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APPENDIX 1

ORAL CANCER AND SMOKELESS TOBACCO

A REVIEW OF THE EPIDEMIOLOGICAL EVIDENCE

RELATING TO WESTERN POPULATIONS

Author : P N Lee

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EXECUTIVE SUMMARY

This review was carried out to investigate in detail the epidemiological evidence relating oral and pharyngeal cancer to smokeless tobacco use by Western populations. Evidence relating to India and other parts of Central and South-Eastern Asia, where smokeless tobacco is often used in conjunction with other products, such as betel nut, areca nut, ash or slaked lime, is not considered.

27 case-control and 5 prospective studies were identified that provided relevant information. 23 of the studies were conducted in the USA, with 5 being conducted in Sweden and one each in Puerto Rico, England, Norway and Brazil. Limitations of many of the studies considered, or of the papers describing them, include the small number of cancer cases who used smokeless tobacco, failure to present results by site of cancer, failure to present results separately for chewing tobacco and for snuff, collection of data from unreliable sources, failure to present results separately for smokers and nonsmokers, failure to take potential confounding variables (in particular smoking and alcohol consumption) into account and failure to conduct dose-response analyses. A few studies had gross weaknesses of design.

In spite of the limitations and weaknesses of the studies a number of conclusions can be drawn from the available data.

The first and clearest conclusion is that Swedish oral snuff carries little or no increased risk of oral/pharyngeal cancer. This conclusion derives mainly from two high quality studies published in 1998 which reported relative risks (for head and neck cancer and for oral cavity cancer respectively) that were close to unity after adjustment for relevant confounders, and partly from a smaller study of lip cancer which also found no association with snuff use. A combined relative risk estimate of 0.97 (95% confidence interval [CI] 0.72-1.30) can be derived from these 3 studies, findings which seem consistent with the results of a poorly reported study conducted over 40 years ago, and with results of a further prospective study for which detailed data are not available.

The results from 11 studies, mainly conducted in the USA, provide no convincing evidence of an effect of chewing tobacco on the risk of oral/pharyngeal cancer. Data on risk by detailed site of cancer within the mouth, on risk in nonsmokers and on dose-response are limited. However, the consistent lack of association of chewing tobacco with oral/pharyngeal cancer seen in studies published since 1969, which provide a combined relative risk estimate of 1.07 (95% CI 0.92-1.24), argues against earlier reports (in 1920, 1957 and 1962) of a significant association of chewing tobacco with, respectively, lip cancer, oral/pharyngeal cancer and mouth/pharynx/larynx cancer.

The evidence relating to snuff use in the USA shows enormous variability between studies. Significant relative risks of oral/pharyngeal cancer related to snuff use of 2.42, 2.67, 3.40, 4.22, 4.81 and 14.6 have been reported in six studies and a further study, of dubious design, reported a relative risk as high as 540. In contrast three other studies have reported non-significant relative risks of 0.42, 0.62 and 0.80, all with an upper 95% confidence limit below 2. Three of the studies showing a positive association reported large relative risks for cancer of the gum and buccal mucosa, where the snuff is typically held, but a much smaller increase in risk for cancers of other sites. Limited evidence suggests that risk estimates are higher in women than men and in never than ever smokers and increase with duration of snuff use. Although the reason for the between-study heterogeneity is unclear, the overall data show a clear relationship of snuff use in the USA to risk of cancer of the gum and buccal mucosa. A possible weaker relationship to risk of cancer of the pharynx or other sites in the mouth has not been so clearly demonstrated.

A number of studies, mainly in the USA, have reported results relating oral/pharyngeal cancer risk to the unspecified use of smokeless tobacco. Relative risks are again heterogeneous, though less so than for snuff, the overall data giving a combined (random-effects) relative risk estimate of 1.93 (95% CI 1.41-2.64; $p<0.001$). The evidence is inconsistent regarding the cancer site showing the strongest relationship. Limited data suggest a higher relative risk in nonsmokers than in smokers, but provide no clear evidence of a dose-response relationship. The data for unspecified smokeless

tobacco use, which take little account of potential confounding variables, taken on their own, do not provide completely convincing evidence of a true effect. However, snuff is part of unspecified smokeless tobacco use and it is reasonable to conclude that the observed increase is, at least in part, a real one.

In summary, oral/pharyngeal cancer risk is increased by smokeless tobacco use in the USA. The increase is related mainly, if not wholly, to the use of oral snuff rather than to chewing tobacco, and predominantly arises where the snuff is held, typically, in the gingival buccal area. Limited evidence suggests that the risk is greater in never smokers and in women. Oral snuff, as used in Sweden, does not appear to increase the risk of oral/pharyngeal cancer.

Results from some relevant random-effects meta-analyses are given below*

Exposure/Studies considered	Studies	Estimates	Relative risk (95% CI)
Chewing tobacco			
All studies	11	14	1.29(0.99-1.68)
Studies published since 1969	8	11	1.07(0.92-1.24)
Studies of nonsmokers	3	4	1.68(1.00-2.80)
All studies except two with major weaknesses	9	12	1.27(0.96-1.69)
Snuff			
All studies	14	14	2.31(1.23-4.32)
All studies except two with major weaknesses	12	12	1.80(1.00-3.27)
- conducted in Sweden	3	3	0.97(0.72-1.30)
- conducted in USA	9	9	2.26(1.08-4.75)
Smokeless tobacco use			
All studies	11	17	1.93(1.41-2.64)
All studies except two with outlying results	9	13	1.59(1.30-1.95)

*See sections 4.2-4.4 for fuller details of these meta-analyses

INDEX

* Bracketed dates are years of publication

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1. Introduction

1.1 Usage of smokeless tobacco

Smokeless tobacco is mainly used orally, and nasal use has become rare.[1] The two major products used in North America and Europe are chewing tobacco and snuff. There are several types of chewing tobacco and snuff, differing in their formulation and how the tobacco is treated.

Chewing usually involves placing a plug of tobacco in the gingival buccal area, where it is held or chewed. Many users chew tobacco for many hours in a day.

Snuff is usually described as moist or dry.[1] Moist snuff is mainly used in the USA and Scandinavia. In Sweden it is generally placed under the upper lip, while in Denmark the lower lip is preferred, and in the USA it is generally kept in the gingival buccal area.[2] Dry snuff is placed in the oral cavity or administered through the nasal passage.

In the United States, smokeless tobacco has formed an important part of total tobacco consumption for many years. Available data[3] show that chewing tobacco and snuff represented 11.2% of all tobacco products by weight in 1950, 6.5% in 1965, 9.6% in 1980 and 12.1% in 1995. For many years sales of chewing tobacco were two or three times that of snuff, but since the early 1980s sales of snuff have risen sharply so that, by 1995, sales of chewing tobacco and snuff were about equal[3] (see table below). However it should be noted that "there has been a reclassification of products within the two major categories [of smokeless tobacco], and some types of fine-cut smokeless tobacco that were classified as 'chewing tobacco' prior to 1981 are now categorized as 'moist/fine-cut snuff'".[1]

Annual sales in tonnes	1920	1950	1960	1970	1975	1980	1985	1990	1995
Chewing tobacco	NA	38960	28940	30930	36560	48040	38560	32070	28210
Snuff	16370	18140	15740	12110	11430	10840	22040	23270	26940
All tobacco	298640	511990	588190	612290	634653	612037	569865	494054	454542

In the great majority of the other 30 economically developed countries considered by Forey et al.[3] smokeless tobacco forms only an unimportant part of the tobacco market. The most notable exception is Sweden where, though sales of chewing tobacco are negligible, snuff has always formed a large proportion of total sales of tobacco (70% in 1920, 31% in 1950, 19% in 1965, 29% in 1980 and 45% in 1995). As in the USA, the use of snuff has increased sharply in recent decades. In Canada, Iceland and Norway smokeless tobacco forms a few percent of the market, but in the other economically developed countries sales (if any) are very low.

Smokeless tobacco is also widely used in parts of Central and South-East Asia.[1] Tobacco may be used alone or in combination with other products, such as betel nut quid, ash, slaked lime, areca nut and even snail shells. In India there are various forms, called khaini, mishri, zarda and kiwan, in which the tobacco is prepared in different ways. Nass is common in Central Asia, with prevalence rates of up to 20% in some countries. Nass is usually made with local tobacco, ash and cotton or sesame oil, but the composition varies regionally, as in India.[2]

More details of variations over time and country in the extent of tobacco chewing and snuff taking, and of the various types of chew used and snuff taken can be found in IARC Monograph 37 on tobacco habits other than smoking.[1]

1.2 Oral and pharyngeal cancer

The ninth revision of the International Classification of Diseases (ICD9), based on recommendations by a WHO committee in 1975,[4] contains a group of diseases entitled "malignant neoplasm of lip, oral cavity and pharynx" consisting of codes 140-149. The codes represent the following individual neoplasms:

140	Lip (excluding skin of lip)
141	Tongue
142	Major salivary glands
143	Gum (includes gingiva, alveolar mucosa)
144	Floor of mouth
145	Other and unspecified parts of mouth (including cheek mucosa, vestibule of mouth, hard and soft palate, uvula and retromolar area)
146	Oropharynx
147	Nasopharynx
148	Hypopharynx
149	Other and ill-defined sites within the lip, oral cavity or pharynx

Similar classifications have been used in ICD7,[5] ICD8[6] and ICD10.[7]

Oral and pharyngeal cancers are primarily squamous cell (epidermoid) carcinomas, usually well differentiated. Leukoplakia, erythroplasia, lichen planus and submucous fibrosis, each entailing altered tissue morphology, are considered to be precursor conditions.[8]

The American Cancer Society estimated recently that about 28,900 new cases (18,900 in men and 10,000 in women) of oral cavity and pharyngeal cancer will be diagnosed in the United States during 2002, with an estimated 7,400 people (4,900 men and 2,500 women) expected to die from oral cavity and oropharynx cancer in 2002. The incidence rate and death rate have both been declining for 20 years or more.[9]

The incidence of oral cancer differs markedly in different countries. Compared with the USA, it is much more common in France, Hungary and India, for example, and is less common in Japan and Mexico. The strong relationship of oral cancer to tobacco smoking and alcohol consumption, particularly in combination, has been described repeatedly.[9]

1.3 Previous major reviews of the epidemiological evidence relating oral cancer to smokeless tobacco use

Studies relating to the possible role of smokeless tobacco in oral cancer have been conducted for many years, going back (at least) to 1920 in the USA[10] and 1933 in India.[11]

In 1985, the International Agency of Research on Cancer (IARC) published a monograph,[1] number 37 in their series evaluating the carcinogenic risk of chemicals to humans, which contained a section on tobacco habits other than smoking. This monograph found that there was "**sufficient evidence** that oral use of snuffs of the types commonly used in North America and western Europe is carcinogenic to humans," that there was "**limited evidence** that chewing tobacco of the types commonly used in these areas is carcinogenic" and that there was "**inadequate evidence** that nasal use of snuff is carcinogenic to humans."

Evidence considered by the IARC[1] included studies of experimental animals, which were regarded as providing "**inadequate evidence** to evaluate the carcinogenicity of chewing tobacco [or] snuff," epidemiological case-control and cohort study data (which will be considered in detail in this report), and also reports of case series of oral cancer patients. For chewing tobacco they concluded that "Reports of series of oral-cancer patients indicate that a high proportion were tobacco chewers and that the cancer often developed at the site at which the quid was placed habitually. However, data on chewing tobacco often come only from medical records; coexistent smoking habits often were not mentioned." For oral snuff they concluded that "Reports of case series indicated that a high proportion of oral-cancer patients took snuff orally, and that the cancer frequently developed at the site of snuff application." They also noted that three case series that did not distinguish snuff from chewing tobacco confirmed "the high relative frequency of smokeless-tobacco use in oral-cancer patients."

The following year an Advisory Committee to the US Surgeon-General published a report on the health consequences of using smokeless tobacco.[12]

In relation to the epidemiological evidence on cancer and smokeless tobacco (essentially that considered by IARC the year before), they concluded:

"1. The scientific evidence is strong that the use of smokeless tobacco can cause cancer in humans. The association between smokeless tobacco use and cancer is strongest for cancers of the oral cavity.

2. Oral cancer has been shown to occur several times more frequently among snuff dippers than among nontobacco users, and the excess risk of cancers of the cheek and gum may reach nearly fiftyfold among long-term snuff users.

3. Some investigations suggest that the use of chewing tobacco also may increase the risk of oral cancer.

4. Evidence for an association between smokeless tobacco use and cancers outside the oral cavity in humans is sparse. Some investigations suggest that smokeless tobacco users may face increased risks of tumors of the upper aerodigestive tract, but results are currently inconclusive."

A more recent literature review, with meta-analysis, was reported in 1995 by Gross et al.[13] Their review concluded that "the studies in southeast Asia suggest a strong relationship between the risk of oral cancer and the use of chewing tobacco," although they felt that "it is still unclear whether it is the tobacco or the substance added [that] plays the major role." Studies in Europe and Latin America were regarded as containing "insufficient cases to demonstrate an increased risk of oral cancer" due to the use of smokeless tobacco. For the USA, a meta-analysis was carried out based on estimates from 12 studies of the relative risk of oral cancer associated with the use of smokeless tobacco. Although, in three of the largest studies considered, risk estimates were close to 1 (0.99, 1.02 and 1.04) all the other estimates exceeded 1.70, with six being statistically significant (at $p<0.05$). An overall estimate, based on random-effects meta-analysis was calculated as 1.74 (95% confidence interval [CI] 1.32-2.31). Gross et al.[13] referred to this relative risk as representing a weak association and subject to "the biases and confounders that tend to perplex observational studies," pointing also to "the possible existence of study and publication bias."

Limitations of that review include:

(1) failure to try to separate out possible effects of smokeless tobacco on smokers and nonsmokers,

(2) failure to investigate effects of type of oral and pharyngeal cancer, and

(3) failure to separate out possible effects of chewing tobacco and snuff.

The next year, 1996, Pershagen[2] published a review on smokeless tobacco. He noted that "short term tests of genotoxicity provide information of some relevance for the cancer risk assessment. Various extracts of chewing tobacco can induce mutations, micronuclei, sister chromatid exchange and cell transformation" and that "extracts of moist oral snuff can also produce mutations, sister chromatid exchange and chromosomal aberrations." He also noted that carcinogenicity tests in experimental animals of various types of smokeless tobacco administered by different routes have in general "failed to demonstrate a significantly increased tumour production," though he pointed out, as other reviews before him,[1] that tobacco specific nitrosamines present in smokeless tobacco "are potent carcinogens in animal tests" though typically producing upper digestive tract and nasal cavity tumours, and not oral cancer, when administered orally.

He noted that though oral leukoplasia, sometimes referred to as "snuff dipper's lesion," is a "common finding in snuff users," it only "in rare instances develop[s] into a carcinoma" and "is normally reversible following cessation of exposure." He also referred to the "large number of case reports [that] have described oral carcinomas in smokeless tobacco users, sometimes occurring at anatomic locations where the tobacco is routinely placed."

He noted that "relatively few epidemiologic studies of high quality" have investigated the relationship of smokeless tobacco use to oral cancer. For chewing tobacco he regarded the case-control studies as having provided "no consistent evidence of an increased risk of oral cancer" though "methodological limitations in the studies make it difficult to interpret the findings." For oral snuff use he noted that cohort studies provided

"inconclusive evidence" on a relationship with oral cancer, although the studies were noted to have "limited statistical power." Six case-control studies were noted to be available from Sweden and the USA on oral snuff use and oral cancer. Though all the studies did not show an effect, three of the USA studies provided evidence of an association with high relative risks which Pershagen considered made confounding by smoking or alcohol an "unlikely" explanation for the findings. He regarded the most conclusive study as that by Winn et al.[14] which "showed a relative risk of 4.2 (95% confidence interval = 2.6-6.7) for oral and pharyngeal cancer in nonsmoking women from south-eastern US who used oral snuff, and a strong trend with duration of exposure for cancer of the gum and buccal mucosa."

In 1998, Nilsson carried out a review[15] of the risks associated with snuff dipping. He commented that the presence of highly carcinogenic tobacco-specific nitrosamines in snuff has been "a matter of serious concern." Noting that "the levels of TSNA in such products may differ by orders of magnitude depending on origin and manner of processing," he considered that the "mere presence of such agents at low levels ... hardly constitute[s] a meaningful prerequisite for classifying all types of snuff as human carcinogens." He noted "a wide discrepancy" between the estimated cancer risk associated with snuff dipping derived on the one hand from previous studies conducted in the United States and on the other from recent "extensive" Swedish epidemiological studies. Although about "20% of all grown-up Swedish males use moist snuff, it has not been possible to detect any significant increase in the incidence of cancer of the oral cavity or pharynx - the prevalence of which by international standards remains low in this country."

A number of other reviewers have also considered the evidence relating smokeless tobacco to oral cancer.[8] (See also section 6.)[16-22]

1.4 Objectives of this review

The objective of this review is to investigate in detail the epidemiological evidence relating oral and pharyngeal cancer to smokeless tobacco use by Western populations. The evidence relating to India and other parts of Central and South-Eastern Asia is not considered in detail in this review.

2. Methods

Relevant papers were obtained from our in-house files, MEDLINE searches and papers cited by Gross et al.[13] Further relevant papers were sought from the reference lists of papers already obtained. Attention was restricted to papers presenting the results of epidemiological studies relating incidence of oral cancer (or specific forms of it) to whether or not subjects had used smokeless tobacco, or to review papers on the subject. Papers describing smokeless tobacco use in oral cancer cases with no corresponding data on control patients or the population at risk were not considered. Nor were papers relating smokeless tobacco to oral leukoplakia, which is not oral cancer as such.

Though references have been obtained for studies conducted in Indian and other south east Asian populations (see Appendix A), these are not considered in this review. This review considers the evidence from studies mainly in the USA or Sweden that concern the use of snuff or of chewing tobacco unadulterated by betel nut, etc. The review consists of:

1) A brief text summary of the main findings of each study considered in chronological order of year of publication,
2) Tables summarizing features of the study design and results,
3) Meta-analyses of the data collected, with discussion.

Where appropriate, relative risks and 95% confidence intervals (CIs) have been calculated using standard formulae.[23] In some studies this means that relative risks and CIs presented by the authors have been re-estimated for uniformity. For example, where the relative risk for a 2x2 table with cells a, b, c, d was originally estimated as $(a+0.5)(d+0.5)/(b+0.5)(c+0.5)$, the simpler formula ad/bc has been used.

Fixed- and random-effects meta-analysis has been carried out to obtain a combined estimate of relative risk from a set of independent estimates, as described by Fleiss and Gross.[24] Fixed-effects meta-analysis assumes a common underlying relative risk estimate and only takes into account within-study variability in calculating the combined relative risk estimate and its 95%

confidence limit. Random-effects meta-analysis also takes into account between-study variability. Where there is no evidence of heterogeneity between the sets of estimates, the two analyses give the same results.

3. Summary of evidence from studies not conducted in India or South-east Asia

3.1 Case-control studies

STUDY 1 : Broders/USA: Minnesota (1920)

The earliest epidemiological study relating oral cancer to smokeless tobacco, reported in 1920, was conducted in Rochester, Minnesota by Broders[10]. He compared the distribution of (apparently current) tobacco habits in 537 cases of squamous cell epithelioma of the lip, 526 of whom were men, and in 500 control men without epithelioma of the lip. The study is severely limited by the failure to define how the controls were selected, and by the cases being much older than the controls (mean ages 57 and 36 years respectively), no attempt being made to adjust for age (or sex) in analysis. From the data provided the following frequencies (%) can be calculated:

	No tobacco	Chew only	Smoke and chew	Use snuff*	Smoke only
Lip cancer	19.5	5.1	18.9	0.28	56.2
Controls	21.4	3.4	10.0	0.16	65.2

(* Presumably as the percentages for cases add to 100% but those for controls add to 100.2%, the snuff taking cases did not smoke other products, but the snuff taking controls did.)

