THE RELATIONSHIP BETWEEN EUROPEAN AND AMERICAN SMOKELESS TOBACCO AND DISEASES OTHER THAN ORAL AND CARDIOVASCULAR

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Executive summary

This review was carried out to investigate in detail the epidemiological evidence relating diseases other than oral and cardiovascular to smokeless tobacco use by Western populations. Evidence relating to India and other parts of Central and South-Eastern Asia, where the usage of smokeless tobacco differs from that in the West, is not considered.

A total of 75 studies that provided relevant information were identified. Of these, 51 were of a case-control design, 18 were prospective studies, and 6 were cross-sectional. Forty-six of the studies were conducted in the USA, 18 were carried out in Sweden, three took place in Norway and the USA, two each were conducted in Canada, Denmark, and the UK, and one study took place in Puerto Rico. One multi-centre study was conducted in Australia, Denmark, Germany, Sweden and the USA.

In 27 of the studies, the analyses for smokeless tobacco were restricted to lifelong non-smokers, although in one of these studies, smokers were only excluded if this was their main form of tobacco usage. Three studies excluded ever smokers of cigarettes only, but only one of these adjusted for other forms of tobacco. Five studies excluded current smokers, but included former smokers, and none adjusted for this during analysis. In 38 studies the smokeless tobacco users could also have smoked, but in one of these studies analysis for two endpoints was restricted to never smokers. Of these 38 studies, six studies carried out proper adjustment for smoking variables, with another five studies carrying out partial adjustment. In two studies, it was not stated whether smoking had been adjusted for, and in the remaining 25 studies, no attempt was made to adjust the results for smoking. In two studies, it was not possible to determine whether the study group included smokers. Forty-two of the studies adjusted for age, while 36 studies carried out adjustment for a variety of other potential confounders. In four studies, no information on adjustment was given.

Various other problems were noted with some of the studies in this review. These included the small number of cases who also used smokeless tobacco, the collection of data from potentially unreliable sources, and a failure to present results in sufficient detail to allow relative risks to be calculated. Generally, there was also a

failure to present results separately for chewing tobacco and snuff. Despite these limitations, various conclusions can be drawn from the available data.

Firstly, smokeless tobacco carried little increased risk of those cancers investigated in this review. Twenty-six meta-analyses were carried out, but significant increases were seen only for oesophageal cancer and prostate cancer. For oesophageal cancer the relative risk was estimated as 1.37 (95% CI 1.10-1.71, number of estimates = 8) where results for chewing tobacco were included for one study providing separate estimates for chewing tobacco and snuff and 1.43 (1.13-1.81) where results for snuff were included. For prostate cancer, corresponding relative risks were 1.75 (1.09-2.81, n = 5) and 1.33 (0.83-2.13). No significantly reduced relative risks were estimated. For many of the endpoints considered, meta-analysis was based on very limited data. There were also isolated reports of significant increases for connective tissue cancer, bile duct cancer, cervical cancer and nervous system cancer, all cancers where the number of studies was too few to justify meta-analysis. Bearing in mind the multiple endpoints considered, the relatively marginal significances seen, the weaknesses present in many of the epidemiological studies and the possibility of publication bias, none of these associations provide convincing evidence of a true effect of smokeless tobacco use. If there is a true association of cancer of those sites investigated in this review with smokeless tobacco use it is clear that this is much less than that with smoking.

The evidence for a relationship between smokeless tobacco and non-neoplastic diseases other than oral or cardiovascular is slightly stronger. Of the 14 endpoints considered in this section, six - all diseases other than cancer or cardiovascular disease (RR = 1.15, 95% CI 1.06-1.24, n = 2), all diseases of the musculoskeletal system (1.94, 1.06-3.55, n = 2), all diseases of the respiratory system (1.19, 1.01-1.41, n = 3), COPD (1.59, 1.08-2.33, n = 2), and particularly all diseases of the digestive system (1.46, 1.18-1.82, n = 3) and liver cirrhosis (2.00, 1.33-3.02, n = 2) - showed a significantly higher risk in users of smokeless tobacco. There was also a highly significant and markedly reduced risk of Parkinson's disease (0.22, 0.09-0.53, n = 2) in smokeless tobacco users. Again, though, most of the meta-analyses were based on a limited number of studies, and indeed for some of the endpoints cited above the two individual estimates were for males and females in the same study.

Therefore, until more data are available, there is little clear evidence of an effect of smokeless tobacco use on the risk of non-neoplastic diseases other than oral or cardiovascular in Western populations.

This report also includes results of a meta-analysis of those four studies, all prospective, that had provided data relating smokeless tobacco to all cause mortality. This showed a significantly increased risk (RR = 1.19, 95% CI 1.12-1.27) in smokeless tobacco users. In view of the small number of studies, the relatively weak association, and the fact that the results included deaths from oral and cardiovascular disease, the increased risk does not provide any clear evidence of an effect of smokeless tobacco on the diseases of primary interest in this review.

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Index

Index

Footnote
Only the main summary tables are numbered. Tables giving detail for individual studies, which are not cited elsewhere in the report, are not numbered.

Index

1. Introduction

Smokeless tobacco is used in many countries across the world, and there is much variation in the nature of the products used. The tobacco is often processed and treated with additives and flavouring agents, and it may be taken alone or in combination with a variety of other ingredients. In Europe and the USA, the smokeless tobacco products used are most commonly chewing tobacco and snuff. Chewing tobacco is either chewed and /or placed between the buccal mucosa and gum for varying periods of time. Snuff is also generally used orally, and although it may be sniffed through the nasal cavities, this pattern of usage has become rare [International Agency for Research on Cancer, 1985].

Several reviews of the effects of smokeless tobacco use have been published [International Agency for Research on Cancer, 1985; US Surgeon General, 1986; National Cancer Institute, 1993; Pershagen, 1996; Nilsson, 1998; Critchley & Unal, 2003]. Much of the evidence relates to smokeless tobacco use in Asian countries, such as India, and to oral cancer, oral leukoplakia and cardiovascular disease. No major detailed evaluation of the association between smokeless tobacco as used in Western populations and other diseases has been undertaken. Therefore, the aim of this report is to provide a systematic review of the relationship between European and American smokeless tobacco and diseases other than oral and cardiovascular.

2. Materials and methods

2.1 *Identification of studies*

A search was made of reviews of the relationship between smokeless tobacco and oral cancer and cardiovascular disease to identify studies that appeared to have considered other diseases. In addition, major reviews, including IARC monograph 37 [International Agency for Research on Cancer, 1985], the US Surgeon General Report of 1986 [US Surgeon General, 1986] and National Cancer Institute Monograph 2 [National Cancer Institute, 1993], were examined for references to suitable papers for inclusion. A Medline search was also conducted, using the keywords "smokeless tobacco AND disease", and "smokeless tobacco AND cancer NOT oral". In addition, searches were carried out for specific endpoints e.g. diabetes. Abstracts of the papers were examined, and from these, papers suitable for inclusion in the review were chosen. From the papers thus selected, secondary references were then identified and examined.

Studies of prospective, cross-sectional and case-control design were included. In addition, papers that gave other epidemiological evidence were also selected. Due to differences in the formulation and use of smokeless tobacco in Asian populations, studies were only included if they had been carried out in a population that used European or American forms of smokeless tobacco. For several of the studies, more than one paper had been published. In the case of cross-sectional or case-control studies, the earliest publication was selected. However, if a later publication included a larger number of subjects, it was chosen instead. For prospective studies, the paper reporting the longest period of follow-up was chosen. Deviations from this, and instances where study reports may have been duplicated, are noted in the text.

2.2 *Structure of the review*

For each disease endpoint, brief details and results are given for each of the relevant studies. Where a study considered more than one disease, details are given in a special section (section 3) at the beginning of the review, and reference made to this under each disease heading. Details of the studies are given, and are presented in tabular form if the number of studies permits. The findings for each endpoint are summarized and presented in a table. Papers that provided evidence other than results from a case-control, cross-sectional or prospective study are not included in the summary section.

Results are displayed in the form of relative risks for the endpoint in question in current users of smokeless tobacco only compared to never users of tobacco. Where results are not available for these exposure groups, relative risks calculated for the nearest appropriate exposure group are selected. In addition, if unadjusted and adjusted relative risks are reported, the most adjusted risk estimate is included. If a relative risk has not been presented by the authors, wherever possible it has been calculated from the numbers of cases and controls exposed and non-exposed to smokeless tobacco, using a 2 x 2 table. It should also be noted that in this review, the term "relative risk" is taken to include estimates of odds ratios in the summary tables and the text describing them.

If appropriate, fixed and random effects meta-analysis [Fleiss & Gross, 1991] is then carried out. Fixed effects meta-analysis assumes a common underlying relative risk estimate and only takes within-study variability into account when calculating the combined relative risk estimate and its 95% confidence interval. The random effects model also takes between-study variability into account. Where there is no evidence of heterogeneity between the sets of estimates, the two models will produce the same results.

For many endpoints, relative risks are only available for smokeless tobacco use, with no separate findings available for snuff and chewing tobacco. For other endpoints, some studies do provide results by type of smokeless tobacco used. Here, as appropriate, we provide meta-analyses for:

chewing tobacco only,

snuff only,

smokeless tobacco/chewing tobacco (i.e. combining results from all available studies, using results for chewing tobacco where results for separate types of smokeless tobacco are presented), and

smokeless tobacco/snuff (i.e. combining results from all available studies, using results for snuff where results for separate types of smokeless tobacco are presented).

All-cause mortality, cancer, and non-neoplastic diseases are dealt with in sections 4, 5 and 6 respectively. Section 7 provides an overall summary of the evidence relating to smokeless tobacco use and diseases other than oral cancer and CVD, while references to the papers included in this review are given in section 8.

2.3 *Abbreviations used*

Various abbreviations are used in this review. Where these apply to a specific part of the document, an explanation is given in the text of the relevant section. However, the following abbreviations are used throughout this review:

C-C: Case-control
Chew: Chewing tobacco
CI: Confidence interval
COPD: Chronic obstructive pulmonary disease
CS: Cross-sectional
CVD: Cardiovascular disease
F: Females
HR: Hazard ratio
M: Males
NS: Not significant
OR: Odds ratio
P: Prospective
RR: Relative risk
S: Significant
SD: Standard deviation
SMR: Standardized mortality ratio
ST: Smokeless tobacco
STS: Soft tissue sarcoma

3. Studies that considered more than one endpoint

3.1 *Introduction*

Ten studies provide data on a range of endpoints. These are described below before specific endpoints are considered.

Prospective studies (section 3.2)	Winn	:	USA (1982)
	Bolinder	:	Sweden (1994)
	Accortt	:	USA (2002)
	Boffetta	:	Norway/USA (2005)
	Henley	:	USA – CPS I and CPS II (2005)
Case-control/cross-sectional studies (section 3.3)	Williams	:	USA (1977)
	Wynder	:	USA – 8 cities (1977)
	Bolinder	:	Sweden (1992)
	Sterling	:	USA (1992)
Other epidemiological evidence (section 3.4)	Redmond	:	UK - London (1970)

3.2 *Prospective studies*

3.2.1 Winn: USA (1982)

This study, described only in an abstract [Winn et al., 1982], was based on data from the Dorn Study, in which approximately 300,000 US veterans (over 99% men) with life insurance policies were mailed a questionnaire in 1954, in order to obtain information on tobacco use, occupation and demographic characteristics. SMRs were then calculated for deaths occurring among cohort members between 1954 and 1969, using rates derived from the non-tobacco users in the cohort, so presumably (though not stated in the abstract) the SMRs were for smokeless tobacco users who did not smoke. The results were as follows:

Disease	SMR
All malignant neoplasms	≈ 100*
Cancers of digestive system	137
Oesophageal cancer	228
Stomach cancer	151
Pancreatic cancer	165
Liver cancer	281
Lung cancer	60
Tuberculosis	148
Cirrhosis	294

*Stated to be approximately one, but presumably 100 was meant

Increased SMRs for digestive cancers were seen in both blue and white collar workers.

3.2.2 Bolinder: Sweden (1994)

In the study by Bolinder et al., 1994, the population consisted of 135,036 men who had received medical check-ups through the Swedish Construction Industry's Organization for Working Environment Safety and Health during the years 1971 to 1974. Members of the study population who were alive on 1 January 1974 were followed-up for cause-specific mortality until 1985. There were 8293 deaths during follow-up. Analysis of tobacco usage revealed that 6297 men were current users of smokeless tobacco only and 32,546 were never users of tobacco.

Compared to never users of tobacco, a relative risk of 1.4 (95% CI 1.3-1.8), adjusted for age and region of origin, was estimated for all causes of death in users of smokeless tobacco only. The risk estimate for all cancers was 1.1 (95% CI 0.9-1.4). Relative risks were also calculated for men in two specific age groups, as follows:

Cause of death	Age 35-54 years at entry to study			Age 55-65 years at entry to study		
	Non-users	Smokeless tobacco users		Non-users	Smokeless tobacco users	
	No.	No.	RR (95% CI)	No.	No.	RR (95% CI)
At risk	13784	1672		5642	1734	
All causes	410	105	1.9 (1.6-2.4)	820	301	1.2 (1.0-1.3)
All cancer	128	22	1.2 (0.8-1.9)	223	69	1.0 (0.8-1.3)
Lung cancer	5	1	1.2 (0.2-9.1)	8	2	0.8 (0.1-3.9)

Drawbacks with this study include the possibility of misclassification of both exposure, as no follow-up recording of subjects' smoking habits was made, and disease. However, it was felt that the effects of this would be small. Additionally, information on alcohol consumption was not collected. In a critique of this study, Rodu & Cole, 1995 maintained that the non-user group had a substantially lower death rate from all causes than the general Swedish male population, and therefore the general population would have been a more appropriate choice as a reference group.

3.2.3 Accortt: USA (2002)

Accortt et al., 2002 conducted a prospective study of all-cause and disease-specific mortality, based on data from the First National Health and Nutrition Examination Survey (NHANES I) and the NHANES I Epidemiologic Followup Survey (NHEFS). NHANES I consisted of a national probability sample of the non-institutionalized US population which oversampled the elderly, poor, and women of childbearing age. The initial survey, which was conducted between 1971 and 1975, consisted of an in-person interview covering a wide array of health behaviours and a physical examination. The NHEFS surveys were conducted after approximately 10, 15 and 20 years of follow-up. The original cohort consisted of 14,407 adults, aged 25-74 years, who underwent physical examination. Of these, 13861 (96%) were successfully traced in at least one follow-up survey. After 20 years, 4604 (32%) subjects had been identified as deceased, with death certificates being available for 98% of these individuals. In the initial survey, only a random sample of 3847 subjects were asked about smokeless tobacco use, but all those who completed the 10 year follow-up survey provided information on this variable. Data from the 10 year survey were used to infer smokeless tobacco use at baseline where necessary. There were 1503 ever users of smokeless tobacco in the study. Of these, 505 (33.6%) had never smoked and were considered "exclusive" smokeless tobacco users, 952 (63.3%) had smoked and were termed "combined" users, and the remaining 46 (3.1%) had an unknown smoking status.

Due to the difference in age between exclusive smokeless tobacco users and non-tobacco users, and the low prevalence of smokeless tobacco use among subjects aged less than 45 years, mortality analyses were restricted to the 6805 subjects aged 45-75 years at baseline. In this subsample, there were 1068 smokeless tobacco users, 414 of whom were never smokers. After adjustment for age, race, gender and poverty index ratio[*], the hazard ratios for exclusive smokeless tobacco users compared to non-tobacco users were estimated at 1.1 (95% CI 0.9-1.3) for all causes, and 1.1 (95% CI 0.6-1.9) for all cancers. For all causes for which there were at least 30 deaths, the following hazard ratios were estimated, stratified by gender:

[*] A poverty index equal to 1.0 designates the poverty level, with ratios less than 1.0 below and ratios greater than 1.0 above the poverty level. Full definitions are provided elsewhere [National Center for Health Statistics, 1977].

	Males		Females	
	Hazard ratios (95% CI)		Hazard ratios (95% CI)	
Disease classification	Crude	Adjusted[1]	Crude	Adjusted
All causes	1.5 (1.1-1.9)	1.0 (0.8-1.3)	1.7 (1.2-2.4)	1.3 (0.9-1.7)
Malignant neoplasms	1.1 (0.5-2.4)	0.9 (0.3-2.3)	1.6 (1.0-2.6)	1.7 (1.0-2.8)
Endocrine, nutritional and metabolic disease and immunity disorders	2.7 (0.7-10.9)	2.4 (0.7-8.8)	2.9 (0.6-13.4)	1.4 (0.1-13.5)
Diseases of the nervous system and sense organs	1.6 (0.2-10.2)	1.1 (0.2-5.2)	0.3 (0.1-1.3)	0.6 (0.1-2.6)
Diseases of the circulatory system	1.5 (1.1-2.0)	1.0 (0.7-1.5)	1.8 (1.0-3.1)	1.2 (0.7-1.9)
Diseases of the respiratory system	2.1 (0.7-5.8)	0.9 (0.3-2.5)	0.7 (0.2-2.5)	0.6 (0.1-2.3)
Diseases of the digestive system	3.1 (0.7-12.7)	1.9 (0.4-9.8)	0.0[2]	0.0[3]

[1] Adjusted for age, race and poverty index ratio
[2] Based on 0 cases in exclusive smokeless tobacco users and 29 cases in non-tobacco users
[3] Based on 0 cases in exclusive smokeless tobacco users and 24 cases in non-tobacco users

In addition, hazard ratios for exclusive smokeless tobacco users were estimated for several specific diseases, stratified by smoking status and gender:

	Never smokers		Ever smokers	
	Hazard ratios (95% CI)		Hazard ratios (95% CI)	
Cause of death	Crude	Adjusted	Crude	Adjusted
Males:				
Lung cancer	0.0[1]	0.0[2,3]	0.5 (0.1-3.8)	22.6[3] (6.4-80.3)
Digestive cancers	1.2 (0.5-3.1)	0.9[4] (0.3-2.3)	0.3 (0.1-1.0)	0.7[4] (0.3-1.8)
Females:				
Lung cancer	7.0 (1.6-30.9)	9.1[3] (1.1-75.4)	8.7 (3.3-22.4)	1.2[3] (0.2-8.9)
Digestive cancers	0.8 (0.3-2.4)	0.8[4] (0.3-2.7)	0.7 (0.3-1.7)	0.2[4] (0.1-1.1)

[1] Based on 0 cases in exclusive smokeless tobacco users and 9 cases in non-tobacco users
[2] Based on 0 cases in exclusive smokeless tobacco users and 6 cases in non-tobacco users
[3] Adjusted for age, race, poverty index ratio, region of residence, alcohol, recreational physical exercise, and fruit/vegetable intake
[4] Adjusted for age, race, poverty index ratio, alcohol, and dietary fat intake

A second paper [Accortt et al., 2005] gave the following results for prostate cancer in men and breast cancer in women:

Cause of death	Observed cases[1]	Hazard ratios (95% CI) Crude	Adjusted[2]
Men:			
Prostate cancer	19	1.1 (0.5-2.9)	1.2 (0.5-3.4)
Women:			
Breast cancer	5	0.6 (0.2-2.0)	1.8 (0.5-6.5)

[1] Among exclusive smokeless tobacco users
[2] Adjusted for age, race and poverty index ratio

Analyses investigating the combined effects of smokeless tobacco use and smoking on specific disease outcomes were restricted to men because of the low prevalence of combined use among women (n = 62). Adjusted hazard ratios were estimated as follows:

Tobacco usage	Hazard ratios (95% CI) Lung cancer[1]	All cancers[2]
Non-tobacco users	1.0	1.0
Exclusive smokeless tobacco users	0.0[3]	1.0 (0.3-2.5)
Exclusive smokers	13.2 (4.5-38.2)	1.3 (0.8-2.1)
Current smokers	24.7 (8.3-73.5)	1.8 (1.1-3.1)
Former smokers	7.0 (2.1-23.2)	1.0 (0.5-1.8)
Combined tobacco users	22.6 (6.4-80.3)	1.6 (0.9-2.7)
Smokeless tobacco and current smokers	33.9 (8.0-143.7)	2.2 (1.2-3.7)
Smokeless tobacco and former smokers	9.0 (2.0-40.8)	0.9 (0.4-1.8)

[1] Adjusted for age, race, poverty index ratio, region of residence, alcohol frequency, recreational physical exercise, and fruit/vegetable intake
[2] Adjusted for age, race, poverty index ratio, alcohol, recreational physical exercise, fruit/vegetable intake, dietary fat intake, and family history of cancer
[3] Based on 0 cases in exclusive smokeless tobacco users and 6 cases in non-tobacco users

The study was criticised by Ebbert et al., 2003 because the 'non-tobacco users' group contained pipe and/or cigar smokers. It was argued that if pipe and cigar smoking increased the risk of death in this cohort, no increased risk of death from smokeless tobacco use would be observed when compared with non-tobacco users. This null effect would be more obvious in men than in women, because more men than women smoke pipes and cigars. However, in a reply to these criticisms, Accortt et al., 2003 state that only about 5% of the non-tobacco users group were pipe and/or cigar smokers, and that the prevalence was higher among smokeless tobacco users. Additionally, there may be differences between the sexes in the form of smokeless tobacco used, with men preferring chewing tobacco and women favouring snuff. The lower levels of tobacco-specific N-nitrosamines, and thus potentially lower

carcinogenicity, of chewing tobacco may be reflected in the observed hazard ratios estimated for men and women. Finally, the issue of the amount of smokeless tobacco used was not adequately addressed, with one-time users being combined with daily heavy users.

3.2.4 Boffetta: Norway/USA (2005)

The cohort in the study by Boffetta et al., 2005 consisted of two groups of men: a systematic sample of the general adult population of Norway identified from the 1960 census, and relatives of Norwegian migrants to the US. Study subjects completed questionnaires on lifestyle habits in 1964 and 1967. Information on use of smokeless tobacco was available for 10,136 men alive on 1 January 1966. Of these, 1999 (19.7%) were regular current users, 1216 (12.0%) were regular former users, and the remaining 6921 (68.3%) were never or occasional users. No re-assessment of smokeless tobacco use was carried out during follow-up. Cohort members were followed-up until 31 December 2001. During this time, there were a total of 1052 incident cases of cancer.

