorial Hospital in Bombay with oesophageal cancers. Time period not stated	649 cases, 649 controls No of ST users not stated	Some description of ST used. Limited information about sites included Some limited control of confounders (age, sex, location) may have been achieved by matching, but this is not very clear, and results are presented separately for chewers who do not smoke.	OR for pan chewing with tobacco among non-smokers was 2.8 for men ($p<0.001$) and 2.0 for women (NS). ORs for pan chewing without tobacco were much higher at 12.1 for men, and 7.0 for women	Limited information concerning selection of controls. The higher risk of pan chewing without tobacco may be explained by the habit of swallowing the liquid extract among these chewers, whilst those chewing with tobacco spit out the liquid as it is too pungent to swallow. Quality: F

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
34	Simarak et al, 1977[68] Betel chewing, frequently including air-sun dried tobacco	Patients attending University hospital, Chiang Mai, Thailand, with cancer of the oral cavity, oropharynx, hypopharyx, larynx and lung (patients attending radiological department of University Hospital). Jan 1971 to April 1972	299 cases, 1113 controls Betel chewers: 169 cases, 516 controls	Some description of types of ST used. Sites included were adequately described (though without ICD codes) Confounders controlled for included age, and province of residence by M-H (Mantel-Haenszel stratification), education, types of smoking, agricultural employment and rural residence by logistic regression	On multivariate analysis, the OR associated with oral and oropharyngeal cancers was 2.27 for men and 3.16 for women ($p<0.05$ in both cases). Positive associations also found with larynx and hypopharynx cancers in men (OR = 2.36, $p<0.01$), but too few cases in women. There was no correspondence between the site where the quid was usually kept and site of the cancer, but numbers were small and often difficult to determine exactly place of origin of tumours within oral cavity due to advanced stage of disease	Selection of controls is well described. Unclear what proportion of betel chewers added tobacco to betel: states that 25 of 26 betel chewing cancer patients with oral and oropharyngeal cancers added tobacco to betel compared with less than 2/3 of controls – however these figures do not correspond with the proportion of betel chewers in Table 1. Quality: A

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
35	Krishnamurthy and Shanta, 1976[120]	India - unclear how controls were selected, or criteria on which they were matched, response rates unclear	1243 cases, 5824 controls No. of ST users not stated	Type of ST use not clear, limited information on possible dose-response relationships. Outcomes not clearly described. Potential confounders not controlled for.	Among cases with cancers of buccal mucosa, anterior tongue, posterior tongue, pharynx, 87.9%, 67.9%, 55.1% and 33.6% chewed betel nut and tobacco, compared with 11.2% of controls: (OR= 0.79, 95% CI 0.57 to 1.11) comparing heavy or chain with light smokers.	Conference abstract – Impossible to calculate OR for most outcomes as raw numbers of neoplasms at each location not stated. Calculation of OR for heavy versus light smokers does not support authors statement that intensity of the chewing habit also seems significant. Quality: F

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
36	Jussawalla et al. 1971[121] Betel nut and tobacco	Greater Bombay. Population controls (matched by age, sex and religion) obtained from registered voters lists. 1968	2005 cases, 2005 controls 1152 cases, 665 controls chewed tobacco	No clear definition of ST but some description of types of ST provided. Outcomes clearly defined (ICD codes 140-148, 150, 161), and all cases confirmed histologically Very limited control of confounding - analyses of those who chewed only compared with non-tobacco uses tended to find higher risks than analyses of chewers compared with non-chewers.	Risk of developing cancer in buccal mucosa is 7.7 times higher in chewers than non-chewers (95% CI 5.3 to 11.1). Also calculated for cancers of anterior 2/3 of mouth, alveolus, hard palate, oral cavity, base tongue, tonsils, orophayrnx, nasopharynx, hypopharynx, larynx, and oesophagus. Odds ratios tend to be higher when smokers are excluded. Risks associated with both smoking and chewing are greater than additive compared with smoking alone and chewing alone.	Cancers of salivary glands and unspecified areas were excluded. Quality: A

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
37	Hirayama, 1966[10] Tobacco and lime chewing	Ceylon and India (Vellore, Bombay, Bihar). Selection of controls was not clear – patients with diseases other than cancer from Government General Hospitals in Ceylon. 1964	India and Ceylon, 545 cases, (369 males, 163 females) 440 controls (277 males, 163 females) In India and Ceylon, approx. 152 female cases and 122 male cases, 64 male controls and 69 female controls chewed betel quid with tobacco. A further 10 female cases and 1 control chewed betel quid with tobacco and smoked, compared with 191 cases and 69 controls (figures read off a graph)	Definitions of ST not provided. Outcome not clearly defined. Possible confounders were not considered (though it is stated that there were no differences in smoking between the two groups).	RR of developing oral or pharyngeal cancer at particular sites – lip RR = 5, cheek RR = 7, gingiva RR = 2.8, anterior tongue RR = 3.6 (all the above statistically significant with $p<0.01$). Other sites palate RR = 1.4, posterior tongue RR= 0.8, rest of oropharynx RR = 0.4. Strong dose response relationships with frequency of chewing per day, duration of chewing each quid in minutes, and age at which chewing habit started (e.g. chewing 6 or more quids per day RR = 81.1 compared with 8.5 for <3 quids per day. Retaining quid in sleep associated with RR of 63.7. The side affected almost always corresponded to the side where the quid was kept.	Separate analyses have been performed on sub-groups and the exact numbers in each analysis is not always clear. Quality: F

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
38	Shanta and Krishnamurthi, 1963[122] Betel nut and tobacco chewing, described in paper	Patients with cancers of upper alimentary tract Years of recruitment not stated	882 cases, 400 controls (males 628 cases, 300 controls; females 300 cases, 100 controls) Tobacco chewers: Males 395 cases, 28 controls; Females 174 cases, 11 controls.	Some description of types of ST used. Sites included are clearly stated, All cancers are SCC and histologically confirmed. No control of confounding, though cigarette smoking was rare among women.	Very strong associations with cancers of lip and buccal cavity (OR= 47.26, 95% CI 28.2 to 79.74) in males, (OR=45.51, 95% CI 20.08 to 105.72) in females. Also high OR for cancers of anterior and posterior tongue and pharynx. OR for cancers of hypopharynx and oesophagus were statistically significantly raised only in males.	Large sample size, but the methods of selection of cases and controls is unclear. Dose-response relationships not calculated but stated that all chewers had been heavy chewers over a period of 20-40 years. Quality: F
39	Sarma, 1958[123] Betel chewing, sometimes tobacco and lime added	Unselected patients >20 years attending Assam Medical College, India 1954-1955	238 oral cancer cases, 84 other cancers, 3678 non-tumour controls No. of ST users not stated	Some description of types of ST used. Cancer sites included clearly stated (larynx, oesophagus, tonsil, pharynx, tongue, palate, lip, cheek, gum). No control of confounding.	Out of 238 upper alimentary tract cancers, 230 addicted to betel nut chewing, of 84 tumours at other sites, 47 addicts. Crude OR = 7.02, 95% CI 3.35 to 15.38) for oral cancers compared with non-tumours	Not clear how many betel nut chewers added tobacco. Quality: F

Cross-sectional study

ID	Study Type of ST	Setting Years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
40	Chakrabarti et al. 1991[124] Chewing betel and tobacco, no further details	Patients attending cancer detection centre of the National Cancer Institute, Calcutta, India Time period not stated	3205 1523 chewed betel nut with tobacco, 1677 non-chewers	ST use not clearly described, and no attempt to measure dose-response relationships. Outcomes clearly defined and oral malignancies confirmed by biopsy. No control of confounding	The crude OR for malignancies was 5.58, 95% CI 2.21 to 14.95, and for oral dysplasia 2.28, 95% CI 1.79 to 2.92) for ST users compared with non-users.	Cross-sectional study Quality: F

Other Regions

Case-control studies

ID	Study Type of ST	Subjects, setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
41	Idris et al. 1995[59] Toombak Tobacco sp. *N. rustica* – coarse powder of dried toombak leaves mixed with concentrated solution of natron (sodium bicarbonate) in water until the product is moist and hardened	Patients attending radiation and isotope Centre, Khartoum, only hospital in Sudan for treatment of patients with malignant neoplasms. Used two control series, hospital controls with non-SCC oral neoplasms and neoplasms of non-oral sites unrelated to tobacco use; and volunteers attending oral health education programmes in Sudan 1970-1985	646 cases (375 group 1,271 group 2), 3024 controls (204 hospital and 2820 population) 157 cases in group 1, 52 cases in group 2, 23 hospital controls, 597 population controls)	Types of ST used clearly described. Sites included clearly stated ICD-O codes 141.5, 143.8, 144.9, 145.0) for group 1, 141.9 and 145.5 for group 2. ORs adjusted for age, sex, ethnicity, and cigarette use.	Group 1 SCC of lip, buccal cavity, floor of mouth (OR= 7.3, 95% CI 4.3 to 12.4) with hospital controls, (OR= 3.9, 95% CI 2.9 to 5.3) with population controls. All neoplasms at sites of preference for placement of quid. Group 2 SCC of tongue, palate and maxillary sinus (OR= 1.4, 95% CI 0.8 to 2.5) compared with hospital controls; (OR= 0.7, 95% CI 0.5 to 1.0) compared with population controls. All neoplasms located at oral sites having little or no direct contact with quid. Some dose-response relationship for first group with both control groups e.g.<10 years of use, (OR= 0.7, 95% CI 0.3 to 1.8) >11 years (OR= 11.0, 95% CI 4.8 to 25.1).	Good study Quality: A