Based on the above data the following relative risks can be estimated:

Exposure	Smoking habits	Adjustment Factors	Lip cancer RR (95% CI)
Chewing	Nonsmokers	None	1.65(0.85-3.19)
	Smokers	None	2.19(1.51-3.18)
	Any	Smoking	2.05(1.48-2.83)
Snuff	Any	None	1.75(0.12-26.5)

The CI above are calculated assuming that all the subjects provided data on smoking/chewing snuff. However, it is unclear if this is so as the data in the source table, taken at face value, imply the number of cases using snuff was (0.28x537)/100 = 1.5! The CI, therefore, may be wider than indicated.

From the frequencies above it can also be calculated that chewing is not related to smoking in the control population. Among both chewers and non-chewers about 75% smoke.

STUDY 2 : Moore/USA: Minnesota (1952, 1953)

In a case-control study conducted in Minneapolis, Minnesota and reported in 1952 and 1953, Moore et al.[25,26] compared tobacco use history between patients with cancer of the face, lip, mouth or with oral leukoplakia and control surgical out-patients with non-malignant disease by a general interview procedure for clinic patients. The subjects were all white men aged 50 or older. Relevant data for cancers of the lip and mouth regarding the use of chewing tobacco and/or snuff for 20 or more years were as follows:

	Smokeless tobacco use		
Cancer site	Yes	No	Relative risk(95% CI)
Lip	39	33	2.56(1.12-5.85)
Mouth	26	14	4.02(1.57-10.3)
Lip or mouth	65	47	3.00(1.37-6.54)
Controls	12	26	

No details are given of how the control patients were selected and the study is clearly limited by failure to adjust for any potential confounding variable, even age. The information above was taken from other reviews,[1,12,13] the two papers cited[25,26] not being available from the British Library.

STUDY 3 : Wynder 1/USA: New York (1957)

In 1957 Wynder and Bross[27] reported findings from a case-control study conducted in Whites in New York. It involved 543 male and 116 female patients with microscopically confirmed squamous cell cancer of the oral cavity and 207 male and 246 female control patients with benign diseases of the head and neck, lymphomas, benign diseases of the thoracic region, cancer of the lower gastro-intestinal tract or skin cancer. Cases and controls were matched on age and religion. Data were collected through trained interviewers. Data on the use of smokeless tobacco were only available for men. It was noted that 17% of male cases were tobacco chewers as compared with only 8% of the male controls. With one exception, a patient with cancer of the gum, all the tobacco chewers were also tobacco smokers. The authors noted that in the case of lip and gum cancer, the lesion was usually found at the site where the tobacco was held, but no relationship to tobacco chewing was found with cancer of the pharynx, floor of the mouth and tonsil. The highest percentage of tobacco chewers were among patients with cancer of the palate, 22%, and buccal mucosa, 20%. The authors concluded that "though tobacco chewing appears to have some influence on the development of some cancer sites of the mouth, it is less important than tobacco smoking." The study is limited by the failure to present estimates adjusted for other risk factors.

From the material presented in this and in a second paper,[28] the following numbers of male cases and controls by smoking habits can be estimated:

Cancer	No tobacco	Chew only	Smoke only	Smoke and chew	Total
Lip	2	0	57	15	74
Tongue	11	0	140	29	180
Gum	0	1	35	5	41
Floor of mouth	0	0	76	10	86
Buccal mucosa	0	0	32	8	40
Palate	1	0	31	9	41
Tonsil	2	0	46	9	57
Pharynx	1	0	20	3	24
All oral cancer	17	1	437	88	543
Controls	21	0	169	17	207

The data are clearly inadequate to assess the role of chewing tobacco in the absence of smoking, but among smokers the relative risk for chewing can be estimated as follows:

Cancer site	Relative risk (95% CI)
Lip	2.62(1.23-5.57)
Tongue	2.06(1.09-3.90)
Gum	1.42(0.49-4.11)
Floor of mouth	1.31(0.57-2.99)
Buccal mucosa	2.49(0.99-6.24)
Palate	2.89(1.18-7.06)
Tonsil	1.95(0.81-4.65)
Pharynx	1.49(0.40-5.54)
All oral and pharyngeal cancer	2.00(1.16-3.47)

Gross et al.[13] give an estimate of 2.36 (1.36-4.08) for all oral cancer but that is for all subjects, ignoring smoking.

STUDY 4 : Wynder 2/Sweden: Stockholm (1957)

In 1957 Wynder et al[29] reported findings from a case-control study conducted in Stockholm involving 810 cancer patients, 380 male and 430 female. Detailed environmental and medical histories were obtained by interview. None of the female patients chewed and the analyses for the male patients compared 265 cases with squamous cell cancers of the upper alimentary and respiratory tracts (including 14 of the lip, 33 of the tongue, 19 of the gum, 8 of the buccal mucosa, 51 of the nasopharynx and maxilla and 41 of the hypopharynx) and 115 similarly interviewed controls with cancer of the skin, cancer of the head and neck region other than squamous cell cancer, cancer of the stomach, lymphoma, salivary-gland tumours, leukaemia, sarcoma and cancer of the rectum and colon. The cases and controls were not matched. Ridit analyses were carried out suggesting that tobacco chewing (of Kentucky and Virginia tobaccos to which little else is usually added) was "suggestively related to cancer of the gum and buccal cavity." The authors noted that "nearly half of the patients with cancer in these areas were habitual chewers and had chewed for many years" and "in the majority of these cases, the cancer appeared in the area in which the chewed tobacco was held." Other sites studied (lip, tongue, nasopharynx, hypopharynx) showed no apparent relationship to tobacco chewing as judged by a graphical presentation of the ridit analysis. Numbers of cases and controls who chewed were not given, so that relative risk estimates could not be calculated. None of the differences between cases and controls appear to be statistically significant.

The study is limited by incomplete reporting and the lack of control of potential confounding factors. One wonders whether the smokeless tobacco use referred to in this paper was actually moist snuff, and not chewing tobacco. According to national statistics[3] chewing tobacco has been a negligible part of the Swedish tobacco market for many years. In 1930, for example, snuff formed 62.5% of the sales by weight and chewing tobacco only 1.8%.

STUDY 5 : Peacock/USA: North Carolina (1960)

Peacock et al.[30] carried out a study in North Carolina between 1952 and 1958 involving 56 cases of oral cancer (including buccal mucosa, alveolar ridge and floor of the mouth) diagnosed by tissue biopsy, 45 of whom provided information on tobacco use. As controls, 146 patients with diagnoses other than oral cancer and 217 outpatients aged over 40 were interviewed. A table was presented giving the breakdown of the cases and each group of controls by age, sex, race and economic status according to use of snuff or chewing tobacco for more than 20 years. The authors concluded that "the North Carolina Memorial Hospital survey revealed a significant association between oral cancer and the prolonged use of snuff and [chewing] tobacco only in those patients who were over 60 years of age and in the lower economic or staff group."

From the data presented the following table can be constructed showing the number of cases and controls by sex and age:

Sex	Age	Oral cancer Cases Users*	Non Users	Inpatient Controls Users	Non Users	Outpatient Controls Users	Non Users
Male	40-59	4	6	12	33	19	49
	60+	10	5	10	19	28	21
	Total	14	11	22	52	47	70
Female	40-59	3	5	17	27	24	36
	60+	8	4	10	18	23	17
	Total	11	9	20	45	47	53

(*Users = history of chewing tobacco and/or snuff)

From this the following age-adjusted relative risks can be calculated:

	Using inpatient controls	Using outpatient controls	Using combined controls
Males	2.72(1.03-7.16)	1.59(0.64-3.95)	1.95(0.81-4.68)
Females	1.96(0.68-5.61)	1.19(0.43-3.26)	1.48(0.56-3.92)

It was not possible to calculate relative risks adjusted also for race and/or economic group because of the limited amount of data. The study is limited by failure to adjust for smoking and alcohol and by the failure to define more precisely how the controls were selected. Gross et al.[13] suggest that, in the two control groups but not the cases, non-users may have included those not answering the questions on smokeless tobacco use. It is unclear from the paper if this potential source of bias actually occurred.

STUDY 6 : Vogler/USA: Atlanta (1962)

Vogler et al.[31] interviewed 1918 patients in a clinic in Atlanta in 1956-1957. They fell into four groups:

(1) 333 patients with cancer of the mouth, pharynx and larynx,

(2) 214 patients with diseases of the mouth other than cancer (e.g. leukoplakia),

(3) 584 patients with cancer of other sites and

(4) 787 patients with no cancer, the mouth not examined.

All the patients were white and over 20 years old.

From data presented on numbers of male cases by group and urban/rural residence and on percentages of male cases who chewed tobacco, the following table can be constructed. Note that percentages for group 1 (urban and rural) and group 2 (rural) come from the text, but other percentages are estimated (inevitably inaccurately) from a very small figure.

Group	Residence	Male Subjects	% chewers
1	Urban	140	17
	Rural	91	36
2	Urban	64	8
	Rural	45	36
3	Urban	133	8
	Rural	84	12
4	Urban	141	2
	Rural	44	6

Group 2, containing leukoplakia patients, is clearly not a valid control for the group 1 cases. Based on a comparison of group 1 with groups 3 and 4 combined the relative risk of cancer of the mouth, pharynx and larynx combined associated with chewing tobacco (adjusted for residence) can be estimated as 4.48 (95% CI 2.71-7.41). Although imprecise, it is clear the difference is highly statistically significant. The authors note that differences are consistently evident by age within the urban and rural patients. It should

be noted that the validity of using groups 3 and 4 combined as the control group is dubious as the prevalence of chewing varies between these two groups.

Data were also presented, for all ages and urban/rural residence combined, on the percentage of chewers and excessive chewers by site of cancer in group 1. Using the same combined control group, unadjusted relative risks for chewing can be estimated as shown below (numbers of controls are not shown for excessive chewing):

	Cases		
Cancer site	Total	Chew	Relative risk(95% CI)
Lip	46	11	4.51(2.06-9.89)
Buccal cavity	94	35	8.52(4.79-15.2)
Pharynx-larynx	81	13	2.74(1.34-5.60)

Few women chewed tobacco and Vogler et al. concentrated attention on snuff dipping. Here the percentages were given numerically as:

Group	Residence	Female Subjects	% snuff
1	Urban	38	40
	Rural	55	75
2	Urban	57	2
	Rural	37	11
3	Urban	170	3
	Rural	129	20
4	Urban	377	1
	Rural	150	11

More detailed data are also given by age. Based on this, the relative risk of mouth, pharynx and larynx cancer combined for snuff dipping among women, adjusted for age and residence, can be estimated as 14.6 (95% CI 8.19-26.0). The authors noted a non-significant tendency for the risk to increase with the amount of time snuff was held in the mouth per day.

Data were also presented for all ages and urban/rural residence combined on the percentage of snuff dippers and excessive snuff dippers by

site of cancer in group 1. Using the same combined control group, unadjusted relative risks for snuff dipping can be estimated as follows:

Cancer site	Cases	Relative risk(95% CI)
Lip	3	7.28(0.65-81.6)
Buccal cavity	72	40.6(22.5-73.6)
Pharynx-larynx	18	1.82(0.41-8.13)

The study is limited by incomplete reporting, by failure to adjust for smoking or alcohol use and by the unexplained difference in smokeless tobacco use between the two control groups used in the relative risk estimation above.

STUDY 7 : Vincent/USA: New York (1963)

In 1963 Vincent and Marchetta[32] reported results of a comparison of two groups of patients at the Roswell Park Memorial Institute in Buffalo, New York. The first group consisted of 106 successive patients who entered the Head and Neck Clinic with a malignant lesion of any part of the oral cavity, larynx or pharynx. The second, control group, consisted of 100 successive male and 30 successive female patients in the same age group in the Gastrointestinal Clinic. Patients answered questions about drinking and smoking habits. The paper presented a table giving the distribution of tobacco use separately for males who (i) had oral cavity cancer, (ii) had pharynx cancer, (iii) had intrinsic or extrinsic larynx cancer or (iv) were control patients, the tobacco use categories being apparently based on current habits used. Based on the data presented, one can calculate:

Cancer site	Used snuff	Did not use snuff	Relative risk (95% CI)
Oral cavity	9	24	7.13(2.19-23.2)
Pharynx	3	30	1.90(0.43-8.42)
Oral cavity and pharynx	12	54	4.22(1.41-12.6)
Intrinsic and extrinsic larynx	2	21	1.81(0.33-9.97)
All head and neck	14	75	3.55(1.22-10.3)
Controls	5	95	

The association of snuff use with head and neck cancer is stronger for "oral cavity" cancer (defined to include soft and hard palate, gingiva, floor of the mouth, buccal mucosa and anterior two-thirds of the tongue) than for the "pharynx" and "intrinsic and extrinsic larynx" groups. The authors state that "the use of snuff, chewing tobacco and pipe tobacco was higher among male patients with cancer of the oral cavity than patients in the control group," citing a table which actually gives no data on chewing tobacco. The authors also state that two of the female patients chewed tobacco, but does not state whether these patients were cases or controls. The results are limited by failure to adjust for age or smoking habits.

STUDY 8 : Martinez/Puerto Rico (1969)

Martinez[33] conducted a case-control study in Puerto Rico in 1966 involving 400 histologically confirmed cases of epidermoid cancer, 179 of the oesophagus (120 in males and 59 in females), 153 of the mouth (115 in males and 38 in females) and 68 of the pharynx (55 in males and 13 in females). For each cancer patient three controls were matched on age (within five years) and sex. One of the three controls was a patient without any of the cancers of interest admitted at the same time and from the same hospital or clinic as the matched case. The other two controls were selected from the same community as the case. Trained interviewers asked questions about a wide range of topics, hospital and neighbourhood controls being noted to be "very homogeneous for most variables."

The authors presented information (in their Table 13) on the numbers of cases of each type and their matched controls subdivided by type of product smoked. The data relating to the categories "none" and "chewing only" (which relate to habits in the last 20 years) allow estimation of the effect of chewing in the absence of smoking, as shown below:

Cancer site		Cases Chewing only	Never tobacco	Controls Chewing only	Never tobacco	RR(95% CI)
Mouth	Males	1*	9	7*	43	0.68(0.07-6.25)
	Females	1*	12	11*	45	0.34(0.04-2.91)
Pharynx	Males	3	5	2	29	8.70(1.15-65.9)
	Females	0	3	2	21	0.00
Mouth and pharynx combined	Males	4	14	9	72	2.29(0.62-8.47)
	Females	1	15	13	66	0.34(0.04-2.79)
Oesophagus	Males	3	10	13	51	1.18(0.28-4.90)
	Females	7	15	13	75	2.69(0.92-7.87)
Combined	Males	7	24	22	123	1.63(0.63-4.24)
	Females	8	30	26	141	1.45(0.60-3.50)

It is important to note that the data marked with an asterisk in the table above for chewing only and mouth cancer were actually those presented in the

table for pipe only and mouth cancer. Two reasons make it clear that the data for chewing only and pipe only for mouth cancer had been transposed in the source Table 13. One is that transposing the rows will make the data for the individual cancers add up to that given for the combined data. The other is that the combined cancer data and those for cancers of the pharynx and oesophagus show no women cases or controls who are smokers of pipes only and some who chew only, whereas the data for mouth cancer, as presented, implausibly show the reverse. It is notable that the US Surgeon-General[12] did not detect this error and calculated an inappropriate relative risk for mouth cancer for males of 11.9.

The source Table 13 shows that there are large numbers of mixed smokers but does not distinguish mixed chewers and smokers from e.g. mixed smokers of pipes and cigars. This makes it impossible to estimate the risk associated with chewing among smokers. Further detailed data are given in the next source table, but only for the three cancers combined. From these data one can calculate the following:

		Cases		Controls		
Cancer site	Sex	Chew and smoke	Smoke only	Chew and smoke	Smoke only	RR(95% CI)
Mouth, pharynx and oesophagus cancer	Males	38	217	86	626	1.27(0.84-1.92)
	Females	10	68	30	152	0.75(0.34-1.61)

Taken together, the data do not clearly show an increased risk of oral cancer associated with chewing tobacco either in nonsmokers or smokers. The estimate for pharynx cancer in males in nonsmokers is significant, but only marginally so, while estimates for mouth cancer are not elevated. Note that none of these analyses are adjusted for age or other risk factors such as alcohol.

STUDY 9 : Browne/UK: Stoke-on-Trent (1977)

Browne et al.[34] carried out a study in Stoke-on-Trent, England involving 75 cases (46 males and 29 females) of squamous cell carcinoma of the mouth notified to the Cancer Registry in 1957-1971, 56 of which were confirmed histologically, and two controls matched for age, sex, occupation and residential area living at the time of the survey. Interviewing was direct in 17% of cases and 96% of controls, and with relatives or friends in the remainder. None of the cases or controls used snuff. Seven of the cases and 20 of the controls chewed tobacco, giving a relative risk for chewing ignoring tobacco for the sexes combined of 0.67 (95% CI 0.27-1.66). Data are not presented which allow estimate of the effect of chewing separately for smokers and nonsmokers. However, it is noted that whereas all seven of the cases who chewed also smoked a pipe, only five of the 20 controls did ($p<0.001$). On the other hand, among the chewers, there were only two cases (29%) who smoked a cigarette compared with 11 controls (55%). It was also noted that tobacco chewing was solely practised by workers in coal mines (where smoking is not allowed).

The study design is clearly not a satisfactory one. Any trends over time in use of chewing tobacco may cause bias, as may differences in the respondent supplying the data. The data are not presented in a way that allows very useful estimation of risks to be carried out, data are not separated by sex, or adjusted for any factor and it is unclear which period of life chewing and tobacco use referred to.

STUDY 10 : Williams/USA (1977)

Williams and Horm[35] obtained personal interviews for 7,518 incident cases of invasive cancer from the Third National Cancer Survey in the USA. Subjects were classified by cancer type and analyses for chewing tobacco or snuff were carried out for eight cancer sites (lip-tongue, salivary, gum-mouth, pharynx, oesophagus, larynx, lung and bladder) using cases of all other cancer types combined as controls. Data were presented on number of cases and controls by level of chewing tobacco or snuff use as well as relative risks, adjusted for age, race and cigarette-years. These data are summarized below, with estimates of 95% confidence limits attached.

Cancer site	Sex	Number of cases by smokeless tobacco use			Relative risks (95% CI)	
		None	Low	High	Low*	High*
Lip-tongue	Male	71	1	2	0.36 (0.05-2.62)	0.36 (0.45-7.75)
	Female	20	0	0	0.00	0.00
Gum-mouth	Male	42	8	3	3.88 (1.77-8.49)	6.65 (2.01-22.0)
	Female	23	2	0	4.92 (1.10-22.1)	0.00
Pharynx	Male	45	2	0	0.45 (0.11-1.88)	0.00
	Female	18	0	0	0.00	0.00
Controls	Male	1690	98	66		
	Female	3135	23	30		

(* The actual levels were not stated, but were chosen so as to divide the distribution of exposure about equally)

The estimates of the 95% CI are based on a variance calculation dependent simply on the numbers of exposed and unexposed cases and controls. In practice, this will understate the variance (and the width of the 95% CI) for the estimate adjusted for age, race and cigarette years. The source paper claims the relative risk of 3.88 for gum-mouth/low smokeless tobacco use in males is significant at $p<0.01$ but the other two high relative risks for gum-mouth (6.65 for high use in males and 4.92 for low use in females) are not significant even at $p<0.05$.