Relative risks, adjusted for age and smoking of cigarettes, cigars and pipes were estimated for various cancer sites for users of smokeless tobacco compared to never users, as follows:

Cancer site	Never users	Ever users (Pack years=61335)		Former users (Pack years=23452)		Current users (Pack years=37883)	
	Cases	Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)
Oesophagus	18	9	1.40 (0.61-3.24)	5	1.90 (0.69-5.27)	4	1.06 (0.35-3.23)
Stomach	143	74	1.11 (0.83-1.48)	32	1.29 (0.87-1.91)	42	1.00 (0.71-1.42)
Pancreas	60	45	1.67 (1.12-2.50)	18	1.80 (1.04-3.09)	27	1.60 (1.00-2.55)
Lung (all types)	271	72	0.80 (0.61-1.05)	28	0.80 (0.54-1.19)	44	0.80 (0.58-1.11)
Lung (adeno-carcinoma)	39	11	0.83 (0.42-1.65)	4	0.86 (0.30-2.43)	7	0.81 (0.36-1.85)
Kidney	66	22	0.72 (0.44-1.18)	13	1.17 (0.63-2.16)	9	0.47 (0.23-0.94)
Bladder	169	69	0.83 (0.62-1.11)	30	0.98 (0.66-1.47)	40	0.72 (0.52-1.06)

Relative risks, stratified by smoking status, were also given for pancreatic and lung cancer in ever users of smokeless tobacco, compared to never smokers:

Smoking status	Pancreatic cancer			Lung cancer		
	Cases	RR[1]	95% CI	Cases	RR[1]	95% CI
Never smokers	3	0.85	0.24-3.07	3	0.96	0.26-3.56
Former smokers	14	1.37	0.59-3.17	7	0.64	0.24-1.68
Current smokers	28	1.86	1.13-3.05	62	0.68	0.51-0.90

[1] Adjusted for age and, among current smokers, for amount of tobacco smoking

Despite their attempts at adjusting for smoking status, the authors stated that residual confounding by tobacco smoking, or by other potential risk factors, such as alcohol intake or diet, could not be completely ruled out, but that the lack of a corresponding increase in lung cancer risk meant that residual confounding by tobacco smoking was less likely to have occurred. However, the lack of information on smoking and smokeless tobacco use during follow-up may be of more concern. As misclassification is not likely to have occurred differentially with respect to outcome, it should have the effect of under-estimating the difference between current and former smokeless tobacco users.

Over 20 years earlier Heuch et al. [1983] had presented results for pancreatic cancer derived from follow-up until 1978 of three groups of subjects. The first two (1960 census sample of Norway, relatives of Norwegian migrants to the US) were those considered by Boffetta et al. [2005], while the third were spouses and siblings of individuals interviewed in a case-control study of gastrointestinal cancer. The analyses concerned 63 new cases of pancreatic cancer, 39 of which were histologically verified. Tobacco chewing was classified into three groups; never use (score 0), former of occasional use (score 1) and regular current use (score 2) and the relevant results reported were as follows:

	Observed/expected cases[1]				Odds ratio (95% CI)[2]	
	Never use	Former or occasional use	Regular use	Total cases	Regular vs never use	p for positive trend
All cases of pancreatic cancer						
Among those with chewing data	32/36.2	12/8.2	12/11.6	56	1.34 (NA)	0.210
Histologically verified cases						
Among those with chewing data	20/23.7	5/4.4	9/5.9	34	2.20 (0.89-5.4)	0.045
Among those with data on alcohol, cigarettes and chewing	9/11.9	4/3.2	6/3.9	19	2.31 (NA)	0.067
As above, but with adjustment for alcohol and cigarettes	9/11.4	4/4.1	6/3.5	19	2.85 (NA)	0.060

[1] All calculations with adjustment for region, urban and rural residence, age and sex
[2] NA = not available in source

In view of the overlap with the later report of Boffetta et al. [2005], these results will not be included in summaries of data for pancreatic cancer.

3.2.5 Henley: USA – CPS I and CPS II (2005)

Henley et al., 2005 analyzed data from two large prospective studies, Cancer Prevention Study I (CPS I) and Cancer Prevention Study II (CPS II). In both cohorts, participants were recruited by American Cancer Society volunteers, and consisted of all family members aged at least 30 years in households where at least one person was aged 35 years or older. Each participant completed a mailed questionnaire. In CPS I, 456,487 men and 594,544 women from 25 states were enlisted in 1959. In CPS II, 676,306 women and 508,351 men were enrolled nationwide in 1982. Vital status was determined through personal enquiry by the volunteers for 12 years in CPS I and the first six years in CPS II. Follow-up in CPS II then continued through automated linkage with the National Death Index until December 2000. At the end of the follow-up periods, a total of 23.8% of the participants of CPS I and 34.6% of the participants of CPS II were identified as deceased, with death certificates being available for 97% and 98.9% of these deaths, respectively. Information on smokeless, or 'spit', tobacco use was obtained at baseline, but not updated during the follow-up of either cohort. After excluding subjects who also used cigarettes, cigars and pipes, a total of 7745 men in CPS I and 2488 men in CPS II were classified as current users of smokeless tobacco, and 69,662 and 111,482 men, respectively, were identified as never users. A further 839 men in CPS II were former users of smokeless tobacco. No information on the use of smokeless tobacco in women was available.

Mortality hazard ratios for current male users of smokeless tobacco compared to never users in CPS I were estimated as follows:

Cause of death	No. of deaths		HR[1] (95% CI)	HR[2] (95% CI)
	Never users	Current users		
All causes[3]	9819	2052	1.24 (1.18-1.30)	1.17 (1.11-1.23)
All cancers[4]	1975	357	1.10 (0.98-1.23)	1.07 (0.95-1.20)
Digestive system cancer	760	153	1.26 (1.05-1.50)	1.26 (1.05-1.52)
Lung cancer	116	18	1.04 (0.63-1.72)	1.08 (0.64-1.83)
Genitourinary system cancer	461	98	1.07 (0.86-1.34)	0.97 (0.77-1.22)
Other cancers	631	85	0.91 (0.73-1.15)	0.90 (0.71-1.14)
Causes other than cancer or cardiovascular disease	2290	507	1.31 (1.18-1.44)	1.17 (1.06-1.30)
Diabetes[5]	97	20	1.08 (0.66-1.75)	0.88 (0.53-1.47)
Respiratory system diseases	433	123	1.39 (1.13-1.70)	1.28 (1.03-1.59)
Influenza, pneumonia	299	79	1.22 (0.94-1.57)	1.16 (0.88-1.51)
Chronic obstructive pulmonary disease	65	25	2.03 (1.27-3.25)	1.86 (1.12-3.06)
Digestive system diseases	298	85	1.70 (1.33-2.17)	1.49 (1.14-1.93)
Colitis and other intestinal diseases	124	35	1.45 (0.99-2.13)	1.42 (0.94-2.12)
Cirrhosis	81	19	2.00 (1.20-3.34)	1.49 (0.87-2.56)
Genitourinary system diseases	222	64	1.56 (1.18-2.07)	1.34 (1.00-1.80)
Nephritis and other kidney diseases	174	51	1.60 (1.16-2.20)	1.37 (0.98-1.92)
External causes	613	98	1.17 (0.94-1.46)	1.05 (0.84-1.32)

[1] Adjusted for age
[2] Adjusted for age, race, educational level, body mass index, exercise, alcohol consumption, fat consumption, fruit/vegetable intake and aspirin use
[3] Excludes men who reported prevalent cancer, heart disease, diabetes or stroke in 1959
[4] All analyses for cancers exclude men who reported prevalent cancer in 1959
[5] Excludes men who reported prevalent diabetes in 1959

The following results were reported using data from CPS II:

Cause of death	Smokeless tobacco use	No. of deaths	Hazard ratio[1] (95% CI)	Hazard ratio[2] (95% CI)
All causes[3]	Never	18824	1.00	1.00
	Current	567	1.29 (1.18-1.40)	1.18 (1.08-1.29)
	Chew, never snuff	366	1.26 (1.13-1.40)	1.16 (1.05-1.29)
	Snuff, never chew	70	1.37 (1.08-1.73)	1.25 (0.98-1.58)
	Chew and snuff	82	1.49 (1.20-1.85)	1.36 (1.09-1.69)
	Chew, former snuff	20	1.11 (0.71-1.73)	0.96 (0.61-1.50)
	Snuff, former chew	29	1.12 (0.77-1.63)	1.01 (0.69-1.47)
	Former	197	1.06 (0.92-1.22)	0.98 (0.85-1.13)
All cancers[4]	Never	5921	1.00	1.00
	Current	162	1.24 (1.06-1.45)	1.19 (1.02-1.40)
	Chew, never snuff	113	1.28 (1.06-1.54)	1.23 (1.02-1.49)
	Snuff, never chew	14	0.99 (0.58-1.67)	0.93 (0.55-1.57)
	Chew and snuff	18	1.08 (0.68-1.71)	1.02 (0.64-1.63)
	Chew, former snuff	6	1.38 (0.62-3.06)	1.30 (0.58-2.89)
	Snuff, former chew	11	1.68 (0.93-3.03)	1.58 (0.87-2.87)
	Former	57	1.09 (0.84-1.41)	1.04 (0.80-1.36)
Digestive system cancer	Never	1932	1.00	1.00
	Current	48	1.11 (0.84-1.48)	1.04 (0.77-1.38)
	Former	19	1.09 (0.69-1.71)	0.99 (0.63-1.57)

Cause of death	Smokeless tobacco use	No. of deaths	Hazard ratio[1] (95% CI)	Hazard ratio[2] (95% CI)
Lung cancer	Never	378	1.00	1.00
	Current	18	2.18 (1.35-3.50)	2.00 (1.23-3.24)
	Chew, never snuff	12	2.12 (1.19-3.78)	1.97 (1.10-3.54)
	Snuff, never chew	2	2.37 (0.59-9.53)	2.08 (0.51-8.46)
	Snuff, former chew	4	10.2 (3.78-27.7)	9.78 (3.58-26.7)
	Former	4	1.26 (0.47-3.38)	1.17 (0.43-3.14)
Genitourinary system cancer	Never	1649	1.00	1.00
	Current	44	1.20 (0.89-1.61)	1.15 (0.85-1.56)
	Former	16	1.01 (0.61-1.65)	0.97 (0.59-1.59)
Hematopoietic cancers	Never	895	1.00	1.00
	Current	19	0.98 (0.62-1.54)	0.95 (0.60-1.51)
	Former	9	1.18 (0.61-2.28)	1.16 (0.60-2.25)
Other cancers	Never	1022	1.00	1.00
	Current	32	1.48 (1.04-2.10)	1.49 (1.04-2.14)
	Former	9	1.16 (0.60-2.23)	1.19 (0.61-2.30)
Causes other than cancer or cardio-vascular disease	Never	8712	1.00	1.00
	Current	262	1.23 (1.09-1.40)	1.11 (0.97-1.25)
	Chew, never snuff	166	1.18 (1.01-1.38)	1.07 (0.92-1.25)
	Snuff, never chew	29	1.22 (0.85-1.76)	1.07 (0.74-1.54)
	Chew and snuff	41	1.47 (1.08-1.99)	1.29 (0.95-1.76)
	Chew, former snuff	10	1.22 (0.65-2.28)	1.00 (0.53-1.87)
	Snuff, former chew	16	1.35 (0.82-2.21)	1.20 (0.73-1.97)
	Former	120	1.21 (1.01-1.45)	1.10 (0.92-1.33)
Diabetes[5]	Never	250	1.00	1.00
	Current	8	1.45 (0.71-2.94)	1.12 (0.55-2.29)
	Former	6	2.72 (1.21-6.13)	2.16 (0.95-4.91)
Respiratory system diseases	Never	1685	1.00	1.00
	Current	56	1.27 (0.97-1.66)	1.11 (0.84-1.45)
	Former	28	1.23 (0.84-1.80)	1.10 (0.75-1.62)
Influenza, pneumonia	Never	930	1.00	1.00
	Current	24	0.93 (0.62-1.41)	0.85 (0.56-1.29)
	Former	18	1.27 (0.78-2.06)	1.18 (0.73-1.92)
Chronic obstructive pulmonary disease	Never	269	1.00	1.00
	Current	12	1.81 (1.01-3.23)	1.28 (0.71-2.32)
	Former	8	2.40 (1.18-4.87)	1.88 (0.92-3.84)
Digestive system diseases	Never	689	1.00	1.00
	Current	25	1.57 (1.05-2.34)	1.38 (0.92-2.07)
	Former	9	1.21 (0.63-2.34)	1.05 (0.54-2.03)
Colitis and other intestinal diseases	Never	467	1.00	1.00
	Current	14	1.28 (0.75-2.19)	1.12 (0.65-1.92)
	Former	9	1.71 (0.88-3.33)	1.54 (0.79-3.01)
Cirrhosis	Never	157	1.00	1.00
	Current	11	3.38 (1.83-6.23)	3.02 (1.60-5.69)
Genitourinary system disease	Never	501	1.00	1.00
	Current	17	1.30 (0.80-2.13)	1.02 (0.62-1.69)
	Former	5	0.77 (0.32-1.86)	0.62 (0.26-1.51)
Nephritis and other kidney disease	Never	299	1.00	1.00
	Current	10	1.32 (0.70-2.50)	1.01 (0.53-1.93)
	Former	3	0.75 (0.24-2.36)	0.59 (0.19-1.86)
External causes	Never	1318	1.00	1.00
	Current	45	1.43 (1.06-1.93)	1.26 (0.93-1.70)
	Former	15	1.15 (0.69-1.92)	1.04 (0.62-1.74)

[1] Adjusted for age
[2] Adjusted for age, race, educational level, body mass index, exercise, alcohol consumption,

employment status and type, fat consumption, fruit/vegetable intake and aspirin use
[3] Excludes men who reported prevalent cancer, heart disease, diabetes or stroke in 1982
[4] All analyses for cancers exclude men who reported prevalent cancer in 1982
[5] Excludes men who reported prevalent diabetes in 1982

Further information was available for some disease endpoints regarding the frequency and duration of smokeless tobacco use in current users, although none of the trends reached statistical significance:

Cause of death	Never	Smokeless tobacco use					
		<7 times/week		7 times/week		>7 times/week	
	No.	No.	HR[1] (95% CI)	No.	HR (95% CI)	No.	HR (95% CI)
All causes[2]	18824	99	1.22 (1.00-1.49)	279	1.14 (1.01-1.28)	81	1.20 (0.96-1.49)
All cancers[3]	5921	30	1.25 (0.88-1.80)	75	1.10 (0.87-1.39)	28	1.13 (0.76-1.68)
Lung cancer	378	3	1.95 (0.62-6.09)	9	2.01 (1.03-3.93)	3	2.00 (0.64-6.27)
Causes other than cancer or CVD	8712	42	1.09 (0.80-1.48)	132	1.09 (0.91-1.29)	48	1.25 (0.94-1.66)
COPD	269	3	2.45 (0.77-7.74)	5	1.02 (0.41-2.49)	2	1.41 (0.35-5.74)

COPD = Chronic obstructive pulmonary disease; CVD = Cardiovascular disease; HR = Hazard ratio
[1] Hazard ratios adjusted for age, race, educational level, body mass index, exercise, alcohol consumption, employment status and type, fat consumption, fruit/vegetable intake and aspirin use
[2] Excludes men who reported prevalent cancer, heart disease, diabetes or stroke in 1982
[3] All analyses for cancers exclude men who reported prevalent cancer in 1982

Cause of death	Never	Smokeless tobacco use					
		1-10 years		11-30 years		30+ years	
	No.	No.	HR[1] (95% CI)	No.	HR (95% CI)	No.	HR (95% CI)
All causes[2]	18824	73	1.08 (0.86-1.36)	94	1.22 (1.00-1.49)	309	1.20 (1.07-1.35)
All cancers[3]	5921	25	1.16 (0.79-1.73)	33	1.24 (0.88-1.75)	78	1.14 (0.91-1.43)
Lung cancer	378	2	1.39 (0.34-5.60)	3	1.64 (0.53-5.15)	13	2.96 (1.67-5.24)
Causes other than cancer or CVD	8712	34	1.11 (0.79-1.56)	38	1.09 (0.79-1.50)	153	1.15 (0.98-1.35)
COPD	269	1	1.10 (0.15-7.88)	2	1.18 (0.45-7.34)	7	1.17 (0.54-2.53)

COPD = Chronic obstructive pulmonary disease; CVD = Cardiovascular disease; HR = Hazard ratio
[1] Hazard ratios adjusted for age, race, educational level, body mass index, exercise, alcohol consumption, employment status and type, fat consumption, fruit/vegetable intake and aspirin use
[2] Excludes men who reported prevalent cancer, heart disease, diabetes or stroke in 1982
[3] All analyses for cancers exclude men who reported prevalent cancer in 1982

Although information was collected on alcohol consumption, and the results adjusted for this data, the authors stated that the raised hazard ratios estimated for cirrhosis in CPS II suggested that residual confounding by alcohol consumption may be a problem in this study.

3.3 *Case-control/cross-sectional studies*

3.3.1 Williams: USA (1977)

The study by Williams & Horm, 1977 was based on personal interviews obtained from 7518 incident cases of invasive cancer as part of the Third National Cancer Survey. Detailed information on the criteria used to select cases was not given, but men and women aged at least 25 years were included in the study. For the purposes of analysis, subjects with cancer at one site were compared to subjects with cancer of other sites. In the case of cancer sites known to be associated with tobacco, each site was compared individually with all remaining non tobacco-related sites serving as controls. Each unrelated site was then compared to all other non-related sites combined. The analyses make this equivalent to a case-control study.

From the data given, it was possible to estimate relative risks and confidence intervals, adjusted for age and race, for smokeless tobacco use in relation to cancer of various sites, as follows:

Cancer site	Men			Women		
	No.[1]	RR[1]	95% CI	No.[1]	RR[1]	95% CI
Oesophagus	3	0.79	0.24-2.56	0	-[2]	-
Lung	38	0.65	0.45-0.94	1	(0.84)	0.12-6.13
Bladder	29	1.42	1.94-2.17	1	(1.46)	0.20-10.70
Stomach	13	1.20	0.67-2.17	2	(0.96)	0.23-3.98
Small intestine	2	2.23	0.48-10.26	0	-[2]	-
Colon	30	1.18	0.78-1.77	8	1.54	0.72-3.29
Rectum	14	0.86	0.49-1.52	2	0.92	0.22-3.80
Liver	1	(0.71)	0.10-5.21	0	-[2]	-
Gallbladder/bile ducts	1	(0.74)	0.10-5.47	0	-[2]	-
Pancreas	3	0.29	0.09-0.93	0	-[2]	-
Breast	0	-[2]	-	11	0.49	0.25-0.95
Cervix, invasive	-	-	-	10	2.70	1.34-5.43
Uterine corpus	-	-	-	7	1.69	0.76-3.77
Ovary	-	-	-	2	(1.60)	0.39-6.64
Vulva	-	-	-	1	(3.40)	0.46-25.43
Prostate	67	1.37	0.99-1.89	-	-	-
Male genitalia	2	(1.45)	0.35-6.02	-	-	-
Kidney	3	(0.72)	0.22-2.31	1	(2.08)	0.28-15.29
Connective tissue	1	(0.43)	0.06-3.13	0	-[2]	-
Melanoma	1	(0.50)	0.07-3.69	0	-[2]	-
Nervous system	1	(0.47)	0.06-3.40	2	(13.43)	3.20-56.44
Thyroid gland	1	(0.65)	0.09-4.83	1	(1.73)	0.24-12.67
Lymphosarcoma	2	0.61	0.15-2.54	0	-[2]	-
Hodgkin's disease	3	1.74	0.54-5.65	0	-[2]	-
Other lymphomas	2	1.80	0.42-7.75	0	-[2]	-
Multiple myeloma	4	1.07	0.38-3.05	1	(1.87)	0.25-13.85
Acute lymphocytic leukaemia	1	(2.63)	0.35-19.68	0	-[2]	-
Chronic lymphocytic leukaemia	4	1.21	0.42-3.46	2	5.48	1.28-23.46
Acute granulocytic leukaemia	1	(1.25)	0.17-9.26	0	-[2]	-
Chronic granulocytic leukaemia	0	(1.11)	0.06-19.07	0	-[2]	-

Cancer site	Men			Women		
	No.[1]	RR[1]	95% CI	No.[1]	RR[1]	95% CI
Other primaries	12	1.64	0.88-3.05	3	2.21	0.68-7.20
Unknown primaries	4	0.78	0.28-2.15	1	(1.00)	0.14-7.31

[1] Adjusted for age and race; see text for meaning of bracketed relative risks
[2] Not estimated as no cases in smokeless tobacco users

Relative risks adjusted for smoking, age and race could also be estimated from the data presented in the study. These results were as follows:

Cancer site	Men			Women		
	No.[1]	RR[1]	95% CI	No.[1]	RR[1]	95% CI
Oesophagus	2	(0.73)	0.17-3.07	0	-[2]	-
Lung	36	0.69	0.47-1.00	1	(0.63)	0.09-4.62
Bladder	29	1.67	1.09-2.55	1	(1.75)	0.24-12.84
Stomach	12	1.31	0.71-2.43	2	(1.02)	0.24-4.28
Small intestine	2	3.11	0.65-14.77	0	-[2]	-
Colon	30	1.36	0.90-2.07	7	1.28	0.58-2.87
Rectum	13	0.75	0.42-1.35	2	0.87	0.21-3.62
Liver	1	(1.20)	0.16-9.05	0	-[2]	-
Gallbladder/bile ducts	1	(1.77)	0.24-13.13	0	-[2]	-
Pancreas	3	0.29	0.09-0.92	0	-[2]	-
Breast	0	-[2]	-	11	0.60	0.31-1.17
Cervix, invasive	-	-	-	10	4.18	2.08-8.43
Uterine corpus	-	-	-	7	1.92	0.86-4.28
Ovary	-	-	-	2	(1.37)	0.33-5.69
Vulva	-	-	-	1	(2.95)	0.39-22.07
Prostate	65	1.32	0.94-1.84	-	-	-
Male genitalia	2	(2.75)	0.66-11.45	-	-	-
Kidney	3	(0.86)	0.26-2.78	1	(2.10)	0.28-15.49
Connective tissue	1	(0.64)	0.09-4.72	0	-[2]	-
Melanoma	1	(0.73)	0.10-5.41	0	-[2]	-
Nervous system	1	(0.45)	0.06-3.30	2	(14.99)	3.52-63.87
Thyroid gland	1	(0.57)	0.08-4.21	1	(1.64)	0.22-12.00
Lymphosarcoma	1	(0.38)	0.05-2.79	0	-[2]	-
Hodgkin's disease	2	(1.30)	0.31-5.40	0	-[2]	-
Other lymphomas	2	1.58	0.36-6.97	0	-[2]	-
Multiple myeloma	3	0.94	0.29-3.09	1	(1.95)	0.26-14.52
Acute lymphocytic leukaemia	1	(5.24)	0.63-43.79	0	-[2]	-
Chronic lymphocytic leukaemia	3	0.92	0.28-3.05	2	4.80	1.11-20.72
Acute granulocytic leukaemia	1	(1.93)	0.25-14.69	0	-[2]	-
Chronic granulocytic leukaemia	0	-[2]	-	0	-[2]	-
Other primaries	11	1.64	0.85-3.18	3	3.36	1.03-10.99
Unknown primaries	4	0.68	0.24-1.89	1	(1.77)	0.24-12.97

[1] Adjusted for smoking, age and race; see text for meaning of bracketed relative risks
[2] Not estimated as no cases in smokeless tobacco users

(It should be noted that the source paper provided adjusted relative risks without confidence levels by two levels of exposure to smokeless tobacco. It also provided numbers of cases and controls who were unexposed and exposed at the two levels from which confidence levels for the adjusted relative risks could be calculated assuming that the variances of the adjusted and crude relative risks were the same. The relative risks by level were then combined by fixed-effects meta-analysis [Fleiss & Gross, 1991]. Where there were no cases of a cancer among smokeless tobacco users, no attempt was made to estimate relative risk or confidence intervals. Where a relative risk was given for one level, but there were no cases among smokeless tobacco users at the other level, an approximate relative risk was estimated by adding 0.5 to each cell of the relevant 2x2 table. Such estimates are particularly uncertain, and are shown in brackets.)