ID	Study Type of ST	Subjects, setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
42	Van Wyk et al 1993[125] Betel chewing and snuff use	Indian patients with oral SCC, Natal, South Africa. Controls from same ethnic group were recruited in a separate house-to-house survey in 1983 in Natal. 1983-1989	150 cases, 1029 controls 32 female cases and 21 controls chewed betel with tobacco, 18 female cases, 5 male cases used snuff	Some description of types of ST used. Sites included clearly stated – tongue ICD 141, cheek incl. cuccal mucosa (ICD 143, 145.0), floor of mouth, palate and oropharynx (ICD 144, 145.1, 145.8, 146.0), all histologically confirmed. Poor control of confounding, though smoking was rare in women (only 7% of cases).	OR for areca nut chewing with tobacco in women was 47.42 (95% CI 20.34 to 110.54) and the attributable risk for oral cancer was 91%. OR for areca nut chewing without tobacco was 43.9 (95% CI 18.6 to 103.57). Controls matched on age. Unable to show a relationship with snuff use as 87% of the snuff dippers have additional habits, and no relationship found with duration of chewing in years.	Could not calculate OR for men as areca nut chewing was rare. Not stated how many controls used snuff. All patients suffered from submucous fibrosis, regarded as a pre-malignant condition. Quality: F

ID	Study Type of ST	Subjects, setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
43	Franco et al 1989[126] ST use not described	Patients with newly diagnosed cancers of tongue, gum, floor of mouth and other parts of oral cavity in three areas of Brazil. Controls were patients from same hospital to which cases had been admitted, or neighbouring general hospitals, matched on sex, age and trimester of hospital admission. 1986-1988	232 cases, 464 controls ST users: 9 cases and 13 controls	No description of ST use. Sites included clearly stated (ICD 9 141 and 143-145, cases confirmed histopathologically. Adjusted by matching for smoking and drinking status, sex, and anatomical site.	Use of ST, either as snuff or chew, was not associated with risk of oral cancer	Cases and controls were interviewed blind to the hypothesis under investigation, and small numbers only. Quality: F

ID	Study Type of ST	Subjects, setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
44	Cook-Mozaffari et al 1979[127] Nass – chewing tobacco and lime – no further details	Cases registered at Caspian Cancer Registry, Province of Mazandaran and Gilan along the Caspian Sea. 1974-1976	344 cases oesophageal cancer, 181 tumours at other sites, 1050 controls Number of ST users not stated	Limited information on exposure, and no information on dose-response relationships. Sites included not clearly stated, very few cases confirmed histologically, and 21% were diagnosed solely on clinical grounds. OR adjusted for age and location by matching.	Among males, chewing of nass associated with OR of 0.87, (95% CI 0.5 to 1.52) –No females chewed.	Prevalent cases, controls randomly selected of same age and sex and resident in same village or town. Many cases not interviewed directly as too ill or dead. Very high rate of non-response (55% of oesophageal cases, 39% of other cancer cases interviewed), partly due to high frequencies of incorrect addresses and funding problems. Some small discrepancies in numbers reported within paper. Quality: F

ID	Study Type of ST	Subjects, setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
45	Whitaker et al 1979[128] Chewing tobacco – no further details	Patients with oral and pharyngeal cancers in the two main textile regions of England (Christie Hospital, Manchester, Cookridge Hospital, Leeds) No. of ST users not stated	280 cases, 280 controls 10 cases, 10 controls	No further information on ST use. Sites included clearly stated (ICD – 8 141 - tongue, 143-145 mouth, 146-149 pharynx, all SCC. Age and sex matched, but no further control of confounding and all tobacco chewers smoked cigarettes	No associations between chewing tobacco and oral & pharyngeal cancers	Main focus of study was occupational risk, and controls were patients with primary malignancies not known to be associated with textile work. Quality: F

Cross sectional study

ID	Study Type of ST	Setting Years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
46	Salem et al 1984[129] 'Shammah' dipping, includes powdered tobacco leaves and hydrated sodium carbonates, placed in buccal or lower labial vestibule.	Adults over 15 living in Gizan region of Saudi Arabia Time period not stated	661 of whom 187 used shammah, 474 were non-users	Type of ST described in detail. Examination of oral mucosa and type of ST use clearly described. No control of confounding	Oral mucosal lesions were diagnosed in 78 individuals. All of these had used 'shammah' consistently for more than 5 years, and no lesions were observed among cigarette smokers. Biopsy specimens were obtained from 30 of these individuals, and 2 had carcinoma in situ. Seven had SCC, but these were all obtained from a separate group of hospital patients, not the main study group.	Investigator could not have been 'blind' to shammah use, as oral surfaces were reported to be frequently stained yellow to brown with remnants of shammah still in place. Response rates to the survey not reported, and only 30 of the 78 found to have lesions gave permission for biopsy samples. Quality: F

Other Cancers

US studies
Prospective Cohorts

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
47	Heineman 1994[130] Chewing T and oral Snuff	The study includes only men. Focuses on tobacco consumption and colorectal cancer association. US World War I veterans, 1954-1957, 26 years follow-up.	248,046 veterans included in the follow-up. Person years of follow up was 41,124 for ST users.	Tobacco use status was ascertained only at the beginning. Misclassification of exposure is highly possible and this may dilute the association. ST use was defined as 'only ST use without current or past smoking history'. Dose-response relation was studied. Colorectal cancer deaths obtained from death certificates (underlying cause of death). Most of the confounders were controlled in the analyses but data on the major confounder, diet was not available.	RR of deaths from colon ca for users of chewing tobacco or snuff versus never used tobacco: RR = 1.2 (95% CI 0.9 to 1.7). For Rectal Ca: RR = 1.9 (95% CI 1.2 to 3.1) – adjusted for age, calendar time, year of questionnaire response, socioeconomic status and sedentary occupation. Dose-response relation: RR for colon ca; amount ST use versus never used tobacco': Never heavy use RR = 2.0 (95% CI 1.4 to 3.0). Ever heavy use RR=0.6 (95% CI 0.4 to 1.1). For Rectal Ca: Never heavy use RR = 2.5 (95% CI 1.3 to 5.0). Ever heavy use RR=1.5 (95% CI 0.7 to 3.0).	Veterans who reported heavy ST use (defined as using 'practically every day') showed lower risk for both cancer outcomes than those who reported having used these products but never heavily This counter-intuitive finding is not discussed in the paper. Quality: F

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
48	Zheng 1993[131] Chewing T and oral Snuff	Focuses on risk factors for pancreatic cancer. In 1966 a cohort of white male policy holders of the Lutheran Brotherhood Insurance Society aged 35+ were included. They were mostly from California, Minnesota, Missouri & Dakota, US, followed up for 20 years.	17,633 people included in the study ST use 27,025 person years	Tobacco use status was ascertained only at the beginning. Misclassification of exposure is highly possible. ST use was not the main focus of the study. ST use was defined as 'ever use', no information was presented on intensity and duration. No dose-response relation analyses were performed. Outcome (pancreatic cancer deaths), obtained from death certificates, coded by an oncologist. RR was adjusted for most confounders.	Among 'ever users of ST' the age, alcohol, and smoking adjusted RR= 1.7 (95% CI 0.9-3.1) based on 16 deaths.	Quality: F

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
49	Zahm et al 1992[104] Chewing tobacco and oral snuff	US military veterans, ages 31-84, who held active US government life-insurance policies in 1953 and died from soft tissue sarcoma (STS) by 1980. Enrolled in 1953.	293,958 of whom 248,046 provided tobacco use histories on a questionnaire in either 1954 or 1957 48,304 ST user (854,453 P-Y of ST use), 21 died from STS.	Frequent and infrequent ST use clearly defined. No information on any changes in ST use over time (23-26 years follow-up). Concern over misclassification of outcomes for STS – 3rd National Cancer Survey showed that only 54.8% of those diagnosed with STS have STS on their death certificate. In this study, only 56.3% of persons with STS on death certificates had diagnosis confirmed by hospital records. Histologic type and tumour location were unspecified on most veterans death certificates – high and low risk sub-groups of STS were probably combined and therefore risks diluted. Results adjusted for age and calendar time only.	Veterans who ever chewed tobacco or used snuff had a non-significant 40% excess of STS compared with those who never used any tobacco products (RR=1.4, 95% CI 0.8 to 2.6). Highest risk was for frequent users during first 10 years of follow-up (RR = 3.4, 95% CI 1.1 to 10.7).	Most veteran users of chewing tobacco or snuff also used other tobacco products. Higher risks found in ex-users than current users, and higher in those who started young, but risk did not increase with duration of use. Items left blank on questionnaire were coded as 'NO' which may underestimate risks. ST users also used other cigarette products – there were no deaths among the 2,308 veterans who used only ST products. Quality: F