It is also possible to use the data above to provide some overall unadjusted estimates of risk for any smokeless tobacco use and for combined cancer categories as follows:

Cancer site	Sex	Cases Exposed	Unexposed	Relative risk (95% CI)
Lip-tongue	Male	3	71	0.44(0.14-1.40)
	Female	0	20	0.00
Gum-mouth	Male	11	42	2.70(1.36-5.34)
	Female	2	23	5.14(1.18-22.4)
Oral cavity	Male	14	113	1.28(0.72-2.28)
	Female	2	43	2.75(0.65-11.7)
Pharynx	Male	2	45	0.46(0.11-1.91)
	Female	0	18	0.00
Oral cavity and pharynx	Male	16	158	1.04(0.61-1.79)
	Female	2	61	1.94(0.46-8.14)
Controls	Male	164	1690	
	Female	53	3135	

While the study provides some evidence for an association of smokeless tobacco use with gum-mouth cancer and not with lip-tongue or pharynx cancer, it is limited by the extremely small number of cases who used smokeless tobacco. It is difficult to see how one can get very reliable estimates for a relative risk adjusted for three factors when the number of exposed cases never exceeds eight in any analysis. The authors concluded that "At least for cancers of the gum and mouth, chewing and snuff tobacco seem to play a primary role because they show the strongest association (more than for pipes, cigars, or cigarettes)" though they noted that "the number of users of unsmoked tobacco was too small to allow an analysis stratifying on pipes and cigar use."

STUDY 11 : Wynder 3/USA: Six states (1977)

Wynder and Stellman[36] interviewed 22,101 patients during the years 1969 to 1975. 3716 with cancer of one of six categories, most of the remainder forming a pool of controls selected on the basis of absence of a history of tobacco-related disease. Oral cavity cancer was one of the case categories considered, with 593 males and 280 females interviewed. Female use of chewing tobacco and snuff was very low, so results were only presented for males. It was noted that in males the smoking habits of users of chewing tobacco did not differ significantly from those of non-users. The authors noted that the relative risks computed for chewing tobacco or snuff for any of the 6 disease categories considered (which also included lung Kreyberg I, lung Kreyberg II, larynx, oesophagus and bladder) were all not significant at the 99% confidence level. Numbers of cases of oral cavity cancer and age, sex, race and city matched controls in males by use of chewing tobacco and snuff are given below, together with relative risks (and 95% CIs) based on them. Note that the controls also include those matched to the other five diseases, so that the relative risk estimates are not properly adjusted for the matching factors considered.

	Oral cavity cancer cases		Controls		
Exposure	Exposed	Unexposed	Exposed	Unexposed	RR (95% CI)
Ever chewed tobacco	61	530	233	2327	1.15 (0.85-1.55)
Ever used snuff	10	581	69	2491	0.62 (0.32-1.21)

STUDY 12 : Westbrook/USA: Arkansas (1980)

Westbrook et al.[37] compared the medical records of 55 female patients with cancer of the alveolar ridge or buccal mucosa who were treated at the University of Arkansas between 1955 and 1975 with those of 55 randomly selected female hospital controls of similar age and period of admission to the cases. Fifty of the cases, but only one control, were snuff dippers, with the tumours typically appearing at the site where the snuff was usually placed. Taken at face value, this gives a relative risk estimate of 540 (95% CI 61.0-4783). However, as pointed out by both IARC[1] and the US Surgeon-General[12], this estimate is very unreliable as the probability of snuff use being mentioned in medical records, had it occurred, seems likely to be much greater for the cases than controls.

STUDY 13 : Winn/USA: N Carolina (1981)

Using hospital records and death certificates available for 1975-1978, Winn et al.[14] identified 255 women residing in 67 counties in central North Carolina with oral or pharyngeal cancer. They also sought two female controls for each case, matched on age, race, source of ascertainment (hospital or death certificate) and county of residence. Prospective controls were ineligible if they had cancers of the oral cavity, pharynx, larynx or oesophagus as well as other oral or pharyngeal disease or mental disorders. Interviews were conducted with 232 of the 255 cases and with 410 of the 502 controls. The proportion of next-of-kin interviews was higher for cases than for controls.

The authors first presented the results of analyses showing the number of cases and controls according to snuff dipping, smoking and race. These data, together with various relevant relative risks for ever/never snuff dipping, are described below:

		Cases of oral or pharyngeal cancer		Controls		
Smoking habits	Race	Ever snuff	Never snuff	Ever snuff	Never snuff	RR(95% CI
Never	White	79	36	80	153	4.20(2.60-6.77)
	Black	12	5	25	16	1.54(0.49-2.64)
	Combined (adjusted for race)					3.67(2.35-5.73)
Ever	White	11	70	14	101	1.13(0.49-2.64)
	Black	5	14	5	16	1.14(0.27-4.79)
	Combined (adjusted for race)					1.14(0.55-2.35)
Any	Combined (adjusted for race and smoking)					2.67(1.83-3.90)

Note that these data also show that, in the control population, the frequency of smoking is lower in snuff users (15%) than in non-users (41%).

In a further analysis based on the hospital sample only, the authors presented data separately for cancer of the gum and buccal mucosa and for other mouth and pharynx by duration of snuff use among nonsmokers.

Cancer site	Duration of snuff use (yrs)	Cases	Controls	RR(95% CI)*
Gum and buccal mucosa	0	2	34	1.00(base)
	1-24	3	3	17.0(1.99-145)
	25-49	10	11	15.5(2.93-81.6)
	50+	15	4	63.8(10.5-387)
	Any	28	18	26.4(5.65-124)
Other mouth and pharynx	0	22	61	1.00(base)
	1-24	3	5	1.66(0.37-7.55)
	25-49	14	10	3.88(1.51-10.0)
	50+	8	18	1.23(0.47-3.23)
	Any	25	33	2.10(1.03-4.28)

(*Relative risks and 95% CI have been recalculated from the numbers.)

The authors note that the elevated risk associated with snuff dipping among nonsmokers was not decreased by adjustment for age, alcohol consumption, urban or rural residence, source of case ascertainment or employment in various occupations. Nor did statistical control for smoking reduce the risk for snuff dipping seen in the smokers and nonsmokers combined. They estimated that snuff dipping alone was attributable for 31% of cases of oral and pharyngeal cancer. They referred to "the carcinogenic hazard of oral snuff" being of "special concern in view of the recent upswing in consumption of smokeless tobacco in the United States."

Although this study is much better in many ways that those previously cited, it is limited by the use of proxy respondents, which was greater in cases (51%) than in controls (21%) in the hospitalized series. Also they do not give enough attention to the heterogeneous nature of the evidence on the possible effect of snuff dipping. It is easy to understand why relative risk estimates for snuff dipping in nonsmokers should be much higher for the gum and buccal mucosa which come into direct contact with the snuff. However it is less clear why snuff dipping should increase the risk significantly for never smoking whites, but not for never smoking blacks or for ever smoking blacks or whites ($p<0.05$ for heterogeneity for the four relative risks in the table on the previous page).

STUDY 14 : Wynder 4/USA: Five states (1983)

Wynder et al.[38] carried out a case-control study in 1977-1980 in five US States involving 414 male and 157 female patients with a histologically confirmed diagnosis or oral and pharyngeal cancer and an equal number of control patients without a tobacco-related disease individually matched to the cases on age, sex, race, hospital and hospital status (private, semi-private, ward). Patients were interviewed in hospital. The paper was aimed at studying the possible effect of mouthwash use on oral cavity cancer and only limited results relating to smokeless tobacco were presented. Chewing tobacco was not reported by women, but was reported by "approximately 9% of both male cases and controls." This suggests an approximate relative risk of 1.00 (95% CI 0.62-1.61) for chewing tobacco. 59% of cases who chewed tobacco had done so for more than 20 years, as against 69% of controls. This suggests an approximate relative risk of 0.86 (95% CI 0.48-1.54) for long-term chewing tobacco and of 1.32 (95% CI 0.61-2.88) for short-term chewing tobacco versus no chewing tobacco use.

Among men, fewer cases (3) than controls (7) used snuff, which represents a relative risk of 0.42 (95% CI 0.11-1.65). Among women, more cases (2) than controls (0) used snuff for more than 30 years.

Although these data do not indicate any effect of chewing tobacco or snuff in this study, they are limited by failure to adjust for any variable, particularly smoking and drinking. The limited reporting is also a problem, especially for snuff use, where no results for overall snuff use are given for women.

STUDY 15 : Stockwell/USA: Florida (1986)

Stockwell et al.[39] conducted a case-control study based on incident cancer cases reported to the Florida Cancer Data System in 1982. 2351 patients with head and neck cancer were compared with 8285 control patients with cancer of the colon, rectum, cutaneous melanoma and endocrine neoplasms. Smoking histories were sought on all subjects and were available for 79%. Patients were classified by the primary tobacco product used, with a total of 18 cases and 31 controls reporting primary use of smokeless tobacco. The table below summarizes numbers of cases by type of head and neck cancer as well as relative risks (compared to those reporting never having used tobacco at all) adjusted for age, race and sex.

	Number of patients			
Cancer site	Primary SLT* use	No tobacco	Total	Relative risk (95% CI)**
Lip	0		72	0.0
Tongue	1		312	2.3(0.2-12.9)
Salivary gland	2		114	5.3(1.2-23.4)
Mouth and gum	5		443	11.2(4.1-30.7)
Pharynx	2		450	4.1(0.9-18.0)
Nasopharynx	1		71	5.3(0.7-41.6)
Nasal cavity/paranasal sinuses	1		92	3.3(0.4-25.9)
Larynx	6		797	7.3(2.9-18.3)
Total cases	18	340	2351	6.58(3.64-11.9)
- male	15		1696	
- female	3		655	
Controls	31	3852	8285	
- male			4164	
- female			4121	

*SLT = smokeless tobacco, **Adjusted for age, race and sex, except for total cases which is unadjusted.

Although the frequency of primary smokeless tobacco use among cases (0.77%) was only about twice as high as that among controls (0.37%), indicating a relative risk of 2.05 (95% CI 1.15-3.68) for primary/non-primary use, the proportion of primary smokers in the head and neck cancer group was much higher than in the controls. This meant that the relative risks presented in the above table, which are restricted to those who are not primary smokers, are substantially higher.

Limitations of the study include the lack of tobacco use data on 18.3% of cases and 22.1% of controls, indicating inadequacies in the data collection system which "was obtained by chart and histopathology review at reporting institutions," the failure to record use of multiple tobacco products (so that one cannot carry out analyses restricted to nonsmokers or smokers), the small number of subjects reporting primary smokeless tobacco use and the limited number of confounding variables adjusted for.

STUDY 16 : Young/USA: Wisconsin (1986)

In 1986 Young et al.[40] reported results from a case-control study based on patients registered in the Wisconsin Head and Neck Cancer Network. Detailed interviews were carried out with three groups of cancer cases; oral cavity (150 males and 52 females), oropharynx (59 males and 19 females) and hypopharynx (29 males and 8 females). Interviews were also carried out with two control groups, 70 males and 57 females with cancers not thought to be related to tobacco use (salivary gland, paranasal sinus and nasopharynx) and 180 males and 19 females with larynx cancer.

Use of a tobacco product other than cigarettes was noted to be rare for females (<1%). Among males 3.5% had ever used snuff or chewing tobacco, but no statistically significant differences between cancer site groups were noted. No detailed data were given. The study is limited by the incomplete reporting and the inadequacy of the control groups, particularly the larynx cancer group, for the purposes of investigating possible effects of smokeless tobacco. Numbers of exposed cases, 17 across all case and control groups combined, were also very low.

STUDY 17 : Blot/USA: Three states (1988)

Blot et al.[41] identified incident cases of pathologically confirmed primary oral and pharyngeal cancer (excluding salivary gland and nasopharynx cancer) aged 18-79, diagnosed in 1984 and 1985 in areas of Georgia, California and New Jersey. In each area population-based controls aged under 65 were identified by random digit dialling, while those aged 65+ were selected from rosters of residents provided by the Health Care Financing Administration. Controls were selected to have a similar age, sex and race distribution to the cases. Interviews were completed for 762 male and 352 female oral and pharyngeal cancer cases and for 837 male and 431 female controls, 22% of the interviews for cases and 2% of those for controls being with next-of-kin respondents. The study was primarily concerned with risk associated with smoking and drinking, and results were only reported very briefly for smokeless tobacco.

The authors noted that among males 6% of cases and 7% of controls had used smokeless tobacco (primarily chewing tobacco), but nearly all were also smokers. The only relative risk that can be calculated (approximately) from this is an unadjusted one of 0.85 (95% CI 0.57-1.26) for any smokeless tobacco use regardless of smoking.

They also noted that among women 3% of cases and 1% of controls used smokeless tobacco (primarily snuff), but users were generally nonsmokers. This leads to an unadjusted relative risk estimate for any smokeless tobacco use regardless of smoking of 3.06 (95% CI 0.99-9.47). The authors also report a relative risk of 6.2 (95% CI 1.9-19.8) for users of smokeless tobacco among nonsmoking women, which is adjusted for age, race, study location and self versus next-of-kin respondent. They noted that this analysis involved six cases, all occurring in the oral cavity, and for controls.

The study is limited by the relative infrequency of female cases and controls using smokeless tobacco and particularly by the very limited

reporting of results for males, where numbers of cases and controls using smokeless tobacco were substantially larger (about 46 cases and 59 controls). One would have liked to see results by cancer site and by smoking habit.

STUDY 18 : Spitz/USA: Texas (1988)

Spitz et al.[42] conducted a study in Texas involving 131 male and 54 female white patients with histologically confirmed squamous cell carcinoma of the upper aerodigestive tract attending the hospital in 1985-1987 and an equal number of randomly selected age and sex matched white control patients, frequency matched on age and sex, who did not have a squamous cell carcinoma. Data were collected from a self-administered risk factor questionnaire given as part of the hospital registration procedure. the distribution of cancer site of the cases was larynx 65, tongue 37, orohypopharynx 23, floor of mouth 17 and other oral cavity 43. Only limited results were reported for smokeless tobacco. It seems from the text that they relate to men (and this has been assumed below), but this is unclear and they may relate to sexes combined.

The authors report that the same number of cases and controls, 23, admitted to chewing tobacco. This provides a relative risk estimate of 1.00 with a 95% CI of 0.53-1.89 assuming the results relate to men.

Nine cases and four controls reported snuff dipping, which would lead to a relative risk estimate of 2.34 (95% CI 0.70-7.81). However the authors report an estimate of 3.4 (95% CI 1.0-10.9) which perhaps is adjusted for age or other variables (though this is not stated). The authors note that of the nine cases who dipped snuff, all drank alcohol, all smoked cigarettes, pipes or cigars and seven also chewed tobacco. Three of the four controls who dipped snuff were stated to have smoked, with no information given on alcohol consumption.

The authors stated that there was no difference in distribution of sites of malignancy for snuff dippers compared with all other cases, with four snuff dippers having laryngeal cancer, four having oral cavity cancer and one having a pharyngeal cancer. The distribution of control snuff dippers by site was not given so relative risks by site cannot be calculated.

The study is limited by the relatively small number of cases and controls who used smokeless tobacco and by incomplete reporting. The inability to be able to separate out larynx cancer cases from the total is unfortunate for the purposes of this review.

STUDY 19 : Franco/Brazil: São Paulo and Goiânia (1989)

Franco et al.[43] carried out a study in three hospitals in São Paulo and Goiânia in Brazil involving interviews with 201 male and 31 female patients with histopathologically confirmed cancer of the tongue, gum, floor of mouth and other parts of the oral cavity newly diagnosed in 1986-1988 and 464 control patients without neoplastic disease or mental disorder admitted from the same or neighbouring hospitals. Two controls were matched to each case on the basis of sex, age and period of hospital admission. The study is concerned with a wide range of risk factors, with very little information provided on use of smokeless tobacco. The authors reported that use of smokeless tobacco, either as snuff dipping or tobacco chewing, was not associated with risk of oral cancer, with 9 cases and 13 controls reporting using tobacco in this form. Based on these data, an unadjusted relative risk for ever/never smokeless tobacco use for the sexes combined can be estimated as 1.40 (95% CI 0.59-3.33). The authors note that "RR estimates by matched analyses for this variable were independent of smoking or drinking status, sex, or anatomical site" but do not actually present any relative risk estimates.

STUDY 20 : Blomqvist/Sweden: Göteborg (1991)

In 1991 Blomqvist et al.[44] reported results from a study in Göteborg, Sweden involving 57 men and 4 women with squamous cell carcinoma of the lower lip and age and sex matched control patients who were tumour free and had not previously been treated for cancer. Of the 59 cases and 61 controls who provided tobacco history data in the interview, 2 cases and 2 controls reported having used snuff and not having smoked. Compared with the 12 cases and 8 controls with no tobacco use, one can estimate a relative risk of 0.67 (95% CI 0.08-5.75) in relation to snuff use among nonsmokers. It was also noted that there were 17 cases and 15 controls who had "mixed" tobacco habits, but this would have included those who, for example, smoked cigarettes and pipes or cigars, and the number of the "mixed" group who used snuff and smoked cannot be estimated. Limitations of this study include failure to give details of the control diagnoses, to give fuller information on mixed snuff use and smoking and to take any potential confounding variables into account.

STUDY 21 : Maden/USA: Washington State (1992)

Maden et al.[45] carried out a study in western Washington state, USA in 1985-1989 involving 241 male cases of oral cancer (tongue, gum, mouth or oropharynx) aged 18 to 65 who had a telephone and 210 male population controls, frequency matched on age and reference year (the year of diagnosis of the cases), obtained by random digit dialling. 131 cases and 136 controls were successfully interviewed at home or at another place of their choice. 53% of the interviewed cases were in situ and 47% invasive cancer. 19 of the cases and 5 of the controls had used smokeless tobacco (stated to include plug, minipouches and snuff), with the relative risk, adjusted for age, given as 4.5 (95% CI 1.5-14.3). The main purpose of the study was to investigate viral risk factors for oral cancer and tobacco use was only considered briefly.

STUDY 22 : Sterling/USA: National (1992)

Sterling et al.[46] investigated the relationship between smokeless tobacco and cancer based on the combined data of the 1986 National Mortality Followback Survey (NMFS), a probability sample of the USA deaths (cases) and of the 1987 National Health Interview Survey (NHIS), a probability sample of the living, non-institutionalized US population (controls). There were 6976 oral cancer deaths (ICD 140-149), of which 5863 had used smokeless tobacco less than 100 times, 11 had used it 100-9999 times, 266 had used it 10,000 or more times and 836 had no information available. For the purpose of analysis, Sterling et al. considered decedents with no information as having used it 100-9999 times, but controls with no information as having no use. Based on a multiplicative model, Sterling et al. estimated that the relative risks of oral cancer associated with lifetime use of smokeless tobacco, adjusted for sex, race, age, lifetime smoking, alcohol drinking and occupation, were as follows:

Lifetime use of smokeless tobacco	Oral cancer relative risk (95% CI)
0-99	1.00
100-9999 (including unknown)	0.92(0.25-3.42)
10,000+	1.21(0.32-4.63)

The NMFS questionnaire depends on responses by surrogates while the majority of individuals in the NHIS sample are interviewed directly. In the discussion, based partly on a series of simulation experiments using varying levels of assumed misclassification of smokeless tobacco use by surrogates, the authors argue that this difference does not lead to significant bias.

The analyses by Sterling et al. also showed that alcohol was a major factor in the risk of oral cancer, with the relative risk for daily drinking versus less than once a week being 7.20 (95% CI 3.74-13.88). They argued that the strong association of snuff dipping with oral cancer noted by Winn et al.[14] (Study 13) may have been due to failure to adjust for alcohol use.

As support for this view they carried out a further analysis of the NMFS/NHIS data relating ever/never snuff use to oral cancer adjusted for age, sex and race but not for smoking, alcohol or occupation. here a significant relationship was seen, with a relative risk of 2.42 (95% CI 1.28-4.59). It is surprising that Sterling et al. did not also give the more fully adjusted relative risk for snuff use specifically (rather than for combined smokeless tobacco use as above) so that the effects of confounding for smoking, alcohol and occupation could be more directly seen.