The authors presented relative risk estimates for each of the cancer sites according to the number of smokeless tobacco-years of exposure. For men, these were as follows:

Cancer site	1-50 smokeless tobacco-years			51+ smokeless tobacco-years		
	No.[1]	Relative odds[2]	Adjusted relative odds[3]	No.[1]	Relative odds[2]	Adjusted relative odds[3]
Oesophagus	2	0.82	0.90	1	0.73	-
Lung	27	0.73	0.65	11	0.51	0.79
Bladder	19	1.61	1.61	10	1.15	1.78
Stomach	7	1.06	1.00	6	1.40	1.73
Small intestine	1	1.77	1.72	1	2.81	5.64
Colon	15	0.93	1.11	15	1.51	1.70
Rectum	9	0.95	0.76	5	0.73	0.73
Liver	1	0.89	1.59	0	-	-
Gallbladder/bile ducts	0	-	-	1	1.20	4.18
Pancreas	2	0.31	0.31	1	0.26	0.25
Prostate	38	1.54	1.47	29	1.17	1.13
Male genitalia	2	2.27	5.00	0	-	-
Kidney	3	0.91	1.08	0	-	-
Connective tissue	1	0.51	0.92	0	-	-
Melanoma	1	0.61	1.06	0	-	-
Nervous system	0	-	-	1	0.91	0.80
Thyroid gland	1	0.78	0.65	0	-	-
Lymphosarcoma	1	0.42	0.44	1	0.90	-
Hodgkin's disease	2	1.31	1.96	1	3.05	-
Other lymphomas	1	1.10	0.70	1	2.94	3.58
Multiple myeloma	1	0.36	0.26	3	1.59	1.84
Acute lymphocytic leukaemia	1	5.44	9.16	0	-	-
Chronic lymphocytic leukaemia	1	0.43	0.48	3	1.76	1.30
Acute granulocytic leukaemia	1	1.96	3.08	0	-	-
Other primaries	9	2.05	2.12	3	0.90	0.89
Unknown primaries	3	0.90	0.78	1	0.51	0.45

[1] Numbers of cases are for the first of the two odds ratio estimates following. Those for the second may be slightly less due to missing smoking data for some subjects
[2] Adjusted for age and race
[3] Adjusted for smoking, age and race

The relative odds ratios estimated for women were as follows:

Cancer site	1-50 smokeless tobacco-years			51+ smokeless tobacco-years		
	No.[1]	Relative odds[2]	Adjusted relative odds[3]	No.[1]	Relative odds[2]	Adjusted relative odds[3]
Lung	1	1.49	-	0	-	-
Bladder	0	-	-	1	1.78	2.43
Stomach	0	-	-	2	1.05	1.09
Colon	1	0.40	0.33	7	1.96	1.69
Rectum	1	1.05	0.94	1	0.80	0.81
Breast	3	0.26	0.26	8	0.64	0.67
Cervix, invasive	6	3.08	4.71	4	2.29	3.60
Uterine corpus	5	2.66	3.07	2	0.66	0.72
Ovary	0	-	-	2	2.32	1.88
Vulva	0	-	-	1	4.06	3.40
Kidney	1	2.97	2.98	0	-	-
Nervous system	2	28.16	29.32	0	-	-
Thyroid gland	0	-	-	1	2.49	2.35
Multiple myeloma	1	2.36	2.22	0	-	-
Chronic lymphocytic leukaemia	1	8.77	-	1	3.44	3.07
Other primaries	1	1.58	2.94	2	2.63	3.60
Unknown primaries	1	1.24	2.65	0	-	-

[1] Numbers of cases are for the first of the two odds ratio estimates following. Those for the second may be slightly less due to missing smoking data for some subjects
[2] Adjusted for age and race
[3] Adjusted for smoking, age and race

Although the authors reported that, in men, the use of smokeless tobacco correlated negatively with education and income, and positively with alcohol consumption, there was no attempt to adjust the results for these factors. Other problems noted with this study, apart from the very small number of cases for some cancers, included the high non-response rate of eligible participants, and the choice of cancer patients as a control group.

3.3.2 Wynder: USA - 8 cities (1977)

In this case-control study, Wynder & Stellman, 1977 interviewed patients in 20 hospitals in 8 American cities during the years 1969 to 1975, using a standardized questionnaire. The 3716 patients with histologically proven cancer of one of the six sites under study (lung Kreyberg type I, lung Kreyberg type II, oral cavity, larynx, oesophagus and bladder) were considered as cases. There were 892 patients with type I lung cancer, 473 with type II lung cancer, 873 with cancer of the oral cavity, 467 with cancer of the larynx, 264 with cancer of the oesophagus, and 747 with bladder cancer. The remaining 18,385 interviewed patients served as a control group. Controls were selected on the basis of the absence of a history of tobacco-related disease. Approximately 37% of the male controls and 49% of the female controls were diagnosed with a malignant neoplasm. In the control group, 9% of men had ever used chewing tobacco and 2.7% had ever used snuff. Female usage of chewing tobacco was very low (< 0.5%), and less than 1% of the women had ever used snuff. The authors reported that all the relative risks calculated for the various sites had 99% confidence intervals that included 1.00. Relative risks among snuff users ranged from 0.5 for type II lung cancer to 1.7 for oesophageal cancer, and again all the 99% confidence intervals included 1.00.

From the data given by the authors, it was possible to estimate the following relative risks for male chewing tobacco and snuff users:

Cancer site	Ever used chewing tobacco			Ever used snuff		
	Yes	No	RR (95% CI)	Yes	No	RR (95% CI)
Matched controls	233	2327	-	69	2491	-
Lung cancer type I	91	637	1.43 (1.10-1.85)	29	698	1.50 (0.96-2.33)
Lung cancer type II	26	294	0.88 (0.58-1.35)	6	314	0.69 (0.30-1.60)
Oesophagus	20	163	1.23 (0.76-1.99)	8	175	1.65 (0.78-3.49)
Bladder	47	539	0.87 (0.63-1.21)	11	576	0.69 (0.36-1.31)

Although the analyses area not adjusted for smoking, the authors noted that the smoking habits of users of chewing tobacco did not differ significantly from that of non users of chewing tobacco in any cancer diagnosis category. No similar statement was made for snuff, though the authors commented that their data included insufficient cases to demonstrate an increased risk due to chewing tobacco and snuff only.

The authors noted that the data on smokeless tobacco use may not be strictly comparable either among cancer sites or between cases and matched controls, because the underlying age distribution is not identical. The age distribution was not appreciably altered if the entire control series was considered. Further problems include recall bias, if subjects with certain cancers are more likely to report higher tobacco consumption than those with other diseases. Another issue involves the histological classification of lung cancer type II, where the relationship with tobacco may depend on the type of lesion under consideration.

3.3.3 Bolinder: Sweden (1992)

This study by Bolinder et al., 1992 was based on the same participants as in the prospective study by Bolinder et al., 1994 reported above. However, as this study was of cross-sectional design and the endpoints considered were different to those of the previous study, it has been considered separately. Subjects comprised 97,586 male construction workers, aged 16-65 years, who underwent medical check-ups between 1971 and 1974. Participants completed a questionnaire which asked about various symptoms and disorders, as well as smoking information, while data on sick-leave frequency and disability pension diagnoses were obtained from the Swedish National Social Insurance Board. In the study cohort, there were 23,885 never users of any form of tobacco and 5014 subjects who used smokeless tobacco daily but had never been regular smokers.

The results of the study were as follows:

Symptom	Non-users		Smokeless tobacco users	
	%	OR	OR[1]	95% CI
Cough in the morning	3.0	1.0	2.1	1.8-2.4
More than 3 months cough/year	2.1	1.0	1.4	1.1-1.7
Breathlessness on slight effort	4.1	1.0	1.4	1.3-1.6
Heartburn	19.4	1.0	0.9	0.8-0.9
Peptic ulcer	3.6	1.0	1.1	0.9-1.2
Sleeping disturbances	5.6	1.0	1.2	1.1-1.4
Nervous problems	4.6	1.0	1.2	1.1-1.4
Low back pain in past year	22.0	1.0	1.1	1.0-1.2
Frequent sick-leave	-	1.0	1.1	1.0-1.2
Long sick-leave	-	1.0	1.2	1.1-1.2
Disability pension for musculoskeletal diagnosis, age 46-55	43[2]	1.0	2.8[3]	1.6-4.8
Disability pension for musculoskeletal diagnosis, age 56-65	318[2]	1.0	1.5[3]	1.2-1.8

[1] Adjusted for age
[2] Number of subjects
[3] Unadjusted

Approximately 25% of eligible men did not participate in the study, which may have resulted in selection bias. Additionally, no information on confounding factors appears to have been collected, despite the authors noting that alcohol consumption, which could influence the incidence of various diseases, is often higher in users of tobacco. The authors felt that it was "unlikely that the higher risks among

smokeless tobacco users could be explained solely by exposure to risk factors other than tobacco".

3.3.4 Sterling: USA (1992)

The study by Sterling et al., 1992 was based on data from the 1986 National Mortality Followback Survey (NMFS) and the 1987 National Health Interview Survey (NHIS). The NMFS was based on a stratified probability sample of death certificates of persons aged 25 years or over who died during 1986. The strata were based on racial origin, cause of death, and within certain causes, age at death. A questionnaire was sent to a member of each decedent's family. The final NMFS sample consisted of 18,733 decedents, with questionnaire data available for 16,598 of these. The NHIS collects information from a weekly representative sample of civilian non-institutionalised households as part of an ongoing study, with the weekly samples being additive over time. For the majority of respondents, personal interviews were conducted. Details of the number of subjects included in this part of the study were not given. Users of smokeless tobacco were classified into one of three groups, depending on the number of times they had used either chewing tobacco or snuff, with the groupings being 0-99, 100-9999 and 10,000+ times, respectively.

Relative risks, adjusted for sex, race, age, smoking, alcohol consumption and occupation, were estimated as follows:

Smokeless tobacco use	All cancers		Digestive cancers	
	RR	95% CI	RR	95% CI
0-99	1.00	-	1.00	-
100-9999	0.37	0.26-0.54	0.15	0.04-0.52
10000+	0.88	0.69-1.12	0.61	0.34-1.10

The authors noted that the differing methods used to collect data from the decedent and living populations could result in varying amounts of misclassification occurring in the two groups. However, they discussed the results of several studies that showed good agreement between information obtained from a primary respondent and from a proxy respondent, usually next of kin. It was argued that as the use of smokeless tobacco is more conspicuous than other habits, it would be very unlikely to go unreported by surrogate respondents. Another potential source of error arose from the classification of all decedents whose usage of smokeless tobacco was unknown as never users, although it was estimated by the authors that in order to achieve an estimate for which the lower confidence interval exceeded 1.00 it would be necessary to reclassify 22% of never-using decedents as users. Conversely, in order for misclassification to have masked a significantly elevated risk, 82% of users would have to have been classified as never users. It was felt that misclassification on such a large scale would be very unlikely.

3.4 *Other epidemiological evidence*

3.4.1 Redmond: UK - London (1970)

In a paper published in 1970 [Redmond, 1970], Redmond described case reports of "polypusses" of the nose, and other sites including the oesophagus, associated with snuff use dating back to 1761. It is likely that in at least some of these cases, the disease being described was cancer.

4. **All cause mortality**

4.1 *Introduction*

Three studies have provided information on all cause mortality. These are described in section 4.2 and the results summarized in section 4.3.

4.2 *Prospective studies*

4.2.1 Bolinder: Sweden (1994)

See section 3.2.2

4.2.2 Accortt: USA (2002)

See section 3.2.3

4.2.3 Henley: USA – CPS I and CPS II (2005)

See section 3.2.5

4.3 *Summary*

Four prospective studies presented results for all causes of death combined in users of smokeless tobacco compared to non-users. (Note that such an analysis will include deaths from oral and cardiovascular disease not within the scope of this review.) Three of the studies were conducted in the USA, while the fourth took place in Sweden. In all four studies, cigarette, cigar and pipe smokers were excluded from the analysis. All of the studies also carried out adjustment for age, and for various other potentially confounding factors.

The results are summarized below in table 4.1. Significantly raised relative risks of 1.4 (95% 1.3-1.8), 1.17 (95% CI 1.11-1.23) and 1.18 (95% CI 1.08-1.29) were reported by three of the studies. The fourth study also estimated a raised relative risk, but this failed to reach statistical significance.

A meta-analysis of the results from these four studies gave a relative risk estimate of 1.18 (95% CI 1.13-1.23) using a fixed effects model and 1.19 (95% CI 1.12-1.27) using a random effects model. There was no evidence of significant heterogeneity between the studies (heterogeneity chisquared = 4.90 on 3 d.f., $p \geq 0.1$).

Table 4.1: Summary of results for all-cause mortality

Study	Non-users		Smokeless tobacco users		Product[1]	Sex	RR	95% CI	Adjustment factors[2]
	At risk	Cases	At risk	Cases					
Accortt	-	-	414	-	ST	M+F	1.1	0.9-1.3	Age, smoking, other[3]
Bolinder	32546	-	6297	-	ST	M	1.4	1.3-1.8	Age, smoking, other[4]
Henley-CPS I	69662	9819	7745	2052	ST	M	1.17	1.11-1.23	Age, smoking, other[5]
Henley-CPS II	111482	18824	2488	567	ST	M	1.18	1.08-1.29	Age, smoking, other[6]

[1] ST = smokeless tobacco
[2] Adjustment for smoking includes studies restricted to non-smokers
[3] Race, sex and poverty status
[4] Region of origin
[5] Race, education, BMI, exercise, alcohol intake, fat consumption, fruit/vegetable intake and aspirin use
[6] Race, education, BMI, exercise, alcohol intake, employment status and type, fat consumption, fruit/vegetable intake and aspirin use

5. **Cancer**

5.1 *Introduction*

In the sections that follow, for all cancers combined and for 16 types of cancer, studies providing relevant data are described and results summarized.

Table 5.1: Number of studies for cancer

Section	Cancer	Number of studies: Prospective	Case-control/ cross-sectional	Other	Total
5.2	All cancers	5	1	0	6
5.3	Bladder cancer	3	12	0	15
5.4	Brain cancer	0	1	0	1
5.5	Breast cancer	1	2	1	4
5.6	Connective tissue cancers	1	2	0	3
5.7	Digestive cancers	10	16	2	28
5.8	Female genital organ cancers	0	1	0	1
5.9	Haematopoietic cancers	3	6	0	9
5.10	Kidney cancer	1	10	0	11
5.11	Lung cancer	6	3	0	9
5.12	Male genital organ cancers	0	1	0	1
5.13	Nasal cancer	0	2	3	5
5.14	Nervous system cancers	0	1	0	1
5.15	Prostate cancer	3	2	0	5
5.16	Skin cancer	1	1	2	4
5.17	Thyroid gland cancer	0	1	0	1
5.18	Other cancers	2	2	0	4

Finally, in section 5.19, the overall results are summarized.

5.2 *All cancers*

5.2.1 Prospective studies

5.2.1.1 Winn: USA (1982)

See section 3.2.1

5.2.1.2 Bolinder: Sweden (1994)

See section 3.2.2

5.2.1.3 Accortt: USA (2002)

See section 3.2.3

5.2.1.4 Henley: USA – CPS I and CPS II (2005)

See section 3.2.5

5.2.2 Case-control/cross-sectional studies

5.2.2.1 Sterling: USA (1992)

See section 3.3.4

5.2.3 Summary

Six studies, five prospective and one case-control, investigated the relationship between smokeless tobacco use and all cancers combined. (Although all cancers combined includes oral cancers which are beyond the scope of this review, the results are considered here as non-oral cancers will form the great majority of the cancers considered.) Details of the studies are given in table 5.2.1. Four of the studies excluded all smokers and one excluded cigarette smokers from the smokeless tobacco analyses. The sixth study appeared to include smokers of all products, but only adjusted for cigarette smoking during analysis. Five of the studies adjusted their findings for age and for various other potential confounders. The sixth study did not provide information on the factors adjusted for.

The results of the six studies are summarized in table 5.2.2, where the most adjusted risk estimate is reported where applicable. Four raised relative risks were estimated, although only one was significantly so (1.19, 95% CI 1.02-1.40). A significantly reduced relative risk was reported by the cross-sectional study (0.68, 95% CI 0.55-0.83). Finally, a standardized mortality rate of approximately 100 was reported.

The study by Winn could not be included in a meta-analysis, as no relative risk estimate or confidence interval was available. However, a meta-analysis based on the results of the other five studies gave a relative risk estimate of 1.04 (95% CI 0.96-1.12) using a fixed effects model and 1.01 (95% CI 0.83-1.21), using a random effects model. It was noticeable that the results from the one cross-sectional study were markedly different from those from the prospective studies, and indeed there was significant heterogeneity between the studies (heterogeneity chisquared = 19.85 on 4 d.f., $p < 0.001$). Meta-analysis based on the results from the prospective studies alone gave a relative risk estimate of 1.11 (95% CI 1.02-1.21) for both models.

Table 5.2.1: Summary of studies of all cancers

Study	Study Type	Location	Treatment of smoking in analysis		Other adjustment factors
			Smokers excluded	Smoking variables adjusted for	
Accortt	P	USA	Ever cigarette	-	Age, race, poverty index, alcohol intake, dietary fat intake
Bolinder	P	Sweden	Ever smokers	-	Age, region of origin
Henley-CPS I	P	USA	Ever smokers	-	Age, race, education, BMI, exercise, alcohol intake, fat consumption, fruit/ vegetable intake, aspirin use
Henley-CPS II	P	USA	Ever smokers	-	Age, race, education, BMI, exercise, alcohol intake, employment status and type, fat consumption, fruit/vegetable intake, aspirin use
Sterling	C-C	USA	None	Cigarette smoking	Age, sex, race, alcohol intake, occupation
Winn	P	USA	Ever smokers	-	Not stated

Table 5.2.2: Summary of results for all cancers combined

Study	Non-users		Smokeless tobacco users		Product[a]	Sex	RR	95% CI	Adjustment factors[b]	Notes[c]
	Controls	Cases	Controls	Cases						
Accortt	-	-	414	-	ST	M	1.1	0.6-1.9	Age, smoking, other	1
Bolinder	32546	-	6297	-	ST	M	1.1	0.9-1.4	Age, smoking, other	1
Henley-CPS I	69662	1975	7745	357	ST	M	1.07	0.95-1.20	Age, smoking, other	1
Henley-CPS II	111482	5921	2488	162	ST	M	1.19	1.02-1.40	Age, smoking, other	1
Sterling	-	-	-	-	ST	M+F	0.68	0.55-0.83	Age, smoking, other	2
Winn	Total population ~ 300,000				ST	M	~1.00	-	Smoking, others not stated	3

[a] ST = smokeless tobacco

[b] Adjustment for smoking includes studies restricted to non-smokers; refer to table 5.2.1 for full details of adjustment factors.

[c] Key to notes:

1 Number of controls refers to population at risk

2 Relative risk estimated from data given

3 Standardized mortality ratio/100. The ratio itself was actually given as ~1 by authors, but presumably ~100 was intended

5.3 *Bladder cancer*

5.3.1 Prospective studies

5.3.1.1 Boffetta: Norway/USA (2005)

See section 3.2.4

5.3.1.2 Henley: USA - CPS I and CPS II (2005)

See section 3.2.5

5.3.2 Case-control/cross-sectional studies

5.3.2.1 Lockwood: Denmark - Copenhagen/Frederiksberg (1961)

The case group in the study by Lockwood, 1961 was made up of 282 men and 87 women with bladder cancer reported to a tumour registry between 1942 and 1st March 1956, who were resident in the city of Copenhagen or the borough of Frederiksberg. One control, identified from electoral rolls, was selected for each case, matched for sex, age, marital status, occupation and residence. All participants were interviewed and asked for information on a number of lifestyle factors. Among the men, two cases and nine controls cited smokeless tobacco as their main form of tobacco usage. Twenty-four cases and 38 controls were non-smokers. In addition, 49 female cases and 57 female controls were non-smokers, and none of the women used smokeless tobacco. Using the entire study population, a relative risk of 0.29 (95% CI 0.06-1.38) could be estimated for the risk of bladder cancer in users of smokeless tobacco compared to non-smokers. When the analysis was restricted to men, this increased to 0.35, but remained non-significant (0.07-1.77).

Although the interview asked about all types of tobacco used, subjects were then categorized according to their preferred smoking habits. Thus, smokers of other products who also used smokeless tobacco less frequently than their main tobacco product would be omitted from analysis. In addition, no form of adjustment for potentially confounding variables was carried out in this study, despite the fact that such information was collected at interview.

5.3.2.2 Wynder: USA - New York (1963)

Cases in this study [Wynder et al., 1963] consisted of 200 male bladder cancer patients interviewed at one of seven hospitals in New York during the period from January 1957 until December 1960. An equal number of controls, matched for sex and age, were also interviewed. In a separate study, data on a further 100 male bladder cancer patients and 100 male age-matched controls were collected. As separate analysis of the two groups revealed no differences between them, they were combined. Each bladder cancer case was confirmed by histological diagnosis. In the control group, 73 men had malignant tumours of sites other than the bladder, and 227 had benign diseases. Tobacco chewing was reported by 11% of the case group and 8% of controls, while snuff was used by 2% of cases and 3% of controls. The authors reported that neither of these differences reached statistical significance. From these data, it was possible to estimate relative risks for bladder cancer of 1.42 (95% CI 0.82-2.47) for tobacco chewing and 0.66 (0.23-1.88) for snuff use. These analyses do not adjust for smoking, the results for smoking and smokeless tobacco being presented independently. It is not stated how smoking habits differed between users and non-users of chewing tobacco and of snuff.

5.3.2.3 Dunham : USA - New Orleans (1968)

In the study by Dunham et al., 1968, 402 of the cases came from an incidence study of bladder cancer carried out in New Orleans between 1 February 1958 and 31 January 1964. Patients with bladder cancer were identified from hospital records and other registries. A further 91 cases, who were diagnosed before this date and/or were not resident in New Orleans, were also included. The control group consisted of 527 subjects without cancer of the bladder who were interviewed in the same hospital during the same period of study. Proportions of cases and controls were similarly distributed for age, sex and race categories, and also for ward, semi-private and private patients, and residence in metropolitan New Orleans. From the data presented, it was possible to calculate that 128 of the cases and 161 of the controls were never users of tobacco, and seven cases and nine controls used some form of smokeless tobacco.

Relative risks for bladder cancer in relation to various forms of tobacco use could be calculated as follows:

Tobacco use	Controls	Cases	RR	95% CI
Never users	161	128	-	-
Smokeless tobacco only	9	7	0.98	0.35-2.70
Chewing tobacco only	3	5	2.10	0.49-8.94
Chewing tobacco and snuff only	2	1	0.63	0.06-7.01
Snuff only	4	1	0.31	0.03-2.85
Cigarettes only	209	216	1.30	0.96-1.75
Cigarettes and other[1]	97	100	1.30	0.90-1.86
Cigar only	14	10	0.90	0.39-2.09
Cigars and other[2]	20	19	1.19	0.61-2.33
Pipe only	10	6	0.75	0.27-2.13
Pipe and other[3]	5	7	1.76	0.55-5.68

[1] Includes users of pipes, cigars and smokeless tobacco
[2] Includes users of pipes and smokeless tobacco
[3] Includes users of smokeless tobacco

Adjustment for sex and race increased the relative risk estimate for bladder cancer among exclusive users of all types of smokeless tobacco to 1.14 (95% CI 0.39-3.31). It was not possible to adjust this estimate for any other factors, although information on other potential confounders was collected.