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
50	Heineman 1992[132] Chewing T and oral Snuff	The study includes only men. Focuses on tobacco consumption and myeloma association. US World War I veterans. 1954-1957	248,046 veterans included in the follow-up. Person years of follow up was 41,124 for ST users.	ST use is not defined, no information on dose-response relationships. Smoking status was ascertained only at the baseline. Follow-up information was complete for 96% and death certificates obtained 97% of those identified as deceased. Cause of death was detected from death certificates (ICD8) No attempt to control for confounding factors.	RR of deaths from Multiple Myeloma for users of chewing tobacco or snuff versus never used tobacco: (RR = 1.0 95% CI 0.4 to 2.3). Risk did not increase with heavier use of CT or snuff (used occasionally: RR=1.7; and used 'practically everyday': RR=0.6) all CIs included 1.	US Veterans cohort - no information on any changes in ST use or cigarette smoking over time (23-26 years follow-up). High potential for misclassification bias. Quality: F
51	Kneller 1991[133] Chewing T and oral Snuff	Stomach ca in white men of US, Norwegian and German descent living in 8 US cities 1966-67.	17,818 people included in the study 1420 persons used ST	Outcome measured using death certificates – coded by a nosologist. ST use is not defined, no information on dose-response relationships. Limited attempts to control for confounding factors (5-year age group, stratification by pack-years of smoking).	No statistically significant association was seen among current or former users of ST compared with tobacco abstainers (18 cases; RR=2.3; 95% CI 0.98 to 5.22). Stratification by pack years of smoking reduced this risk estimate (RR=1.6; 95% CI 0.58 to 4.50).	Quality: F

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
52	Hsing, 1991[134] Chewing T and oral Snuff	US veterans who served in US Army during 1917-1940 and were aged 31-84 in 1953 and responded to the questionnaires in 1954 and 1957. They were followed-up for 26 years for prostate cancer mortality. 250,000 men	250,000 men Number of ST users was not given.	ST use was defined as 'only ST use without current or past smoking history'. No information on dose-response relationships. Death certificates - follow-up information was complete for 96%, certificates obtained for 98% of those identified as deceased. Limited control for confounders (only age and smoking history).	Age adjusted RR of death from prostate cancer: 1.17 (95% CI 0.88 to 1.56)	In total there were 4,607 deaths in the cohort, 48 of them in the ST user group. Tobacco use status was ascertained only at the beginning – high potential for misclassification bias. Quality: F

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
53	Hsing 1990[135] Chewing T and oral Snuff	In 1966 a cohort of white male policy holders of the the Lutheran Brotherhood Insurance Society who were 35+ included into study. They were followed-up for prostate ca mortality. They were mostly from Minnesota- US, had Norwegian and Scandinavian heritage, rural and farmers.	17633 men ST use only=4,025 py[3] ST+cigarettes =7,613py ST+pipe/cigar =2,729 ST +cigarettes + pipe/cigar=22,896 py	Information on tobacco habits was ascertained only at the beginning. Misclassification of exposure is highly possible. No information was given about intensity and duration of ST use. Dose-response relation was not analysed. Underlying cause of death obtained from death certificates. Analyses controlled for age, education, smoking, alcohol, diet, marital status and rural/urban residence.	RR of deaths from Prostate Ca for 'ever users of chewing tobacco or snuff versus never used tobacco': RR = 4.5 (95% CI 2.1 to 9.7). RR of deaths from Prostate Ca for 'ST user and cigarettes versus never used tobacco': RR =2.9 (95% CI 1.3 to 6.5). RR of deaths from Prostate Ca for 'any tobacco user versus never used tobacco': RR =1.8 (95% CI 1.1 to 2.9).	Loss to follow-up was high (23%) due to lapsed policies. Study group may not represent US population. Quality: F
54	Bjelke 1982[105] Chewing T and oral Snuff	Norwegian men and US men	12,945 Norwegian and 16,930 American men followed up 10 years for cancer mortality Number of ST users not given	Abstract – no information on measurements of outcome, exposure or confounders.	Men with ST habit have an increased risk of cancer of the oesophagus and pancreas. The results were consistent with a multiplicative effect of alcohol and chewing T and using snuff. (No numerical information)	This is an abstract from a congress presentation. There is not sufficient information about the methodology, results and discussion. Quality: F

[3] py – Person-Years

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
55	Winn et al. 1982[106] ST use (chewing tobacco and snuff)	DORN study - US veterans with life Insurance Policies. 1954 - 1969	Approximately 300,000. Number of ST users not stated.	Abstract – no information on measurements of outcome, exposure or confounders.	In the absence of smoking, ST related SMRs were higher for cancer of digestive system (137), cancer of oesophagus (228), cancer of stomach (151), pancreas (165), and liver (281).	Abstract only - small numbers for some outcomes (only one death from cancer of oesophagus). Quality: F

Case-Control Studies

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
56	Brown *et al* 1992[136] ST use not described.	All newly diagnosed cases of leukaemia among white men aged 30 years or above from Iowa Health Registry, a member of SEER, or from a special surveillance network of hospitals and pathology laboratories instituted in Minnesota Controls selected by random digit dialling, Medicare records, and state death certificate files, and frequency matched by 5-year age group, state of residence and vital status. 1981 to 1984	578 cases, 820 controls ST users: 24 cases 23 controls.	ST use is not a main focus of the study and is not described. Cases from population-based cancer registry, definitions clearly stated and slides reviewed by regional pathologist. Control of confounding was limited to state and age group, but it is stated that education, occupational exposures and family history of ca were not confounders (& smoking by restriction).	The OR for all leukaemias (compared with non-tobacco users) was 1.8, 95% CI 0.9 to 3.3. No statistically significant relationships for any sub-type, but there are small numbers of cases for each, and risks above unity for all but one of the sub-types studied	Response rates high (86% ca, between 77% and 79% for different co series Dead controls (n=425) were excluded from main analyses since there is evidence that smokers are over-represented in such groups. Leukaemia subtypes studied include acute non-lymphocytic, chronic myelogenous, chronic lymphocytic, acute lymphocytic, myelodysplasia. Quality: F

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
57	Brown et al 1992[137] ST use not described	All newly diagnosed cases of Non Hodgkin's lymphoma (NHL) or multiple myeloma (MM). Case and control selection as above (Brown et al 1992[137]	NHL: 622 cases, 820 controls MM: 173 cases, 650 controls ST users (NHL): 19 cases, 23 controls ST users (MM): 5 cases, 8 controls	As above (Brown et al 1992)[137]	OR for ST use of all NHL subtypes was 1.3 (95% CI 0.7 to 2.5). OR for multiple myeloma was 1.9 (95% CI 0.5 to 6.6).	Number of cases and controls are small, and ORs therefore imprecisely estimated. Quality: F
58	Zahm et al 1989[138]	All newly diagnosed soft-tissue sarcoma, non-Hodgkin's lymphoma and Hodgkin's disease among white male Kansas residents aged 21+ General population controls were selected by random digit dialling (<64 years) or Medicare file if over 65, matched by age. 1976 to 1982	133 cases, 948 controls; 4 upper GI tract cases, 5 lung, pleura and thorax cases; 3 head, neck and face cases, 16 other 28 cases, 127 controls	No information collected on duration, amount, or age at starting ST use. Sites included clearly defined by ICD codes, all confirmed histologically. Control of confounding limited (age adjusted only).	For all cases combined, OR = 1.8 (95% CI 1.1 to 2.9). No statistically significant associations for individual cancer types or sites e.g. upper GI tract (OR = 3.3 95% CI 0.8 to 12.6), lung, pleura & thorax (OR = 3.1, 95% CI 0.9 to 10.5), head, face and neck (OR = 2.4, 95% CI, 0.5 to 10.2), other areas of the body (OR = 1.4, 95% CI, 0.7 to 2.5).	Tobacco chewing histories taken up until a key date 5 years prior to cancer diagnosis for cases (range 1971 to 1977) and 1977 for controls – who therefore had more opportunity to report exposures than cases, which may dilute risk estimates Overall response rate 93%. For dead cases, controls were selected from Kansas state mortality files and additionally matched on year of death. Quality: F

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
59	Burch 1989[139] Oral Snuff and chewing tobacco	Cases of primary bladder cancer diagnosed during 1979-82, aged 35-79 yrs and age, sex & area of residence matched controls, randomly selected from population included. The study was carried out in Alberta and South central Ontario, Canada.	826 cases and 792 controls. 9 cases and 18 controls were snuff users. 26 of the cases and 34 of the controls used chewing tobacco.	ST use was defined ever/never, no information about length and intensity of consumption or concomitant smoking. Outcome described as 'primary bladder cancer'. OR adjusted for lifetime cigarette consumption.	Analyses for ST were restricted to men as women did not use ST. OR snuff use = 0.47, (95% CI 0.21 to 1.07). OR chewing tobacco use = 0.60, (95% CI 0.34 to 1.06).	High non-response rates in cases and controls (33% & 56% respectively). Small numbers of cases and controls used ST. Quality: F

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
60	Slattery 1988[60] Oral snuff and chewing tobacco	White, male, 21-84 yrs old, newly diagnosed bladder cancer cases between 1977-83, from Utah cancer registration and population controls.	332 cases and 686 age matched (categorically) pop controls. 16 of the cases and 32 of the controls used snuff. 21 of the cases and 45 of the controls used chewing tobacco.	ST use was not defined in detail (only ever/never). Cases were defined according to ICD-9 and confirmed histologically. Study restricted to white men and stratified by smoking status but except for this no attempt was made to control for confounders.	Crude OR of snuff use for bladder cancer compared with non-users (OR=1.0, 95%CI 0.54 to 1.85) OR of snuff use for bladder ca in smokers was 0.70, 95% CI 0.36 to 1.35. OR of snuff use for bladder ca in never smokers was 2.73, 95% CI 0.48 to 15.57. Crude OR of chewing tobacco for bladder ca: was 1.08, 95% CI 0.63 to 1.87). OR of chewing tobacco for bladder ca in smokers was 1.22, 95% CI 0.68 to 2.19). OR of chewing tobacco for bladder ca in never smokers: was OR=2.78, 95% CI 0.38 to 20.20.	Numbers of snuff users or tobacco chewers were small in cases and controls. Stratification demonstrated possible interactions between smoking and ST use, (OR for association of snuff use and chewing tobacco with bladder cancer are both higher among those who have never smoked) but these associations are not statistically significant. Quality: A