Sterling et al. describe their treatment of missing data on smokeless tobacco as intended to be a "worst case scenario." The effect of this assumption is difficult to see as no data are given on the distribution of smokeless tobacco use in the living population to correspond with that given for the decedents (0-99, 100-9999, 10,000+, unknown). However it seems surprising that the calculated relative risk estimates for the 100-9999 group, which includes decedents but not living population with unknown smokeless tobacco use, were not enormously high, given that there were 836 oral cancer decedents with unknown use and only 11 with known use in the range 100-9999. In this context it should be noted that the distribution of smokeless tobacco use in the oral cancer cases (calculated from Table 1 of the source paper) was very different from that of decedents from digestive cancer, from cancers of sites other than oral or digestive or from causes other than cancer.

		Lifetime smokeless tobacco use				
Cause of death		0-99	100-9999	10,000+	Unknown	Total
Oral cancer	N	5863	11	266	836	6976
	%	84.0	0.16	3.81	12.0	100.0
Digestive cancer	N	96004	1296	4254	7960	109514
	%	87.7	1.18	3.88	7.27	100.0
Other cancer	N	302265	5647	13502	21888	343302
	%	88.0	1.64	3.93	6.38	100.0
Other causes	N	1309689	25499	72303	119394	1526885
(not cancer)	%	85.8	1.67	4.74	7.82	100.0

While the percentage of subjects with use 0-99 or 10,000+ in the four cause of death groups is reasonably similar, it is remarkable that there is a marked deficiency of oral cancer cases with use 100-9999 compared to other

groups. It could be argued that in view of the differences between the NMFS decedents and the NHIS living population in treatment of missing data, it might have been better to base analysis on NMFS data only, using some appropriate disease group as controls. This would clearly produce a very low relative risk of oral cancer in the 100-9999 use group. Using other causes (not cancer) as controls, for example, the following can be estimated:

Usage	Oral cancer relative risk (95% CI)
0-99 (base)	1.00
100-9999	0.10(0.05-0.17)
10,000+	0.82(0.73-0.93)
Unknown	1.56(1.45-1.68)

Although not adjusted even for age and sex, these relative risks are so implausible, particularly for the 100-9999 use group, as to cause worry about the whole analysis.

Clarification from the authors is necessary before any final conclusions could be reached.

STUDY 23 : Mashberg/USA: New Jersey (1993)

Mashberg et al.[47] carried out a study in New Jersey among US Veterans involving 359 male patients with invasive squamous cell carcinoma or carcinoma in situ of the oral cavity or oropharynx histologically diagnosed during 1972-1983 and 2280 male control patients without evidence of cancer or dysplasia of the pharynx, larynx, lung or oesophagus. At interview, 52 cases and 255 controls reported ever having used snuff or chewing tobacco. After adjustment for age, race, smoking and drinking, no increased risk of oral cancer was found for use of snuff (RR = 0.8, 95% CI 0.4-1.9) or chewing tobacco (RR = 1.0, 95% CI 0.7-1.4). One can also calculate an unadjusted relative risk estimate for total smokeless tobacco use of 1.35 (95% CI 0.98-1.86). The authors note that "the negative results of this study could be due to imprecision in the risk estimate given the small number of exposed individuals. However, the numbers are in fact higher than in many other studies and the upper confidence limits of the relative risks reported for both snuff and chewing tobacco are considerably below estimates from a number of other studies.

STUDY 24 : Perry/USA: Michigan (1993)

Gross et al.[13] cite results from a paper by Perry et al.[48] in 1993 referenced only as "available from the author." This related to a case-control study of oral cancer risk conducted at a hospital in Detroit, Michigan over a two-year period, involving 80 males and 53 females with oral cancer and 533 males and 145 females admitted for cardiovascular conditions. 10 cases (9 male) and 31 controls (all male) were users of smokeless tobacco. Various relative risks (adjusted using a log linear model) were reported as summarized below:

Exposure usage	Adjustment factors	Oral cancer relative risk (95% CI)
Any	None	1.70(0.81-3.55)
100-9999 times	Sex, race, age, cigarettes, alcohol, job type	1.86(0.69-4.98)
10000+ times	Sex, race, age, cigarettes, alcohol, job type	0.93(0.23-3.69)
100-9999 times	Sex, race, age	2.51(1.01-6.26)
10000+ times	Sex, race, age	1.30(0.35-4.85)

Gross et al. comment on the lack of a clear dose-response and the tendency for adjustment for cigarettes, alcohol and occupation to reduce the association from a significant to a non-significant one.

As may have been guessed from the method of analysis used, many of the authors of the Perry paper are common to the earlier paper by Sterling et al.[46] considered in Study 22.

STUDY 25 : Kabat/USA: Eight cities (1994)

Between 1977 and 1990 Kabat et al.[49] enrolled incident cases of histologically confirmed primary cancers of the lung, oral cavity and pharynx, larynx, oesophagus, bladder, kidney and pancreas in 28 hospitals in eight US cities as part of a case-control study of tobacco-related cancers. Each case was matched on age, sex, race, hospital and time of admission to a control patient with a disease thought not to be associated with tobacco or alcohol use and with no prior history of tobacco-related cancer. The analyses concerned 1097 male and 463 female cases of oral cancer (tongue, floor of mouth, gums, gingiva, buccal mucosa, palate, retromolar area, tonsil and other pharynx, but not nasopharynx) and 2075 male and 873 female controls.

Only limited results are reported for smokeless tobacco. For chewing tobacco results for men were as follows:

		Oral cancer cases		Oral cancer
Population	Adjustment	Total	Exposed	relative risk (95% CI)
Never smoked	None	82	4	2.25(0.69-7.34)
Ever smoked	None	1015	63	1.06(0.76-1.46)
Total	Ever/never smoked	1097	67	1.14(0.81-1.53)

Among the controls, the proportion ever having smoked was higher among chewers (91%) than among non-chewers (78%).

For women it was noted that the proportion of chewers was below 2% (with none among never smokers) but no information to calculate a relative risk was given.

As regards snuff use, it is noted that for males none of the 82 never smoking cases but 4 of the 448 never smoking controls did, giving a relative risk of 0.00 which is clearly non-significant. It is also noted that the proportion of snuff users was below 2% but no further information to calculate a relative risk was given.

It was also noted that the proportion of snuff users among women was below 2%. No further details are given for smokers, but among never smokers 4/113 cases, as compared to 0/470 controls, used snuff. A relative risk for this relation is given as 34.5 (95% CI 8.49-140.1) but it is unclear how this was calculated. Adding ½ to each entry of the 2x2 table, as is sometimes done, gives an estimate of 38.7. It is clear that the unadjusted association with snuff use in women is statistically significant, an exact test giving a two-sided p value of 0.0027.

Subsequently, Muscat et al.[50] reported further results from the same study. This time they were based on 687 male and 322 female cases of cancer of the oral cavity and pharynx (excluding salivary gland and nasopharynx) and 619 male and 304 female control patients enrolled between 1981 and 1990. Again only limited results were reported.

Among males 38 cases and 33 controls reported using chewing tobacco regularly (at least once a week for as long as a year), leading to an unadjusted relative risk estimate of 1.04 (95% CI 0.64-1.68), quite similar to that reported by Kabat et al.[49] No females reported regular use of chewing tobacco.

In males, regular use of snuff was reported by 9 cases and 10 controls, giving an unadjusted relative risk estimate of 0.81 (95% CI 0.33-2.00). In females, only 2 cases and 1 control reported regular snuff use, with the unadjusted relative risk 1.89 (95% CI 0.17-21.0).

Inasmuch as the data provided by Muscat et al.[50] relate to a shorter enrolment period and only to regular use, only the data provided by Kabat et al.[49] will be used in subsequent meta-analyses to avoid overlap.

STUDY 26 : Lewin/Sweden: Stockholm and southern region (1998)

Lewin et al.[51] attempted to identify all incident cases of cancer of the head and neck (squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, larynx and oesophagus) among men aged 40-79 living in Stockholm county or the southern healthcare region of Sweden in January 1988 to January 1991. Controls were selected by random sampling from a population register, stratified on region and age. Interviews were obtained from 545 of 605 (90%) identified cases and from 641 of 756 (85%) identified controls. Among the interviewed cases there were 128 with oral cavity cancer and 138 with pharyngeal cancer (75 oropharynx and 63 hypopharynx).

Relative risks for all cancers of the head and neck combined in relation to oral snuff use were as follows:

Population	Head and neck cancer cases Total	Snuff use	Head and neck cancer cases Users	Adjustment	Head and neck cancer relative risk (95% CI)
Never smokers	44	Ever	9	Age, region	4.7(1.6-13.8)
		Current			3.3(0.8-12.0)
		Former			10.5(1.4-118)
Former smokers	116	Ever	24	Age, region	1.1(0.6-1.9)
		Current			1.4(0.7-2.8)
		Former			0.8(0.4-1.8)
Current smokers	385	Ever	50	Age, region	0.8(0.5-1.2)
		Current			0.6(0.3-1.1)
		Former			1.0(0.5-2.0)
Total	545	Ever	83	Age, region,	1.1(0.7-1.5)
		Current	43	alcohol,	1.0(0.6-1.6)
		Former	40	smoking	1.2(0.7-1.9)

After adjustment for age, region, alcohol and smoking risk associated with snuff use did not significantly increase with:

(i) age at start of snuff use – RRs 1.0, 1.0 (0.6-1.6), 1.1 (0.7-1.8) for never, <25 years, 25+ years use;

(ii) duration of snuff use – RRs 1.0, 1.0 (0.70-1.6), 1.1 (0.6-2.0) for never, <30 years, 30+ years;

(iii) lifetime snuff consumption – RRs 1.0, 1.0 (0.7-1.6), 1.1 (0.6-2.0) for never, <125 kg, 125+ kg; or

(iv) intensity of usage of snuff – RRs 1.0, 0.8 (0.5-1.3), 1.6 (0.9-2.6) for never, ≤50 g/wk or >50 g/wk.

Relative risks associated with snuff use, again adjusted for age, region, smoking and alcohol intake, were presented by site of cancer. No significant associations were seen. For oral cavity and pharynx the results were as follows:

Cancer site	Cases Total	Snuff use	Cases Users	Relative risk (95% CI)
Oral cavity	128	Ever	25	1.4(0.8-2.4)
		Current	10	1.0(0.5-2.2)
		Former	15	1.8(0.9-3.7)
Pharynx	138	Ever	15	0.7(0.4-1.3)
		Current	8	0.7(0.3-1.5)
		Former	7	0.8(0.3-1.9)

In the discussion the authors point out that "Swedish" oral snuff is a moist unfermented tobacco, mainly produced from dark Virginia tobacco mixed with Kentucky tobacco and is used mainly in Sweden, to a lesser extent in the other Nordic countries and not at all elsewhere. They also note that, in comparison with countries where oral snuff is used, Sweden has a much lower incidence of head and neck cancer, especially cancer of the buccal mucosa or gingiva. This well designed study, which found a dose-dependent excess risk of cancer of the head and neck from tobacco smoking and alcohol consumption among Swedish males, concluded that "no increased risk was found for the use of Swedish oral snuff."

STUDY 27 : Schildt/Sweden: Northern counties (1998)

Schildt et al.[52] carried out a case-control study in the four most northerly counties of Sweden involving 410 cases of oral cancer (lip, tongue, gum and mouth) diagnosed during 1980-89 and 410 population controls. For the 175 living cases, an age/sex/county matched control was drawn from the National Population Registry, while for the 235 deceased cases a deceased control was selected from the National Registry for Causes of Death, matched also on year of death. Mailed questionnaires were sent to living subjects or to next-of-kin of relatives. Completed questionnaires were obtained from 354 matched pairs (237 male and 117 female; 143 alive and 211 deceased).

Only 13, 5 cases and 8 controls, had regularly chewed tobacco. A relative risk estimate taking the matching factors into account was calculated as 0.6 (95% CI 0.2-2.0).

67 cases and 72 controls had ever used snuff. Relative risks were 0.9 (95% CI 0.6-1.4) adjusted for the matching factors only and 0.8 (95% CI 0.5-1.3) in a multivariate analysis adjusted additionally for smoking and four aspects of alcohol consumption (light beer, beer, wine and liquor).

In further analysis adjusted for the matching factors only, relative risks were estimated as 0.7 (95% CI 0.4-1.1) for current snuff users and 1.5 (95% CI 0.8-2.9) for former snuff use, relative to never snuff use.

An analysis was also presented giving risk (relative to those who had never smoked or used snuff) for nine categories of snuff by smoking. These can be converted to give risk estimates for snuff use (relative to never snuff use) by level of smoking.

Smoking habits	Oral cancer cases Total	Snuff	Oral cancer cases Exposed	Oral cancer relative risk (95% CI)
Never	152	Former	9	1.80(0.90-3.50)
		Current	19	0.70(0.40-1.20)
		Any	28	1.01(0.66-1.56)
Former	85	Former	16	1.78(0.80-3.96)
		Current	15	0.67(0.30-1.50)
		Any	31	1.09(0.59-2.03)
Current	122	Former	3	1.82(0.77-4.33)
		Current	10	0.71(0.32-1.54)
		Any	13	1.10(0.58-2.06)

The source table can also be used to demonstrate that, among the controls, the proportion ever having smoked was somewhat higher in those who had ever used snuff (40/67 = 60%) than in those who had never done so (138/282 = 49%). The proportion ever having drunk alcohol was also higher in ever snuff users (42/53 = 79%) than in never snuff users (134/259 = 52%).

Analyses were also carried out relating to lifetime oral snuff use. Relative risks were estimated as 0.8 (95% CI 0.4-1.5) for lifetime consumption of less than 156.0 kg and 1.1 (95% CI 0.5-2.0) for greater consumption than this.

For lip cancer considered alone, the risk was 1.8 (95% CI 0.9-3.7) among former snuff users, but "close to unity" for current users. For all other sites combined a decreased risk was found for current users, with a relative risk of 0.4 (95% CI 0.1-0.9).

The results are generally consistent with a lack of effect of Swedish oral snuff (and chewing tobacco) on risk of oral cancer. The authors comment on the much higher concentration of nitrosamines in American snuff (up to 18-fold higher) compared with Swedish snuff, as well as a 1.5 to 2 fold higher concentration of nicotine in American snuff, as a possible explanation for differences in findings between Swedish and American studies.

3.2 Prospective studies

STUDY 28 : Smith/USA: Tennessee (1970, 1975)

In 1970 Smith et al.,[53] from the University of Tennessee College of Dentistry, reported results from a study in which 20,000 patients in clinics received oral cytology smears. Over 15,000 patients were snuff users (many for 30-60 years), of which 1,751 showed "any type of visible oral mucosal membrane change that offered criteria for further diagnostic study." Of these 1,751, 157 showed "tissue changes that clinician thought should undergo biopsy." None of the biopsies showed "changes consistent with dyskeratosis or malignancy." Over 75% of the patients (apparently but not clearly the 1,751) had, at the time of publication, been followed clinically with repeat cytological smears at six-month intervals for 5½ years and none showed "any mucosal change or findings other than those from the original testing."

Later, in 1975, Smith[54] reported on an attempt to follow up the 1,751 patients for a further 4½ years. 201 were lost to follow-up but in the remaining 1,550 no oral cancers were seen. Smith[54] concluded that "the type of snuff used in this country cannot logically be considered as carcinogenic in view of the large number of patients who have used snuff for many years with no clinical or histological evidence of tissue change." It is interesting to note, however, that in their first paper Smith et al.[53] also referred to an additional study of 500 snuff users from hospital, with an average duration of snuff use of 47 years, where two epithelial carcinomas were seen.

Both IARC[1] and the US Surgeon-General[12] have criticized the study for failure to give details of the methods employed for follow-up. Inasmuch as no deaths among cohort members were reported, it seems likely that persons who died and persons who developed cancer may have been lost to follow-up. IARC[1] also complain that the "consistent lack of clear specification as to which subset of the study group reference is being made makes it difficult to determine who was examined or followed-up." The US Surgeon-General[12] considers Smith's data uninterpretable.

STUDY 29 : Schuman 1/Norway (1982)

In two abstracts Bjelke and Schuman[55] and Schuman et al.[56] reported results from a cohort study of 12,945 men in Norway followed from 1967-1978. Regular users of oral tobacco were found to have a relative risk of 2.8 for cancer of the buccal cavity and pharynx. This was noted to be statistically significant but further detail was not available. [Note that this text was derived from the reports by the IARC[1] and the US Surgeon-General[12], only the first of the source papers so far having been obtained, the other apparently being incorrectly cited in the two reports.]

STUDY 30 : Schuman 2/US Insurance policy holders (1982)

In the same two abstracts Bjelke and Schuman[55] and Schuman et al.[56] also reported results from a cohort study of 16,930 USA men who had been policy holders of an insurance association and who had been followed up from 1966-1981. Tobacco use had been assessed by postal questionnaire. Somewhat increased relative risks in relation to smokeless tobacco use were reported for various types of cancer (pancreas, prostate and oesophagus) but presumably were not seen for cancer of the oral cavity or pharynx as results were not given. [Note that this text was derived from the reports by the IARC[1] and the US Surgeon-General[12], only the first of the source papers so far having been obtained, the other apparently being incorrectly cited in the two reports.]

STUDY 31 : Zahm/US Veterans (1992)

In the US Veterans study 248,046 veterans (virtually all white males) provided tobacco-use histories on a mailed questionnaire in 1954 or 1957. Zahm et al.[57] investigated the relationship of tobacco use to mortality by 1980 from soft tissue sarcoma (the main interest of the paper), buccal cavity cancer and pharynx cancer. There were 74 deaths from buccal cavity cancer and 55 from pharynx cancer. The authors reported the following relative risks for smokeless tobacco use adjusted for age and period of follow-up:

Cancer site	Exposure to smokeless tobacco	Relative risk (95% CI)*
Buccal cavity	Ever	3.0(2.0-4.5)
	Frequent**	3.4(2.1-5.6)
	Infrequent	1.9(1.0-3.5)
Pharynx	Ever	8.7(4.1-18.3)
	Frequent**	11.2(5.0-25.0)
	Infrequent	4.5(1.7-11.7)

* Relative to those who never used smokeless tobacco
** Practically every day

The authors noted that the risk of pharyngeal cancer rose with younger age at first use of smokeless tobacco, with those starting before age 14 having a relative risk of 20.7 (95% CI 8.0-53.7). No corresponding data were given for buccal cavity cancer. No striking trends in risk were seen for other use characteristics (ex/current status, duration, age at cessation) for either buccal cavity or pharyngeal cancer.

Those who reported smokeless tobacco use were far more likely to be smokers than those who did not, as shown in the table below (in which veterans with unknown smokeless tobacco or smoking habits are excluded):

		Smoked other tobacco products	
Smokeless tobacco use	Persons	Number	Percent
Yes	45759	43451	95.0
No	197684	144943	73.3

The authors commented on the potential for confounding by smoking when studying relationships with smokeless tobacco use, but did not attempt any analyses adjusted for smoking. Possible confounding by alcohol was not discussed.

STUDY 32 : Nyren/Sweden (1998)

In his review of the evidence on snuff dipping, Nilsson[15] referred to three studies conducted that do not support an association between oral cancer and the use of the special brand of non-fermented moist snuff (snus) used in Sweden. Two were the case-control studies described earlier by Lewin et al.[51] and by Schildt et al.[52] The other was a prospective study by Nyren et al. which Nilsson described as "" very large prospective study that was recently completed by researchers at the well-known Karolinska Institute and has provided essentially the same results as the two Swedish investigations mentioned above." However the paper cited was noted to be submitted for publication, and a Medline search did not reveal that such a paper had in fact been published. Nor did Nilsson present any detailed findings from the study.