5.3.2.4 Cole: USA - Massachusetts (1971)

In the study by Cole et al., 1971, the case group consisted of all residents of the Boston and Brockton Standard Metropolitan Statistical Areas, aged 20-89 years, with a newly diagnosed neoplasm of the lower urinary tract during the 18 months ending on 30 June 1968. A total of 470 cases were interviewed, and in all but 28 subjects, the tumour was located in the bladder. Controls were drawn at random from annual population lists, matched on year of diagnosis, age and sex. Interviews took place with 500 controls. Interviews were rated as reliable, doubtful or unreliable. Doubtful interviews, obtained from 20 cases and 22 controls, were retained, but the two cases and two controls who gave unreliable interviews were excluded from further analysis. Data on smokeless tobacco use were only available for men. In the case group, three men used snuff and 46 men used chewing tobacco. Equivalent numbers for the controls were not given, but it was stated that the proportion of cases using smokeless tobacco did not differ from the numbers expected, which were estimated at 2.9 for snuff and 42.3 for chewing tobacco. No mention was made of adjustment for cigarette smoking.

5.3.2.5 Williams: USA (1977)

See section 3.3.1

5.3.2.6 Wynder: USA - 8 cities (1977)

See section 3.3.2

5.3.2.7 Howe: Canada - British Columbia/Newfoundland/Nova Scotia (1980)

Cases in the study by Howe et al., 1980 consisted of all newly diagnosed bladder cancers occurring in the provinces of British Columbia, Newfoundland and Nova Scotia between April 1974 and June 1976. Neighbourhood controls were matched to each of the cases by age and sex. Interviews were carried out with 480 pairs of male cases and controls and 152 pairs of female cases and controls. The relative risk for men who reported using chewing tobacco at any time compared to those who had never used chewing tobacco was estimated at 0.9 (95% CI 0.5-1.6), based on a discordant pair ratio of 29:32. Controlling for cigarette smoking did not affect this estimate.

5.3.2.8 Mommsen: Denmark - Aarhus (1983)

The case group in the study by Mommsen et al., 1983 comprised 165 men and 47 women with newly diagnosed primary bladder cancer who were consecutively admitted to an oncology department in Aarhus during a two-year period for the men, and a three-year period for the women, both of which started in September 1977. Male patients were matched to controls on a one-to-one basis, while for the female patients there were two controls to every case, giving a total of 259 controls. Matching was based on age, sex, geographic area and degree of urbanization. Cases were interviewed in hospital, while the controls were mailed a questionnaire and then interviewed by telephone a few days later. Tobacco chewing was reported by 39 cases and 26 controls, giving an unadjusted relative risk estimate for bladder cancer of 2.02 (95% CI 1.19-3.42). A logistic regression analysis, which included smoking of cigarettes, cigarillos and pipes, industrial work, saccharin and alcohol consumption, previous venereal disease, and work with petroleum or asphalt, oil or gasoline, or chemical materials as independent variables, estimated relative risks of between 1.67 and 1.87 for tobacco chewing. A second publication on this study [Mommsen & Aagaard, 1983] estimated a relative risk of bladder cancer in men who had ever chewed tobacco of 1.7 (95% CI 1.0-2.9), compared to men who had never used chewing tobacco, adjusted for cigarette, pipe and cigar/cigarillo smoking. None of the women in the study appeared to have used chewing tobacco.

5.3.2.9 Hartge: USA - multicentre (1985)

Hartge et al., 1985 interviewed 2982 cases and 5782 controls as part of the National Bladder Cancer Study, a population-based case-control study conducted in 10 geographic areas. The case group included all residents of the study areas, aged 21-84 years, who were diagnosed with bladder cancer during a one-year period, starting between December 1977 and March 1978, depending on the area. Controls aged 21-64 years were selected through random digit dialling, while controls aged 65 -84 years were selected from Health Care Financing Administration rosters. As so few women used smokeless tobacco, analysis was restricted to male cases and controls. Among the 4282 male controls, 5% had ever used snuff and 12% had ever used chewing tobacco. Corresponding information for the cases was not given. A relative risk of 0.77 (95% CI 0.38-1.56) was estimated for bladder cancer in men had never smoked cigarettes but who used snuff exclusively, compared to men who did not use any tobacco. This estimate was adjusted for use of pipes, cigars and chewing tobacco. The relative risk for men who used chewing tobacco was estimated at 1.02 (95% CI 0.67-1.54), after adjustment for use of pipes, cigars and snuff.

5.3.2.10 Kabat: USA - Six cities (1986)

Kabat et al., 1986 drew data from a large case-control study of smoking and cancer that interviewed cancer cases in 18 hospitals in six US cities. In this study, all bladder cancer cases interviewed between 1976 and 1983 were selected to participate. This time period included 751 male and 197 female bladder cancer cases. Seventy-six participants of both sexes stated that they had never smoked, and for each of these, three controls were sought from among hospitalized patients with a current diagnosis of a non tobacco-related disease. Controls were matched on age, sex, race, hospital, year of interview and lifetime non-smoking status. In total, 238 male and 254 female controls were obtained. One female case and one male case chewed tobacco, and no male cases reported ever having used snuff. However, in women, three cases compared to one control had ever used snuff, a difference that was statistically significant ($p = 0.04$). From this data, a relative risk of 10.4 (95% CI 1.07-101.5) could be estimated. Although information on confounding variables was collected, no attempt was made to adjust the results for these factors.

5.3.2.11 Slattery: USA - Utah (1988)

Slattery et al., 1988 compared all Utah residents, aged 21-84 years, with a positive histology of carcinoma of the bladder diagnosed between 1 December 1977 and 31 March 1983 with population controls, matched to the cases by age and sex, using a two-to-one ratio. Controls were selected by random digit dialling, with those aged 65 or over also being obtained through social security records. Analyses were restricted to white men, and were based on 332 cases and 686 controls. Participants were interviewed at home. Overall, 76 cases and 307 controls were never smokers. Sixteen cases and 32 controls had ever used snuff, while the corresponding numbers for chewing tobacco were 20 and 45 respectively. However, the majority of these subjects also used cigarettes, as shown below:

Smokeless tobacco use	Cases		Controls	
	Never smoked cigarettes	Ever smoked cigarettes	Never smoked cigarettes	Ever smoked cigarettes
Snuff				
Never	74	239	304	348
Ever	2	14	3	29
Chewing tobacco				
Never	75	234	296	343
Ever	1	19	11	34

Odds ratios for the risk of bladder cancer for users of smokeless tobacco were estimated, using non-users as the comparison group:

	Snuff		Chewing tobacco	
	OR	95% CI	OR	95% CI
All subjects - unadjusted	1.00	0.54-1.85	1.08	0.63-1.87
Never smokers - unadjusted	2.73	0.48-15.57	2.78	0.38-20.20
Ever smokers - unadjusted	0.70	0.36-1.35	1.22	0.68-2.19
All subjects – adjusted[1] for:				
Smoking group[2]	0.92	0.47-1.79	0.75	0.41-1.35
Pack years[3]	0.90	0.46-1.75	0.68	0.38-1.23
Age started[3]	0.92	0.47-1.82	0.76	0.42-1.39
Years stopped	0.99	0.50-1.96	0.78	0.45-1.36

[1] Adjusted in multiple logistic regression analysis
[2] Never, ex- or current smokers
[3] Includes ex- and current smokers

Information on caffeinated coffee and tea consumption was collected, but analyses for smokeless tobacco use were not adjusted for this.

5.3.2.12 Burch: Canada - Alberta/Ontario (1989)

Eligible cases in the study by Burch et al., 1989 consisted of all individuals, aged 35-79 years and resident in Alberta, metropolitan Toronto or south-central Ontario, who were diagnosed with primary histologically confirmed bladder cancer between 1979 and 1982. Cases were identified from a cancer institute, a tumour registry and hospital and medical records relating to the study area. Controls were randomly selected from province-wide annually updated listings, and were matched to cases on a one-to-one basis for age, sex and area of residence. A total of 826 cases and 792 controls took part in the study. Each participant completed an interviewer-administered questionnaire. Among the male subjects, 26 cases and 34 controls had ever used chewing tobacco, and 601 cases and 568 controls had never used it, with a relative risk estimate of 0.60 (95% CI 0.34-1.06) in a matched analysis. Snuff was used by 9 cases and 18 controls, leaving 618 cases and 584 controls as never users. The relative risk of bladder cancer in ever users of snuff compared to never users was estimated at 0.47 (95% CI 0.21-1.07). The authors reported that analyses restricted to subjects who had never smoked cigarettes produced virtually identical results.

5.3.3 Summary

Fifteen studies reported findings for the risk of bladder cancer in users of smokeless tobacco, and details of these studies are given in Table 5.3.1. Three studies were prospective in design, and the remaining 12 were case-control studies. In four of the 15 studies the smokeless tobacco analysis was restricted to non-smokers of any product. One study included smokers of cigars and/or pipes only and adjusted for this during analysis, and one only included smokers where smoking was a less important source of tobacco than was smokeless tobacco. In eight studies smokers of all tobacco products were included, with three adjusting for smoking of all products, two adjusting for cigarette smoking only, and three not accounting for smoking in analysis. In one study it was not stated whether the exposed group included smokers, and no adjustment for smoking variables took place.

A summary of the results of the studies is shown in Table 5.3.2, where the most adjusted relative risk is reported where applicable. Twelve of the relative risks estimated were below 1.00, although none of them was significantly so. Ten relative risks were raised, but only two reached statistical significance, although a third was of borderline significance. In one study, the observed numbers of users of both snuff and chewing tobacco did not vary significantly from those expected, but as the observed numbers were slightly higher than the expected numbers, the relative risk estimates would have exceeded 1.00.

Table 5.3.3 gives the results of meta-analysis of the studies of bladder cancer. Results from the study by Cole could not be included in a meta-analysis, as valid relative risks and confidence intervals could not be estimated. Four analyses were conducted, to take account of the varying tobacco products considered by the studies. Firstly, results for chewing tobacco and snuff were analysed alone. Two analyses were then carried out for all types of smokeless tobacco, using results for chewing tobacco and snuff respectively, where both were considered separately by a study. The relative risk estimates for chewing tobacco alone, smokeless tobacco/chewing tobacco, and smokeless tobacco/snuff were quite similar, with no real association with bladder cancer emerging. However, the overall risk estimates for snuff use only were markedly lower, although they failed to reach statistical significance. In the analysis that included smokeless tobacco and chewing tobacco, there was significant heterogeneity between the studies ($p < 0.05$).

Table 5.3.1: Summary of studies of bladder cancer

Study	Study Type	Location	Treatment of smoking in analysis		Other adjustment factors
			Smokers excluded	Smoking variables adjusted for	
Boffetta	P	Norway/ USA	None	Smoking of cigarettes, cigars and pipes	Age
Burch	C-C	Canada	None	None	Age, area of residence
Cole	C-C	USA	Not stated	None	None
Dunham	C-C	USA	Ever smokers	-	Sex, race
Hartge	C-C	USA	Ever cigarette	Cigar, pipe smoking, use of snuff or chewing tobacco[1]	None
Henley-CPS I	P	USA	Ever smokers	-	Age, race, education, BMI, exercise, alcohol intake, fat consumption, fruit/ vegetable intake, aspirin use
Henley-CPS II	P	USA	Ever smokers	-	Age, race, education, BMI, exercise, alcohol intake, employment status and type, fat consumption, fruit/ vegetable intake, aspirin use
Howe	C-C	Canada	None	Cigarette smoking	Age, sex
Kabat	C-C	USA	Ever smokers	-	None
Lockwood	C-C	Denmark	Ever smokers[2]	-	None
Mommsen	C-C	Denmark	None	Smoking of cigarettes, cigars and pipes	Age, geographic area, degree of urbanization
Slattery	C-C	USA	None	Smoking status	None
Williams	C-C	USA	None	Cigarette smoking	Age, race
Wynder 1963	C-C	USA	None	None	None
Wynder 1977	C-C	USA	None	None	None

[1] Snuff was adjusted for in the chewing tobacco analyses and chewing tobacco was adjusted for in the snuff analyses

[2] Only those for whom smoking was the main form of tobacco usage were excluded

Table 5.3.2: Summary of results for bladder cancer

Study	Non-users		Smokeless tobacco users		Product[a]	Sex	RR	95% CI	Adjustment factors[b]	Notes[c]
	Controls	Cases	Controls	Cases						
Boffetta	6921	169	3215	69	ST	M	0.72	0.52-1.06	Age, smoking	1
Burch	568	601	34	26	Chew	M	0.60	0.34-1.06	Age, other	
	584	618	18	9	Snuff	M	0.47	0.21-1.07		
Cole	-	-	-	3	Snuff	M	Expected no. of cases 2.9		None	2
	-	-	-	46	Chew	M	Expected no. of cases 42.3			2
Dunham	161	128	9	7	ST	M+F	1.14	0.39-3.31	Smoking, other	
Hartge	-	-	-	-	Snuff	M	0.77	0.38-1.56	Smoking	
	-	-	-	-	Chew	M	1.02	0.67-1.54		
Henley-CPS I	69662	461	7745	98	ST	M	0.97	0.77-1.22	Age, smoking, other	1,3
Henley-CPS II	111482	1649	2488	44	ST	M	1.15	0.85-1.56	Age, smoking, other	1,3
Howe	Total population 960				Chew	M	0.90	0.50-1.60	Age, smoking	
Kabat	238	75	0	1	Chew	M	9.48	0.38-235	Smoking	4,5
	254	75	0	1	Chew	F	10.1	0.41-250		4,5
	253	73	1	3	Snuff	F	10.4	1.07-102		5
Lockwood	38	24	9	2	ST	M	0.35	0.07-1.77	None	5
Mommsen	139	126	26	39	Chew	M	1.7	1.0-2.9	Age, smoking, other	6
Slattery	652	313	32	16	Snuff	M	0.92	0.47-1.79	Smoking	
	639	309	45	20	Chew	M	0.75	0.41-1.35		
Williams	1624	177	164	29	ST	M	1.67	1.09-2.55	Age, smoking, other	5
	3135	72	53	1	ST	F	1.75	0.24-12.84		5
Wynder	276	267	24	33	Chew	M	1.42	0.82-2.47	None	5
1963	291	294	9	6	Snuff	M	0.66	0.23-1.88		5
Wynder	2327	539	233	47	Chew	M	0.87	0.63-1.21	None	5
1977	2491	576	69	11	Snuff	M	0.69	0.36-1.31		5

[a] ST = smokeless tobacco

[b] Adjustment for smoking includes studies restricted to non-smokers; refer to table 5.3.1 for full details of adjustment factors. Where study presents multiple RR estimates, adjustment factors relate to all RRs unless otherwise stated

[c] Key to notes:

1 Number of controls refers to population at risk
2 Cancer of lower urinary tract
3 Genitourinary system
4 No subjects in one exposure group, 0.5 added to each cell to obtain relative risk estimate
5 Relative risk estimated from data given
6 Data came from Mommsen & Aagaard, 1983

Table 5.3.3: Summary of meta-analysis results for bladder cancer studies

Tobacco product	No. of studies	Fixed effects estimate RR	95% CI	Heterogeneity chisquared	p value	Random effects estimate RR	95% CI
Chewing tobacco only	9	0.99	0.82-1.18	14.06	NS	1.01	0.78-1.32
Smokeless tobacco/ chewing tobacco	16[1]	1.01	0.90-1.13	25.79	<0.05	1.02	0.86-1.22
Snuff only	6	0.75	0.54-1.04	6.87	NS	0.76	0.51-1.13
Smokeless tobacco/snuff	13[2]	0.97	0.85-1.11	21.36	NS	0.94	0.75-1.17

NS = Not significant

[1] Combines results from all available studies, using results for chewing tobacco if results for separate types of smokeless tobacco are presented

[2] Combines results from all available studies, using results for snuff if results for separate types of smokeless tobacco are presented

5.4 *Brain cancer*

5.4.1 Case-control/cross-sectional studies

5.4.1.1 Zheng: USA - Iowa (2001)

Cases in the study by Zheng et al., 2001 consisted of 375 subjects, aged 40-85 years, with histologically confirmed incident glioma. A total of 2434 population-based controls, matched for sex and age, were selected with a matching ratio of 6.5:1. Controls aged less than 65 years were randomly selected from state drivers licence records, while those aged 65 years or above were chosen from the United States Health Care Financing Administration records. A postal questionnaire was used to collect information from the study subject or their next-of-kin. No details of the numbers of subjects who used smokeless tobacco were given, but the authors reported that neither the use of snuff nor chewing tobacco was associated with the risk of brain glioma in this study. The authors felt that the use of proxy respondents may actually be beneficial in this study, due to the effects of the disease on memory.

5.4.2 Summary

Only one study on the association between brain cancer and the use of smokeless tobacco was available. The study was of a case-control design, and was conducted in the USA. Smokers of cigarettes, cigars and pipes were included in the study. As relative risks were not presented, it was not possible to ascertain whether adjustment for any smoking variables or other factors had been carried out. The authors reported that neither the use of snuff nor chewing tobacco was associated with the risk of brain cancer in either men or women.

Table 5.4.1: Summary of results for study on brain cancer

Study	Non-users		Smokeless tobacco users		Product	Sex	RR (95% CI)	Adjustment factors
	Controls	Cases	Controls	Cases				
Zheng	-	-	-	-	Snuff	M	No association	Not stated
	-	-	-	-	Snuff	F	No association	Not stated
	-	-	-	-	Chew	M	No association	Not stated
	-	-	-	-	Chew	F	No association	Not stated

5.5 *Breast cancer*

5.5.1 Prospective studies

5.5.1.1 Accortt: USA (2002)

See section 3.2.3

5.5.2 Case-control/cross-sectional studies

5.5.2.1 Spangler: USA - North Carolina (2001)

In this study [Spangler et al., 2001], 1070 Cherokee women aged at least 18 years, residing on tribal lands, were interviewed using a 96-item questionnaire. During the interview, a personal history and age at diagnosis of breast cancer were obtained. A total of eight breast cancer cases were identified: five diagnosed before age 55 and three diagnosed after this age. In the entire study group, 64 women reported current use of smokeless tobacco, and 228 women reported former use. In the five women with breast cancer diagnosed before the age of 55 years, three had ever used smokeless tobacco, and two had not. Among the controls, the corresponding numbers were 172 and 893 respectively. From these numbers, the authors estimated a crude odds ratio for the risk of breast cancer associated with smokeless tobacco use of 7.79 (95% CI 1.05-66.0). None of the women who were older than 55 years when diagnosed with breast cancer used smokeless tobacco. Among the controls in this age group, there were 50 users and 122 non-users of smokeless tobacco. This gave rise to an estimated odds ratio of 0 (95% CI 0-5.67). Limitations of the study discussed by the authors included a failure to obtain menstrual histories from the participants, and the self-reporting of smokeless tobacco use and breast cancer. Deaths from breast cancer would necessarily be excluded. Additionally, the study was carried out in a small population with a small number of breast cancer cases, which precluded the ability to control for confounding.

In a later paper, Spangler et al., 2002 presented corrections to their original data. Although the study was still based on eight cases of breast cancer, it was now reported that three had been diagnosed before the age of 55 years, and five cases occurred in women older than this. In the younger cases, one had used smokeless tobacco and the other two had not. For the controls, the corresponding figures were 274 and 693. From this, a new odds ratio of 1.26 (95% CI 0.12-13.9) was estimated. Two of the five older breast cancer cases had ever used smokeless tobacco, compared

to 46 controls who were smokeless tobacco users and 85 controls who were not. Here, the new odds ratio was estimated at 1.23 (95% CI 0.14-9.52).

5.5.2.2 Williams: USA (1977)

See Section 3.3.1

5.5.3 Other epidemiological evidence

5.5.3.1 McBride: USA - North Carolina (2000)

McBride, 2000 reported that rates of smokeless tobacco use among women in North Carolina were higher than the national rate, at 2.5% compared to 0.6%. The rate in Cherokee women was 8%, while that in Lumbee women was 23%. However, between 1993 and 1997, breast cancer rates in North Carolina were lower in Native American women than among white or African American women, although the rate of 23.2 per 100,000 was higher than the 18.9% reported for white women, but lower than the 26.6% seen in African Americans.

5.5.4 Summary

One prospective and two case-control studies reported on the association between smokeless tobacco use and breast cancer. All three of the studies were conducted in the USA. One study [Accortt et al., 2002] was based on non smokers of cigarettes. One study [Williams & Horm, 1977] included smokers of all products in the analyses of smokeless tobacco use, but only adjusted for cigarette smoking. Although the third study also included cigarette smokers, there was no attempt to adjust the results for this. Two of the studies adjusted for age during analysis, while one study provided risk estimates for different age groups. Two of the studies [Williams & Horm, 1977; Accortt et al., 2002] also adjusted for various other potential confounders.

The results of the three studies are summarized in table 5.5.1. Three relative risks were non-significantly raised, and one was below 1.00.

For the purposes of meta-analysis the results for male breast cancer patients in the study by Williams were excluded. The combined results for female patients gave overall relative risk estimates of 0.80 (0.46-1.40) for both the fixed and random effects models. There was no evidence of significant heterogeneity between these studies (heterogeneity chisquared = 2.56) on 3 d.f., $p < 0.1$).

Table 5.5.1: Summary of results for breast cancer

Study	Non-users		Smokeless tobacco users		Product[a]	Sex	RR	95% CI	Adjustment factors[b]	Notes[c]
	Controls	Cases	Controls	Cases						
Accortt	-	-	-	5	ST	F	1.8	0.5-6.5	Age, smoking, poverty index	1
Spangler	693	2	274	1	ST	F	1.26	0.12-13.9	None	2,3
	85	3	46	2	ST	F	1.23	0.14-9.52	None	2,4
Williams	1615	9	164	0	ST	M	-	-	Age, smoking, race	5,6
	2028	1107	42	11	ST	F	0.60	0.31-1.17		5

[a] ST = smokeless tobacco

[b] Adjustment for smoking includes studies restricted to non-smokers. Where study presents multiple RR estimates, adjustment factors relate to all RRs unless otherwise stated

[c] Key to notes:

1 Data taken from Accortt et al., 2005
2 Data taken from Spangler et al., 2002
3 Aged <55 years at diagnosis
4 Aged >55 years at diagnosis
5 Relative risk estimated from data given
6 Not estimated as no cases in smokeless tobacco users

5.6 *Connective tissue cancers*

5.6.1 Prospective studies

5.6.1.1 Zahm: USA (1992)

This study [Zahm et al., 1992] was based on 248,046 US veterans, aged 31-84 years, who held active US government life insurance policies in 1953 and responded to a questionnaire in 1954 or 1957. Over 99% were male. Mortality was ascertained from 1 January 1954, or 1 January 1957 for respondents to the second questionnaire, until 30 September 1980. Death certificates were obtained for 97% of those identified as deceased, and were used to ascertain cause of death. There were 119 deaths due to soft-tissue sarcoma (STS). A total of 48,304 veterans used smokeless tobacco, and 52,741 were non-users of any tobacco product.