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
61	Goodman, 1986[63] Chewing tobacco and oral snuff At least once a day and 1 year or more	Cancer of the kidney from 18 hospitals of 6 cities in US were included in the study. 1977-83	267 cases and 267 controls 13 male cases, 4 male controls and 1 female control used chewing tobacco	ST use is defined as ever-never use. No information on dose-response relationships. Incident cases of kidney adenocarcinoma, histologically confirmed. Adequate matching, analysing and control of confounding.	The crude OR for renal cell cancer in ever tobacco chewers versus never chewers: (OR = 4.0, 95% CI 1.1 to 14.2) for men. OR was not calculated for women since no females cases chewed. In logistic regression model (BMI, decaffeinated coffee use, pack years smoking, and interaction term for chewing tobacco and pack years smoking), the adjusted OR for chewing tobacco was 0.9 (95% CI 0.1 to 5.1). Positive interaction between smoking and chewing tobacco for renal cell cancer. OR for smoking (pack-years) was 1.1 (95% CI 0.9 to 1.4), chewing tobacco use 0.9 as above, but pack-years x chewing tobacco OR = 26.0 (95% CI 4.4 to 153.0).	Small number of cases and controls used chewing tobacco without concurrent smoking. Interaction between chewing tobacco and pack years of smoking was checked. The fitted OR for persons who chewed tobacco and had 30 pack years of smoking compared to never users was 26 (95% CI 4.4 to 153.0). Quality: A

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
62	Hartge 1985[140] Chewing tobacco and oral snuff	Population based case-control study. National bladder ca study, US. 1977-78.	2982 cases, 5782 controls Number of ST users not given	ST use was defined as 'ever used for 6 months or more in life' no information provided on dose-response relationships. Histologically confirmed bladder ca. Registered to 9 cancer registries of NCI. ST cancer association analysed in men who had never smoked cigarettes, and basic confounders (race, age, sex, residence, pipes, cigars) were included in multivariate analysis.	Among men who never smoked, snuff dippers and tobacco chewers were not at increased risk for bladder cancer (OR for snuff use = 0.77; 95% CI 0.38 to 1.56), and for chewing tobacco (OR= 1.02; 95% CI 0.67 to 1.54). OR adjusted for race, age, sex, residence, use of pipes and cigars.	The study focuses on non-cigarette tobacco use and bladder ca association. Since non-cigarette tobacco use was small in women the analyses were restricted to men. Quality: F

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
63	Howe 1980[141] Chewing tobacco	Newly diagnosed bladder cancer cases from 3 provinces of Canada 1974-77	(480 m and 152 w) and age-sex matched neighbourhood controls included (632 pairs=1264 persons). Number of ST users was not presented in the paper.	ST use was not main focus of study and wasn't defined well (ever/never). Cases from cancer registries and co-operating pathologists & urologists. Limited results were presented for ST, only crude OR for bladder ca. States that controlling for cigarette smoking did not change the estimate (no data presented).	The OR of Chewing tobacco use (ever vs never) for bladder ca was 0.90 (95% CI 0.5 to 1.6). This estimate was calculated only for men.	Study focuses on tobacco use, occupation, coffee, various nutrients and bladder ca association. Small numbers of ST users among both cases and controls. Quality: F
64	Williams and Horm, 1977[109] Chewing tobacco and snuff (cans or plugs per week * years of use)	Part of the Third National Cancer Survey – a random 10% sample of all incident cases in survey areas in the US. 1969-72.	7518 cases (controls are inter-case comparisons) ST users: Males, 132 cases 169 controls. Females 5 cases 53 controls	Some information and frequency and quantity of ST used. Sites clearly described (though not in this paper). Basic confounders (age, sex, race and cigarette smoking) are considered, but could not control for cigar / pipe smoking	A relationship was 'suggested' for bladder cancer (OR 1.61 and 1.78 in males for 1-50 and >50 'chewing years' respectively; OR = 2.43 in females with > 50 chewing years) and lymphoma (e.g. OR = 1.31 and 3.05 at each exposure level in males for Hodgkin's disease).	Controls are cancers from sites not thought related to tobacco or alcohol consumption in the TCNS – may dilute estimates of risk. Very high non-response bias – only 67% of sample interviewed. Quality: R

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
65	Wynder and Stellman 1977[110] Chewing tobacco and oral snuff	Patients with cancer of lung (Kreyberg types I and II), larynx, oesophagus or bladder from 20 hospitals in 8 American Cities – New York, Houston, Los Angeles, Birmingham, Miami, New Orleans. 1969-1975	3716 cases, and 3716 controls Distribution of cases by site: Lung I – 91; Lung II – 26; oral cavity 61; larynx 46; oesophagus 20; bladder 47. 291 cases, 233 controls had ever used chewing tobacco, 79 cases and 69 controls had ever used snuff	No description or definition of ST use. Sites included clearly stated (lung cancer ICD 162, oesophagus 150, bladder 188) and histologically proven. Limited consideration of confounders (age, race and city), but smoking habits of users of chewing tobacco did not differ significantly from non-users of chewing tobacco in any cancer diagnosis category.	OR among snuff users ranged from 0.5 (Lung II cancer) to 1.7 (oesophagus) but none were significant. Re-analysis of raw numbers in EPI-INFO found one statistically significant association for Lung I cancer, crude OR = 1.43, 95% CI 1.09 to 1.86). Lung cancer (type I) had the largest number of cases (n=91).	Controls were from same hospitals but without tobacco-related disease, clearly defined. Insufficient cases to demonstrate increased risk due to chewing tobacco or snuff use alone. Quality: F

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
66	Cole, 1971[142] Oral Snuff and chewing tobacco	Incident, histologically confirmed transitional or SCC of lower urinary tract cases and sex-age matched population controls. Participants were aged 20- 89 years old, from 96 hospitals in Boston Brockton Standard metropolitan Statistical Areas and 15 hospitals from peripheral areas	470 cases 500 controls In cases only 3 persons used snuff and 46 cases were using chewing tobacco	ST use is not clearly defined, no information on dose-response relationships. No ICD codes, but most cases confirmed histologically. Limited control for confounding factors.	There were no differences between observed and expected numbers of cases (lower urinary tract cancer) who had used snuff (3 vs 2.99) or chewing tobacco (46 vs 42.3) – restricted to men.	ST use was not main focus of study. Limited results were presented about snuff use and chewing tobacco. Results were not properly analysed (ie methods for matched designs were not used). Quality: F

Cross sectional Studies

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
67	Spangler 2001[143] Chewing T and oral Snuff	Women from Cherokee tribal land, US interviewed 1990-91.	1408 women included and 292 women reported using ST	No information about duration and intensity of ST. Breast ca. diagnosis self-reported. No control of confounders.	OR of ST for breast ca diagnosed before 55 years age = 7.79 (95% CI 1.05 to 66.0) OR of ST for breast ca diagnosed after 55 years age= 0.0 (95% CI 0.0 to 5.67)	A cross sectional study based on self reported data. Small study population and small number of breast cancer cases. Quality: F
68	Sterling 1992[144] Chewing T and oral Snuff	The study analyses the link between ST use and oral and digestive organ cancers in a cross sectional design. People who died in 1986 in US were study population.	16,598. Number of decedents by lifetime use of ST > 100 times estimated using information from 1986 National Mortality Follow-up Survey	Dose-response relationship was considered. Outcome from death certificates. Potential confounders included into multivariate analyses (adjusted for sex, race, age, smoking, drinking and occupation).	RR for all cancer mortality RR=0.37, 95% CI 0.26 to 0.54 among those who had ever used ST 100 to 9,999 times, and RR 0.88, 95% CI 0.69 to 1.12 among those who used ST over 10,000 times. No statistically significant relationships for oral cancers. RR for cancer of digestive organs among those who had ever used ST 100 to 9,999 times, RR 0.15, 95% CI 0.04 to 0.52 and among those who used ST over 10,000 times RR 0.61 95% CI 0.34 to 1.10).	Information about tobacco and other factors obtained from their families. Recall bias is possible. No validation for exposure information. Non-response rate was 11.4% to questionnaire. Reference category are those who used ST 0 to 99 times (rather than never-users) which could underestimate risk. Quality: F

Scandinavian Studies

Prospective cohort

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
69	Heuch 1983[97] Chewing tobacco	In 1964-67 tobacco habits of the study population defined. The study population was a set of 3 groups: 1) a sample of pop recorded in 1960 census 2) a set of brothers, living in Norway, of a sample of migrants to the US 3) spouses-siblings of individuals interviewed for a case control study of gastrointestinal ca. Followed up for 11 –14 yrs for pancreatic ca. Norway	16,713 persons were included in the study. Number of ST users not presented.	ST use was defined as 'never used group, former users and regular users' but no information was provided about those with several tobacco habits. Outcomes assessed using cancer register and death registry (only 62% of cases histologically verified). ORs were adjusted for region, place of residence (urban/rural), age and sex, and some analyses smoking and alcohol.	OR chewing tobacco for <u>all pancreas cancers</u> (n=63) was 1.34. No trend in pancreas ca cases from never used group, former users and regular users p=0.21 OR of chewing tobacco for <u>histologically verified</u> pancreas cancers was 2.20 (95% CI 0.89 to 5.4) Positive trend in pancreas ca cases p=0.045. Among men: OR of chewing tobacco for histologically verified pancreas cancers was= 2.31. No trend in pancreas ca cases, p=0.067 OR= 2.85 and test for trend, p=0.06 among men after adjustment for alcohol and smoking	16,713 persons were followed up for 11–14 yrs for pancreatic ca. In total 63 cases occurred, only 39 of them histologically verified. Quality: F