3.3 Other epidemiological data

In a letter to the Lancet in 1987, Davis and Severson[58] reported data on trends in tongue cancer in the USA in 1973-1984 based on the SEER programme of the National Cancer Institute which consists of cancer registers encompassing about 13% of the population. They reported that over this period tongue cancer incidence rates had risen about 3-fold in men aged 30-39, though much less clear trends were evident in women or, in either sex, in other age groups. They noted that in the past 15 years, the production of smokeless tobacco products has increased by 42% and speculated that the rise in tongue cancer in men may be a result of this.

In 1992 Sterling et al.[46] noted that regional analyses of cancer mortality have shown a higher risk of cancer of the buccal cavity and pharynx in white Southern women relative to white Northern women and this may possibly underlie major studies exploring a potential relationship between cancer of the oral region and use of smokeless tobacco having centred on the American South-East.

In 1995 Vigneswaran et al.[59] commented on the earlier proposal of Rodu[60] that smokeless tobacco be considered as "an alternative nicotine source for smokers who are unable or unwilling to quit smoking entirely." Based on the study of Winn et al.[14], they note that "the relative risk of oral cancer with smokeless tobacco use is 4.2, about half the risk from smoking (relative risk = 10 to 15)." They pointed out that "mortality data from populations with sustained high-frequency smokeless tobacco use do not support the mistaken prediction of an epidemic of oral cancer with increasing smokeless tobacco use." They estimated that, assuming an incidence rate of smokeless tobacco-induced oral cancer of 26 cases per 100,000 long-term users[14], and that the nation's current 46 million smokers used smokeless tobacco instead, "12,000 new cases of oral cancer would occur annually." These 12,000 cases "represent less than 5% of all smoking-related cancers, less than 10% of smoking-related lung cancers, and less than 50% of the 27,000 oral cancers now attributed to smoking each year." In terms of mortality, "the 6,000 deaths

that would result pales in comparison with the [estimated] 419,000 Americans [who] die yearly from smoking-related illnesses."

In 1998 Bouquot and Meckstroth[61] presented estimates by U.S. state of the percent use of smokeless and of smoked tobacco among males older than 18 years of age in 1993 and the age-adjusted mortality rate from oral/pharyngeal cancer for males in 1990-1994. No correlation was seen between smokeless tobacco use and oral/pharyngeal cancer rates. West Virginia, the state with the highest smokeless tobacco use in men, had only the 26th highest rate, while Washington State, the state with the highest mortality rate, had a very low rate, only 47th of the 51 states with data. The authors also noted that:

"
- there seems to be no increase in the prevalence of oral cancer among US baseball players, who are frequent users of snuff and chewing tobacco,
- malignant transformation of smokeless tobacco keratosis seems to be a rare event,
- very few oral cancers have been produced in laboratory animals by the exclusive use of smokeless tobacco (i.e. without the use of extreme concentrations or added etiologic factors)."

4. Summary of the epidemiological evidence

4.1 Study details

Table 1 summarizes information from each of the 32 epidemiological studies considered in section 3.1 (case-control) and 3.2 (prospective) concerning their year of publication, location and study design.

Of the 32 studies considered, 1 was reported in the 1920s, 3 in the 1950s, 4 in the 1960s, 4 in the 1970s, 11 in the 1980s and 9 in the 1990s. About half of the studies were not available at the time of the 1986 review by the US Surgeon-General.[12]

23 studies were conducted in the USA, 5 in Sweden and one each in Puerto Rico, England, Brazil and Norway. The distribution is unsurprising given that USA and Sweden are the major users of smokeless tobacco. Within the USA the distribution of study regions was as follows:

Area		Studies	Study numbers*
National		4	10, 22, 30, 31
8 cities (unstated)		1	25
North East	: New England	0	-
	: Middle Atlantic	6	3, 7, (11), (14), (17), 23
Mid West	: East North Central	3	(14), 16, 24
	: West North Central	2	1, 2
South	: South Atlantic	6	5, 6, (11), 13, 15, (17)
	: East South Central	2	(14), 28
	: West South Central	3	(11), 12, 18
West	: Mountain	0	-
	: Pacific	4	(11), (14), (17), 21

*Bracketed numbers indicate studies conducted in more than one area.

Five of the studies were of prospective design, with the other 27 case-control. Most, 20, of the case-control studies used diseased controls, mainly hospital patients, while 6 used healthy population controls and 1 used both types. The studies with diseased controls used a variety of selection criteria. Inasmuch as diseases associated with smokeless tobacco use are little understood and many of the studies did not have smokeless tobacco as their major concern anyway (see Table 3 later), it is not unexpected that no common criteria were used. Of

the 21 studies using diseased controls, 7 (studies 3,4,10,11,14,15,25), mainly those conducted by Wynder or his colleagues, excluded diseases associated with smoking and a further 5 (studies 2,8,19,20,23) excluded all other cancers. However, some (studies 1,5,7,12,18,23) were happy to accept essentially all patients other than those with the case diseases. Of course, if smokeless tobacco has little effect on disease rates generally, it should not matter too much which control group is used provided it does not contain a high proportion of those with a disease quite strongly related to smokeless tobacco use.

In most of the studies, data were collected directly from the subjects by interview or by mailed questionnaire. However in five studies data were provided partly or wholly by next-of-kin or other surrogate. In study 9 data for 83% of cases and 4% of controls were provided by surrogates, while the corresponding percentages were 51% and 21% in study 13 and 22% and 2% in study 17. In study 22 all data for (decedent) cases came from surrogate interviews, whilst the majority of interviews with subjects were conducted directly. The higher rate of surrogate interviews in cases than in controls in these studies is unsatisfactory as a surrogate may be less aware of the subject's history of smokeless tobacco use (and of smoking, alcohol use, etc) than the subject him or herself. In study 27 controls were matched with cases on vital status, with the questionnaires sent to subjects if alive and to next-of-kin if dead. This design is preferable to that used in studies 9, 13, 17 and 22. In two studies, the medical records appear to have been the source of information. In study 12, it is likely that this would have led to a much greater likelihood of smokeless tobacco use being reported by cases than controls.[1] In study 15, information on cases and controls was stated to have been obtained "by cohort and histopathology review at reporting institutions" and it is difficult to judge whether the questions asked of cases and controls would have been comparable. In some studies, the source of information on smokeless tobacco use was not stated at all or unclearly described.

Table 2 gives information on the number of cases and controls considered as well as details of the types of oral and pharyngeal cancer

considered and whether histological confirmation was insisted on. The total number of cases of oral and pharyngeal cancer considered by the various studies can be summarized as follows.

Number of cases	Number of studies	Study numbers
<50	2	5,28
50-99	4	7,9,12,20
100-199	5	2,18,21,24,31
200-499	10	4,6,8,10,13,16,19,23,26,27
500-999	4	1,3,11,14
1000+	4	15,17,22,25
Unknown	3	29,30,32

The study involving most cases is study 22, with 6976 oral and pharyngeal cancer cases.

For specific sites, or combinations of sites, the number of studies providing data are as follows:

Site	Number of studies	Study numbers
Lip	7	1,3,4,6,10[a],15,20
Tongue	5	3,4,10[a],15,18
Gum	2	3,4
Mouth	4	3,4,8,18
Gum and mouth	6	2,5,9,10,12,15
Oral (buccal) cavity	11	6,7,11,16,18,19,24,26,27,28,31
Pharynx	11	3,4,6[b],7,8,10,15,16,18,26,31
Oral and pharyngeal	20	3,4,6[b],7,8,10,13,14,15,16,17, 18[b],21[c],22,23[c],25,26[d],29,30,31
Unknown	1	32

([a] Only lip and tongue combined, [b] Includes larynx, [c] Except hypopharynx, [d] Includes larynx and oesophagus)

This table is not completely reliable as few studies reported ICD codes, for many of the studies the definition was not precisely stated, and for one study was unknown.

In the five prospective studies (28-32) and the study based on the NMFS (22), death certificates were used and presumably histological confirmation was not insisted upon. In the remaining 26 case-control studies, histological confirmation was known to have been insisted on in 16 of the studies. Histological confirmation of all cases may also have been a requirement in some of the other studies. In practice, the requirement may be relatively unimportant, because accuracy of diagnosis is far less of a problem for tumours of the oral cavity and pharynx than it is for tumours of internal organs.

In case-control studies, the relative frequency of controls to cases varied markedly by study. In 9 studies (5,6,8,10,11,15,22,23 and 24), there were many more controls than cases, while in 4 studies (9,13,19,25), there were about twice as many. With the exception of study 2, where there were markedly more cases than controls, the number of cases and controls were equal or about equal in the other studies.

Table 3 summarizes information about availability of results relating to smokeless tobacco. 13 of the studies (2,5,12,13,15,22,24,26-30,32) particularly concerned chewing tobacco, snuff or smokeless tobacco, as judged by inclusion of these words in the title of the paper. Others tended to be concerned with smoking and/or alcohol or be more wide-ranging. For the majority of studies, information on lifetime history of use appears to have been collected (although sometimes this is inferred by statements in the paper concerning having collected smoking and alcohol history data). Two studies (2 and 5) only gave information relating to 20+ years of use while one study (8) restricted attention to those using smokeless tobacco in the last 20 years. For some of the early studies (1,7,9), it appeared that the investigators had only asked about current use though this was not totally clear. 13 of the studies (1,3,4,6,8,9,11,14,16,18,23,25,27) provided results relating specifically to chewing tobacco, though for one of these (4) there are doubts as to whether this is correct. 17 of the studies (1,6,7,11-14,16,18,20,22,23,25-28,32) provided results relating specifically to snuff use, while 13 studies (2,5,10,15,17,19,21-24,29-31) provided information on total smokeless

tobacco use, most of these not presenting separate results for chewing tobacco or snuff.

In the great majority of the studies, analyses just compared users and nonusers. Only in 8 studies (6,10,13,14,22,24,26,27) was any further detail available on such factors as duration of use, time spent in mouth per day, total lifetime consumption and current/former use.

Table 4 gives details of how potential confounding variables have been taken into account (not known for study 32). As regards the sexes, the great majority of the studies were of males or females only or presented results separately for the two sexes. 4 studies (15,22,24,27) presented results for the sexes combined with adjustment for sex made in analysis. 4 studies did not take sex into account at the analysis stage, 3 studies (9,19,20) relying on the matching and the other (1) comparing cases that were 98% male with controls that were 100% male.

4 studies (1,4,8,16) did not take age into account at all, in one of which (1) the cases and controls were very different in average age. A further 8 studies (3,7,9,12,14,19,20,25) matched their cases and controls on age, but did not follow the recommended standard procedure[23] of adjusting in analysis for any factor thought important enough to match on.

Adjustment for race was carried out in 8 studies (10,11,13,15,17,22,23,24) with a further study (2) restricting attention to Whites. Two further studies (14,25) matched but did not adjust for race. Only US studies took race into account by adjustment or matching.

It was notable that, when analysing data for smokeless tobacco use, smoking and alcohol consumption were rarely taken into account, despite their known importance in the aetiology of oral and pharyngeal cancer. Only 6 studies (13,22-24,26,27) adjusted for both. No other study took alcohol into account but, for some other studies (1,2,10,15,20), results adjusted for, or stratified on, smoking were available.

As shown in Table 4, some studies adjusted or matched for other variables also. Often these related to features of the study such as location, hospital, vital status of respondent and admission period. Occupation/employment was adjusted for in 3 studies (13,22,24).

Relatively few studies provided information on the joint distribution of smokeless tobacco and either smoking or alcohol in their control populations. While study 1 reported a similar frequency of smoking in chewers and non-chewers, study 25 reported a higher frequency in chewers and study 31 reported a higher frequency in smokeless tobacco users. Study 13 reported a lower frequency of smoking in snuff users than in non-users but study 27 reported a higher frequency of smoking and alcohol consumption in snuff users.

4.2 Relative risk estimates for chewing tobacco

Table 5 gives all available relative risk estimates for oral and pharyngeal cancer associated with chewing tobacco. A total of 12 studies, all conducted in the USA except study 8 (Puerto Rico) and study 27 (Sweden) provide data, and all are of case-control design. Study 4 merely gave information that there was either no association (for 4 sites) or there was a non-significant increase (for 2 sites) and its estimates cannot be used in meta-analyses. As there was doubt as to whether its results actually related to chewing tobacco or snuff, it is unclear whether one would have wanted to include its results anyway. Study 1 is of obviously weak design, comparing cases of mean age 57 with controls of mean age 36. Study 9 is also weak, partly because there is a large time difference between when the cases got cancer and when the controls were interviewed and partly because of a much higher proxy response for cases than for controls.

Table 5 presents a total of 32 relative risks with confidence limits, relating to a variety of site/sex/smoking habits/adjustment factors, of which 11 are statistically significant (at $p<0.05$). The distribution of significant results is, however, clearly non-random, with two in study 1, four in study 3, four in study 6 and one in study 8 and none in any of the studies published since 1970 (9,11,14,18,23,25,27).

A first-meta-analysis was conducted using the 14 estimates shown overleaf. These use the widest site definition available, and, apart from study 8, where independent estimates are available by sex and smoking, each study provides only one estimate. Based on these estimates, a fixed-effect estimate of 1.33 (95% CI 1.18-1.51) was obtained with a highly significant ($p<0.001$) heterogeneity χ^2 statistic of 46.3 on 13 d.f. Using random-effects meta-analysis gave an estimate of 1.29 (95% CI 0.99-1.68). Omitting the very weak studies (1 and 9) gave a fixed-effects estimate of 1.25 (95% CI 1.09-1.44), but the heterogeneity remained ($\chi^2 = 36.6$ on 11 d.f., $p<0.001$), the random effects estimate now being 1.27 (95% CI 0.96-1.69).

Relative risks of oral/pharyngeal cancer associated with chewing tobacco

Study No.	Name	Cancer site	Sex	Relative risk (95% CI)	Adjustment factors
1	Broders	Lip	M+F	2.05 (1.48-2.83)	Smoking
3	Wynder 1	Oral/pharyngeal	M	2.00 (1.16-3.47)	Smoking (smoker)
6	Vogler	Mouth/pharynx/larynx	M	4.48 (2.71-7.41)	Residence
8	Martinez	Mouth/pharynx/oesophagus	M	1.27 (0.84-1.92)	Smoking (smoker)
			F	0.75 (0.34-1.61)	
		Mouth/pharynx	M	2.29 (0.62-8.47)	Smoking (nonsmoker)
			F	0.34 (0.04-2.79)	
9	Browne	Mouth/gum	M+F	0.67 (0.27-1.66)	None
11	Wynder 3	Oral cavity	M	1.15 (0.85-1.55)	None
14	Wynder 4	Oral/pharyngeal	M	1.00 (0.62-1.61)	None
18	Spitz	Oral/pharyngeal/larynx	M	1.00 (0.53-1.89)	None
23	Mashberg	Oral cavity/oropharynx	M	1.00 (0.70-1.40)	Age,race,smoking,alcohol
25	Kabat	Oral/pharyngeal	M	1.14 (0.81-1.53)	Smoking
27	Schildt	Oral	M+F	0.60 (0.20-2.00)	Age,sex,region,vital status
					Heterogeneity
Include		Meta-analysis			
All studies		Fixed-effects		1.33 (1.18-1.51)	$\chi^2 = 46.33$ on 13 df ($p<0.001$)
		Random effects		1.29 (0.99-1.68)	
Exclude		Fixed-effects		1.25 (1.09-1.44)	$\chi^2 = 36.59$ on 11 df ($p<0.001$)
studies 1 and 9		Random effects		1.27 (0.96-1.69)	

These data do not provide convincing evidence of a true effect of chewing tobacco for a number of reasons. First, the random-effects estimates are not significant (at $p<0.05$). Second, estimates from studies conducted since 1969 (8,9,11,14,18,23,25,27) show no indication of an effect with a fixed-effect estimate of 1.07 (95% CI 0.92-1.24) and no indication of heterogeneity ($\chi^2 = 6.52$ on 10 d.f., $p = 0.77$). Third, of the 14 estimates only 1 adjusts for alcohol consumption and 8 for smoking, with 4 unadjusted for any factor including age. Confounding cannot be ruled out.

Although the analyses above do not show any convincing evidence of an effect of chewing tobacco, it is nevertheless theoretically possible that it might have an effect on a specific part of the oral cavity and pharynx. Three of the studies provided relative risks by site. In study 3, there was no real evidence of variation in risk by site, with relative risks for the 8 sites studied varying between 1.31 and 2.89 and all being statistically consistent with the overall estimate of 2.00 for all oral and pharyngeal cancer. In study 8, where such data were variable and had huge sampling variation, no reliable conclusions could be drawn. In study 6, relative risk estimates were higher for the buccal cavity (RR = 8.52, 95% CI = 4.79-15.2) than for the lip (RR = 4.51,

95% CI = 2.06-9.89) or pharynx/larynx (RR = 2.74, 95% CI = 1.34-5.60). However, the overall estimate for mouth/pharynx/larynx combined for this study of 4.48 (95% CI 2.71-7.41) was clearly atypically high compared to that seen in the other studies, and was mainly responsible for the heterogeneity seen in the original meta-analyses, making the relevance of this site variation difficult to interpret. It is clearly unfortunate that none of the studies of chewing tobacco conducted since 1970 have attempted to present results by site.

Three studies have looked at the relationship of oral/pharyngeal cancer to chewing tobacco specifically in nonsmokers. Study 1 has been noted already to be weak, while studies 8 and 25 were based on very few exposed cases, 5 and 4 respectively. Relative risks were 1.65 (95% CI 0.85-3.19) for lip cancer in study 1, 2.25 (95% CI 0.69-7.34) for oral/pharyngeal cancer in study 25 and 2.29 (95% CI 0.62-8.47) in males and 0.34 (95% CI 0.04-2.79) in females for mouth and pharynx cancer in study 8. Together these give a combined relative risk estimate of 1.68 (95% CI 1.00-2.80), or 1.72 (95% CI 0.76-3.87) omitting the weak study 1.

None of the studies provided any useful information on any aspect of the dose-response relationship of chewing tobacco to risk of oral/pharyngeal cancer.

Overall the data do not provide convincing evidence of an effect of chewing tobacco specifically on the risk of oral/pharyngeal cancer.

4.3 Relative risk estimates for snuff use

Table 6 gives results from 15 studies that have reported results relevant to the relationship of snuff use with oral and pharyngeal cancer risk. Results from the only study of prospective design (study 28), which merely noted that no such cancers were seen in snuff users in the patients followed up, cannot usefully be considered in meta-analysis. The remaining studies, which provide more useful data, are all of case-control design and all conducted in the USA except for three (studies 20, 26 and 27) that were conducted in Sweden. As noted in the previous section, there is an additional case-control study (study 4) which may have provided results on snuff use, but again its findings cannot be used in meta-analysis. Of the 14 studies providing actual relative risk estimates, two are of obviously weak design. One is study 1 which, as noted above, compared cases and controls of very different mean age. the other is study 12, which has been criticized[1] for using a design which made snuff use far more likely to be detected in cases than in controls. It is clear from inspection of Table 6 that the results are quite heterogeneous, with some studies (1,11,14,20,23,26,27) providing little or no evidence of a relationship of snuff use with cancer at any of the sites considered and some studies (6,7,12,13,25) including relative risk estimates that are large and very highly significant indeed.