Relative risks, adjusted for age and calendar time, were calculated for various aspects of smokeless tobacco use, as follows:

Tobacco use	No. of persons	Person-years	STS deaths	RR	95% CI
Never used any tobacco products	52741	1020199	20	1.0	
Used smokeless tobacco	48304	854453	21	1.4	0.8-2.6
Smokeless tobacco only	2308	41124	0	-	
Smokeless tobacco and other tobacco products	43451	767493	20	1.5	0.8-2.7
Smokeless tobacco and unknown smoking history	2545	45836	1	1.1	0.1-8.2
Ex-user			16	1.5	0.8-2.8
Current user			3	0.9	0.3-3.1
Frequency of use:					
Infrequent user			6	1.3	0.5-3.2
Frequent user			8	1.5	0.7-3.5
Age started:					
15-19 years			6	1.6	0.7-4.1
20-24 years			6	1.8	0.7-4.4
25+ years			4	1.2	0.4-3.6
Duration:					
<5 years			9	2.9	1.3-6.3
5-9 years			3	1.9	0.6-6.4
10-19 years			1	0.5	0.1-3.4
20+ years			4	0.9	0.3-2.5
Age stoppped:					
<25 years			5	2.3	0.9-6.0
25-29 years			6	3.9	1.6-9.8
30+ years			2	0.4	0.1-1.8

Subjects with unknown smokeless tobacco use status (n=2), frequency (n=7), age started (n=5), duration (n=4) and age stopped (n=5) were excluded from respective analysis

Possible drawbacks with this study include the failure to update smoking information during follow-up. Any changes in smokeless tobacco use that occurred during the study period would not have been recorded. Additionally, there may have been inaccuracies in the information recorded on the death certificates. It has been observed that only about half of persons diagnosed with soft-tissue sarcoma have the condition recorded on their death certificate. Similarly, less than 60% of subjects with soft-tissue sarcoma recorded on their death certificate have the diagnosis confirmed by hospital records. There was also a failure by this study to collect information on potential confounding factors.

5.6.2 Case-control/cross-sectional studies

5.6.2.1 Williams: USA (1977)

See section 3.3.1

5.6.2.2 Zahm: USA - Kansas (1989)

In the study by Zahm et al., 1989, the case group comprised all newly diagnosed cases of soft-tissue sarcoma among white male residents of Kansas, aged 21 years or older, that occurred during 1976-1982. Three white male controls were selected for each case from among the general population of Kansas, frequency matched by age and vital status to the combined age distribution of the study's original three cancer case series. Controls younger than 65 years of age were selected by random digit dialling, while those aged 65 years or older were identified from Medicare files. For deceased cases, controls were selected from state mortality files, with year of death being an additional matching factor. Telephone interviews were obtained with 133 cases and 948 controls, or their next-of-kin if deceased. Of these, 105 cases and 819 controls were non-users of smokeless tobacco, and 28 cases and 127 controls had ever used either chewing tobacco or snuff.

The results of the study were as follows:

	No. smokeless tobacco users		Odds ratio	95% CI
	Cases	Controls		
All subjects	28	127	1.8	1.1-2.9
Location of tumour				
Upper gastrointestinal tract	4		3.3	0.8-12.6
Lung, pleura, thorax	5		3.1	0.9-10.5
Head, neck, face	3		2.4	0.5-10.2
Other	16		1.4	0.7-2.5
Soft-tissue sarcoma cell type				
Fibromatous	7		1.8	0.7-4.7
Adipose	3		1.1	0.2-4.2
Myomatous	7		2.1	0.8-5.3
Other	11		1.9	0.9-3.9
Age in years at diagnosis				
20-39	4	22	2.3	0.6-8.2
40-59	6	20	1.7	0.6-4.9
60-79	9	50	1.3	0.5-2.9
80+	9	35	3.2	1.0-10.1

There was no attempt to adjust the findings for any potential confounding factors.

5.6.3 Summary

One prospective and two case-control studies gave information on the relationship between connective tissue cancers and smokeless tobacco use. All three of the studies were carried out in the USA. One study [Zahm et al., 1992] restricted the analysis of smokeless tobacco use to lifelong non-smokers. One study [Williams & Horm, 1977] included smokers of all tobacco products, but only adjusted for cigarette smoking during analysis. The third study [Zahm et al., 1989] also included smokers of all products, but did not adjust for any smoking variables. Two of the studies adjusted their results for age [Williams & Horm, 1977; Zahm et al., 1992], and one study [Williams & Horm, 1977] also adjusted for race.

The results of the three studies are summarized in table 5.6.1. It can be seen that only one study [Zahm et al., 1989] provided useful information, the total number of cases in the other studies combined in smokeless tobacco users being only one. The Zahm et al., 1989 study did in fact report a significant increase (1.8, 95% CI 1.1-2.9).

Table 5.6.1: Summary of results for connective tissue cancer

Study	Non-users		Smokeless tobacco users		Product[a]	Sex	RR	95% CI	Adjustment factors[b]	Notes[c]
	Controls	Cases	Controls	Cases						
Williams	1587	37	163	1	ST	M	0.64	0.09-4.72	Age, smoking, race	1
	3109	26	53	0	ST	F	-	-		1,2
Zahm 1989	819	105	127	28	ST	M	1.8	1.1-2.9	Age	
Zahm 1992	1020199	20	41124	0	ST	M	-	-	None	1,2,3

[a] ST = smokeless tobacco
[b] Adjustment for smoking includes studies restricted to non-smokers. Where study presents multiple RR estimates, adjustment factors relate to all RRs unless otherwise stated
[c] Key to notes:
1 Relative risk estimated from data given
2 Not estimated as no cases in smokeless tobacco users
3 Person-years at risk

5.7 *Digestive cancers*

5.7.1 Prospective studies

5.7.1.1 Bjelke: Norway/USA (1982)

In an abstract, Bjelke & Schuman, 1982 described the results from two studies, one based on 12,945 Norwegian men and the other on 16,930 insured American men. Follow-up lasted for more than 10 years in each study. Details of the numbers of cases and controls, and the proportions that used smokeless tobacco were not given, but analyses were stratified for age, residence characteristics and cigarette smoking. It was found that men who used smokeless tobacco had an increased risk of cancer of the oesophagus and pancreas, and that these results were consistent with the multiplicative effects of alcohol and smokeless tobacco use. Cigarette smoking was reported to be negatively associated with tobacco chewing.

In their monograph on tobacco habits other than smoking, [International Agency for Research on Cancer, 1985] gave some more detailed results, referring also to an abstract by Schuman et al (1982) which has proved to be unobtainable and appears to have been incorrectly cited by IARC. For the Norwegian men, statistically significant relative risks for regular users of oral tobacco were given as 3.1 for oesophageal cancer and 2.2 for histologically-confirmed cases of pancreatic cancer. For the US men, former snuff users/tobacco chewers had a significant relative risk of 3.3 for pancreatic cancer, but that associated with regular snuff use/chewing was not as high, 2.1 based on 5 deaths in regular users, and not significant. The relative risk of oesophageal cancer for tobacco chewing and snuff use was stated to be a non-significant 2.6. No confidence intervals were presented for any of the relative risks, and the data available are not sufficient to estimate them reliably.

5.7.1.2 Winn: USA (1982)

See section 3.2.1

5.7.1.3 Kneller: USA - 9 states (1991)

In the study by Kneller et al., 1991, a questionnaire was sent to 17,818 white male life insurance policy holders, aged at least 35 years, in October 1966. To increase the number of men of Norwegian descent, recipients were limited to residents of California, New Jersey, Washington, Michigan, Minnesota, Missouri, North Dakota, Ohio and Wisconsin. Over 76% of the study participants were born either in Norway, Sweden or Germany, or had at least one parent born in one of these countries. Compared to the general US population, there was a higher proportion of farmers and never smokers, and a lower proportion of labourers or semi-skilled workers. The cohort was then followed-up for 20 years, during which time death certificates were coded for underlying cause of death, other contributory causes of death, and other significant conditions. During the study period, there were 75 deaths from stomach cancer, and this was the underlying cause of death in 72 of these subjects. The proportion of subjects who used smokeless tobacco was not stated. However, it was reported that the risk of stomach cancer was higher among ever users of smokeless tobacco compared to tobacco abstainers, with a relative risk of 2.3 (95% CI 0.98-5.22) being estimated, based on 18 cases. Stratification by pack-years of smoking reduced this estimate to 1.6 (95% CI 0.58-4.50), but an excess risk of borderline significance was seen among subjects who used smokeless tobacco exclusively (RR = 3.8, 95% CI 1.00-14.32), based on three cases. No attempt appeared to have been made to adjust this result for other potentially confounding variables.

5.7.1.4 Zheng: USA - 9 states (1993)

The population for the study by Zheng et al., 1993 consisted of 17,818 white men, aged at least 35 years, who held a life insurance policy with the Lutheran Brotherhood Insurance Society, and who answered a questionnaire sent to them in October 1966. Follow-up lasted for 20 years, during which time death certificates were obtained for all deceased subjects, and coded for underlying cause of death, other contributory causes of death, and other significant conditions. There were 57 deaths due to pancreatic cancer. Never users of any tobacco product contributed 58,888 person-years to the study, and there were 9 deaths from pancreatic cancer. For exclusive users of tobacco other than cigarettes, the corresponding figures were 27,025 and 5. This gave an age-adjusted relative risk estimate of 0.9. Adjustment for age and alcohol index reduced this estimate to 0.8. A 95% confidence interval of 0.3-2.5 was given for the adjusted relative risk. For ever users of smokeless tobacco, the age, alcohol and smoking adjusted relative risk was 1.7 (95% CI 0.9-3.1), based on 16 deaths.

5.7.1.5 Heineman: USA (1995)

In this study [Heineman et al., 1995], a total of 293,958 veterans were enrolled in a cohort study between 1954 and 1957. Eligible subjects were aged 31-84 years, had served in the armed forces between 1917 and 1940, and held an active US Government life insurance policy in 1953. Less than 0.5% of policy-holders were women, and most were white. Tobacco use was determined by questionnaires mailed in 1954, and again in 1957 to non-responders to the original questionnaire. Replies to either questionnaire were received from a total of 248,046 individuals. Mortality was ascertained for the period from 1 January 1954, or 1957 for responders to the second questionnaire, until 30 September 1980. Death certificates were available for 97% of those reported to have died during this time. By the end of follow-up, there had been 164,785 deaths, of which 3812 were due to colon cancer and 1100 to rectal cancer. No details of the numbers of subjects who used smokeless tobacco were given, but analyses were based on 1,020,199 person-years for never users of tobacco, and 41,124 person-years for users of smokeless tobacco exclusively.

Relative risks, adjusted for age, calendar time, year of questionnaire response, socioeconomic status and sedentary job, were calculated for various cancer sites in smokeless tobacco users compared to never tobacco users, as follows:

Cancer site	Number of deaths		RR (95% CI)
	Never used tobacco	Exclusive smokeless tobacco users	
Colon	782	39	1.2 (0.9-1.7)
Rectum	201	17	1.9 (1.2-3.1)
Ascending colon	67	3	1.1 (0.3-3.4)
Transverse colon	15	0	-
Descending colon	15	0	-
Sigmoid colon	67	3	1.1 (0.3-3.4)

There was little evidence of an increase in risk with increasing amount of smokeless tobacco used, for either colon or rectal cancer:

Exposure group	Colon cancer			Rectal cancer		
	No.	RR[1]	95% CI	No.	RR[1]	95% CI
Never used tobacco	782	1.0		201	1.0	
Exclusive smokeless tobacco users:						
Never heavy use	27	2.0	1.4-3.0	9	2.5	1.3-5.0
Ever heavy use	12	0.6	0.4-1.1	8	1.5	0.7-3.0

[1] Adjusted for age, calendar time, year of questionnaire response, socioeconomic status and sedentary job

5.7.1.6 Accortt: USA (2002)

See section 3.2.3

5.7.1.7 Chao: USA – CPS II (2002)

Chao et al., 2002 reported on the second Cancer Prevention Study (CPS II), which consisted of a cohort of 467,788 men and 588,053 women aged at least 30 years. Follow-up lasted for 14 years, during which time 996 men and 509 women died from stomach cancer. At enrollment, participants completed a questionnaire that gave information on use of tobacco. Among the men, 2855 individuals were current users of smokeless tobacco, while 17% had ever used more than one type of tobacco. Of these, 25% smoked cigarettes and used smokeless tobacco, 14% used smokeless tobacco and smoked cigars or pipes, and the remaining 61% smoked both cigarettes and cigars or pipes. Information on smokeless tobacco use in women was not collected.

The results of the study for the main groups of male tobacco users were as follows:

Type of tobacco use	No. of study subjects	Person-years	Stomach cancer deaths	Age-adjusted RR (95% CI)	Multivariate[1]-adjusted RR (95% CI)
Never users	117968	1558552	169	1.00	1.00
Current smokeless tobacco only	2855	35673	8	1.79 (0.88-3.65)	1.58 (0.76-3.28)
Current cigarette only	93468	1166280	230	2.41 (1.96-2.96)	2.16 (1.75-2.67)
Current >1 type tobacco[2]	39678	500785	96	1.85 (1.44-2.38)	1.81 (1.40-2.35)
Former smokeless tobacco only	881	10812	2	1.21 (0.30-4.92)	1.11 (0.27-4.50)
Former cigarette only	126604	1618013	285	1.56 (1.29-1.89)	1.55 (1.28-1.88)
Former >1 type tobacco[2]	40590	517527	94	1.44 (1.12-1.85)	1.57 (1.22-2.03)

[1] Model includes age, race, education, family history of stomach cancer, consumption of high-fibre grain foods, vegetables, citrus fruits or juices, and use of vitamin C, multivitamins and aspirin

[2] Includes combined smokers of cigarettes and cigars or pipes

The authors commented on the association between infection with helicobacter pylori and gastric disease, but did not provide any direct information on such infection in the study population.

5.7.1.8 Boffetta: Norway/USA (2005)

See section 3.2.4

5.7.1.9 Henley: USA – CPS I and CPS II (2005)

See section 3.2.5

5.7.2 Case-control/cross-sectional studies

5.7.2.1 Wynder: Sweden - Stockholm (1957)

In the study by Wynder et al., 1957, 39 men with cancer of the oesophagus were compared to 115 men with cancer of the skin, head and neck region other than squamous cell cancer, stomach, rectum and colon, lymphomas, salivary gland tumours, leukemia, and sarcoma. All subjects were patients at the Radiumhemmet hospital in Stockholm during the period 1952 to 1955. There was no attempt to match the case and control groups. Each participant was interviewed and their charts reviewed for laboratory data. Numbers of chewing tobacco users were not given, but the authors stated that there was no relationship with cancer of the oesophagus. From a graph presented, it appeared that the duration of use of chewing tobacco was shorter in the case group than in the controls, but the difference did not reach statistical significance. There was no discussion of confounding by various other factors.

5.7.2.2 Wynder: USA - New York (1961)

This study [Wynder & Bross, 1961] was based on interview data obtained during 1956-1959 from patients with cancer of the oesophagus and control patients at three hospitals in New York. There were 150 male cases and an equal number of male controls. All of the cases had a confirmed diagnosis of epidermoid cancer. Some 64% of the control group also had a malignant tumour, with the commonest being basal cell carcinoma of the skin (29%). A total of 21% of the cases and 10% of the controls chewed tobacco, a difference that was reported as significant. However, there was no difference between the two groups in the duration of tobacco chewing. From the data given, the following crude relative risks could be estimated:

Chewing tobacco use	Cases		Controls			
	%	No.	%	No.	RR	95% CI
Never users	79	119	90	135	-	-
Ever users	21	32	10	15	2.42	1.25-4.69
Duration of use:						
<10 years	7	11	3	5	2.50	0.84-7.39
10-19 years	7	11	1	2	6.24	1.36-28.72
20-29 years	3	5	3	5	1.13	0.32-4.01
30-39 years	1	2	1	2	1.13	0.16-8.18
40-49 years	1	2	1	2	1.13	0.16-8.18
50+ years	1	2	1	2	1.13	0.16-8.18

One major drawback of this study was the fact that all of the tobacco chewers were also smokers, and no attempt was made to separate out the effects of these two exposures.

5.7.2.3 Martinez: Puerto Rico (1969)

In the study by Martínez, 1969, the case group was made up of patients with histologically confirmed epidermoid carcinoma of the oesophagus, identified in all hospital and clinics in Puerto Rico during 1966. For each case, three controls were selected, matched for age and sex. The next suitable patient admitted at the same hospitals or clinic as the case was chosen as a hospital control, while two population controls were identified from the same community as the case. Participants were interviewed in person, but where this was not possible, a family member acted as a proxy respondent. To ensure comparability, all members of a matched group gave information through proxy respondents. The total study group consisted of 179 cases and 537 controls. Of these, 25 cases and 126 controls had never used any form of tobacco, while 10 cases and 26 controls used chewing tobacco only.

From the data given in the study, the following crude relative risks could be estimated for both sexes combined:

Tobacco use	No. cases	No. controls	Relative risk	95% CI
Never users	25	126	-	-
Chewing tobacco only	10	26	1.94	0.83-4.52
Cigarettes only	56	170	1.66	0.98-2.81
Mixed[1]	64	149	2.16	1.29-3.64

1 Includes users of pipes and/or cigars

Data were also available for men and women separately:

Tobacco use	No. cases	No. controls	Relative risk	95% CI
Men:				
Never users	10	51	-	-
Chewing tobacco only	3	13	1.18	0.28-4.90
Cigarettes only	37	124	1.52	0.70-3.29
Mixed[1]	52	123	2.16	1.02-4.57
Women:				
Never users	15	75	-	-
Chewing tobacco only	7	13	2.69	0.92-7.87
Cigarettes only	19	46	2.07	0.96-4.46
Mixed[1]	12	26	2.31	0.96-5.57

[1] Includes users of pipes and/or cigars

It was not possible to adjust these results for any potentially confounding variables.

5.7.2.4 Bjelke: Norway/USA (1974)

Bjelke, 1974 reported on two studies, one conducted in Norway and the other in the USA. In the first study, 228 stomach cancer and 278 colorectal cancer cases, admitted to six hospitals in Oslo and the adjoining counties, were compared to 1394 controls. No further details were available, but it was reported that there was an association of 'high stomach cancers' with tobacco chewing. In the second study, 52 oesophageal, 83 stomach and 373 colorectal cancer cases, admitted to six Minneapolis hospitals, were compared to 1657 controls. Again, no details were given, but a synergistic effect of tobacco chewing and alcohol on oesophageal cancer risk was observed.

5.7.2.5 Williams: USA (1977)

See Section 3.3.1

5.7.2.6 Wynder: USA - 8 cities (1977)

See section 3.3.2

5.7.2.7 Pottern: USA - Washington (1981)

In this study [Pottern et al., 1981], all deaths, identified from a computerized mortality tape, among black male residents of Washington D.C. attributed to primary oesophageal cancer during the years 1975-77 formed the case group. Controls were randomly selected from among other causes of death, excluding oral, pharyngeal and laryngeal cancers. Two controls were selected for each case, and were matched for race, sex, age and year of death. Interviews were conducted with next of kin or close friends for 120 cases and 250 controls. Among the cases, the prevalences of tobacco chewing and snuff taking were 3.3% and 1.7%, respectively. Details were not given for the controls, but it was stated that the prevalence of tobacco chewing was slightly higher, while snuff taking was less common than among the cases. No attempt was made to estimate relative risks. One major drawback of this study was the inclusion in the control group of subjects with tobacco-related diseases, such as lung cancer and heart disease.

5.7.2.8 Weinberg: USA - Pennsylvania (1985)

The case group in the study by Weinberg et al., 1985 was identified by reviewing all deaths attributed to stomach cancer among residents of four counties in Pennsylvania for the years 1978-1980. Hospital records were then used to verify the cause of death. Three controls were selected for each case: a patient who had died of cancer of the digestive organs other than the stomach, a patient who had died of arteriosclerotic heart disease, and a living neighbourhood control. The digestive cancer and heart disease controls were identified from the same death certificate file as the cases, and were matched on sex, race, county of residence and age. From the address listed on the case's death certificate, a neighbourhood control was sought who resided as close as possible to the case, and was also of the same sex and age. For the cases and the two groups of diseased controls, interviews were conducted with next of kin, while the neighbourhood controls were interviewed in person. A total of 178 cases, 178 digestive cancer controls, 178 heart disease controls and 138 neighbourhood controls took part in the study. Overall, about 16% of male participants had ever chewed tobacco but no women reported this habit. There were no differences between the cases and any of the control groups in the prevalence of tobacco chewing.

5.7.2.9 Falk: USA – Louisiana (1988)

In the study by Falk et al., 1988, 363 incident cases of pancreatic cancer identified at hospitals in high risk areas of Louisiana in 1979 to 1983 were compared with 1,234 age, sex and race matched patients from the same hospitals. Subjects admitted with chronic conditions suspected from altering diet or lifestyle were not included as controls. Among the male subjects, 12% chewed tobacco and less than 3% used snuff. Among females, use was much less, only 2% reporting use of any of cigars, pipes, chewing tobacco or snuff. The authors reported that no excess risks were associated with smokeless tobacco, but no odds ratios (or numbers to calculate them from) were provided. Nor were any details presented of any factors adjusted for.

5.7.2.10 Farrow: USA - Washington State (1990)

Cases in the study by Farrow & Davis, 1990 were identified through the cancer surveillance system of the Fred Hutchinson Cancer Research Center. Eligible cases (n = 148) included all married men, aged 20-74 years, newly diagnosed with cancer of the pancreas between 1 July 1982 and 30 June 1986, who resided in King, Pierce or Snohomish county, Washington. Only about half of the cases were histologically confirmed. The control group (n = 188) consisted of married men living in the three counties from which the cases arose, frequency-matched by five-year age categories, who were identified by random digit dialling. Due to the rapidly fatal nature of pancreatic cancer, all interviews were conducted with the subjects' spouses. Details of the numbers of smokeless tobacco users were not given, but it was reported that among all subjects combined, 6.9% had chewed tobacco. There was no association between ever use of chewing tobacco and the risk of pancreatic cancer, with the odds ratio being estimated at 0.8, after adjustment for race and education. The confidence interval for this estimate was not given, but was stated to include 1.00. Additional adjustment for age and dietary factors did not materially affect this estimate.

5.7.2.11 Ghadirian: Canada (1991)

Ghadirian et al., 1991 identified patients with cancer of the pancreas, gall bladder and bile duct in greater Montreal in 1984 to 1988, and then interviewed a total of 179 individuals with pancreatic cancer, 97 men and 82 women. 75% of the interviews were with a proxy respondent and 25% were direct. 83% of the cases were confirmed histologically, with 17% diagnosed clinically or radiologically. 239 population-based controls, 123 men and 116 women, matched for age, sex and place of residence, were identified by random digit dialling. 17% of the controls were interviewed by proxy, and 83% direct. The authors reported that consumption of chewing tobacco was not associated with increased risk, but noted the limited numbers of chewers available for analysis. No odds ratios for chewing or relevant numbers of cases and controls were presented. Analyses were stated to be adjusted for age, sex, smoking, schooling and response status.