Case-Control Studies

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
70	Lagergren et al. 2000[65] Snuff, defined as taking a quid of snuff at least once a week for 6 months or more	Whole of Sweden, except those >80 and individuals born abroad. All patients with a new diagnosis of AC of oesophagus or gastric cardia and half with oesophageal SCC (born on even dates). Controls were selected from the population, 1995-97.	618 patients, 189 oesophageal ACC, 262 cardia AC, 167 oesophageal SCC, 820 controls. 35 oeso AC cases, 53 gastric cardia AC, 33 oesophageal SCC, 126 controls	Snuff use clearly defined & includes trend information. Outcomes clearly defined, and 97% confirmed by biopsies and / or re-examination of surgical specimens by a pathologist. Many potential confounders considered (age, sex, education, cigarette smoking, alcohol consumption, dietary intakes of fruit and vegetables and energy intake, BMI, reflux symptoms, physical activity).	Snuff users had OR of 1.2 (95% CI 0.7 to 2.0) for oesophageal AC compared with never users. No trend found for duration of use (in years) or intensity (number of quids per week). Results similar for gastric cardia AC (OR=1.2, 95% CI 0.8 to 1.8). For oesophageal SCC, adjusted OR of 1.4 (95% CI 0.9 to 2.3). No apparent dose-response but point estimates of borderline significance observed in single high-dose or long-duration categories e.g. 15-35 quids/week, (OR = 2.1, 95% 1.0 to 4.4).	Very good study – Encompasses whole population of Sweden, and uses population controls, randomly selected from age and sex strata. Response rates were good (between 73% and 87% for each cancer type and controls). Quality: A

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
71	Ye 1999[66] Chewing tobacco and oral snuff	Gastric cancer cases and population controls from 5 counties with different incidence rates of gastric cancer in Northern and Central Sweden included, 1989-1995	567 gastric ca cases and 1534 controls. Only 8 cases and 14 controls reported having ever chewed tobacco, and none of the females had ever used moist snuff. 83 of the male cases (375) and 192 of the male controls (779) were snuff users.	Use of ST was defined as at least once a week for 6 months or more. Snuff dipping was analysed in detail as age at starting, duration of use, times per day (dose response). Gastric ca were analysed in the study: Cardia ca and distal stomach ca (intestinal type-diffuse type), defined histologically and according to locality. Main confounders adjusted in multivariate models (age, residence area, BMI, SES and smoking)	OR of snuff dipping for <u>cardia ca</u> Never users OR = Ref Ex user OR = 0.8, (95% CI 0.3-1.9), current users OR = 0.5, (95% CI 0.2-1.0), Ever users OR = 0.6, 95% CI 0.3-1.2. No statistically significant trends were found for age at starting use, duration of use in years, or number of times used per day. OR of snuff dipping for distal stomach ca <u>intestinal</u> type Ex-user OR = 0.9 95% CI 0.5-1.6, Current user OR= 0.8, 95% CI 0.5-1.3, ever users 0.8, 95% CI 0.5-1.2). Again, no statistically significant dose-response relationships observed. OR of snuff dipping for distal stomach ca <u>diffuse</u> type Ex-users, OR 0.7, 95% CI 0.3-1.6, current user 0.6, 95% CI 0.3-1.2, ever users 0.7, 95% CI 0.4-1.2. No statistically significant dose-response relationships.	Controls were selected from the population register. Only 8 cases and 14 controls reported having ever chewed tobacco, and none of the females had ever used moist snuff. Therefore analysis of the effect of ST use was restricted to snuff use among males. Joint effect of smoking and snuff dipping analysed and presented for total gastric and cardia ca. 28 (3.1%) of the cases and 245 (16%) of the controls refused to participate. Their smoking and ST use habits may differ. Quality: A

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
72	McLaughlin 1995[145] Chewing tobacco and oral snuff	A multicentre case control study based in Sydney, Berlin, Heidelberg, Uppsala, Minnesota, & Denmark. The study was planned to explore tobacco and renal cell ca relation. Four of the 6 centres obtained the cases from the cancer registers. Controls were selected from the population. 1989-91	1723 renal cell cases (adenoma) and 2309 controls. 11 cases and 13 controls used ST	Cases obtained from cancer registries. ST use was not defined in terms of frequency. Results adjusted for age, sex, centre and BMI. Unclear how many ST users used only this tobacco product.	The OR of ST vs no tobacco use for renal cell ca was 1.3, (95% CI 0.6 to 3.1). No interaction observed between ST and cigarette smoking.	Very few cases or controls used ST. Unclear whether these are also exclusive ST users, or whether they smoke cigarettes too, and whether analyses were adjusted for cigarette smoking. Quality: F
73	Hansson 1994[66] Oral snuff	Histologically confirmed incident gastric cancer cases and population controls were selected from low gastric ca counties and 2 high gastric ca counties in Sweden, 1989-92.	338 gastric ca cases and 679 controls. No of ST users not given.	ST use not defined or described. Histologically confirmed incident gastric cancer cases. Adjusted for age, gender, SES, vegetable intake and other tobacco use.	There was no statistically significant association between gastric ca and snuff dipping (OR=0.7; 95% CI, 0.47 to 1.06 after adjustment in a multivariate model.	Population controls were used. Non-response rate was higher in controls. The number of snuff dipping cases and controls was not presented in this study. It was stated that the number of chewing tobacco users was too small to allow any reliable statistical analysis. Quality: F

Asian Studies

Case-control studies:

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
74	Phukan et al. 2001[69] Chewing of several different types of betel (red, green and fermented) with or without tobacco, also chewing tobacco alone (chardha)	Cancer of oesophagus presenting at Dr. Bhubaneswar Barooah Cancer Institute in Guwahati, Assam. Controls were matched on age and sex, and chosen from those accompanying patients. July 1997 – June 1998	502 cases, 1004 controls Tobacco chewers: 438 cases, 592 controls	Description of types of betel and tobacco very clear and detailed. Cancer of oesophagus, site not stated. Major confounders were considered (smoking, alcohol consumption) but unclear whether matching taken into account.	Highest risks for men chewing betel nut and tobacco when unfermented betel nut was used (OR= 7.1, 95% CI 3.5 to 6.7 (error in original paper)). Chewing 'Zarda' (finely cut, scented tobacco) and dried tobacco alone also has significantly raised risk. Clear trends in dose-response relationships observed for men and women, including frequency of use per day, duration of use in years, age at starting and spitting versus keeping in mouth. For example, the OR associated with chewing for over 20 years was 10.6 (95% CI 5.6 to 17.3) in men and 7.2 (95% CI 2.6 to 14.2) in women, compared with (OR=1.8 95% CI 0.09 to 7.1) and (OR=1.2 95% CI 0.07 to 5.2) for men and women who had chewed for under 10 years respectively	Inclusions and exclusions clearly defined. Evidence of dose-response relationships. Quality: A

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
75	Dikshit and Kanhere 2000[52] Tobacco quid chewing, no further details Same study as ID24	Bhopal Population-Based Cancer Registry, Bhopal, India 1986-1992	247 163 lung cases, 260 controls 52 tobacco quid chewers among lung cases, 108 controls	No clear definitions of ST use, but detailed trend information reported. Sites included clearly defined using ICD-O codes, histologically confirmed. Controls for age, sex, education, religion and cigarette smoking (but does not specify how variables were measured or adjusted for). Stated that risk estimates could not be adjusted for alcohol use.	No association between tobacco quid chewing and lung ca (OR= 0.7, 95% CI 0.4 to 1.2) compared with non-chewers.	Information on controls collected from a separate survey of 2500 males in Bhopal – based on a random sample of voter list of Bhopal cancer registry, 1989-1992. Response rates unclear – cases for which detailed information about smoking or chewing history was unavailable or cases registered from death certificates were excluded (unclear how many). Quality: A

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
76	Nandakumar et al 1996[70] Chewing tobacco	Patients with oesophageal cancer registered in Bangalore population based cancer registry, Kidwai Memorial Institute of Oncology. Controls patients who attended the same Institute during same time period, but proved not to have cancer. Randomly selected and matched on sex, age, area of residence, calendar time 1982-1985	343 cases, 686 controls 79 cases and 96 controls chewed tobacco	No clear definition, but some description of types of ST used and trend information. Outcome of interest, portion of oesophagus affected (upper, middle, or lower third), type of cancer all clearly stated. Most cases confirmed microscopically (78%). Many potential confounders were considered and controlled (including bidi and cigarette smoking, alcohol and non-tobacco chewing).	Chewing with or without tobacco was associated with an elevated risk of oesophageal cancer in both males (OR=2.1, 95% CI 1.2 to 3.8) and females (OR = 2.2, 95% CI 1.4 to 3.3). Most dose-response variables (duration in years and number of times chewed per day) did not show a trend with increased risk except for the period of time that the quid was retained in the mouth (OR = 3.9, 95% CI 1.9 to 7.9 for over 30 minutes, compared with (OR=1.3, 95% CI 0.8 to 2.1) for under 5 minutes. After adjusting for alcohol, (OR = 4.3 95% CI 1.6 to 11.6) in non-smokers (10 ca, 16 co). The risk was highest for the lower third of oesophagus (OR = 6.6, 95% CI 2.1 to 21.2), and not statistically significant for the other locations.	Information was collected by the registry for cases and controls. Possible response bias, only 62.5% of patients were interviewed for the study. In adjusted analyses, there was little difference between the risks associated with tobacco chewing (OR = 2.9, 95% CI 1.5 to 5.4), and chewing paan only (OR = 2.8, 95% CI 1.5 to 5.2). Use of snuff was not a significant factor for either males or females. Quality: A