The table overleaf presents relative risk estimates from each study using the widest site definition available. With the exception of studies 20 and 25, where the only available estimates are for never smokers, the estimates selected are relevant to smokers and nonsmokers combined. Where there is a choice, the estimate selected is adjusted for the most potential confounding factors. In the case of studies 26 and 27 results relating to ever use (rather than current or former use) are selected for conformity with other studies. Based on the 14 estimates, a fixed-effects meta-analysis relative risk estimate of 1.85 (95% CI 1.55-2.22) can be calculated which has a very large heterogeneity chisquared statistic of 123.7 on 14 d.f. ($p<0.001$). For these data the random-effects estimate of 2.31 (95% CI 1.23-4.32) is larger, still significant, but with wider variation. Removing studies 1 and 12, noted to be

Relative risks of oral/pharyngeal cancer associated with snuff use

Study No.	Name	Cancer site	Sex	Relative risk (95% CI)	Adjustment factors
1	Broders	Lip	M+F	1.75 (0.12-26.5)	None
6	Vogler	Mouth/pharynx/larynx	F	14.60 (8.19-26.0)	Age,residence
7	Vincent	Oral cavity/pharynx	M	4.22 (1.41-12.6)	None
11	Wynder 3	Oral cavity	M	0.62 (0.32-1.21)	None
12	Westbrook	Gum/buccal mucosa	F	540 (61.0-4783)	None
13	Winn	Oral/pharyngeal	F	2.67 (1.83-3.90)	Race,smoking
14	Wynder 4	Oral/pharyngeal	M	0.42 (0.11-1.65)	None
18	Spitz	Oral/pharyngeal/larynx	M	3.40 (1.00-10.90)	Age?
20	Blomqvist	Lower lip	M+F	0.67 (0.08-5.75)	None
22	Sterling	Oral/pharyngeal	M+F	2.42 (1.28-4.59)	Age,sex,race
23	Mashberg	Oral cavity/oropharynx	M	0.80 (0.40-1.90)	Age,race,smoking,alcohol
25	Kabat	Oral/pharyngeal	M+F	4.81 (1.19-19.4)	None
26	Lewin	Head and neck	M	1.10 (0.70-1.50)	Age,region,smoking,alcohol
27	Schildt	Oral cavity	M+F	0.80 (0.50-1.30)	Matching factors,smoking,alcohol

Include	Meta-analysis		Heterogeneity
All studies	Fixed-effects	1.85 (1.55-2.22)	χ^2 = 123.7 on 13 df (p<0.001)
	Random effects	2.31 (1.23-4.32)	
Exclude 1,12	Fixed-effects	1.78 (1.49-2.14)	χ^2 = 79.5 on 11 df (p<0.001)
	Random effects	1.80 (1.00-3.27)	
Exclude 1,12,20, 26,27	Fixed-effects	2.59 (2.06-3.26)	χ^2 = 69.7 on 8 df (p<0.001)
	Random-effects	2.26 (1.08-4.75)	
20,26,27 only	Fixed-effects	0.97 (0.72-1.30)	χ^2 = 1.16 on 2 df (p=0.56)

of inadequate design, the fixed-effects estimate reduces to 1.78 (95% CI 1.78-2.14) but again heterogeneity is substantial (p<0.001), the random-effects estimate now being 1.80 (95% CI 1.00-3.27). One obvious source of heterogeneity is country. The three Swedish studies show no evidence of effect or heterogeneity, with the overall relative risk estimate 0.97 (95% CI 0.72-1.30). In contrast, there is evidence of an association and heterogeneity (p<0.001) in the US studies (again omitting studies 1 and 12) with the fixed-effects estimate 2.59 (95% CI 2.06-3.26) and the random-effects estimate 2.26 (95% CI 1.08-4.75).

Looking further at the data from the Swedish studies in Table 6, it can be seen that the detailed analyses available from study 27 provide no indication at all of an effect of snuff in any site, smoking group or snuff use group. Those for study 26 shown no evidence of an effect of current, former or ever use at any site or overall in current or former smokers. The only

significant relative risks relate to use of snuff in never smokers, where estimates are 4.7 (95% CI 1.6-13.8) for ever use, 3.3 (95% CI 0.8-12.0) for current use and 10.5 (95% CI 1.4-117.8) for former use. None of these estimates is highly significant and, taken in conjunction with the lack of evidence of an effect in never smokers in studies 20 and 27, and in current or former smokers in studies 26 and 27, the overall data can be regarded as consistent with Swedish oral snuff having no effect on risk of oral/pharyngeal cancer. This view is strengthened by further analyses from study 26 showing no significant trend in risk of head and neck cancer with age at start of snuff use, duration of snuff use, lifetime snuff consumption or intensity of usage of snuff, and by study 32 which was reported as finding no association of oral cancer with snuff use but with no actual data being available for analysis.

The association seems to be restricted to the US studies and it is useful to investigate further the evidence from the nine studies of interest (6,7,11,13,14,18,22,23 and 25). These fall into three groups.

1. Three studies (11,14,23) reported a non-significantly **lower** risk of oral/pharyngeal cancer associated with snuff use and reported no further results by site of cancer or by smoking habit.
2. Three studies (18,22,25) reported an increased risk of oral/pharyngeal cancer associated with snuff use and reported no further results by site of cancer or by smoking habit. Study 25 reported a high relative risk for female never smokers, based on only four exposed cases, but saw no cases in never smoking males and did not report results for smokers. Study 18 reported an increased risk that was not statistically significant, based on only nine exposed cases. Study 22 was much larger and reported a relative risk of 2.42 (95% CI 1.28-4.59) after adjustment for age, sex and race. This relative risk was only cited to indicate the dangers of bias due to failure to adjust for smoking, occupation and particularly alcohol consumption, it being reported by the authors[46] that there was no association when these factors were adjusted for in analysis. However, the data presented showing a lack of association were for **smokeless tobacco use** and not snuff use.

3. Three studies (6,7,13) reported a markedly increased risk of oral/pharyngeal cancer associated with snuff use and did report fuller details. As shown in the table below, all three studies reported a much higher relative risk for cancer of the buccal cavity than for cancers of the pharynx (or the rest of the mouth).

Study No	Name	Sex	Cancer site	Relative risk (95% CI)	Cancer site	Relative risk (95% CI)
6	Vogler	F	Buccal cavity	40.6 (22.5-73.6)	Pharynx/larynx	1.82 (0.41-8.13)
7	Vincent	M	Oral cavity	7.13 (2.19-25.2)	Pharynx	1.90 (0.43-8.42)
13	Winn*	F	Gum/buccal mucosa	26.4 (5.65-120)	Other mouth/pharynx	2.10 (1.03-4.28)

(*Results for never smokers)

The set of relative risks for cancer of the oral/buccal cavity is strikingly high, particularly those in the two studies of women. Note also that study 12, though clearly flawed, reported a huge relative risk of cancer of the gum and buccal mucosa in women associated with snuff use, which seems unlikely to be wholly due to over-reporting in cases relative to controls.

Meta-analyses of data from these three studies seem inappropriate since the relative risk (fixed-effects) for oral/pharyngeal cancer as a whole was so much greater for these three studies (4.43, 95% CI 3.27-6.00) than for the other six (1.27, 95% CI 0.89-1.80, $p<0.001$). However there does seem to be a clear association of cancer of the gum and mouth to snuff use. The estimates from studies 6 and 7 were not adjusted for smoking or alcohol use and may be subject to confounding. However those for study 13 were restricted to never smokers and the authors, Winn et al.,[14] reported that adjustment for a variety of factors including alcohol did not affect the associations materially. Winn et al. also reported a marked tendency for risk of cancer of the gum and buccal mucosa to increase with duration of exposure to snuff.

Although there does seem to be an association of snuff use with cancers other than of the gum or mouth in the data shown above, it is unclear whether this is a real effect, partly because the association is much weaker, so more liable to the effects of confounding or other biases, and partly because

corresponding relative risks were not available for the other studies which reported a much weaker association with oral/pharyngeal cancer generally.

4.4 Relative risk estimates for unspecified smokeless tobacco use

Table 7 gives results from 14 studies that have reported results relevant to the relationship of unspecified smokeless tobacco use with oral and pharyngeal cancer risk. Results from study 29, which reported a significant increase in buccal cavity/pharynx cancer risk cannot be included in meta-analysis as confidence limits are not available. Nor, for similar reasons, can results from studies 16 and 30 be included, these studies finding no significant increase in the cancers studied associated with smokeless tobacco use. Of the 11 studies providing more useful data, 10 are of case-control design, only study 31 being prospective. Ten were conducted in the US, study 19 being carried out in Brazil.

The table overleaf presents relative risk estimates from each study using the widest site definition available. Estimates from studies 22 and 24 are given separately for low and high smokeless tobacco use, while estimates for study 31 are given separately for buccal cavity and for pharynx. Although these two estimates in each pair are strictly not completely independent, they will be taken to be so for the purposes of meta-analysis, any resultant error being likely to be minimal. All the estimates relate to smokers and nonsmokers combined. Where there is a choice, the estimate selected is the one adjusted for the most potential confounding factors.

Five of the 17 estimates selected are statistically significant at $p<0.05$. The fixed-effects relative risk estimate is 1.73 (95% CI 1.48-2.03). However, there is highly significant heterogeneity between estimates ($\chi^2 = 49.4$ on 16 d.f., $p<0.001$) and a random-effects estimate is rather higher at 1.93 (95% CI 1.41-2.64). The heterogeneity arises mainly because of the relatively low estimate for males of 0.85 (95% CI 0.57-1.26) in study 17 and the relatively high estimates of 3.00 (95% CI 2.00-4.50) for buccal cavity and of 8.70 (95% CI 4.10-18.30) for pharynx cancer in study 31, each with a relatively high weight. If studies 17 and 31 were omitted from analysis on the basis that they produce outlying results, this would remove the significant heterogeneity

Relative risks of oral/pharyngeal cancer associated with unspecified smokeless tobacco (SLT) use

Study No.	Name	Cancer site (SLT use)	Sex	Relative risk (95% CI)	Adjustment factors
2	Moore	Lip/mouth	M	3.00 (1.37-6.54)	Race
5	Peacock	Gum/mouth	M	1.95 (0.81-4.68)	Age
			F	1.48 (0.56-3.92)	
10	Williams	Lip/tongue/gum/mouth	M	1.28 (0.72-2.28)	None
			F	2.75 (0.65-11.7)	
15	Stockwell	Oral/pharynx/larynx/ nasal cavity/sinuses	M+F	2.05 (1.15-3.68)	None
17	Blot	Oral/pharyngeal	M	0.85 (0.57-1.26)	None
			F	3.06 (0.99-9.47)	
19	Franco	Tongue/gum/mouth	M+F	1.40 (0.59-3.33)	None
21	Maden	Tongue/gum/mouth/ oropharynx	M	4.50 (1.50-14.30)	Age
22	Sterling	Oral/pharyngeal (low SLT)	M+F	0.92 (0.25-3.42)	Age,sex,race,alcohol,
		(high SLT)		1.21 (0.32-4.63)	smoking,occupation
23	Mashberg	Oral cavity/oropharynx	M	1.35 (0.98-1.86)	None
24	Perry	Oral (low SLT)	M+F	1.86 (0.69-4.98)	Age,sex,race,alcohol,
		(high SLT)		0.93 (0.23-3.69)	smoking,occupation
31	Zahm	Buccal cavity	M	3.00 (2.00-4.50)	Age
		Pharynx	M	8.70 (4.10-18.3)	

Include	Meta-analysis		Heterogeneity
All studies	Fixed-effects	1.73 (1.48-2.03)	$\chi^2 = 49.41$ on 16 df ($p<0.001$)
	Random effects	1.93 (1.41-2.64)	
Omit studies 17 and 31	Fixed-effects	1.59 (1.30-1.95)	$\chi^2 = 10.45$ on 12 df ($p=0.58$)

completely ($\chi^2 = 10.45$ on 12 d.f., $p = 0.58$) and reduce the overall estimate to 1.59 (95% CI 1.30-1.95) but the association would still remain highly significant ($p<0.001$).

For 4 of the studies considered in Table 7, relative risk estimates are available by site. In studies 2, 10 and 15 the relative risk estimates are higher for mouth or gum/mouth than for other sites, but in study 31 estimates are lower for the buccal cavity than for the pharynx. Numbers of exposed cases are quite low in studies 10 and 15 and the estimates by site have large sampling variation.

Only 2 of the studies present relative risks for nonsmokers. In study 15 smokeless tobacco use was associated with an increased risk of cancer of various sites, which was significant for mouth/gum (11.2, 95% CI 4.1-30.7), salivary gland (5.3, 95% CI 1.2-23.4) and for the combined grouping

5. Discussion and conclusions

In an ideal world, evidence relating to smokeless tobacco use and oral/pharyngeal cancer would be available from a number of large and valid case-control or prospective studies involving adequate numbers of exposed cases, in which relative risk estimates were presented adjusted for age, smoking, alcohol consumption and other potential confounding factors, with clear separation of possible effects of chewing tobacco and of snuff and analyses conducted by site of cancer. Separate results would also be available for nonsmokers and for smokers and for males and for females. Although results from 27 case-control and 5 prospective studies have been collated in this review, it is clear that most of these fall very far from the ideal requirements. This is not totally surprising, given that many of the studies were conducted 25 or more years ago and that many were clearly more concerned with evaluating the role of risk factors such as smoking or alcohol than with smokeless tobacco, for which usage is sometimes quite low in the populations studied.

Many of the studies considered (or the papers describing them) have one or more of the following weaknesses:

(i) A small number of oral/pharyngeal cancer cases, and particularly of cases exposed to smokeless tobacco;

(ii) Failure to insist on histopathological confirmation of diagnosis;

(iii) Failure to present results by site of cancer, especially in view of suggestions that risk may be higher at the place where the smokeless tobacco is actually held in the mouth;

(iv) Failure to describe clearly how cases and controls were selected;

(v) Doubts about whether the control groups used are representative of the population at risk in respect of smokeless tobacco use;

(vi) Failure to describe clearly how the exposure data were collected;

(vii) Collection of exposure data from unreliable sources, such as medical records, and in ways that may not be fully comparable for cases and controls (e.g. differential use of next-of-kin response);

(viii) Consideration of smokeless tobacco as a single exposure when responses to chewing tobacco and to snuff may be different;

oral/pharynx/larynx/nasal cavity and sinuses (6.58, 95% CI 3.64-11.9). In study 17, smokeless tobacco use was associated with an increased risk of 6.2 (95% CI 1.9-19.8). These limited results suggest a stronger association in nonsmokers. However it is unfortunate that some other studies (22,23), which, based on a relatively large number of cases, found at most a weak association of smokeless tobacco use with oral/pharyngeal cancer, only reported results for smokers and nonsmokers combined.

Relatively few of the studies adjusted for multiple potential confounding factors. The only two studies (22 and 24) which adjusted for smoking and alcohol consumption (as well as age, sex, race and occupation) reported relative risks which gave a combined estimate of 1.28 (95% CI 0.69-2.35, χ^2 = 1.00 on 3 d.f.) which did not show any marked or significant increase in risk associated with smokeless tobacco use.

Four studies reported results by level of smokeless tobacco use. Study 10 showed no clear pattern, but there were only 18 exposed cases of which 13 were classified as having low exposure and 5 as having high exposure. In study 22 relative risk estimates for oral/pharyngeal cancer were slightly higher for high than for low lifetime use, but both were close to unity and the difference not statistically significant. In study 24 relative risks of oral cancer were lower for high than for low lifetime use, but again the difference was not statistically significant. In study 31 relative risks for both buccal cavity and pharynx cancers were higher for frequent than for infrequent smokeless tobacco use, but the differences were again not statistically significant.

The overall data suggest that smokeless tobacco use may be associated with a somewhat increased risk of oral/pharyngeal cancer, with the relationship stronger in those who have never smoked. However, the heterogeneity of relative risk estimates, the lack of clear evidence of a stronger association at particular subsites and of a dose-response, and the failure of most studies to adjust for smoking and alcohol consumption preclude a confident conclusion.

(ix) Failure to present results separately for smokers and nonsmokers when relative risks associated with effects of smokeless tobacco use may plausibly be larger for nonsmokers in view of their lower background risk;

(x) Failure to present results for men and women separately and more generally to report results adequately;

(xi) Failure to adjust relative risk estimates for potential confounding factors, in particular age, smoking and alcohol consumption. Note that even where analysis is restricted to smokers, adjustment for smoking is necessary as the amount and duration of smoking may differ according to smokeless tobacco use; and

(xii) Failure to conduct dose-response analyses relating to aspects of smokeless tobacco use including frequency of use, time spent in mouth per day, length of use and current/former use.

Some studies have already been noted to have gross weaknesses which render inclusion of their results in any meta-analyses as doubtful.

In spite of these weaknesses, it is possible to reach a number of conclusions from the data presented.

The first and clearest conclusion is that Swedish oral snuff carries little or no increased risk of oral/pharyngeal cancer. This conclusion derives mainly from two recently conducted studies,[51,52] both of which reported that those using snuff had a relative risk, of head and neck cancer and of oral cavity cancer respectively, that was close to unity (1.1, 95% CI 0.7-1.5 and 0.8, 95% CI 0.5-1.3) after adjustment for potential confounding variables that included age, smoking and alcohol. These studies, which fitted best the requirements outlined above for an ideal study, also found no clear evidence of an increased risk in subgroups defined by type of cancer or smoking status. Unpublished results from a very large prospective study cited by Nilsson[15], a smaller study of lip cancer[44] and a poorly reported study of upper alimentary tract cancer conducted over 40 years ago[29] do nothing to reverse this conclusion.

Chewing tobacco also shows no clear association with oral/pharyngeal cancer risk. 11 studies, mainly conducted in the USA, provided relative risk estimates. Three studies published in 1920, 1957 and 1962 reported a significantly increased risk, but eight studies published between 1969 and 1998 have not, generally providing relative risk estimates that are close to unity. Omitting two studies of obviously weak design, a random-effects meta-analysis gave a combined relative risk estimate of 1.27 (95% CI 0.96-1.69) which was not statistically significant. Little evidence is available on risk by site of cancer, the only study showing evidence of variation (with risks higher for the buccal cavity than for the lip or pharynx/larynx) being the study, published in 1962, that provided by far the highest and most statistically significant estimate in the meta-analysis. The limited information on risk specifically in nonsmokers again provides no clear evidence of an increased risk, and no useful information on dose-response. The lack of information on risk for particular sites of cancer within the mouth, on risk in nonsmokers and on dose-response is undesirable, but the complete lack of relationship seen in studies conducted in the last 35 years suggests that it is unlikely that chewing tobacco causes oral/pharyngeal cancer.

The evidence relating to snuff use in US studies is more difficult to interpret because of enormous variability in relative risk estimates between the studies. Three studies reported non-significantly lower risks of oral/pharyngeal cancer associated with snuff use of 0.42, 0.62 and 0.80, all with upper 95% confidence limits below 2. However a further six studies reported relative risks of 2.42, 2.67, 3.40, 4.22, 4.81 and 14.6, all of which were statistically significant, and another study, which collected data by a method that has been criticized for being far more likely to detect snuff use in cases than in controls, reported data suggesting a relative risk of 540. Omitting this last study, the other nine studies give a combined, random-effects, relative risk estimate of 2.26 (95% CI 1.08-4.75) but the meaning of this estimate in view of the huge heterogeneity is dubious.

Relative risks specifically for never smokers were only reported in two studies. One study only reported risks for never smokers, with the relative risk 4.81. The other study, by Winn et al.,[14] interestingly presented data which showed a highly significant relation risk of oral/pharyngeal cancer of 3.67 in never smokers and a non-significant relative risk of 1.14 in smokers.

The Winn et al. study also presented results of detailed further analyses of never smokers showing that the relative risk associated with snuff dipping was much higher, for cancer of the gum and buccal mucosa (RR = 26.4) than it was for other mouth and pharynx, and that risk of cancer of the gum and buccal mucosa (but not of other mouth and pharynx) rose with duration of snuff use, to be more than 50-fold increased in those who had used snuff for 50+ years. A much higher relative risk for buccal cavity than for pharynx cancer has also been reported in two other studies (40.6 vs. 1.8 and 7.1 vs. 1.9), the high relative risk of 40.6 being, as for the Winn et al. study, for female snuff-dippers.