5.7.2.12 Sterling: USA (1992)

See section 3.3.4

5.7.2.13 Chow: USA - Los Angeles (1994)

The case group in this study [Chow et al., 1994] consisted of all histologically confirmed extrahepatic bile duct cancer cases diagnosed between 1 March 1985 and 31 October 1989 among white residents, aged 30-84 years, of Los Angeles County. Controls were selected by random digit dialling for subjects aged less than 65 years, and from Health Care Financing Administration files for subjects aged 65 years or older. Controls were matched to the cases for sex and age. All of the control group and cases who were living completed an in-person interview. For the 58% of the cases who were deceased, next-of-kin were interviewed. Full information was available for 105 cases and 255 controls. Among the case group, 64 tumours were located in the extrahepatic duct and 41 in the ampulla of Vater. No details of the numbers of smokeless tobacco users were given. In men, chewing tobacco was associated with an increased risk of cancer of ampulla of Vater, with an odds ratio of 18 (95% CI 1.4-227.7) being given, based on three cases and four controls. All of the cases who used chewing tobacco also used at least one other form of tobacco. No association between smokeless tobacco use and tumours of the extrahepatic duct was observed. Although information on potential confounding factors was collected, it was not stated whether the odds ratio estimate was adjusted for any of these. It was also not stated whether or not chewing tobacco was associated with risk of extrahepatic duct tumours.

5.7.2.14 Muscat: USA - New York (1997)

Muscat et al., 1997 based their study on newly diagnosed incident cases of pancreatic cancer, aged 21-80 years, admitted to hospital in New York City between 1985 and 1993. Control subjects were also hospital patients who had conditions unrelated to tobacco use. Approximately one third of the controls had a diagnosis of cancer. Controls were matched to cases by hospital, sex, age, race and year of diagnosis, and two controls were selected for each case. Interviews were obtained with a total of 290 male cases and 572 male controls and 194 female cases and 382 female controls. Among the men, 66 cases and 157 controls had never used tobacco. Six cases and five controls had chewed tobacco regularly, and did not currently smoke cigarettes. When compared to never users and long-term quitters combined, a crude odds ratio of 3.6 (95% CI 1.0-12.8) was estimated for pancreatic cancer in tobacco chewers. Long-term quitters were defined as subjects who had given up smoking 20 or more years previously, but the numbers of such individuals were not given. Two male cases and three male controls reported using snuff for at least one year. Compared to never smokers, an odds ratio of 1.59 (0.26-9.71) could be estimated. No women reported using smokeless tobacco.

5.7.2.15 Lewin: Sweden - Stockholm county/southern Sweden (1998)

In this study [Lewin et al., 1998], cases were drawn from a study base consisting of all men born in Sweden, aged 40-79 years, living in Stockholm county or the southern healthcare region of Sweden during the period from January 1988 until January 1991. Cases were identified at weekly conferences at all of the six ear, nose and throat departments in the study area, and from surgery departments in the two regions. Referents were selected by stratified random sampling every six months during the study period from a population register for each region. Stratification was by region and age. A total of 122 cases of oesophageal cancer were interviewed, along with 641 referents. Of these, 103 cases and 550 referents were never users of oral snuff, and 19 cases and 91 referents were ever users. The relative risk of oesophageal cancer in ever snuff users compared to never users was estimated at 1.2 (95% CI 0.7-2.2), after adjustment for age, region, smoking status and alcohol intake. Relative risks for current and ex-snuff users were estimated at 1.1 (95% CI 0.5-2.4) and 1.3 (95% CI 0.6-3.1), respectively. In current users, usage of more than 50 grams of snuff per week was associated with a moderately increased risk of oesophageal cancer (RR = 1.9, 95% CI 0.8-3.9).

5.7.2.16 Ye: Sweden - 5 counties (1999)

The base population of the study by Ye et al., 1999 consisted of all individuals, aged 40-79 years, who were born in Sweden and were living in one of five counties in the north and centre of the country between February 1989 and January 1995. All subjects with a new histologically confirmed gastric cancer were eligible as cases. Cases were identified through surgery and pathology departments and national and regional cancer registries. Approximately two controls per case were selected from continuously updated population registers covering the entire study base, frequency matched on age and sex. Face to face interviews were performed with 567 cases and 1164 controls. Chewing tobacco was used by only 8 cases and 14 controls, from which a relative risk of 1.18 (95% CI 0.49-2.82) could be estimated for users compared to non-users. None of the female subjects had ever used moist snuff, but the prevalence in men was 22% in the cases and 25% among the controls.

Relative risks for snuff use in males, adjusted for age, residence area, body mass index, socio-economic status and smoking, were estimated for various subtypes of gastric cancer, as follows:

Snuff dipping	Controls	Cardia cancer		Distal stomach cancer			
		All histologic types		Intestinal type		Diffuse type	
	No.	No.	OR (95% CI)	No.	OR (95% CI)	No.	OR (95% CI)
Never users	587	56	-	146	-	68	-
Ex-users	74	6	0.8 (0.3-1.9)	18	0.9 (0.5-1.6)	8	0.7 (0.3-1.6)
Current users	118	9	0.5 (0.2-1.1)	26	0.8 (0.5-1.3)	11	0.6 (0.3-1.2)
Ever users	192	15	0.6 (0.3-1.2)	44	0.8 (0.5-1.2)	19	0.7 (0.4-1.2)
Age at start (years)							
21+	114	6	0.4 (0.1-1.0)	23	0.7 (0.4-1.2)	13	0.8 (0.4-1.5)
16-20	77	9	1.0 (0.4-2.0)	21	1.0 (0.6-1.7)	6	0.5 (0.2-1.1)
Duration (years)							
1-10	60	6	0.9 (0.3-2.2)	11	0.7 (0.3-1.3)	5	0.6 (0.2-1.3)
11-30	65	6	0.7 (0.2-1.7)	9	0.5 (0.2-1.1)	11	1.1 (0.5-2.2)
31+	66	3	0.3 (0.0-1.1)	24	1.2 (0.7-2.0)	3	0.4 (0.1-1.0)
Times/day							
≤ 5	113	7	0.5 (0.2-1.2)	26	0.8 (0.5-1.3)	7	0.4 (0.2-0.9)
> 5	78	8	0.8 (0.3-1.8)	18	0.9 (0.5-1.6)	12	1.0 (0.5-2.0)

Results were also presented for the joint effects of snuff use and cigarette smoking for all gastric cancers combined, as follows:

Smoking	Snuff use	Cases	Controls	OR (95% CI)
Never smokers	Never users	80	217	-
	Ever users	11	36	0.5 (0.2-1.2)
Ex-smokers	Never users	111	235	1.2 (0.9-1.8)
	Ever users	56	114	1.2 (0.8-1.9)
Current smokers	Never users	101	135	2.0 (1.3-2.9)
	Ever users	16	42	1.0 (0.5-1.8)

Although information on alcohol consumption was collected, there was no attempt to adjust the results for smokeless tobacco use for this factor.

5.7.2.17 Lagergren: Sweden (2000)

Cases in the study by Lagergren et al., 2000 consisted of all patients with a new diagnosis of adenocarcinoma of the oesophagus or gastric cardia, and all patients with oesophageal squamous-cell carcinoma who were born on an even date occurring within a study base encompassing the entire Swedish population during the period 1995-1997, with the exception of individuals aged 80 years or older, and those born abroad. A total of 189 oesophageal adenocarcinoma patients, 262 gastric cardia adenocarcinoma patients and 167 squamous cell carcinoma patients were interviewed. Control patients were randomly selected from age and sex strata in the base population to resemble the age and sex distributions among the oesophageal adenocarcinoma cases. A total of 820 controls were interviewed. Ever having used snuff was reported by 126 controls (15%) and 35 cases (19%) with oesophageal adenocarcinoma, 53 cases (20%) with gastric cardia adenocarcinoma and 33 cases (20%) with oesophageal squamous cell carcinoma.

Odds ratios for the various forms of cancer in relation to use of snuff were estimated as follows:

Cancer type	Snuff use status		Duration of snuff use (years)			Intensity of snuff use (no. of quids used per week)		
	Never	Ever	1-10	11-25	>25	1-14	15-35	>35
No. of controls	694	126	44	45	37	45	34	45
Oesophageal adenocarcinoma								
No. of cases	154	35	10	10	15	11	17	7
OR[1]	1.0	1.2	1.0	1.0	1.7	1.0	2.2	0.7
(95% CI)	-	(0.8-1.9)	(0.5-2.1)	(0.5-2.0)	(0.9-3.3)	(0.5-2.1)	(1.2-4.1)	(0.3-1.6)
OR[2]	1.0	1.2	0.9	0.8	1.9	1.0	2.0	0.8
(95% CI)	-	(0.7-2.0)	(0.4-2.2)	(0.3-1.8)	(0.9-4.0)	(0.4-2.3)	(1.0-4.3)	(0.3-2.0)
Gastric cardia adenocarcinoma								
No. of cases	209	53	18	19	15	19	15	18
OR[1]	1.0	1.3	1.2	1.3	1.4	1.3	1.5	1.2
(95% CI)	-	(0.9-1.9)	(0.7-2.2)	(0.7-2.3)	(0.7-2.6)	(0.8-2.3)	(0.8-2.8)	(0.7-2.1)
OR[2]	1.0	1.2	1.0	1.1	1.1	1.2	1.3	1.3
(95% CI)	-	(0.8-1.8)	(0.5-1.8)	(0.6-2.0)	(0.6-2.2)	(0.6-2.1)	(0.7-2.5)	(0.7-2.4)
Oesophageal squamous cell carcinoma								
No. of cases	134	33	11	8	14	10	15	7
OR[1]	1.0	1.7	1.6	1.2	2.8	1.4	2.8	1.1
(95% CI)	-	(1.1-2.7)	(0.8-3.2)	(0.5-2.6)	(1.4-5.4)	(0.7-2.9)	(1.5-5.5)	(0.5-2.6)
OR[2]	1.0	1.4	1.2	0.9	2.0	1.2	2.1	1.0
(95% CI)	-	(0.9-2.3)	(0.5-2.5)	(0.4-2.1)	(0.9-4.1)	(0.5-2.5)	(1.0-4.4)	(0.4-2.4)

[1] Adjusted for age and sex

[2] Adjusted for age, sex, tobacco smoking, alcohol use, educational level, body mass index, reflux symptoms, intake of fruit and vegetables, energy intake and physical activity

There was no evidence of a statistically significant trend of increasing risk with either duration or intensity of snuff use for any of the cancers investigated.

5.7.2.18 Alguacil: USA - Atlanta/Detroit/New Jersey (2004)

Alguacil & Silverman, 2004 included all cases of carcinoma of the exocrine pancreas newly diagnosed between August 1986 and April 1989 among 30-79 year old residents of the cities of Atlanta and Detroit and the state of New Jersey. The control series was drawn from the general population of the study areas and was frequency matched to the expected age, race and gender distribution of the cases. Controls aged 30-64 years were selected by random digit dialling. Controls aged 65-79 years were a stratified random sample drawn from the Centers for Medicare and Medicaid Services rosters of the population aged >65 years in each study area. Cigarette smokers were excluded from the analysis, leaving a total of 154 cases and 844 controls. In the case group, there were 123 non-tobacco users, 16 ever users of cigars, 9 ever users of pipes and 7 ever users of smokeless tobacco. The corresponding figures for the control group were 682, 85, 62 and 44 respectively. Compared to non-tobacco users, subjects who had ever used smokeless tobacco had a relative risk for pancreatic cancer of 1.4 (95% CI 0.5-3.6), after adjustment for race, sex, geographic site, cigar smoking and age. For subjects who were exclusive smokeless tobacco users, the relative risk estimate was 1.1 (95% CI 0.4-3.1). There was some evidence of an increase in risk with amount of smokeless tobacco used per week ($\leq$ 2.5 ounces/week: 0.3, 95% CI 0.04-2.5; > 2.5 ounces/week: 3.5, 95% CI 1.1-10.6; p for trend = 0.04), but for duration of use, this was less convincing ($\leq$ 20 years of use: 1.1, 95% CI 0.1-11.0; >20 years of use: 1.5, 95% CI 0.6-4.0; p for trend = 0.42). The use of chewing tobacco and snuff were highly correlated in this study, but when relative risks were calculated for each type of smokeless tobacco separately, the risk of pancreatic cancer was higher for chewing tobacco (1.7, 95% CI 0.6-4.5) than for snuff (1.1, 95% CI 0.4-3.5). Subjects who chewed tobacco used more ounces of tobacco per week (mean 7.2 oz) compared to those who used snuff (mean 2.4 oz) and experienced a significant increase in pancreatic cancer risk with increased use of chewing tobacco (p = 0.04).

5.7.3 Other epidemiological evidence

5.7.3.1 Zacho: Denmark - Copenhagen (1968)

In an early Danish study, Zacho et al., 1968 reported on a series of 535 patients with stomach cancer. None of the 150 female cases used smokeless tobacco, but among the men, the prevalence of usage was 25.2% overall. Usage increased with age, with 8.5% of men aged 40-49 years reporting tobacco chewing or snuff use, compared to 40.4% of men aged 70 years or older. There was also a higher proportion of users in rural compared to urban areas, and in men of lower socio-economic status. For different sites of cancer, the proportion of smokeless tobacco users ranged from 18.9% for tumours affecting the body of the stomach to 39.3% for pyloric tumours. The majority of smokeless tobacco users (86.6%) were also current or ex-smokers. No control group was collected in this study, making the estimation of relative risks impossible. In a later publication [Zacho et al., 1975], based in part on the same subjects, the authors reported that of 202 male smokers with gastric cancer, 29.7% also used smokeless tobacco, while 23 of the 67 non-smokers (34.3%) were smokeless tobacco users. In this update, smokeless tobacco users were most likely to have a tumour in the body of the stomach. Among male pipe smokers with tumours of the pylorus, there was a significantly higher proportion of men who had also used snuff or chewing tobacco than those who had smoked pipes exclusively ($p < 0.05$). However, among cigarette smokers with cardial tumours, the percentage of exclusive cigarette smokers was significantly higher than men who had also used smokeless tobacco ($p < 0.02$).

5.7.3.2 Redmond: UK - London (1970)

See section 3.4.1.

5.7.4 Summary

Details of the 26 studies that investigated the relationship between digestive cancers and usage of smokeless tobacco are given in Table 5.7.1. In nine of the studies the analysis of smokeless tobacco use was restricted to never smokers of any product and in one it was restricted to never smokers of cigarettes. One study did not provide information on whether smokers were included in the study group. The remaining 15 studies included smokers of all products, although in one of these studies the analysis for pancreatic cancer was restricted to non-smokers. However, only six studies carried out adjustment for smoking variables, with three of these adjusting for cigarette smoking only. The other nine studies either did not adjust for smoking, or did not state whether such adjustment had taken place. It should also be noted that for the majority of studies where details of the number of participants were given, it was apparent that the number of cases who were also smokeless tobacco users was very small.

A summary of results from the individual studies and from selected meta-analyses are presented in Tables 5.7.2 and 5.7.3 respectively. The results for each individual endpoint are discussed below.

5.7.4.1 All digestive cancers

Five studies, four prospective and one case-control, gave information on the relationship between smokeless tobacco use and all digestive cancers combined. Of the five relative risks presented, two were raised, one significantly so (1.26, 95% CI 1.05-1.52), and the other three were below 1.00. One of these also reached statistical significance (0.48, 95% CI 0.28-0.82). One study reported an SMR of 137.

There was no evidence of an association between all digestive cancers combined and the use of smokeless tobacco from meta-analysis of the available data. However, there was significant heterogeneity between the studies included in this analysis ($p < 0.02$).

5.7.4.2 Bile duct cancer

Only one case-control study provided information for this endpoint, and estimated a significantly raised relative risk for tumours of the ampulla of Vater of 18.0 (95% CI 1.4-227.7) for users of chewing tobacco compared to non-users, but found no association between smokeless tobacco and tumours of the extrahepatic

duct. It was not stated whether adjustment for smoking or other factors was carried out in this study.

5.7.4.3 Colon cancer

One prospective and two case-control studies examined the relationship between colon cancer and smokeless tobacco use. All of the relative risks presented were above 1.00, although none was significantly so. The third study failed to find any association between smokeless tobacco and cancer of the colon.

Meta analysis of these results failed to find any evidence of a significant relationship between smokeless tobacco use and the risk of colon cancer.

5.7.4.4 Gall bladder cancer

Data relating to the risk of gall bladder cancer in users of smokeless tobacco were available from only one case-control study. As only one case was seen in smokeless tobacco users, no conclusions can be drawn.

5.7.4.5 Liver cancer

Two studies investigated the possible relationship between smokeless tobacco use and the risk of liver cancer. One study was prospective in design and the other was case-control. Only one case was seen in smokeless tobacco users in the case-control study. The prospective study reported an SMR of 281 for liver cancer in smokeless tobacco users, but did not give any indication of the significance of this finding. No conclusions can be drawn.

5.7.4.6 Oesophageal cancer

Thirteen studies presented data relating to oesophageal cancer risk in users of smokeless tobacco. Four of the studies were prospective and nine were case-control in design. Eleven of the 13 relative risks reported were above 1.00, but only two reached statistical significance (2.42, 95% CI 1.25-4.69; 3.1, 95% CI not available), one coming from a study in which no adjustment for smoking or any other potential confounders was carried out. For three of the 13 relative risks the significance of the findings was not available. One other found no association of oesophageal cancer to smokeless tobacco use. One study reported an SMR of 228 but did not present a confidence interval or p value for this result.

Two meta-analyses of the above results were carried out, one including all studies but using results for chewing tobacco where findings for separate tobacco products were given, and the other using results for snuff. For both analyses, the overall risk of oesophageal cancer was significantly raised in users of smokeless tobacco (smokeless tobacco or snuff: 1.37, 95% CI 1.10-1.71; smokeless tobacco or chewing tobacco: 1.43, 95% CI 1.13-1.81).

5.7.4.7 Pancreatic cancer

Eleven studies investigated the possible relationship between use of smokeless tobacco and the risk of pancreatic cancer. Five of the studies were of prospective design and the remaining six were case-control studies. Six of the nine relative risks presented were above 1.00, with one of borderline significance (3.6, 95% CI 1.0-12.8) and one (2.2) stated to be significant without CI being presented. The remaining three relative risk estimates were below 1.00, one of them significantly so (0.29, 95% CI 0.09-0.92). In addition, one study reported an SMR of 165 for pancreatic cancer in users of smokeless tobacco compared to non-users, but did not present a confidence interval or p value for this estimate, and two studies reported finding no association, but gave no relative risks or CIs.

As one of the studies provided data for both chewing tobacco and snuff separately, two meta-analyses were carried out, with all the remaining studies being included in both analyses. None of the relative risks estimated suggested a significant association between the use of smokeless tobacco and the risk of pancreatic cancer. However, there was significant heterogeneity between the studies included in the analysis based on smokeless tobacco and chewing tobacco use ($p < 0.05$).

5.7.4.8 Rectal cancer

Data relating to the endpoint of rectal cancer were available from three studies, one prospective and two case-control. Two of the relative risks reported were below 1.00, although neither reached statistical significance, while the third was significantly raised (1.9, 95% CI 1.2-3.1). One study failed to find any association between smokeless tobacco use and the risk of colorectal cancer for either of the populations studied.

A meta-analysis of the three available relative risks failed to find any evidence of a significant association between the risk of rectal cancer and smokeless tobacco use, although there was significant heterogeneity between the studies ($p < 0.05$).

5.7.4.9 Small intestine cancer

Results for small intestine cancer were only available from one case-control study. Only two cases were seen in smokeless tobacco users, and no conclusions can be drawn.

5.7.4.10 Stomach cancer

The association between stomach cancer and usage of smokeless tobacco was investigated by nine studies. Four were of a prospective design and the remaining five were case-control studies. Seven of the relative risks estimated by the studies were raised, but only one reached borderline significance (3.8, 95% CI 1.00-14.32). No confidence interval or p value was given for one of the estimates. One relative risk was non-significantly below 1.00. One study reported an SMR of 151, but did not attempt to estimate the significance of this finding. One study found a relative risk of 1.00 for stomach cancer in smokeless tobacco users, and for four study populations no association was reported between smokeless tobacco usage and this particular endpoint.

Overall, there was no evidence of an association between stomach cancer and the use of smokeless tobacco.