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
77	Harish 1995[67] Chewing tobacco and oral snuff	Penile cancer cases diagnosed in Cancer Institute of Madras and age matched controls. Controls were selected among the partners of breast ca patients. Madras Cancer Inst., India 1960-1990.	503 penile ca cases 503 controls. 171 cases and 78 controls used chewing tobacco/ and 27 cases and 8 controls used snuff	Not clearly defined, but included chewing tobacco, areca nut, snuff use, and years of use. Dose response relation was studied between chewing tobacco and cancer. Controlled for age by matching, also smoking and phimosis.	OR of chewing tobacco for penile carcinoma was 3.11 (95% CI 2.21 to 4.37). A dose-response relationship was observed for less than ten years of chewing, OR was 1.76 (95% CI 0.95 to 3.28). For over ten years, OR was 3.62 (95% CI 2.48 to 5.27). After adjusting for smoking and phimosis: OR for Chewing tobacco was 4.08 (95% CI 2.73 to 6.12) and OR for snuff use 4.23 (95% 1.59 to 11.26).	The study was designed specifically to analyse the association between smoking, chewing tobacco, snuff use and penile ca. Quality: A
78	Notani 1993[146] Chewing tobacco	Not clear whether the cases are incident or prevalent. Two control groups (hospital and population). Maharasthra, India. 1986-90.	246 lung cases, 153 bladder cases and 212 controls Number of ST users not stated	ST use is not defined and validated. Cases histologically confirmed (98%). States that controls were similar to cases in 5-year age group, mother tongue, and socio-economic status. Adjusted for age and smoking.	No statistically significant relationship with lung or bladder cancers. OR of chewing tobacco use for lung ca (compared to population controls) =0.80 (95% CI 0.5 to 1.4) And for bladder ca=0.45 (95% CI 0.3 to 0.8)	This study was planned to evaluate the association between occupation and lung and bladder ca; ST use was not main focus. No. of ST users was not stated, only ORs presented. No information given about non-response in cases or controls. The study included only men. Quality: F

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
79	Sankaranarayanan et al. 1991[13] Chewing betel, defined in paper	Patients with oesophageal cancers at the Regional Cancer Centre Trivandrum, Kerala, India. For selection of controls see Sankaranarayanan et al. 1989[11] (ID 30) 1983-1984	267 cases 895 controls 67 cases, 181 controls chewed pan-tobacco, 7 cases and 7 controls inhaled nasal snuff	ST use defined in paper, and trend information available. Sites included not clearly stated, most (67%) confirmed histologically. Control of confounding good (duration of bidi smoking, daily frequency of bidi and cigarette smoking, alcohol consumption).	No significant effects associated with taking snuff or pan-tobacco chewing, and no dose-response effects when looking at duration of use in years or frequency per day. However, starting use after age 21 has much reduced risk compared with starting earlier (OR = 0.21), and significant risk found with occasional use (OR= 10.18 in males, 95% CI 3.6 to 28.74).	Absence of effect attributed to confounding with bidi smoking (though no effect also found in females, for whom the only prevalent tobacco habit was pan-tobacco chewing), or to habit of spitting out quid and its extracts rather than swallowing. Quality: A

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
80	Sankaranarayanan et al. 1990[50] Chewing betel, defined in paper	Patients with biopsy-proven carcinoma of larynx at the Regional Cancer Centre and Medical College Hospital, Trivandrum, Kerala, India. For selection of controls see Sankaranarayanan et al. 1989[11]. (ID 30) 1983-84	191 cases, 549 controls 50 cases, 181 controls chewed pan-tobacco, 6 cases and 7 controls inhaled nasal snuff	ST use defined in paper, and trend information available. Site included clearly defined (ICD-O 161), all biopsy-proven, SCC carcinoma Control of confounding good (age and religion, see ID 30).	No statistically significant association, e.g. OR for chewing 10+ pieces / day (OR = 0.73, 95% CI 0.36 to 1.46) compared with never users. However, risk is much lower for those who adopt habit after age 21, than for those who start chewing younger (OR = 0.14, 95% CI 0.07 to 0.24). High risks also observed for occasional users (OR= 13.74, 95% CI 4.92 to 38.34). Snuff use OR = 2.82 (95% CI 0.9 to 8.73).	Lack of effect attributed to confounding with bidi smoking, a stronger risk factor for cancer of larynx. Those who chewed were also more likely to smoke, but consumed fewer bidis than non-chewers. Quality: A

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
81	Simarak 1977[68] Pan	Hospital based oral-oropharynx, larynx-hypopharynx, lung cancer cases and hospital controls, Thailand. 1971-72.	88 oral-oropharynx, 96 larynx-hypopharynx, 115 lung cancer cases and 1113 controls. 66 of oral cancer cases, 65 of the larynx cases, 38 of the lung cases and 517 of the controls were betel chewers	For ST use the duration of consumption and frequency is not available. Definition of cases provided, histological confirmation was obtained for only half of the lung cancer cases. Main confounders were controlled for either by stratification or in a model.	Age and province adjusted OR Lung cancers: OR 0.60 (men), 0.73 (women) Age and province adjusted OR of betel chewing for larynx ca: OR= 2.71*** (just for men) Age, province, school attendance, agricultural employment, rural residence, yaamuan smoking, miang# chewing adjusted: OR= 2.36** *:p<0.05 **:p<0.01 ***:p<0.001 #:yaamuan smoking: a kind of cigar miang chewing: doesn't have tobacco	The aim of the study was to investigate the association between 3 cancer outcomes with smoking, chewing and drinking habits. The cases were selected from University hospital and the controls from radiology department, i.e. not from the same pop. Quality: A

All-cause mortality

Asian Studies
Prospective cohorts

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
82	Gupta 2000[72] Bidi, mishri, betel chewing	People over 35 yrs interviewed for tobacco habits and followed up for 5-6 years. Mumbai City centre (pop: 3,418,089), India, 1991-1994.	52,568 people included. Women: 64,414 person years (py) non tobacco users, 114,980 py ST users and 511 py of smokers Men: 27,236 py non tobacco users, 57,890 py ST users and 28,338 py smokers	ST users did not use other tobacco forms. Dose-response relationship was analysed for bidi, mishri and betel quid chewing. Mortality information obtained by active follow-up. Adjustments for age and smoking (by restriction).	**Among women,** RR ST use vs no tobacco= 1.35. **Among men,** RR ST use vs no tobacco= 1.22 **For women**: ***Mishri users:*** RR mishri vs no tobacco use = 1.24 ***Betel quid:*** RR betel vs no tobacco use = 1.19. RR betel frequency vs no tobacco use: 1-5 times a day: 1.10, 6 or more times a day: 1.49 **For men**: ***Mishri users:*** RR mishri vs no tobacco use = 1.06 RR mishri vs no tobacco use: 1-5 times a day: 1.08, 6 or more times a day: 1.13 ***Betel quid:*** RR betel vs no tobacco use = 1.11. RR betel frequency vs no tobacco use: 1-5 times a day: 1.05 6 or more times a day: 1.16	The study was designed to analyse all cause mortality and tobacco use. People over 35 yrs followed up for 5-6 years. Response rate of eligible individuals is 50% (low) & loss to follow-up 26%. 95% CI not given. Quality: A

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
83	Gupta 1984[71] Pan	People over 15 years interviewed for tobacco habits and followed up for 10 years. Ernakulam District, India. Interview date is not clear.	10,287 people over 15. 637 men and 2026 women used chewing tobacco. 1081 men and 27 of women had mixed habits.	Deaths ascertained through household interviews. Chewing tobacco was defined clearly whether current or lifetime. Dose response relation was not studied. Basic confounders age and sex were controlled either in multivariable analyses or stratification.	Age adjusted RR for all cause mortality (reference group 'no tobacco habit'): Men Women Chewing habit = 1.2 1.3* Mixed habit = 1.4* 1.7 Confidence limits are not provided *: Statistically significant	People over 15 years interviewed for tobacco habits and followed up for 10 years. No information about loss to follow-up. The study has large numbers of tobacco chewers and participants with several tobacco use habits. Quality: A

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
84	Gupta 1980[56] Tobacco chewing	Oral leukoplakia cases and sex, age, tobacco habit matched healthy controls recruited (1968-71) and followed up. Maharasthra District, India.	101,761. 1860 of leukoplakia 8526 of controls used CT	Tobacco chewing, described in paper. All-cause mortality follow-up for 8 years. Controls for age and sex by matching.	Among the controls: Age adjusted annual death rates Among smokers= 47/1000 Among chewers=29/1000 RR smk v chewers=1.6 *1.6 Among the leukoplakia cases: Age adjusted annual death rates Among smokers= 75/1000 Among chewers=39/1000 RR smokers v chewers =2.1 *1.9 *: Age adjusted	Oral leukoplakia cases and sex, age, tobacco habit matched healthy controls selected. It is not clear how many of them were followed up (only person years presented). All cause mortality compared between smokers and tobacco chewers within two groups. Females excluded because they rarely practised smoking. The reference group for chewing tobacco is smokers rather than non-tobacco users. No confidence limits provided for RRs. Quality: A