Only one study reported risk estimates adjusted for age, smoking and alcohol consumption and that found no association of snuff use with oral/pharyngeal cancer risk. However, Winn et al.[14] also reported that adjustment for a range of variables did not affect their conclusions. Little information is available from the studies on the association of smoking or alcohol with snuff dipping, but it is extremely unlikely that the very strong associations reported in some studies would be a result of confounding.

The reason for the extreme heterogeneity between studies is unclear. No obvious pattern of variation in relative risk by area of the USA or by when the study was conducted is evident, which might be expected if differences in type of snuff used by region or time was a major factor.

Taken as a whole, the data do appear to show a clear association of oral/pharyngeal cancer risk to snuff use in the USA, mainly due to an increased risk of cancer of the buccal mucosa and gum, the sites where snuff is typically kept in the mouth. Whether there is an increased risk of cancer of

other sites is less clear, because the association is weaker and more subject to potential biases.

The evidence relating use of unspecified smokeless tobacco to risk of oral/pharyngeal cancer is weaker than that for snuff, but stronger than that for chewing tobacco. The data, from 11 studies, 10 conducted in the USA and 1 in Brazil, are again heterogeneous, but less so than for snuff use, and the combined data give a random-effects meta-analysis estimate of 1.93 (95% CI 1.41-2.64) which is highly significant ($p<0.001$). Data relating to specific sites are inconsistent, with three studies reporting a relatively high risk for cancer of the mouth and gum, but the one prospective study reporting higher relative risks associated with smokeless tobacco use for cancer of the pharynx than for cancer of the buccal cavity. Limited evidence suggests a higher relative risk in nonsmokers than in smokers, but provides no clear evidence of a dose-response relationship. Detailed adjustment for potential confounding variables has only been carried out in two studies, neither of which showed a significant association of oral/pharyngeal cancer risk with smokeless tobacco use.

Taken on their own the results do not provide conclusive evidence of a risk associated with unspecified smokeless tobacco use. The heterogeneity of risk estimates, the lack of clear evidence that risk is higher at particular sites and the lack of a demonstrated dose-response, coupled with the limited control for smoking, alcohol and even age in some of the studies, all argue against coming to a more certain conclusion. However, given snuff is part of unspecified smokeless tobacco use, and the stronger evidence of a risk associated with snuff use, it is not unreasonable to conclude that the observed relationship of unspecified smokeless tobacco use to risk of oral/pharyngeal cancer risk is a real one.

In summary, oral/pharyngeal cancer risk is increased by smokeless tobacco use in the USA. The increase is related mainly, if not wholly, to the use of oral snuff rather than to chewing tobacco, and predominantly arises where the snuff is held, typically in the gingival buccal area. Limited evidence suggests that the risk is greater in never smokers and in women. Oral snuff, as used in Sweden, does not appear to increase the risk of oral/pharyngeal cancer.

6. Comparison with conclusions from a very recent review

After this review was virtually finalized a somewhat similar review paper was published by Rodu and Cole,[62] the summary of which is presented below.

"The most recent epidemiologic review of the cancer risks associated with smokeless tobacco use appeared in 1986, when 10 studies were available. This review describes 21 published studies, 20 of which are of the case-control type. We characterize each study according to the specific anatomic sites and according to the type of smokeless tobacco products for which it provides relative risks of cancer. The use of moist snuff and chewing tobacco imposes minimal risks for cancers of the oral cavity and other upper respiratory sites, with relative risks ranging from 0.6 to 1.7. The use of dry snuff imposes higher risks, ranging from 4 to 13, and the risks from smokeless tobacco, unspecified as to type, are intermediate, from 1.5 to 2.8. The strengths and limitations of the studies and implications for future research are discussed."

As in this review, studies from India and other eastern countries "where processed tobacco is not comparable to that used in the West" were not considered and, with one exception,[63] the 21 studies considered by Rodu and Cole were all considered in the main body of this report. They did not consider studies 1,2,12,14,16,19,20,22,24,28,29,30 or 32. Many of these had gross weaknesses (1,12,16), provided very limited data (14,16,19,20,28-30) or were only cited from secondary references in this report (2,24,32). However, it seems surprising that study 22, which presented detailed analysis of a large nationally representative sample, was not referred to.

The paper is quite short and unfortunately does not present the study-specific relative risk estimates used in the meta-analyses, so one cannot make detailed comparisons with our findings.

An interesting feature of the paper is that, rather than use just the three exposure categories used in this review (chewing tobacco, snuff and

unspecified smokeless tobacco), snuff is divided into two categories, moist snuff "used primarily by men" and dry snuff "used by women, especially in the southern United States." The conclusions reached by Rodu and Cole[62] are very similar to those reached in this report. Whereas this report concludes that there is no real increase in risk for chewing tobacco or for snuff as used in Sweden, a substantial increase in risk for snuff as used in the USA and an intermediate risk for use of unspecified smokeless tobacco, Rodu and Cole consider that there is no real increase in risk for chewing tobacco or for moist snuff, a substantial increase in risk for dry snuff and an intermediate risk for use of unspecified smokeless tobacco. The difference is that, whereas Rodu and Cole would only consider dry snuff users (predominantly only women) in the USA to be at risk, this report did not separate risks for US snuff users by type of snuff used.

In attempting to reconcile the two views some points should be noted. Firstly, although some of the most significant increases in risk of oral cancer associated with snuff use in US studies are in women (see results for studies 6, 12, 13 and 25 in Table 6), substantially elevated relative risks have also been reported in men (studies 7 and 18).

Second, there are some concerns about how Rodu and Cole have classified tobacco type in their Table I, partly because some of the studies apparently did not ask questions about the type of snuff used and/or made no statements about whether the snuff was moist or dry, and partly because in some cases they appear to have made some errors in classifying tobacco type. The table on the next page summarizes the problem. It can be seen that there are a number of studies apparently of chewing tobacco which Rodu and Cole have classified as being of smokeless tobacco and that there are many studies where use of moist or dry snuff has been inferred from the sex of the subject involved, rather than from any information given by the author. Notably, exposure in study 7 (Vincent), where there is a high relative risk in men, is classified as being to smokeless tobacco by Rodu and Cole when it is actually for snuff. There may also be a problem with study 18 (Spitz) where a high

Checking the tobacco type classification used by Rodu and Cole[62]

Study author	PNL number	R&C ref	Tobacco type as per R&C	Comment
Wynder 1	3	4	ST	Should be CT
Wynder 2	4	3	ST	Source refers to CT but study conducted in Sweden where this is very rare. Probably MS but data cannot be used in meta-analysis anyway
Peacock	5	5	ST	Agreed
Vogler	6	6	CT, DS	Results given for snuff only for women, described as snuff-dipping so presumably DS
Vincent	7	7	ST	Main results for males and are for snuff not ST. Some reference made to CT but no results given
Martinez	8	8	ST	Should be CT
Browne	9	11	CT	Agreed
Williams	10	9	ST	Agreed
Wynder 3	11	10	CT, MS	Results only given for males. No reference to MS only snuff
Winn	13	12	DS	Snuff dipping so presumably DS
Stockwell	15	13	ST	Agreed
Blot	17	14	CT, DS	Only results given are for ST
Spitz	18	15	MS, CT	Results seem only to be given for males, so MS has been assumed. However the paper refers to snuff-dipping, so why not DS?
Maden	21	16	ST	Agreed
Mashberg	23	18	ST, CT, MS	Results only given for males. No reference to MS, only snuff
Kabat	25	19	CT, MS, DS	Results for both sexes. No reference to MS or DS, only to snuff
(Muscat)	25	20	MS, CT	Results mainly for males. No reference to MS, only snuff
Lewin	26	23	MS	Swedish study, so MS is correct
Schildt	27	21	MS, CT	Swedish study, so MS is correct
Zahm	31	17	ST	Agreed

Abbreviations used: R&C = Rodu and Cole, ST = smokeless tobacco unspecified, CT = chewing tobacco, DS = dry snuff, MS = moist snuff

relative risk is reported for an exposure described as snuff dipping, which apparently (though not certainly as the text of the Spitz paper is unclear) is for men. Rodu and Cole also appear to assume the snuff result is for men, as they state the exposure is to moist snuff, but there is no comment in their paper about the relatively high risk in this study.

P.S. The single study cited by Rodu and Cole not referred to in the main body of this review is a case-control study conducted by Schwartz et al.[63] in Washington State, USA involving 284 cases of oral cancer and 477 general population controls. After adjustment for age, cigarette smoking and alcohol consumption, prior smokeless tobacco use (chewing tobacco, snuff or mini-pouches) among men was similar in cases and controls with the relative risk estimated as 1.0 (95% CI 0.4-2.3). Only one female (a control) reported smokeless tobacco use. Inclusion of this study has no effect on the

conclusions. The meta-analysis estimates for smokeless tobacco use shown in section 4.4 would be reduced slightly, to:

		RR (95% CI)	Heterogeneity
All studies	Fixed-effects	1.70 (1.46-1.99)	$\chi^2 = 50.89$ on 17 df ($p<0.001$)
	Random-effects	1.86 (1.37-2.52)	
Omit studies 17 and 31	Fixed-effects	1.56 (1.28-1.89)	$\chi^2 = 11.49$ on 13 df ($p=0.57$)

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TABLE 1 : Epidemiological case-control and prospective studies of oral cancer and smokeless tobacco

Study No.	First Author	Year of Publication	Location	Study design[a]	Controls	Source of information
1	Broders	1920	USA: Rochester, MN	CCH	Without lip cancer	Unstated
2	Moore	1952,53	USA: Minneapolis, MN	CCH	Non malignant disease	Personal interview
3	Wynder 1	1957	USA: New York	CCH	Various benign diseases, lymphoma, cancer of skin or lower GI tract	Personal interview
4	Wynder 2	1957	Sweden: Stockholm	CCH	Cancer of skin, head and neck (not squamous), stomach, rectum, colon, salivary gland, and female genital tract and lymphoma, leukaemia, sarcoma	Personal interview
5	Peacock	1960	USA: North Carolina	CCH	Not oral cancer	Personal interview
6	Vogler	1962	USA: Atlanta, GA	CCH	1) Disease of mouth other than cancer 2) Cancer of other sites 3) No cancer, mouth not examined	Personal interview
7	Vincent	1963	USA: Buffalo, NY	CCH	Successive patients	Personal interview
8	Martinez	1969	Puerto Rico	CCH/P	1) Patient with no cancer 2) Community controls	Personal interview
9	Browne	1977	England: Stoke-on-Trent	CCP	Community controls	Interview with subject or next-of-kin
10	Williams	1977	USA: National	CCH	Cancers not strongly related to tobacco or alcohol	Personal interview
11	Wynder 3	1977	USA: New York, Houston, Los Angeles, Birmingham, Miami and New Orleans	CCH	No tobacco-related disease	Personal interview
12	Westbrook	1980	USA: Arkansas	CCH	Undefined hospital controls	Medical records
13	Winn	1981	USA: North Carolina	CCH	Patients without cancers of oral cavity, pharynx, larynx or oesophagus, other oral or pharyngeal disease or mental disorders	Interview with subject or next-of-kin
14	Wynder 4	1983	USA: New York, Chicago, Birmingham, Philadelphia, Pittsburgh and San Francisco	CCH	No tobacco-related disease	Personal interview
15	Stockwell	1986	USA: Florida	CCH	Colon or rectal cancer, melanoma or endocrine neoplasms	Medical records
16	Young	1986	USA: Wisconsin	CCH	1) Cancer of salivary gland, paranasal sinus or nasopharynx 2) Cancer of larynx	Personal interview

TABLE 1 : (contd.) Epidemiological case-control and prospective studies of oral cancer and smokeless tobacco

Study No.	First Author	Year of Publication	Location	Study design[a]	Controls	Source of information
17	Blot	1988	USA: Atlanta, Los Angeles, San Francisco area and New Jersey	CCP	Population controls obtained 1) by random digit dialling (age <65) or 2) from resident rosters (age 65+)	Interview with subject or next-of-kin
18	Spitz	1988	USA: Houston, TX	CCH	Randomly selected patients without squamous cell carcinoma	Self-administered questionnaire
19	Franco	1989	Brazil: Saõ Paulo and Goiânia	CCH	No neoplastic disease or mental disorder	Personal interview
20	Blomqvist	1991	Sweden: Goteborg	CCH	No tumour or previous cancer	Personal interview
21	Maden	1992	USA: Washington State	CCP	Population controls by random digit dialling	Personal interview
22	Sterling	1992	USA: National	CCP	Probability sample of the living, non-institutionalized population	Surrogate interview (cases), Personal interview (controls)
23	Mashberg	1993	USA: East Orange, NJ	CCH	No cancer or dysplasia of pharynx, larynx, lung or oesophagus	Personal interview
24	Perry	1993	USA: Detroit, MI	CCH	Cardiovascular patients	?
25	Kabat	1994	USA: 8 cities	CCH	No tobacco-related disease or previous tobacco-related cancers	Personal interview
26	Lewin	1998	Sweden: Stockholm county and southern region	CCP	Population controls	Personal interview
27	Schildt	1998	Sweden: 4 northern counties	CCP	Population controls, deceased for dead cases, alive for living cases	Surrogate interview (decedents), Personal interview (living)
28	Smith	1970,1975	USA: Tennessee	P	Not applicable	Unstated
29	Schuman 1	1982	Norway: National?	P	Not applicable	Postal questionnaire?
30	Schuman 2	1982	USA: National?	P	Not applicable	Postal questionnaire
31	Zahm	1992	USA: Veterans	P	Not applicable	Postal questionnaire
32	Nyren	1998[b]	Sweden	P	Not applicable	?

[a] CCH = Case-control study with hospital (or other diseased or decedent) controls
CCP = Case-control study with population (living healthy) controls
P = Prospective study

[b] Year of secondary citation

TABLE 2 : Numbers of cases and controls considered

Study Number	First Author	Number of cases[a] M	F	Cancers considered in cases	Histological confirmation	Control group[b]	Number of controls[c] M	F
1	Broders	526	11	Lip	Unstated		500	
2	Moore	112		Lip and mouth	Unstated		38	
3	Wynder I	74	2	Lip	Yes		207	246
		180	57	Tongue				
		41	18	Gum				
		86	8	Floor of mouth				
		40	12	Buccal mucosa				
		41	7	Palate				
		57	7	Tonsil				
		24	5	Pharynx				
4	Wynder 2	14	1	Lip	Unstated		115	156
		33	37	Tongue				
		19	17	Gum				
		8	10	Buccal mucosa				
		51	34	Nasopharynx (and maxilla)				
		41	75	Hypopharynx				
5	Peacock	25	20	Gum and mouth	Yes		191	165
6	Vogler	231	96	Mouth, pharynx and larynx	Unstated	(1)	109	96
		(46)	(3)	(Lip)		(2)	217	354
		(94)	(72)	(Buccal cavity)		(3)	185	589
		(81)	(18)	(Larynx-pharynx)				
7	Vincent	33	9	Oral cavity (including anterior part of tongue)	Unstated		100	30
		33	3	Pharynx (including posterior part of tongue)				
8	Martinez	115	38	Mouth	Yes	(1)	290	110
		55	13	Pharynx		(2)	580	220
9	Browne	46	29	Gum and mouth	75%		92	58
10	Williams	85	21	Lip and tongue	Yes		2102	3464
		18	17	Salivary gland				
		57	27	Gum and mouth				
		53	20	Pharynx				
11	Wynder 3	593	280	Oral cavity	Yes		2519	831
12	Westbrook		55	Gum and mouth	Yes			55
13	Winn		232	Oral and pharyngeal	No			410
14	Wynder 4	414	157	Oral and pharyngeal	Yes		414	157
15	Stockwell	58	14	Lip	Yes?		4164	4121
		199	111	Tongue				
		80	34	Salivary gland				
		280	162	Gum and mouth				
		305	140	Pharynx				
		47	24	Nasopharynx				
16	Young	150	52	Oral cavity	Yes	(1)	70	57
		59	19	Oropharynx		(2)	180	19
		29	8	Hypopharynx				
17	Blot	762	352	Oral and pharyngeal	Yes		837	431

TABLE 2 : Numbers of cases and controls considered (cont.d)

Study Number	First Author	Number of cases[a] M	F	Cancers considered in cases	Histological confirmation	Control group[b]	Number of controls[c] M	F
18	Spitz	131	54	Upper aerodigestive tract including larynx	Yes		131	54
		(25)	(12)	Tongue				
		(14)	(3)	Floor of mouth				
		(27)	(16)	Other oral cavity				
		(15)	(8)	Orohypopharynx				
19	Franco	201	31	Oral cavity	Yes		402	62
20	Blomqvist	57	4	Lower lip	Unstated		57	4
21	Maden	131		Tongue, gum, mouth or oropharynx	Yes		136	
22	Sterling	- 6976 -		Oral and pharyngeal	No		Not stated but very large	
23	Mashberg	359		Oral and oropharyngeal	Yes		2280	
24	Perry	80	53	Oral	?		533	145
25	Kabat	1097	463	Oral and pharyngeal (not nasopharynx)	Yes		2075	873
26	Lewin	545		Oral cavity, oropharynx, hypopharynx, larynx or oesophagus	Yes		641	
		(128)		Oral cavity				
		(138)		Pharynx				
27	Schildt	237	117	Lip, tongue, gum and mouth	Yes		237	117
28	Smith	0	0	Oral cavity	NA		About 1500	
29	Schuman 1	?		Buccal cavity and pharynx	No		12945	
30	Schuman 2	?		Oral cavity and pharynx	No		16930	
31	Zahm	74		Buccal cavity	No		248046	
		55		Pharynx				
32	Nyren	?	?		No		Very large[d]	

[a] Bracketed numbers are subsets of main number shown. These are given when some analyses were conducted for a combined site group which also included larynx and/or oesophagus.

[b] See Table 1 for definitions of control groups. Multiple control groups only used in studies 6, 8 and 16.

[c] Numbers at risk for prospective studies (28-31).

[d] According to Nilsson[15].

TABLE 3 : Exposure to smokeless tobacco

Study Number	First Author	Primary concern[a]	Period of exposure	Chewing Tobacco	Snuff	Smokeless Tobacco	Dose Variables
1	Broders	No	Unstated	✓	✓		
2	Moore	Yes	20+ years			✓	
3	Wynder 1	No	Ever	✓			
4	Wynder 2	No	Ever	✓[b]			
5	Peacock	Yes	20+ years			✓	
6	Vogler	No	Ever	✓	✓		Time in mouth
7	Vincent	No	Unstated		✓		
8	Martinez	No	Last 20 years	✓			
9	Browne	No	Unstated	✓			
10	Williams	No	Ever			✓	High/low exposure
11	Wynder 3	No	Ever	✓	✓		
12	Westbrook	Yes	Ever		✓		
13	Winn	Yes	Ever		✓		Duration of use
14	Wynder 4	No	Ever	✓	✓		Duration (of chewing)
15	Stockwell	Yes	Ever			✓	
16	Young	No	Ever	✓	✓		
17	Blot	No	Ever			✓	
18	Spitz	No	Ever	✓	✓		
19	Franco	No	Ever			✓	
20	Blomqvist	No	Ever		✓		
21	Maden	No	Ever			✓	
22	Sterling	Yes	Ever		✓	✓	Lifetime use of SLT
23	Mashberg	No	Ever	✓	✓	✓	
24	Perry	Yes	Ever			✓	Lifetime use of SLT
25	Kabat	No	Ever	✓	✓		
26	Lewin	Yes	Ever		✓		Age at start, duration, total consumption, intensity of usage, current/former use
27	Schildt	Yes	Ever	✓	✓		Total consumption (of snuff), current/former use
28	Smith	Yes	?		✓		
29	Schuman 1	Yes	Ever			✓	
30	Schuman 2	Yes	Ever			✓	
31	Zahm	No	Ever			✓	
32	Nyren	Yes	?		✓		

[a] Primary concern of the authors as judged by inclusion of "chewing tobacco", "snuff" or "smokeless tobacco" in the title of the paper(s).