Table 5.7.1: Summary of studies of digestive cancers

Study	Study Type	Location	Treatment of smoking in analysis		Other adjustment factors
			Smokers excluded	Smoking variables adjusted for	
Accortt	P	USA	Ever cigarette	-	Age, race, poverty index, alcohol intake, dietary fat intake
Alguacil	C-C	USA	Ever smokers	-	Age, race, sex, geographic site
Bjelke 1974	C-C	Norway/ USA	Not stated	-	Not stated
Bjelke 1982	P	Norway/ USA	None	Cigarette smoking	Age, residence characteristics
Boffetta	P	Norway/ USA	None[1]	Smoking of cigarettes, cigars and pipes	Age
			Ever smokers[2]	-	
Chao	P	USA	Ever smokers	-	Age, race, education, family history of stomach cancer, consumption of high-fibre grain foods, vegetables, citrus fruits or juices, use of vitamin C, multivitamins and aspirin
Chow	C-C	USA	None	Not stated	Not stated
Falk	C-C	USA	None	-	Not stated
Farrow	C-C	USA	None	None	Age, race, education, dietary factors
Ghadirian	C-C	Canada	None	Smoking status	Age, sex, schooling, response status
Heineman	P	USA	Ever smokers	-	Age, calendar time, year of questionnaire response, socioeconomic status, sedentary job
Henley-CPS I	P	USA	Ever smokers	-	Age, race, education, BMI, exercise, alcohol intake, fat consumption, fruit/vegetable intake, aspirin use
Henley-CPS II	P	USA	Ever smokers	-	Age, race, education, BMI, exercise, alcohol intake, employment status and type, fat consumption, fruit/ vegetable intake, aspirin use
Kneller	P	USA	Ever smokers	-	None
Lagergren	C-C	Sweden	None	None	None
Lewin	C-C	Sweden	None	Smoking status	Age, region, alcohol intake
Martinez	C-C	Puerto Rico	Ever smokers	-	Sex
Muscat	C-C	USA	Ever smokers	-	None
Pottern	C-C	USA	None	None	None
Sterling	C-C	USA	None	Cigarette smoking	Age, sex, race, alcohol intake, occupation
Weinberg	C-C	USA	None	None	None
Williams	C-C	USA	None	Cigarette smoking	Age, race
Winn	P	USA	Ever smokers	-	Not stated
Wynder 1957	C-C	Sweden	None	None	None
Wynder 1961	C-C	USA	None	None	None

Table 5.7.1 continued

Study	Study Type	Location	Treatment of smoking in analysis		Other adjustment factors
			Smokers excluded	Smoking variables adjusted for	
Wynder 1977	C-C	USA	None	None	None
Ye	C-C	Sweden	None	None	None
Zheng	P	USA	None	Smoking status	Age, alcohol intake

[1] Oesophageal and stomach cancer

[2] Pancreatic cancer

Table 5.7.2: Summary of results for digestive cancers

Study	Non-users		Smokeless tobacco users		Product[a]	Sex	RR	95% CI	Adjustment factors[b]	Notes[c]
	Controls	Cases	Controls	Cases						
All digestive cancers										
Accortt	-	-	-	-	ST	M	0.9	0.3-2.3	Age, smoking, other	
	-	-	-	-	ST	F	0.8	0.3-2.7		
Henley-CPS I	69662	760	7745	153	ST	M	1.26	1.05-1.52	Age, smoking, other	1
Henley-CPS II	111482	1932	2488	48	ST	M	1.04	0.77-1.38	Age, smoking, other	1
Sterling	-	-	-	-	ST	M+F	0.48	0.28-0.82	Age, smoking, other	2
Winn	Total population ~300000				ST	M	1.37	-	Smoking, others not stated	3
Bile duct cancer										
Chow	41 cases, 255 controls				Chew	M	18	1.4-227.7	Not stated	4
	64 cases, 255 controls				Chew	M	No association		Not stated	5
Colon cancer										
Bjelke 1974 - Norway	278 cases, 1394 controls				Chew	Not stated	No association		Not stated	6
Bjelke, 1974 - USA	373 cases, 1657 controls				Chew	Not stated	No association			6
Heineman	1020199	782	41124	39	ST	M	1.2	0.9-1.7	Age, smoking, other	7
Williams	1360	264	134	30	ST	M	1.36	0.90-2.07	Age, smoking, other	2
	2783	352	46	7	ST	F	1.18	0.78-1.77		2
Gall bladder cancer										
Williams	1600	24	163	1	ST	M	1.77	0.24-13.13	Age, smoking, other	2
	3100	35	53	0	ST	F	-	-		2,8
Liver cancer										
Williams	1607	17	163	1	ST	M	1.20	0.16-9.05	Age, smoking, other	2
	3125	10	53	0	ST	F	-	-		2,8
Winn	Total population ~300000				ST	M	2.81	-	Smoking, others not stated	3

Table 5.7.2 continued

Study	Non-users		Smokeless tobacco users		Product[a]	Sex	RR	95% CI	Adjustment factors[b]	Notes[c]
	Controls	Cases	Controls	Cases						
Oesophageal cancer										
Bjelke 1974 - USA	52 cases, 1657 controls				Chew	Not stated	>1.00	-	Not stated	
Bjelke 1982									Age,	
- Norway	Total population 12945				ST	M	3.1	Significant	smoking,	
- USA	Total population 16930				ST	M	2.6	Not sig.	other	
Boffetta	6921	18	1999	4	ST	M	1.06	0.35-3.23	Age, smoking	1
Lagergren	694	288	126	68	Snuff	M+F	1.30	0.94-1.80	None	2
Lewin	550	103	-	-	Snuff	M	1.1	0.5-2.4	Age, smoking, other	
Martinez	126	25	26	10	Chew	M+F	1.97	0.85-4.71	Other	2
Pottern	120 cases, 250 controls				Chew	M	<1.00		None	
					Snuff	M	>1.00			
Williams	1624	36	164	2	ST	M	0.73	0.17-3.07	Age, smoking, other	2
	3135	19	53	0	ST	F	-	-		2,8
Winn	Total population ~300000				ST	M	2.28	-	Smoking, others not stated	3
Wynder 1957	-	-	-	-	Chew	M	No association		None	
Wynder 1961	135	119	15	32	Chew	M	2.42	1.25-4.69	None	2
Wynder 1977	2327	163	233	20	Chew	M	1.23	0.76-1.99	None	2
	2491	175	69	8	Snuff	M	1.65	0.78-3.49		2
Pancreatic cancer										
Alguacil	682	123	28	5	ST	M+F	1.1	0.4-3.1	Age, smoking, other	
Bjelke 1982									Age,	
- Norway	Total population 12945				ST	M	2.2	Significant	smoking,	
- USA	Total population 16930				ST	M	2.1	Not sig.	other	
Boffetta	6921	60	1999	3	ST	M	0.85	0.24-3.07	Age, smoking	1,9
Falk	363 cases, 1234 controls				Chew	M,F	No association		Not stated	
					Snuff	M,F	No association		Not stated	
Farrow	148 cases, 188 controls				Chew	M	0.8	Includes 1.00	Age, other	
Ghadirian	179 cases, 239 controls				Chew	M,F	No association		Age, smoking, other	
Muscat	329	140	5	6	Chew	M	3.6	1.0-12.8	Smoking	10
	157	66	3	2	Snuff	M	1.59	0.26-9.71		2
Williams	1536	88	161	3	ST	M	0.29	0.09-0.92	Age, smoking, other	2
	3050	85	53	0	ST	F	-	-		2,8

Table 5.7.2 continued

Study	Non-users		Smokeless tobacco users		Product[a]	Sex	RR	95% CI	Adjustment factors[b]	Notes[c]
	Controls	Cases	Controls	Cases						
Pancreatic cancer - continued										
Winn	Total population ~300000				ST	M	1.65	-	Smoking, others not stated	3
Zheng	-	-	-	-	ST	M	1.7	0.9-3.1	Age, smoking, other	
Rectal cancer										
Bjelke 1974 - Norway	278 cases, 1394 controls				Chew	Not stated	No association		Not stated	6
Bjelke, 1974 - USA	373 cases, 1657 controls				Chew	Not stated	No association			6
Heineman	1020199	201	41124	17	ST	M	1.9	1.2-3.1	Age, smoking, other	7
Williams	1472	152	151	13	ST	M	0.75	0.42-1.35	Age, smoking, other	2
	2999	136	51	2	ST	F	0.87	0.21-3.62		2
Small intestine cancer										
Williams	1616	8	162	2	ST	M	3.11	0.65-14.77	Age, smoking, other	2
	3128	7	53	0	ST	F	-	-		2,8
Stomach cancer										
Bjelke 1974 - Norway	228 cases, 1394 controls				Chew	Not stated	>1.00	-	Not stated	
Bjelke, 1974 - USA	83 cases, 1657 controls				Chew	Not stated	No association			
Boffetta	6921	143	1999	42	ST	M	1.00	0.71-1.42	Age, smoking	1
Chao-CPS II	1558552	169	35673	8	ST	M	1.58	0.76-3.28	Age, smoking, other	7
Kneller	-	-	-	3	ST	M	3.8	1.00-14.32	Smoking	
Lagergren	694	209	126	53	Snuff	M+F	1.2	0.8-1.8	Age, smoking, other	
Weinberg	178 cases, 178 controls				Chew	M	No association		None	11
	178 cases, 178 controls				Chew	M	No association			12
	178 cases, 138 controls				Chew	M	No association			13
Williams	1516	108	152	12	ST	M	1.31	0.71-2.43	Age, smoking, other	2
	3055	80	51	2	ST	F	1.02	0.24-4.28		2
Winn	Total population ~300000				ST	M	1.51	-	Smoking, others not stated	3
Ye	1150	559	14	8	Chew	M+F	1.18	0.49-2.82	None	2
	587	270	118	46	Snuff	M	0.85	0.59-1.23		2

Table 5.7.2 continued

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[a] ST = smokeless tobacco

[b] Adjustment for smoking includes studies restricted to non-smokers; Refer to table 5.7.1 for full details of adjustment factors. Where study presents multiple RR estimates, adjustment factors relate to all RRs unless otherwise stated

[c] Key to notes:

1 Number of controls refers to population at risk
2 Relative risk estimated from data given
3 Standardized mortality ratio/100
4 Cancer of ampulla of Vater
5 Cancer of extrahepatic duct
6 Colorectal cancer
7 Person-years at risk
8 Not estimated as no cases in smokeless tobacco users
9 Results from Heuch et al., 1983 not included as superseded by results cited
10 Compared to never users and long-term quitters combined
11 Digestive cancer controls
12 Heart disease controls
13 Neighbourhood controls

Table 5.7.3: Summary of meta-analysis results for digestive cancer studies

Tobacco product	No. of studies	Fixed effects estimate RR	95% CI	Heterogeneity chisquared	p value[1]	Random effects estimate RR	95% CI
All digestive cancers							
Smokeless tobacco	5	1.10	0.95-1.27	11.84	<0.02	0.92	0.65-1.30
Colon cancer							
Smokeless tobacco	3	1.24	0.996-1.53	0.29	NS	1.24	0.996-1.53
Oesophageal cancer							
Smokeless tobacco/ chewing tobacco	7[2]	1.37	1.10-1.71	5.06	NS	1.37	1.10-1.71
Smokeless tobacco/ snuff	7[3]	1.43	1.13-1.81	4.98	NS	1.43	1.13-1.81
Pancreatic cancer							
Smokeless tobacco/ chewing tobacco	5[2]	1.25	0.82-1.92	10.08	<0.05	1.13	0.55-2.36
Smokeless tobacco/ snuff	5[3]	1.12	0.73-1.74	7.27	NS	0.98	0.51-1.87
Rectal cancer							
Smokeless tobacco	3	1.28	0.90-1.83	6.17	<0.05	1.15	0.56-2.37
Stomach cancer							
Smokeless tobacco/ chewing tobacco	7[2]	1.19	0.96-1.48	4.61	NS	1.19	0.96-1.48
Smokeless tobacco/ snuff	7[3]	1.09	0.90-1.31	6.94	NS	1.10	0.89-1.37

[1] NS = Not significant

[2] Combines results from all available studies, using results for chewing tobacco if results for separate types of smokeless tobacco are presented

[3] Combines results from all available studies, using results for snuff if results for separate types of smokeless tobacco are presented

5.8 *Female genital organ cancers*

5.8.1 Case-control/cross-sectional studies

5.8.1.1 Williams: USA (1977)

See Section 3.3.1

5.8.2 Summary

Only one case-control study examined the relationship between smokeless tobacco use and cancers of the female genital organs. Although in this study the smokeless tobacco users may also have smoked cigarettes, cigars or pipes, only adjustment for cigarette smoking was carried out during analysis. The study also adjusted for age and race.

The results of this study are summarized in Table 5.8.1. For cancers of the cervix, ovary, uterus and vulva, the relative risk estimates were all above 1.00 for users of smokeless tobacco compared to non-users, and for cervical cancer the difference reached statistical significance (4.18, 95% CI 2.08-8.43).

Table 5.8.1: Summary of results for female genital organ cancers

Study	Non-users		Smokeless tobacco users		Product[a]	RR	95% CI	Adjustment factors[b]	Notes[c]
	Controls	Cases	Controls	Cases					
Cervical cancer:									
Williams	2896	239	43	10	ST	4.18	2.08-8.43	Age, smoking, race	1
Ovarian cancer:									
Williams	2984	151	51	2	ST	1.37	0.33-5.69		1
Uterine cancer:									
Williams	2797	338	46	7	ST	1.92	0.86-4.28		1
Vulval cancer:									
Williams	3106	29	52	1	ST	2.95	0.39-22.07		1

[a] ST = smokeless tobacco
[b] Where study presents multiple RR estimates, adjustment factors relate to all RRs unless otherwise stated
[c] Key to notes:
1 Relative risk estimated from data given

5.9 *Haematopoietic cancers*

5.9.1 Prospective studies

5.9.1.1 Heineman: USA (1992)

Heineman et al., 1992 examined data relating to 293,958 US veterans who were enrolled in a cohort study between 1954 and 1957. Subjects were eligible if they were aged 31-84 years, had served in the armed forces between 1917 and 1940, and held an active US Government life insurance policy in 1953. Although race and gender were not recorded, 99.5% of policy holders were men, and most were white. Tobacco use was determined by questionnaire. Non-responders to the first questionnaire, in 1954, were sent a second questionnaire in 1957. A total of 248,046 men responded to one of these questionnaires, and were subsequently followed-up with regard to mortality until 30 September 1980. Death certificates were identified for the majority of decedents. Details of the number of men who used smokeless tobacco were not given. For men who used chewing tobacco or snuff exclusively, a relative risk for multiple myeloma of 1.0 (95% CI 0.4-2.3) was estimated, compared to men who used no tobacco. This estimate was based on six cases in users of chewing tobacco or snuff and was adjusted for age, calendar time and year of questionnaire response. The risk of multiple myeloma did not increase with heavier use of chewing tobacco or snuff, with relative risks of 1.7 and 0.6 being estimated for those who used smokeless tobacco occasionally and practically every day, respectively.

5.9.1.2 Henley: USA – CPS I and CPS II (2005)

See section 3.2.5

5.9.1.3 Fernberg: Sweden (2006)

The study by Fernberg et al., 2006 was based on some 335,612 subjects who visited clinics provided by the Swedish construction industry's Organization for Working Environment Safety and Health during the period from 1971 to 1992. Participants were invited for a health check-up every two to three years, during which they completed a questionnaire. Follow-up continued until 31st December 2000, and averaged 19.1 years for each subject. At the end of the study period, there were 1309 histologically verified cases of non-Hodgkin's lymphoma (NHL) and 205 cases of Hodgkin's disease.

The results of the study were as follows:

Tobacco use	No. of subjects	Person-years	NHL cases	IRR[1] (95% CI)	HD cases	IRR[1] (95% CI)
Men:						
Never tobacco users	102443	1.98[2]	337	1.0	49	1.0
Ever snuff users	40981	1.81[2]	66	0.77 (0.59-1.01)	15	0.88 (0.49-1.58)
1-30 years of use		0.64[2]	49	0.81 (0.60-1.11)[3]	11	0.70 (0.36-1.37)[3]
30+ years of use		0.04[2]	16	0.69 (0.41-1.15)[3]	4	3.78 (1.23-11.60)[3]
Women:						
Never tobacco users	778	14.19[4]	27	1.0	5	1.0
Ever snuff users	1	0.016[4]	0	-[5]	0	-[5]

HD = Hodgkin's disease; IRR = incidence rate ratio; NHL = non-Hodgkin's lymphoma
[1] Adjusted for age
[2] Person-years in millions
[3] Adjusted for age and body mass index
[4] Person-years in thousands
[5] Not estimated as no cases in smokeless tobacco users

5.9.2 Case-control studies

5.9.2.1 Williams: USA (1977)

See Section 3.3.1

5.9.2.2 Lindquist: Sweden (1987)

Cases in this study [Lindquist et al., 1987] consisted of 125 leukemia patients who were treated during the period from September 1980 to May 1983 at one of five hospitals taking part in the treatment protocols of the Leukemia Group of Middle Sweden. The cases ranged in age from 15-84 years, and there were 76 men and 49 women. One control per case was selected from a population register, matched on location, age and sex. All participants were interviewed face-to-face. Snuff takers numbered 18 in the case group and 19 in the controls. There were 52 cases and 60 controls who were non-smokers. From this data it was possible to estimate a relative risk of 1.09 (95% CI 0.52-2.30) for leukemia for snuff users in non-smokers. The authors reported that multivariate analysis showed no interaction between smoking habits and exposure to organic solvents, x-rays or petroleum products.

5.9.2.3 Morris I: USA - Iowa/Minnesota (1992)

Cases in the study by Morris Brown et al., 1992b consisted of 578 white men (340 living, 238 deceased), aged at least 30 years, diagnosed with leukaemia during 1981-1984 in Iowa and Minnesota. Random digit dialling, Medicare records and death certificates were used to select a population-based stratified sample of white men without lymphatic or haematopoietic cancer who were frequency matched to the cases by five-year age group, state of residence and vital status. Information was collected from a total of 1245 controls (820 living, 425 deceased). However, the authors stated that as exposures that increase overall mortality, including smoking, have been shown to be over-represented in deceased controls, analysis was restricted to the living control group. A total of 105 cases and 197 controls were non-users of tobacco, 24 cases and 23 controls used smokeless tobacco exclusively, and 14 cases and 12 controls used smokeless tobacco in conjunction with pipes and/or cigars.

Odds ratios for smokeless tobacco use, adjusted for age, state of residence and alcohol use, were presented for all leukaemias, and for subtypes of the disease, as follows:

Disease	Non-tobacco users	Smokeless tobacco only			Smokeless tobacco + cigars and/or pipes		
		No.	OR	95% CI	No.	OR	95% CI
Controls	197	23			12		
All leukemia	105	24	1.8	0.9-3.3	14	1.9	0.8-4.2
Acute non-lymphocytic	29	3	0.9	0.2-3.1	2	1.2	0.2-5.6
Chronic myelogenous	8	2	2.1	0.4-10.7	1	2.1	0.2-18.3
Chronic lymphocytic	40	10	1.9	0.8-4.3	5	1.6	0.5-5.0
Acute lymphocytic	5	0	0.0	-	0	0.0	-
Myelodysplasia	10	4	2.7	0.8-9.4	1	1.0	0.1-8.7
Other	13	5	3.0	0.9-9.2	5	5.2	1.5-17.8

Although deceased controls were excluded from analysis, over 40% of the cases were dead, and smoking information for these subjects came from proxy respondents. The authors suggested that the lack of dose-response gradients in analyses including and excluding proxy respondents suggest that misclassification of the amount smoked was not an issue in this study, although the effect of non-differential misclassification of exposure status was discussed.

5.9.2.4 Morris II: USA - Iowa/Minnesota (1992)

In a second study by Morris Brown et al., 1992a, the original control group described above was compared to a series of 622 cases of non-Hodgkin's lymphoma. In addition, 452 controls from Iowa were compared to 173 multiple myeloma patients. All the patients were white men aged at least 30 years. Controls were frequency matched to cases by age, vital status at time of interview, and state of residence. Each participant was interviewed using a standardized questionnaire. As in the previous study, although information was collected from deceased controls, results including them were not presented to eliminate a potential source of bias. Among the lymphoma patients, there were 116 non-users of tobacco, 19 men who used smokeless tobacco exclusively and 22 men who used smokeless tobacco in conjunction with pipes and/or cigars. In the control group, the corresponding figures were 197, 23 and 12 respectively. Forty-one of the myeloma cases were non-users, while 5 cases used only smokeless tobacco and 3 cases used smokeless tobacco and pipes and/or cigars. Among the controls, there were 105 non-users, 8 exclusive smokeless tobacco users and 4 combined smokeless tobacco users.

The results of the study, by disease subtype, were as follows:

Disease	Non-tobacco users	Smokeless tobacco only			Smokeless tobacco + cigars and/or pipes		
		No.	OR[1]	95% CI	No.	OR[1]	95% CI
Non-Hodgkin's lymphoma:							
Controls	197	23			12		
All lymphoma	116	19	1.3	0.7-2.5	22	2.9	1.4-6.1
Follicular	39	7	1.7	0.7-4.3	5	2.3	0.8-6.9
Diffuse	43	5	0.8	0.3-2.3	7	2.3	0.8-6.2
Small lymphocytic	18	4	1.7	0.5-5.4	5	3.9	1.2-12.5
Other							
High grade	7	1	1.3	0.1-10.8	2	4.8	0.9-26.0
Unclassified	9	2	1.5	0.3-7.4	3	4.6	1.1-19.2
Multiple myeloma:							
Controls	105	8			4		
Cases	41	5	1.9[2]	0.5-6.6	3	1.5[2]	0.3-7.0

[1] Adjusted for age and state of residence
[2] Adjusted for age

As in the study above, a significant proportion of the cases were dead, and information on smoking behaviour was gathered from proxy respondents, while, for the purposes of these analyses, the control groups were limited to self-responders.

5.9.2.5 Hardell: Sweden - Umea (1994)

Cases in the study by Hardell et al., 1994 consisted of 105 men, aged 25-85 years, who were admitted to the department of oncology in Umea between 1974 and 1978 with histopathologically confirmed non-Hodgkin's lymphoma. They were compared to 335 controls, who had answered a questionnaire and who were matched on sex, age, place of residence and vital status, and for year of death in the case of deceased subjects. Living controls were drawn from the National Population Registry and deceased controls from the National Registry for Causes of Death. Oral snuff was used by 35 cases and 84 controls. This gave an odds ratio estimate, adjusted for age and vital status, for the risk of non-Hodgkin's lymphoma of 1.5 (95% CI 0.9-2.5). The analyses did not adjust for smoking, but it was found that smoking was not associated with risk of non-Hodgkin’s lymphoma.

5.9.2.6 Bracci: USA - San Francisco (2005)

Bracci & Holly, 2005 included all cases of non-Hodgkin lymphoma diagnosed between January1988 and February 1993, provided the subject was aged 21-74 years and was resident in one of the six San Francisco Bay Area counties at diagnosis. Random digit dialling was used to identify controls, who were frequency-matched to cases by sex, county of residence and age. Each subject underwent a structured face-to-face interview. A total of 1304 cases (579 women, 725 men) and 2402 controls (836 women, 1566 men) took part in the study. None of the women used smokeless tobacco, but among the men, 7 cases and 6 controls were exclusive users, while 204 cases and 551 controls did not use any form of tobacco. Data were also presented separately for users of cigarettes only, cigarettes and other forms of tobacco, and other tobacco only, although the group "other tobacco" also included the use of pipes and cigars, and was not restricted to smokeless tobacco. Indeed, the authors stated that in the grouping "multiple other tobacco", 100% of cases and 82% of controls were smokers of both cigars and pipes, but no mention of the proportion using smokeless tobacco was made. The relative risks for non-Hodgkin lymphoma in men in these smoking categories were as follows:

Smoking category	Cases No.	Controls No.	OR[1]	95% CI	OR[2]	95% CI
Cigarettes only	332	728	1.1	0.88-1.3	1.1	0.85-1.3
Cigarettes and other tobacco[3]	149	231	1.3	1.00-1.7	1.4	1.0-1.8
Multiple other tobacco[3]	15	17	1.8	0.87-3.7	2.1	0.99-4.4
Snuff or chewing tobacco	7	6	4.0	1.3-12	4.0	1.3-12

[1] Adjusted for age
[2] Adjusted for age, education and weekly alcohol consumption
[3] Other tobacco group includes pipe and cigar smokers

Results were also given by histologic subtype of non-Hodgkin lymphoma among male users of various types of tobacco:

Smoking category	Controls	Follicular			Diffuse large cell		
	No.	No.	OR[1]	95% CI	No.	OR[2]	95% CI
Cigarettes only	728	129	1.3	0.93-1.8	119	1.0	0.74-1.4
Cigarettes and other tobacco[3]	231	58	1.5	1.0-2.2	61	1.6	1.1-2.4
Multiple other tobacco[3]	17	2	0.64	0.14-2.9	9	3.9	1.6-9.6
Snuff or chewing tobacco	6	4	7.3	1.9-28	2	2.5	0.47-13

[1] Adjusted for age and education
[2] Adjusted for age, education and weekly alcohol consumption
[3] Other tobacco group includes pipe and cigar smokers

5.9.3 Summary

Nine studies investigated the relationship between haematopoietic cancers and usage of smokeless tobacco, and details of these are given in Table 5.9.1. In four of the studies the analyses of smokeless tobacco use were restricted to non smokers of any product, and in one to non smokers of cigarettes. The remaining four studies all appeared to include smokers of all tobacco products. Only one of these studies carried out any form of adjustment for smoking, and even this study only considered cigarette smoking. All but one of the studies carried out adjustment for age, and for various other factors. It should also be noted that for all of the endpoints considered by the studies the number of cases who used smokeless tobacco was generally very small, with all but one study being based on 35 or fewer exposed cases.