Cardiovascular Disease

Scandinavian Studies
Prospective cohort

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
85	Bolinder 1994[64] Smokeless tobacco users	Swedish construction workers who had health check-ups in 1971-74	135,036 male workers. Women (less than 0.05%) were excluded. 1672 of those aged 35-54 years and 1734 of 55-65 years olds were ST users	ST use was defined as present ST usage reducing misclassification. Nonusers in this study had never used any tobacco. Outcomes clearly defined with ICD codes. Most of CVD risk factors adjusted for ST-outcome association except cholesterol and alcohol use. Also age and regional origin adjusted.	Age group 35-54 RR of ST use for IHD: RR=2.0, (95% CI 1.49 to 2.9) Stroke: RR=1.9 (95% CI 0.6 to 5.7). All CVD: RR=2.1 (95% CI 1.5 to 2.9). All cancer: RR=1.2 (95% CI 0.8 to 1.9). All cause RR=1.9 (95% CI 1.6 to 2.4). Age group 55-65 adjusted RR of ST use for IHD: RR=1.2 (95% CI 1.0 to 1.5). Stroke: RR=1.2 (95% CI 0.7 to 1.8) All CVD: RR=1.1 (95% CI 1.0 to 1.4). All cancer: RR=1.0 (95% CI 0.8 to 1.3). All cause RR=1.2 (95% CI 1.0 to1.3) *Reference category is male never users of tobacco	25% of the workers did not come for checkups, the reason is not clear. Statistical power of the study is high (in total 6297 users of ST were followed up and 172 IHD deaths occurred in this group). Healthy worker effect may play a role in ST CVD mortality association. When potential confounding due to age, area of domicile, BMI, blood pressure, diabetes and history of heart symptoms or blood pressure medication at the time of entering the study was analysed according to Mantel Haenzel procedure, the RR of death from CVD remained essentially unchanged. Quality: A

Case-Control Studies

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
86	Huhtasaari 1992[73] Oral snuff	First MI cases and population controls from Northern Sweden, 1989-1991.	585 cases (first MI) and 589 controls. 59 cases and 87 controls were regular snuff dippers. 32 cases and 31 controls were concomitant smokers and snuff users. Confounders adjusted for: smoking, low level of education, and age	ST was defined clearly (at least once daily), and dose response relation was analysed. Outcomes clearly defined (MONICA protocol) Blood pressure, cholesterol and diabetes prevalence were similar in cases and controls so they were not included in the model.	Age adj. OR of snuff dipping v no tobacco for MI: 35-54 yrs: OR=0.96 (95% CI 0.56 to 1.67) 55-64 yrs: OR=1.24 (95% CI 0.67 to 2.30) All ages: OR=0.89 (95% 0.62 to 1.29) Snuff dippers had no increased risk of MI compared to non-tobacco users. Snuff <=2 cans weekly OR= 0.63 (95% CI 0.41 to 0.98) >3 more cans weekly OR=0.93 (95% CI 0.61 to 1.41) In a logistic regression model for MI, with smoking, snuff dipping, low level of education and age as predictors, snuff dipping was not significant.	The study was planned within Northern Sweden MONICA project. Cases were identified according to MONICA protocol. Controls were selected from population and they were only group matched. Response rate in controls was 81.6%. A telephone survey conducted to check non-participants smoking habits found them to be similar to those of participants. Quality: A

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
87	Huhtasaari 1999[74] Oral snuff From same study as Huhtasaari 1992 (see ID85).	First MI cases and population controls from Northern Sweden, 1991-1993.	687 first MI men cases and 687 matched controls from same county. The cases were MONICA Sweden project. 59 cases and 90 controls were current snuff users and –non current smokers; 20 cases and 11 controls were both smokers and snuff users. 11 of the cases and 13 of the controls were former snuff users but non-smokers.	Detailed information about ST (present use, previous use, amount, type of preparation, age of onset and whether or not snuffing was associated with quitting smoking) obtained. Median consumption of snuff was 2 boxes per week in both cases and controls. Outcomes clearly defined (MONICA protocol) Confounders adjusted for include hypertension, low level of education, not being married or co-habitant, diabetes, known high cholesterol and heredity.	OR for different combinations of snuff user for MI: Current snuff user-non smoker: 0.96 (95% CI 0.65 to 1.41) Current smoker, no current snuff use: 3.65 (2.67-4.99) Current snuff user and smoker: 2.66 (95% CI 1.24 to 5.71) Former snuff user, never smoked: 1.23 (95% CI 0.54 to 2.82) Former snuff user former smoker: 0.99 (95% CI 0.62 to 1.59) In conditional regression model: adjusted OR of snuff use for all MI: 0.58 (95% CI 0.35 to 0.94). Adjusted OR of snuff use for fatal MI: 1.50 (95% CI 0.45 to 5.03)	Of the original set of case-controls 21.8% were excluded because of missing smoking information. This was common amongst the fatal case pairs. To check the validity of ST information obtained from spouses of fatal MI cases, spouses of surviving cases were interviewed by telephone 2 months later. The agreement was high for snuff use (98%). Information on duration of use was not high quality. Median age of starting snuff was 31.5 years explained by the fact that many had started snuff in conjunction with quitting smoking. Proper statistical analyses were carried out. Quality: A

Cross Sectional Study

ID	Study and type of ST	Subjects, Setting and years of recruitment	Sample size and No of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
88	Bolinder 1992[38] Oral snuff From same study as Bolinder 1994 see (ID 84)	16-65 years old Swedish construction workers, 1971-1974	97,586 construction workers who had voluntary health checkups. 5014 of the participants were ST users who had never been regular smokers.	ST users were daily users. Confounding: persons who had mixed tobacco habits were excluded from the analyses to increase validity, also adjusted for age	Reason for disability pension among 46-55 year olds: OR of ST use vs nonusers for CVD diagnosis=1.6 (95% CI 0.7 to 3.5) for Hypertension: 3.0 (95% CI 1.9 to 4.9) Among 56-65 year olds: OR of ST use vs nonusers for CVD diagnosis 1.5 (95% CI 1.1 to 1.9) Age adjusted RR of 'frequent sick leave' (1 day or more for 4 times or more per year) for all kind of diagnosis was 1.1 (95% CI 1.0 to 1.2) for ST users compared to non-users. Age adjusted RR 'Longer sick leave' (>=30 days in a year) was 1.2 (95% CI 1.1 to 1.2) for ST users compared to non-users.	The aim of the study was to evaluate ST effect on blood pressure and other health hazards. In this cross sectional study, reference group was those who had never used any tobacco form. The outcomes were questionnaire reported symptoms, physical examination and disability pension due to cardiovascular and musculoskeletal diagnoses. Healthy worker effect highly possible. Quality: A

Dental Diseases

US Cross-sectional studies

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
89	Tomar and Winn, 1999[76] Chewing tobacco and oral snuff, users defined as those who said they used substances at time of interview	Dentate adults (>18) who had completed clinical data on dental caries and self-reported data on tobacco use as part of NHANES III[4] 1988 – 1994	14,807 Approx. 444 ST users, of whom 252 chewed tobacco, 180 used snuff	ST use clearly defined. Outcomes clearly described – trained dental examiners scored all teeth and tooth surfaces using specific criteria for coronal and root-surface caries. Some confounders considered (age, ethnicity, education, and visited dentist in last year), but other important confounders (such as diet, oral hygiene, brand of chewing tobacco) not included.	After adjusting for age and race, men who used only chewing tobacco had slightly higher mean number of teeth than those who used snuff or smoked cigarettes. However, mean DFT, DFS and RDFS[5] significantly higher for men using chewing tobacco. Significant dose-response relationships with frequency of use per week and years of use and RDFS e.g. (OR = 1.26, 95% CI 0.56 to 2.80) for 1-10 years of use, (OR=2.55, 95% CI 0.93 to 7.04) for 36 or more years of use. OR less than 1 package per week (OR = 0.97, 95% CI 0.43 to 2.17), 5 or more packages per week (OR= 4.35, 95% CI 1.72 to 11.04). Snuff users did not have significantly raised RDFS. Those who reported placing chewing tobacco on right side of mouth tended to have slightly higher mean number and %RDFS on right posterior teeth than on left posterior teeth and vice versa, but this was not statistically significant.	Good study. Higher risk for chewing tobacco compared with snuff attributed to the addition of sugar to many brands of chewing tobacco. Quality: A

[4] NHANES III – a multipurpose health survey conducted in the US

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
90	Robertson et al 1990[147] Snuff and chewing tobacco, defined as use in past month	Baseball players and coaches, Arizona, US 1988	1094 493 never users, 138 ex-users, 40 used within past month, 423 used within past week	ST use clearly defined, and Self-reported use of ST was validated biochemically. Definitions of outcomes of interest described in detail (entire dentition, measurements on a subset of 12 teeth, presence of caries, restorations, stain, plaque index, gingival index, pocket depth, attachment loss, recession. Players asked not to discuss tobacco use with examiners and rinsed mouth before exam to ensure no traces of ST remained. 12 examiners calibrated with high agreement (average kappa never less than 0.75). Confounders not considered.	Use of ST was not necessarily associated with the most severe forms of periodontal disease, but sites adjacent to mucosal lesions in ST users showed significantly greater recession and attachment loss than in sites not adjacent to lesions in users or comparable sites in non-users.	About 85% of players agreed to participate. Quality: F