[b] The source paper[29] describes the habit as chewing tobacco, but according to national statistics[3] chewing tobacco has been a negligible part of the Swedish tobacco market for many years. In 1930, for example, it formed 1.8% of tobacco sales by weight, whereas snuff formed 62.5% of sales.

TABLE 4 : Potential confounding variables that have been adjusted for, matched for or separated on[a]

Study Number	First Author	Sex	Age	Race	Smoking	Alcohol	Other
1	Broders	No[b]	No[c]	No	Adjust	No	No
2	Moore	Male	No	White	No	No	No
3	Wynder 1	Male	Match	No	Smokers	No	Religion (match)
4	Wynder 2	Male	No	No	No	No	No
5	Peacock	Separate	Adjust	No	No	No	No
6	Vogler	Separate	Adjust	No	No	No	Residence (adjust)
7	Vincent	Male	Match	No	No	No	No
8	Martinez	Separate	No	No	No	No	No
9	Browne	Match	Match	No	No	No	Residence, occupation (match)
10	Williams	Separate	Adjust	Adjust	Adjust	No	No
11	Wynder 3	Separate	Adjust[d]	Adjust[d]	No	No	City (adjust)[d]
12	Westbrook	Female	Match	No	No	No	Time of admission (match)
13	Winn	Female	Adjust	Adjust	Adjust	Adjust	Residence, source of ascertainment, education, type of respondent, employment (adjust)[e]
14	Wynder 4	Separate	Match	Match	No	No	Hospital, hospital status (match)
15	Stockwell	Adjust	Adjust	Adjust	Not primary smokers	No	No
16	Young	Separate	No	No	No	No	No
17	Blot	Separate	Adjust	Adjust	No	No	Location, respondent (adjust)
18	Spitz	Separate	Adjust?[f]	No	No	No	No
19	Franco	Match	Match	No	No	No	Admission period (match)
20	Blomquist	Match	Match	No	Nonsmokers	No	No
21	Maden	Male	Adjust	No	No	No	No
22	Sterling	Adjust	Adjust	Adjust	Adjust	Adjust	Occupation (adjust)
23	Mashberg	Male	Adjust	Adjust	Adjust	Adjust	No
24	Perry	Adjust	Adjust	Adjust	Adjust	Adjust	Occupation (adjust)
25	Kabat	Separate	Match	Match	No	No	No
26	Lewin	Male	Adjust	No	Adjust	Adjust	Region (adjust)
27	Schildt	Adjust	Adjust	No	Adjust	Adjust	Region, vital status (adjust)
28	Smith	---------- Not applicable – no deaths seen ----------					
29	Schuman 1	Male	Adjust?	No	No	No	No
30	Schuman 2	Male	Adjust?	No	No	No	No
31	Zahm	Male	Adjust	No	No	No	Follow-up period (adjust)
32	Nyren	---------- Not known ----------					

[a] "Adjust" implies analyses were reported adjusted for the relevant variable, "Match" implies cases and controls were matched on the variable but analyses adjusted on that variable were not reported, and "No" implies no adjustment or matching on that variable took place and results were not presented separately by level of that variable.

[b] 526 of 537 cases were men, all 500 controls were men.

[c] The cases had a very different average age, 57, from the controls, 36.

[d] Analyses were carried out adjusted for age, race and city but results were not reported. Only unadjusted RRs can be calculated.

[e] Some of the variables were adjusted for in analyses unreported in detail.

[f] A relative risk was reported which may have been adjusted for age and possibly other variables.

TABLE 5 : Relative risk of oral and pharyngeal cancer associated with chewing tobacco

Study number	First author	Smoking habits	Adjustment factors	Cancer	Sex	Cases Total	Exposed	RR(95% CI)	Notes
1	Broders	Nonsmoker	None	Lip	M+F	132	27	1.65(0.85-3.19)	A
		Smoker	None			403	101	2.19(1.51-3.18)	
		Any	Smoking			535	128	2.05(1.48-2.83)	
3	Wynder 1	Smoker	None	Lip	M	72	15	2.62(1.23-5.57)	-
				Tongue		169	29	2.06(1.09-3.90)	
				Gum		40	5	1.42(0.49-4.11)	
				Floor of mouth		86	10	1.31(0.57-2.99)	
				Buccal mucosa		40	8	2.49(0.99-6.24)	
				Palate		40	9	2.89(1.18-7.06)	
				Tonsil		55	9	1.95(0.81-4.65)	
				Pharynx		23	3	1.49(0.40-5.54)	
				All oral		525	88	2.00(1.16-3.47)	
4	Wynder 2	Any	None	Lip	M	14	?	No association	B
				Tongue		33	?	No association	
				Gum		19	?	Increase, not significant	
				Buccal mucosa		8	?	Increase, not significant	
				Nasopharynx and maxilla		51	?	No association	
				Hypopharynx		41	?	No association	
6	Vogler	Any	Residence	Mouth/pharynx/larynx	M	231	56	4.48(2.71-7.41)	-
			None	Lip		46	11	4.51(2.06-9.89)	
				Buccal cavity		99	35	8.52(4.79-15.2)	
				Pharynx/larynx		81	13	2.74(1.34-5.60)	

TABLE 5 : Relative risk of oral and pharyngeal cancer associated with chewing tobacco (contd.)

Study number	First author	Smoking habits	Adjustment factors	Cancer	Sex	Cases Total	Exposed	RR(95% CI)	Notes
8	Martinez	Nonsmoker	None	Mouth	M	10	1	0.68(0.07-6.25)	C
					F	13	1	0.34(0.04-2.91)	
				Pharynx	M	8	3	8.70(1.15-65.9)	
					F	3	0	0.00	
				Mouth and pharynx	M	18	4	2.29(0.62-8.47)	
					F	16	1	0.34(0.04-2.79)	
		Smoker		Mouth/pharynx/ oesophagus	M	255	38	1.27(0.84-1.92)	
					F	78	10	0.75(0.34-1.61)	
9	Browne	Any	None	Mouth/gum	M+F	75	7	0.67(0.27-1.66)	D
11	Wynder 3	Any	None	Oral cavity	M	591	61	1.15(0.85-1.55)	-
14	Wynder 4	Any	None	Oral/Pharyngeal	M	414	37	1.00(0.62-1.61)	E
18	Spitz	Any	None	Oral/pharyngeal/larynx	M	131	23	1.00(0.53-1.89)	F
23	Mashberg	Any	Age, race, smoking, alcohol	Oral cavity/oropharynx	M	359	?	1.0(0.7-1.4)	-
25	Kabat	Never	None	Oral/pharyngeal	M	82	4	2.25(0.69-7.34)	-
		Ever	None			1015	63	1.06(0.76-1.46)	
		Any	Smoking			1097	67	1.14(0.81-1.53)	
27	Schildt	Ever	Age, sex, region, vital status	Oral	M+F	354	5	0.6(0.2-2.0)	-

TABLE 5 : Relative risk of oral and pharyngeal cancer associated with chewing tobacco
(contd./2)

A The study is severely limited by the cases being of mean age 57 and the controls being of mean age 36. Also the cases contain 11 women but the controls are all men.
B It is possible that the data are for moist snuff and not chewing tobacco (see section 3.1 description of study 4). Results are taken from ridit analysis presented graphically.
C See section 3.1 description of study 8 for details of data extraction.
D The study is limited by a large time difference between when the cases got cancer and when the controls were interviewed, and by a much higher proxy response for the cases than for the controls.
E Data are also available by duration of chewing, see summary of study 14 in section 3.1.
F The relative risks have been calculated assuming the data in the source paper are for males, though this is not entirely clear.

TABLE 6 : Relative risk of oral and pharyngeal cancer associated with snuff use

Study number	First author	Smoking habits	Adjustment factors	Cancer	Sex	Cases Total	Exposed	RR(95% CI)	Notes
1	Broders	Any	None	Lip	M+F	537	1 or 2	1.75(0.12-26.5)	A
6	Vogler	Any	Age, residence	Mouth/pharynx/larynx	F	93	53	14.6(8.19-26.0)	B
			None	Lip		3	1	7.28(0.65-81.6)	
				Buccal cavity		72	53	40.6(22.5-73.6)	
				Pharynx/larynx		18	2	1.82(0.41-8.13)	
7	Vincent	Any	None	Oral cavity	M	33	9	7.13(2.19-23.2)	-
				Pharynx		33	3	1.90(0.43-8.42)	
				Oral cavity/pharynx		66	12	4.22(1.41-12.6)	
11	Wynder 3	Any	None	Oral cavity	M	591	10	0.62(0.32-1.21)	-
12	Westbrook	Any	None	Gum/buccal mucosa	F	55	50	540(61.0-4783)	C
13	Winn	Never	Race	Oral/pharyngeal	F	196	90	3.67(2.35-5.73)	D
		Ever				36	17	1.14(0.55-2.35)	
		Any	Race, smoking			232	107	2.67(1.83-3.90)	
		Never	None	Gum/buccal mucosa		30	28	26.4(5.65-124)	
				Other mouth/pharynx		47	25	2.10(1.03-4.28)	
14	Wynder 4	Any	None	Oral/pharyngeal	M	414	3	0.42(0.11-1.65)	-
18	Spitz	Any	None	Oral/pharyngeal/larynx	M	131	9	2.34(0.70-7.81)	E
			Age?			131	9	3.4(1.0-10.9)	
20	Blomqvist	Never	None	Lower lip	M+F	59	2	0.67(0.08-5.75)	-
22	Sterling	Any	Age, sex, race	Oral/pharyngeal	M+F	6976	?	2.42(1.28-4.59)	-

TABLE 6 : Relative risk of oral and pharyngeal cancer associated with snuff use (contd.)

Study number	First author	Smoking habits	Adjustment factors	Cancer	Sex	Cases Total	Exposed	RR(95% CI)	Notes
23	Mashberg	Any	Age, race, smoking, alcohol	Oral cavity/oropharynx	M	359	?	0.8(0.4-1.9)	-
25	Kabat	Never	None	Oral/pharyngeal	M	82	0	0.00	-
					F	113	4	34.5(8.49-140.1)	
					M+F	195	4	4.81(1.19-19.4)	
26	Lewin	Any	Age, region, smoking, alcohol	Oral cavity	M	128	25	1.4(0.8-2.4)	Ever use (F)
						128	10	1.0(0.5-2.2)	Current use
						128	15	1.8(0.9-3.7)	Former use
		Any	Age, region, smoking, alcohol	Pharynx		138	15	0.7(0.4-1.3)	Ever use
						138	8	0.7(0.3-1.5)	Current use
						138	7	0.8(0.3-1.9)	Former use
		Never	Age, region	Head and neck		44	9	4.7(1.6-13.8)	Ever use
						44	?	3.3(0.8-12.0)	Current use
						44	?	10.5(1.4-117.8)	Former use
		Former	Age, region	Head and neck		116	24	1.1(0.6-1.9)	Ever use
						116	?	1.4(0.7-2.8)	Current use
						116	?	0.8(0.4-1.8)	Former use
		Current	Age, region	Head and neck		385	50	0.8(0.5-1.2)	Ever use
						385	?	0.6(0.3-1.1)	Current use
						385	?	1.0(0.5-2.0)	Former use

TABLE 6 : Relative risk of oral and pharyngeal cancer associated with snuff use (contd./2)

Study number	First author	Smoking habits	Adjustment factors	Cancer	Sex	Cases Total	Exposed	RR(95% CI)	Notes
		Any	Age, region, smoking, alcohol	Head and neck		545	83	1.1(0.7-1.5)	Ever use
						545	43	1.0(0.6-1.6)	Current use
						545	40	1.2(0.7-1.9)	Former use
27	Schildt	Any	Matching factors only	Oral cavity	M+F	354	67	0.9(0.6-1.4)	Ever use (G)
			Matching factors, smoking and alcohol			354	67	0.8(0.5-1.3)	
		Never	Matching factors only	Oral cavity	M+F	152	28	1.01(0.66-1.56)	
		Former				80	31	1.09(0.59-2.03)	
		Current				122	13	1.10(0.58-2.06)	
		Any	Matching factors only	Oral cavity	M+F	354	39	0.7(0.4-1.1)	Current use
		Never				152	19	0.70(0.40-1.20)	
		Former				80	15	0.67(0.30-1.50)	
		Current				122	10	0.71(0.32-1.54)	
		Any		Lip		?	?	Close to 1.00	
		Any	Matching factors only	Oral cavity	M+F	354	28	1.5(0.8-2.9)	Former use
		Never				152	9	1.80(0.90-3.50)	
		Former				80	167	1.78(0.80-3.96)	
		Current				122	3	1.82(0.77-4.33)	
		Any		Lip		?	?	1.8(0.9-3.7)	
28	Smith	Any	Not applicable	Oral cavity	?	0	0	No cancer seen in snuff users in 1500 patients followed	H

TABLE 6 : Relative risk of oral and pharyngeal cancer associated with snuff use (contd./3)

Study number	First author	Smoking habits	Adjustment factors	Cancer	Sex	Cases Total	Exposed	RR(95% CI)	Notes
32	Nyren	Any	Not known	Precise definition not known	?	?	?	No association	J

A The study is severely limited by the cases being of mean age 57 and the controls being of mean age 36. Also the cases contain 11 women but the controls are all men.
B No association of mouth/pharynx/larynx cancer with time snuff held in the mouth per day.
C The study is limited by a likely much greater probability in cases than controls of snuff use being reported in their medical records.
D Relative risks are also available for never smokers by duration of snuff use (1-24, 25-49, 50+ years), see summary of study 13 in section 3.1.
E The relative risks have been calculated assuming the data in the source paper are for males, though this is not entirely clear. The RR estimate of 2.34 is calculated directly from the data provided. The estimate of 3.4 is as given by the authors and may have been adjusted for age (and perhaps other factors) though this is not stated.
F See summary of study 26 in section 3.1 for details of risk by age of start, duration, total consumption and intensity of use.
G Matching factors are age, sex, region and vital status.
H The study has been criticized for failing to give details of follow-up and being likely to have missed oral cancer cases occurring.
J Unpublished study reported by Nilsson[15] to have provided "essentially the same results" as studies 26 and 27, i.e. no significant increase in oral cancer associated with snuff use.

TABLE 7 : Relative risk of oral and pharyngeal cancer associated with unspecified smokeless tobacco use

Study number	First author	Smoking habits	Adjustment factors	Cancer	Sex	Cases Total	Exposed	RR(95% CI)	Notes
2	Moore	Any	Race (white)	Lip	M	72	39	2.56(1.12-5.85)	-
				Mouth		40	26	4.02(0.57-10.34)	
				Lip/mouth		112	65	3.00(1.37-6.54)	
5	Peacock	Any	Age	Gum/mouth	M	25	14	1.95(0.81-4.68)	A
					F	20	11	1.48(0.56-3.92)	
10	Williams	Any	None	Lip/tongue	M	74	3	0.44(0.14-1.40)	B
					F	20	0	0.00	
				Gum/mouth	M	53	11	2.70(1.36-5.34)	
					F	25	2	5.14(1.18-22.4)	
				Pharynx	M	47	2	0.46(0.11-1.91)	
					F	18	0	0.00	
				Lip/tongue/gum/mouth	M	127	14	1.28(0.72-2.28)	
					F	45	2	2.75(0.65-11.7)	
				Lip/tongue/gum/mouth/	M	174	16	1.04(0.61-1.79)	
				pharynx	F	63	2	1.94(0.46-8.14)	
15	Stockwell	Not primary	Age, sex, race	Lip	M+F	72	0	0.0	C
				Tongue		312	1	2.3(0.2-12.9)	
				Salivary gland		114	2	5.3(1.2-23.4)	
				Mouth/gum		443	5	11.2(4.1-30.7)	
				Pharynx		450	2	4.1(0.9-18.0)	
				Nasopharynx		71	1	5.3(0.7-41.6)	
		Not primary	None	Oral/pharynx/ larynx/nasal cavity and sinuses		2351	18	6.58(3.64-11.9)	
		Any	None			2351	18	2.05(1.15-3.68)	

TABLE 7 : Relative risk of oral and pharyngeal cancer associated with unspecified smokeless tobacco use (contd.)

Study number	First author	Smoking habits	Adjustment factors	Cancer	Sex	Cases Total	Exposed	RR(95% CI)	Notes
16	Young	Any	None	Oral cavity	M	150	?	No sig. increase	-
				Oropharynx		59	?	No sig. increase	
				Hypopharynx		29	?	No sig. increase	
17	Blot	Any	None	Oral/pharyngeal	M	762	46	0.85(0.57-1.26)	-
					F	352	11	3.06(0.99-9.47)	
		Never	Age, race, location, respondent		F	54	6	6.2(1.9-19.8)	
19	Franco	Any	None	Tongue/gum/mouth	M+F	232	9	1.40(0.59-3.33)	-
21	Maden	Any	Age	Tongue/gum/mouth/ oropharynx	M	131	19	4.5(1.5-14.3)	-
22	Sterling	Any	Age, sex, race, alcohol, tobacco, occupation	Oral/pharyngeal	M+F	6976	847	0.92(0.25-3.42)	Low exposure (D)
						6976	266	1.21(0.32-4.63)	High exposure
23	Mashberg	Any	None	Oral cavity/oropharynx	M	359	52	1.35(0.98-1.86)	-
24	Perry	Any	Age, sex, race, alcohol, tobacco, occupation	Oral	M+F	133	?	1.86(0.69-4.98)	Low exposure (E)
						133	?	0.93(0.23-3.69)	High exposure
		Any	Age, sex, race			133	?	2.51(1.01-6.26)	Low exposure
						133	?	1.30(0.35-4.85)	High exposure
		Any	None			133	10	1.70(0.81-3.55)	Ever exposed

TABLE 7 : Relative risk of oral and pharyngeal cancer associated with unspecified smokeless tobacco use (contd./2)

Study number	First author	Smoking habits	Adjustment factors	Cancer	Sex	Cases Total	Exposed	RR(95% CI)	Notes
29	Schuman 1	Any	Age?	Buccal cavity/pharynx	M	?	?	2.8 (Significant)	-
30	Schuman 2	Any	Age?	Oral cavity/pharynx	M	?	?	No significant association	-
31	Zahm	Any	Age	Buccal cavity	M	74	?	3.0(2.0-4.5)	Ever use
						74	?	3.4(2.1-5.6)	Frequent use
						74	?	1.9(1.0-3.5)	Infrequent use
				Pharynx		55	?	8.7(4.1-18.3)	Ever use
						55	?	11.2(5.0-25.0)	Frequent use
						55	?	4.5(1.7-11.7)	Infrequent use

A Adjusted for two age groups (40-59, 60+); RR (CI) are based on data for two control groups combined.
B See summary of study 10 in section 3.1 for relative risks (adjusted for age, race and cigarettes) by level of lifetime use.
C Subjects were classified only by primary tobacco product use. The last relative risk for study 15 is for primary vs. non-primary use, the others for primary use vs. no tobacco product.
D Risk relative to lifetime smokeless tobacco use of 0-99 times in lifetime. See summary of study 22 in section 3.1 for comment on the treatment of missing data by the authors.
E The first and third relative risks relate to 100-9999 times use in lifetime and the second and fourth to 10000+ times use in lifetime, both relative to 0-99 times use. The final relative risk is for ever/never use

APPENDIX A

Some references relevant to epidemiological studies
of smokeless tobacco use in India
and other parts of Central and South-Eastern Asia

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