[5] DFT = number of decayed, missing or filled teeth. DFS = decayed, missing or filled coronal tooth surfaces. RDFS = number of decayed or filled root surfaces. RDS = number of decayed root surfaces

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
91	Ernster et al. 1990[78] Chewing tobacco and snuff, 'non-users', 'former-users' and 'current users' clearly defined	Members of 7 major league professionals, baseball teams, and their associated minor league teams, players and coaching staff in greater Phoenix and Tucson, Arizona, US 1988	1109 463 current users, 423 within past week, 40 within past month, 138 former users	Use of ST clearly defined and validated biochemically (low serum cotinine level and normal serum thiocyanate levels were considered biochemical evidence of non-use of tobacco). Dental outcomes clearly defined (e.g. recession is "displacement of gingival margin of at least 1mm apical to the cementoenamel junction"), and clinical examination standardized and conducted by specially trained dentists. Many potential confounders were considered including age, race, cigarette smoking, alcohol consumption, and dental hygiene practices.	No significant differences in dental caries, gingival bleeding, pocket depth of 4mm or more, or recession in at least one site of 12 teeth examined between ST users and non-users. Attachment loss of 4mm or more was more common in snuff users both with (32.0%) and without (33.6%) oral lesions than in nonusers (27.4%), $p<0.05$. No significant differences in percentage of facial surfaces of mandibular incisor teeth with visible plaque or gingival bleeding. Percentage of facial sites with gingival recession was greater in teeth adjacent to oral leukoplakias in both snuff and chewing users, and also in snuff users without leukoplakia (e.g. 13% for snuff users with oral leukoplakia at adjacent teeth, versus 4.4% for nonusers).	Agreement good, with average kappa never lower than 0.75. Participation rates were high (85% of team members). Examination carried out on a subset of 12 teeth. Quality: A

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
92	Offenbacher and Weathers, 1985[79] Chewing tobacco and oral snuff	Adolescent males (mean age 13.8, range 10-17) in grammar and high schools in greater metropolitan region of Atlanta, US Years not stated	565 26 snuff only, 21 chewing only, 28 snuff and chewing	Information on frequency and duration of use and brand preference was collected, but not reported in the results in relation to risk. Outcomes include gingivitis, gingival recession, mucosal pathology, caries and DMF index, but these are not clearly defined. Potential confounders such as diet not considered	Overall, positive associations with ST use and gingival recession and mucosal pathology, but not with gingivitis (OR gingival recession 9.1, 95% CI 5.2 to 16.1), OR mucosal pathology (6.0, 95% CI 2.9 to 12.4), OR gingivitis = 0.8 (95% CI 0.4 to 1.4). In students free of gingivitis, ST was not associated with changes in prevalence of gingival recession, mucosal pathology, or mean DMF score (e.g. OR gingival recession in sub-population with gingivitis = 20.7, OR with non gingivitis = 1.13). In only 3 cases was gingival recession located in direct juxtaposition to preferred placement site. DMF score for 52 ST users with gingivitis was 4.35 (+-0.44) significantly higher than in non-users without gingivitis (2.69+-0.26), $p<0.001$. Attributable risk of gingival recession for ST use is 30%	Prevalence of cigarette smoking was very low (n=8, 1.4%). Authors suggest that ST users may be more vigorous toothbrushers than users which causes gingival recession. Research funded by Smokeless Tobacco Research Council. Quality: A

Scandinavia

Cross-sectional studies

ID	Study Type of ST	Subjects, Setting and Years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	comments
93	Johansson et al 1994[148] Snuff – defined as daily use	Participants in MONICA surveys of northern Sweden – randomly selected 2000 individuals aged 25-64 Two surveys 1986 and 1990	3308 (1625 in 1986, 1583 in 1990) No. of ST users not stated	Snuff use is not main focus of study, and limited information available – no dose-response relationship considered. Dental status outcome (dentate or edentulous) clearly defined. Unclear whether confounders adjusted for in this analysis.	Regular use of snuff did not differ between dentate and edentulous men and women	Overall response rates to MONICA survey high (81.3%) in 1986 and 79.2% in 1990. Also considered CHD risk factors in relation to ST use. Quality: F
94	Hirsch et al 1991[80] Snuff	Patients aged 14-19 atending yearly dental check-ups at 9 public dental clinics in Gothenburg 1986	2145 197 used snuff	ST use clearly defined. Outcomes clearly defined. Controls for cigarette smoking, but not other potential confounders such as diet, oral hygiene or flouride exposure.	Indices of DMFT[6], DFSp[7] and DIP[8] were all higher in snuff-users compared with non-users of tobacco. Multiple regression showed positive correlation between DMFT and years of snuff use ($p<0.05$).	Very high response rate (99%). Quality: A

[6] DMFT – Decayed missing and filled teeth
[7] DFSp – Decayed filled proximal surfaces
[8] Dip – Initially decayed proximal surfaces i.e. number of proximal surfaces with caries lesions within the enamel

ID	Study Type of ST	Subjects, Setting and Years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	comments
95	Ekfeldt et al 1990[149] Snuff	Jonköping, Sweden. Dentate individuals who had reached age of 20, 30, 40, 50, 60, 70 or 80 in 1983	585 No. of ST users not stated	ST use is not described in detail and no dose-response information is available. Outcome was degree of incisal / occlusal wear, scored from 0 (no wear or negligible wear of enamel to 3 (wear of the dentin up to more than one-third of the crown height; excessive wear of tooth restorative material or dental materials in crown and bridgework; more than one-third of the crown height). Many potential confounders were considered including age, sex, meals, meals containing juice, syrup or apple, bruxism, dry mouth, salivary secretion and buffer capacity (pH), smokers, trauma to jaw, no. of occluding teeth.	Of variables included in linear regression model, beta coefficient for snuff use (yes/no) was –0.487 (i.e. snuff use increased score by 0.487) and including snuff use in the model explained a statistically significant additional 12% of the variability	Main focus of study is to validate a tooth wear index, About 30% of sample excluded due to incomplete data or no incisal or occlusive wear. Significant predictors were number of teeth, sex, bruxism, age, snuff use, and buffer capacity. Quality: F

Asian studies

Cross-sectional

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
96	Doifode, 2000[150] Paan tobacco, not described	2 randomly selected areas, Naigpur, India Date of study unclear	5061 1023 chewed tobacco,	No definition of ST use or information on possible dose-response relationships. Outcomes not clearly defined. Potential confounders not controlled for.	Tobacco chewing significantly associated with dental caries (OR 1.32, 95% CI 1.15 to 1.52), periodontal diseases (OR = 1.67, 95% CI 1.45 to 1.92), dento-facial anomaly (malocclusion, overcrowding and spacing – (OR= 0.73 95% CI 0.61 to 0.86), opacities and enamel disorders (OR= 3.55, 95% CI 3.03 to 4.16), precancerous lesions OR 4.20, 95% CI 2.87 to 6.16) and carcinoma (OR= 15.85, 95% CI 1.69 to 372.66).	Large sample size. High response rate in area (97.5%). Crude OR calculated in EPI-INFO. High risk for carcinoma based on only 1 case. Quality: F

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
97	Moller et al. 1977[151] Paan tobacco	Survey of adults over 15 in 2 villages in Central Java and Bali 1973	982 209 chewed betel, 591 non-chewers (data presumably missing for other 182 in study)	ST use described, but no information on possible dose-response relationships, Outcomes clearly defined (dental caries, DMFS index, WHO classification). No control of possible confounders	Strong negative correlation between prevalence of dental caries and betel chewing (i.e. chewing is protective). Statistically significant in almost all age groups in both regions. Few men chewed tobacco (only 32).	Presumably high levels of non-response among men who were working in fields far from villages. Tobacco mostly not included in betel quid, used only after quid has been chewed for some minutes or expectorated, and used to clean buccal surfaces of the anterior teeth. Quality: F

Adverse Outcomes of Pregnancy

Asian Studies

Case-control study

ID	Study Type of ST	Subjects, Setting and years of recruitment	Sample size No. of ST users	Measurement of exposure, outcomes and confounders	Findings or Results	Comments
98	Krishna, 1978[82] Locally grown and cured tobacco, kept in mouth for around 8-10 hours per day. Wads weigh 6-10 grammes and are renewed hourly.	Pune Hospital, Maharastra, Delhi, India. June 1971 – May 1972	220 tobacco chewers, 1168 non-chewers	Clear description of tobacco chewing use. Outcomes clearly described. Confounders were not considered beyond looking for differences among several strata.	Stillbirth weight increased among chewers, and sex ratios showed a deficit of boy babies among chewers (98 boys born to 220 chewers; ratio of 80 per 100 compared with 609 to 1168 non-chewers, 108.5 per 100). Birthweight stratified by maternal weight, social class and gestation was approximately 100-200g less among chewers in each strata. This is partly explained by the shorter gestation among chewers.	Large sample size and few women were cigarette smokers (5 and these were excluded). Author argues that these effects are similar to, but greater than those associated with tobacco smoking. The magnitude of the effects is attributed to the frequent use (10 hours per day) of chewing tobacco in this population, which may provide continuously high nicotine levels compared with the more intermittent effects of smoking. Quality: A

Additional References for Appendices

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