A summary of results from the individual studies and from selected meta-analysis are presented in Tables 5.9.2 and 5.9.3 respectively. The results for each individual endpoint are discussed below.

5.9.3.1 All haematopoietic cancers

Only one prospective study examined the relationship between smokeless tobacco use and all haematopoietic cancers combined, reporting a slightly reduced relative risk in users compared to non-users, which failed to reach statistical significance.

5.9.3.2 All leukaemia

The association between usage of smokeless tobacco and all leukaemias combined was investigated by two case-control studies. Both estimated a relative risk which was above 1.00, but neither was significantly so.

There was no evidence of a significant association between smokeless tobacco and all leukaemias combined from a meta-analysis of the available results.

5.9.3.3 Acute lymphocytic leukaemia

Two case-control studies provided results for this endpoint, but only a total of one case was seen in smokeless tobacco users. No conclusions can be drawn.

5.9.3.4 Chronic lymphocytic leukaemia

Two case-control studies assessed the risk of this endpoint in relation to the use of smokeless tobacco. Two of the relative risks estimated by the studies were raised, with one statistically significant (4.80, 95% CI 1.11-20.72). The third risk estimate was non-significantly below 1.00.

Meta-analysis of the three relative risks did not provide any evidence of a significant association between smokeless tobacco use and chronic lymphocytic leukaemia.

5.9.3.5 Acute granulocytic leukaemia

Data relating to the possible association between smokeless tobacco use and acute granulocytic leukaemia was available from two case-control studies. With a total of only four cases in smokeless tobacco users, no conclusions can usefully be drawn.

5.9.3.6 Chronic granulocytic leukaemia

Again, only two case-control studies presented data relevant to this endpoint. Here, only two cases were seen in total in smokeless tobacco users, so no conclusions can be drawn.

5.9.3.7 Myelodysplasia

One case-control study investigated the possible relationship between smokeless tobacco use and myelodysplasia, reporting a non-significantly raised adjusted relative risk, based on only four cases in smokeless tobacco users.

5.9.3.8 Other leukaemias

Leukaemias other than those discussed above were considered by just one case-control study. Although the relative risk estimated by this study was above 1.00, it failed to reach statistical significance, being based on only five cases in smokeless tobacco users.

5.9.3.9 Hodgkin's lymphoma

The relationship between smokeless tobacco use and Hodgkin's lymphoma was investigated by just two studies, one prospective and one case-control in design. The prospective study by Fernberg et al., 2006 found no significant association in males, based on 66 cases in smokeless tobacco users. The results for females in that study, and for both sexes in the case-control study, added only a further two cases in smokeless tobacco users, and little affected the evidence.

5.9.3.10 Non-Hodgkin's lymphoma

Five studies reported on the association between non-Hodgkin's lymphoma and the use of smokeless tobacco. One study was prospective and four were of a case-control design. Three of the relative risks reported for this disease in users of smokeless tobacco compared to non-users were above 1.00, although the association was statistically significant for only one of these estimates (4.0, 95% CI 1.3-12). The two remaining relative risks presented were non-significantly reduced.

Neither the fixed or random effects models produced a statistically significant relative risk estimate when meta-analysis was used on the available results. However, there was a significant degree of heterogeneity between the studies included in this analysis ($p < 0.02$).

5.9.3.11 Other lymphomas

This endpoint was considered by a single case-control study. Only two cases were seen in smokeless tobacco users, so no conclusions can be drawn.

5.9.3.12 Multiple myeloma

Three studies examined the possible association between smokeless tobacco and multiple myeloma. One study was prospective and two were case-control in design. Two of the four relative risks estimated were above 1.00, although neither was significantly so, and one was non-significantly reduced. The fourth relative risk was estimated at 1.00.

There was no evidence of a significant relationship between smokeless tobacco use and the risk of multiple myeloma from a meta-analysis of the available results.

Table 5.9.1: Summary of studies of haematopoietic cancers

Study	Study Type	Location	Treatment of smoking in analysis		Other adjustment factors
			Smokers excluded	Smoking variables adjusted for	
Bracci	C-C	USA	Ever smokers	-	Age, education, alcohol intake
Fernberg	P	Sweden	None	None	Age, BMI
Hardell	C-C	Sweden	None	None	Age, vital status
Heineman	P	USA	Ever cigarette	-	Age, calendar time, year of questionnaire response
Henley-CPS II	P	USA	Ever smokers	-	Age, race, education, BMI, exercise, alcohol intake, employment status and type, fat consumption, fruit/ vegetable intake, aspirin use
Lindquist	C-C	Sweden	None	None	None
Morris I	C-C	USA	Ever smokers	-	Age, state of residence, alcohol intake
Morris II	C-C	USA	Ever smokers	-	Age, state of residence
Williams	C-C	USA	None	Cigarette smoking	Age, race

Table 5.9.2: Summary of results for haematopoietic cancers

Study	Non-users		Smokeless tobacco users		Product[a]	Sex	RR	95% CI	Adjustment factors[b]	Notes[c]
	Controls	Cases	Controls	Cases						
All haematopoietic cancers										
Henley-CPS II	111482	895	2488	19	ST	M	0.95	0.60-1.51	Age, smoking, other	1
All leukaemia										
Lindquist	60	52	19	18	Snuff	M	1.09	0.52-2.30	None	2
Morris I	197	105	23	24	ST	M	1.8	0.9-3.3	Age, smoking, other	
Acute lymphocytic leukaemia										
Morris I	197	5	23	0	ST	M	-	-	None	2,3
Williams	1618	6	163	1	ST	M	5.24	0.63-43.79	Age, smoking, other	2
	3133	2	53	0	ST	F	-	-		2,3
Chronic lymphocytic leukaemia										
Morris I	197	40	23	10	ST	M	1.9	0.8-4.3	Age, smoking, other	
Williams	1594	30	161	3	ST	M	0.92	0.28-3.05	Age, smoking, other	2
	3108	27	51	2	ST	F	4.80	1.11-20.72		2
Acute granulocytic leukaemia										
Morris I	197	29	23	3	ST	M	0.9	0.2-3.1	Age, smoking, other	4
Williams	1609	15	163	1	ST	M	1.93	0.25-14.69	Age, smoking, other	2
	3120	15	53	0	ST	F	-	-		2,3
Chronic granulocytic leukaemia										
Morris I	197	8	23	2	ST	M	2.1	0.4-10.7	Age, smoking, other	5
Williams	1615	9	164	0	ST	M	-	-	Age, smoking, other	2,3
	3124	11	53	0	ST	F	-	-		2,3
Myelodysplasia										
Morris I	197	10	23	4	ST	M	2.7	0.8-9.4	Age, smoking, other	

Table 5.9.2 continued

Study	Non-users		Smokeless tobacco users		Product[a]	Sex	RR	95% CI	Adjustment factors[b]	Notes[c]
	Controls	Cases	Controls	Cases						
Other leukaemias										
Morris I	197	13	23	5	ST	M	3.0	0.9-9.2	Age, smoking, other	
Hodgkin's lymphoma										
Fernberg	1980000	337	1810000	66	Snuff	M	0.88	0.49-1.58	Age, other	6,7
	14190	27	16	0	Snuff	F	-	-	None	2,3,6
Williams	1580	44	162	2	ST	M	1.30	0.31-5.40	Age, smoking, other	2
	3112	23	53	0	ST	F	-	-		2,3
Non-Hodgkin's lymphoma										
Bracci	551	204	6	7	ST	M	4.0	1.3-12	Age, smoking, other	
Fernberg	1980000	49	1810000	15	Snuff	M	0.77	0.59-1.01	Age, other	6,7
	14190	5	16	0	Snuff	F	-	-	None	2,3,6
Hardell	251	70	84	35	Snuff	M	1.5	0.9-2.5	Age, other	
Morris II	197	116	23	19	ST	M	1.3	0.7-2.5	Age, smoking, other	
Williams	1583	41	163	1	ST	M	0.38	0.05-2.97	Age, smoking, other	2,8
	3081	54	53	0	ST	F	-	-		2,3
Other lymphomas										
Williams	1609	15	162	2	ST	M	1.58	0.36-6.97	Age, smoking, other	2
	3125	10	53	0	ST	F	-	-		2,3
Multiple myeloma										
Heineman	1020200	141	41124	6	ST	M	1.0	0.4-2.3	Age, smoking, other	6
Morris II	105	41	8	5	ST	M	1.9	0.5-6.6	Age, smoking	
Williams	1590	34	161	3	ST	M	0.94	0.29-3.09	Age, smoking, other	2
	3102	33	52	1	ST	F	1.95	0.26-14.52		2

[a] ST = smokeless tobacco

[b] Adjustment for smoking includes studies restricted to non-smokers; Refer to table 5.9.1 for full details of adjustment factors. Where study presents multiple RR estimates, adjustment factors relate to all RRs unless otherwise stated

[c] Key to notes:

1 Number of controls refers to population at risk
2 Relative risk estimated from data given
3 Not estimated as no cases in smokeless tobacco users
4 Defined as acute non-lymphocytic leukaemia
5 Defined as chronic myelogenous leukaemia
6 Number of controls refers to person-years at risk
7 Incidence rate ratio
8 Defined as lymphosarcoma

Table 5.9.3: Summary of meta-analysis results for haematopoietic cancer studies

Endpoint	No. of studies	Fixed effects estimate RR	95% CI	Heterogeneity chisquared	p value[1]	Random effects estimate RR	95% CI
All leukaemia	2	1.45	0.89-2.36	0.99	NS	1.45	0.89-2.36
Chronic lymphocytic leukaemia	2	1.83	0.99-3.44	2.95	NS	1.88	0.85-4.13
Hodgkin's lymphoma	2	0.93	0.54-1.60	0.25	NS	0.93	0.54-1.60
Non-Hodgkin's lymphoma	5	0.98	0.79-1.21	13.50	<0.02	1.25	0.73-2.14
Multiple myeloma	3	1.19	0.66-2.15	1.04	NS	1.19	0.66-2.15

[1] NS = Not significant

5.10 *Kidney cancer*

5.10.1 Prospective studies

5.10.1.1 Boffetta: Norway/USA (2005)

See section 3.2.4

5.10.2 Case-control studies

5.10.2.1 Bennington I: USA - Washington (1968)

In this study [Bennington & Laubscher, 1968], all patients admitted to the University of Washington affiliated hospitals during 1951-66 with histologically proven renal adenocarcinoma at surgery or autopsy formed the case group. For each case, two controls were selected, matched for age, race, sex, file (surgical pathology or autopsy), year of admission and hospital. Data on smoking habits were available from clinical records compiled on admission to hospital. In the case group, there were 88 men and 12 women, while in the control group men and women numbered 170 and 20 respectively. Detailed information on tobacco use was only given for male participants. Five cases and eight controls chewed tobacco, and six cases and 43 controls did not use any form of tobacco. From this, the authors estimated a relative risk of 4.8 for renal adenocarcinoma in users of chewing tobacco alone compared to non-tobacco users. No confidence interval was given, but it can be estimated as 1.18-19.59. For users of pipes, cigars and chewing tobacco combined, the relative risk estimate was 8.2, with the confidence interval estimated to be 2.78-24.18. The proportion of deceased participants was not given, but presumably in these subjects, some information on smoking habits was obtained from proxy respondents and therefore may be of doubtful reliability.

5.10.2.2 Bennington II: USA - King County (1968)

In the second study by Bennington et al., 1968, the case group consisted of 66 men with renal adenoma, histologically proven at autopsy at King County hospital during 1951-67. (Although renal adenoma is a benign kidney neoplasm and not cancer, it is a precursor to it, so this study has been included in this section rather than in section 6.) For each case, two control patients were selected, matched on age and sex, from the same file and year as the case. A total of 118 controls were identified. Information on smoking habits appears to have been abstracted from hospital records. Only three cases and four controls chewed tobacco, while five cases and 25 controls were non-users of any form of tobacco. The authors reported a relative risk of 5.1 for renal adenoma in tobacco chewers compared to non-tobacco users. A confidence interval was not given, but it could be estimated at 0.86-30.20. For pipe, cigar and smokeless tobacco use combined, the relative risk estimate was 4.6, for which a confidence interval of 1.38-15.37 could be estimated.

5.10.2.3 Armstrong: UK - Oxford (1976)

The cases in this study [Armstrong et al., 1976] consisted of all patients diagnosed between 1 January 1972 and 31 December 1974 as suffering from renal cancer in the Oxford Regional Hospital Board area. For each case, a control was selected at random, matched on sex, age (± five years) and having had a surgical operation in the same hospital and at the same time (± one month). A total of 139 pairs of cases and controls were interviewed. Information on smokeless tobacco use was collected in men only. In the case group, there were 84 never users, 6 ex-users, 5 occasional users and 1 regular user. Among the controls, never, ex-, occasional and regular users numbered 82, 8, 3 and 3 respectively. From the data given, it was possible to estimate a relative risk for renal cancer of 0.84 (95% CI 0.37-1.92) for ever users of smokeless tobacco compared to never users. The relative risk for regular users was estimated at 0.33 (0.03-3.19). Analysis by the site of the tumour produced risk estimates for ever users of smokeless tobacco of 0.90 (95% CI 0.36-2.26) for tumours of the renal parenchyma, and 0.63 (95% CI 0.1-4.22) for renal pelvis tumours. It was not possible to adjust these results for the effects of cigarette smoking.

5.10.2.4 Williams: USA (1977)

See section 3.3.1

5.10.2.5 McLaughlin: USA - Minneapolis-St. Paul (1984)

McLaughlin et al., 1984 reported on a study in which the case group consisted of white residents of the Minneapolis-St. Paul metropolitan area diagnosed with renal cell carcinoma during the period from 1 January 1974 until 30 June 1979. An age and sex stratified random sample of white controls, aged 30-64 years, was obtained from a complete listing of all telephone subscribers in the study area. Controls aged 65-85 years were identified from the Health Care Financing Administration's listing for the same area, and this sample was also stratified for age and sex. A total of 495 cases and 697 controls were interviewed. For 251 cases who were either deceased or too ill to be interviewed, information was obtained from proxy respondents, usually another family member. Next-of-kin interviews were also obtained for 493 white residents of the study area randomly selected from among all persons who died in the relevant time period of causes other than urinary tract cancer. However, these controls do not appear to have been included in analyses. A total of 46 cases and 89 population controls were non-users of tobacco, while 5 cases and 10 controls used smokeless tobacco exclusively. The odds ratios for renal cell cancer were estimated at 1.7 (95% CI 0.5-6.0) for snuff use and 0.4 (95% CI 0.1-2.6) for chewing tobacco use. Both these estimates were adjusted for age and cigarette smoking. Although data on many other potential confounders were collected, there was no attempt to adjust the results for these factors.

5.10.2.6 Goodman: USA - multicentre (1986)

Cases in this study [Goodman et al., 1986] consisted of all newly diagnosed patients, aged 20-80 years, with histologically confirmed primary adenocarcinoma of the kidney occurring between 1977 and 1983 in 18 hospital centres in six US cities. One control was matched to each case on the basis of hospital, sex, race, age and time of admission. Controls were chosen from among those admitted to hospital for non-tobacco and non-obesity related diseases. A total of 189 men and 78 women with renal cell cancer, and an equal number of controls, were included in the study. Among the controls, 38% of the men and 31% of the women had a diagnosis of cancer. Users of chewing tobacco numbered 13 in the male cases and 4 in the male controls. One female control also reported ever use of chewing tobacco. For men, an odds ratio of 4.00 (95% CI 1.13-14.17) was estimated for the risk of renal cell carcinoma in ever users of chewing tobacco compared to never users. When women were included in the analysis, the odds ratio fell to 3.00 and was no longer statistically significant (95% CI 0.97-9.30). Although information on many potential confounders was collected, no attempt was made to adjust the results for any of these factors, including smoking.

5.10.2.7 Asal: USA - Oklahoma (1988)

In the study by Asal et al., 1988, potential risk factors for renal cell carcinoma were studied in 315 cases, 313 hospital controls and 336 population controls. Cases were identified in 29 hospitals in Oklahoma between 1 July 1981 and 30 June 1984. Hospital controls were matched to the cases on age, sex, race, hospital and time of interview. Population controls were selected, using random digit dialling, from the general population of Oklahoma, and were frequency matched to the cases by age and sex. All participants were interviewed using a structured questionnaire. Details of the numbers of smokeless tobacco users were not given, but it was reported that in men there was a significant association, in a matched pairs analysis, between snuff use and renal cell carcinoma compared to the hospital controls (OR = 3.6, 95% CI 1.2-13.3). This association was not seen when population controls were used as the comparison group.

5.10.2.8 McLaughlin: Australia/Denmark/Germany/Sweden/USA (1995)

McLaughlin et al., 1995 reported on an international multi-centre population-based case-control study, in which co-ordinated studies were carried out in five countries. Cases were identified from all inhabitants aged 20-79 years (20-75 years in Germany) resident in the study areas during the period 1989-1991, and comprised all histologically confirmed incident cases of renal cell cancer. Controls were sampled from the populations that gave rise to the cases, and were frequency matched by sex and five-year age group. Information was collected at face-to-face interviews from a total of 1732 cases and 2309 controls. Of these, 11 cases and 13 controls (all male) used smokeless tobacco. It was not made clear whether these individuals also used other tobacco products. A relative risk of 1.3 (95% CI 0.6-3.1) was estimated for renal cell cancer in exclusive users of smokeless tobacco compared to subjects who did not use any form of tobacco, adjusted for age, sex, centre and body mass index. Information on other potential confounders was collected but not adjusted for. The authors reported that there was no evidence of a dose-response relationship between the amount of smokeless tobacco used and renal cell cancer risk, but did not present these data.

5.10.2.9 Muscat: USA - Multicentre (1995)

In the study by Muscat et al., 1995, cases consisted of all newly-diagnosed histologically confirmed renal cell carcinoma patients at teaching hospitals across the US between 1977 and 1993. Control subjects were patients who did not have kidney cancer and who were hospitalized for conditions not associated with tobacco use. Controls were frequency matched to cases for age, race and year of diagnosis. A total of 778 cases (543 men) and 779 controls (529 men) were interviewed. Chewing tobacco use was only reported by male respondents, with 97.4% of the cases and 99.1% of the controls never having used it, giving an odds ratio of 3.2 (95% CI 1.1-8.7), after adjustment for age and education. Only 1.5% of the cases and 0.8% of the controls used chewing tobacco less than 10 times per week, while more frequent usage was reported by 1.1% of cases and 0.2% of controls. From these data, an adjusted odds ratio of 2.5 (95% CI 1.0-6.1) was estimated for the risk of renal cell carcinoma in men who used chewing tobacco less than 10 times per week. The corresponding odds ratio for men who used chewing tobacco at least 10 times per week was 6.0 (95% CI 1.9-18.7), and this trend was statistically significant ($p < 0.05$). Although information on smoking and alcohol consumption was collected, the results were not adjusted for these factors.

5.10.2.10 Yuan: USA - Los Angeles (1998)

Yuan et al., 1998 used the Los Angeles County Cancer Surveillance Program to identify non-Asian patients aged 25-74 years with histologically confirmed renal cell cancer between April 1986 and December 1994. Interviews were completed with 1204 patients who could be matched to a control on the basis of sex, date of birth, race and neighbourhood of residence at the time of diagnosis. A total of 32 cases and 27 controls had ever used smokeless tobacco, giving an odds ratio estimate for renal cell carcinoma of 1.02 (95% CI 0.56-1.85). This estimate was adjusted for education, current smoking status, and the number of cigarettes smoked per day. Odds ratios for cigarette smokers only, and users of both cigarettes and non-cigarette tobacco products, including pipes and cigars, were estimated at 1.37 (95 %CI 1.13-1.66) and 1.30 (95% CI 0.99-1.70).

5.10.3 Summary

Eleven studies provided data on the possible association between smokeless tobacco and kidney cancer, and details of these are given in table 5.10.1. One study was prospective and the remaining 10 were all case-control in design. In three of the studies the analysis of smokeless tobacco use was restricted to lifelong non-smokers while, in the remaining eight, smokers of all tobacco products were included. However, only four of these studies adjusted for smoking during analysis, and two of these considered only cigarette smoking. Ten of the studies carried out adjustment for age, and for various other potential confounders.

Nine of the relative risks presented were above 1.00, with four of these reaching statistical significance (3.6, 95% CI 1.2-13.3; 4.8, 95% CI 1.18-19.59; 4.00, 95% CI 1.13-14.17; 3.2, 95% CI 1.1-8.7). Four reduced relative risks were also reported, one of which reached statistical significance (0.47, 95% CI 0.23-0.94). In addition, one study failed to find any association between smokeless tobacco use and kidney cancer when compared to controls selected from the general population.

As one study gave results for both chewing tobacco and snuff, two meta-analyses were carried out, with one combining results from all the other studies and the risk estimate for snuff from this study, and the other using the relative risk for chewing tobacco. For usage of smokeless tobacco/snuff, results from both the fixed and random effects models just failed to reach statistical significance. There was also no significant evidence of a relationship between smokeless tobacco/chewing tobacco use and kidney cancer. For both analyses, there was evidence of significant heterogeneity between the studies (smokeless tobacco/snuff: $p < 0.01$; smokeless tobacco/chewing tobacco: $p < 0.005$).

Table 5.10.1: Summary of studies of kidney cancer

Study	Study Type	Location	Treatment of smoking in analysis		Other adjustment factors
			Smokers excluded	Smoking variables adjusted for	
Armstrong	C-C	UK	None	None	None
Asal	C-C	USA	None	None	Age, race, hospital, time of interview
Bennington I	C-C	USA	Ever smokers	-	Age
Bennington II	C-C	USA	Ever smokers	-	Age
Boffetta	P	Norway/ USA	None	Smoking of cigarettes, cigars and pipes	Age
Goodman	C-C	USA	None	None	Age, race, hospital, time of admission
McLaughlin 1984	C-C	USA	None	Cigarette smoking	Age
McLaughlin 1995	C-C	5 countries	Ever smokers	-	Age, sex, BMI, study centre
Muscat	C-C	USA	None	None	Age, education
Williams	C-C	USA	None	Cigarette smoking	Age, race
Yuan	C-C	USA	None	Smoking status, number of cigarettes smoked per day	Age, sex, race, education, neighbourhood of residence

Table 5.10.2: Summary of results for kidney cancer

Study	Non-users		Smokeless tobacco users		Product[a]	Sex	RR	95% CI	Adjustment factors[b]	Notes[c]
	Controls	Cases	Controls	Cases						
Armstrong	82	84	3	1	ST	M	0.33	0.03-3.19	None	1
Asal	-	-	-	-	Snuff	M	3.6	1.2-13.3	Age, other	2
	-	-	-	-	Snuff	M	No association			3
Bennington I	43	6	-	-	Chew	M	4.8	1.18-19.59	Age, smoking	4
Bennington II	25	5	4	3	Chew	M	5.1	0.86-30.20	Age, smoking	4,5
Boffetta	6921	66	1999	9	ST	M	0.47	0.23-0.94	Age, smoking	6
Goodman	185	176	4	13	Chew	M	4.00	1.13-14.17	Age, other	
	77	78	1	0	Chew	F	-	-		
McLaughlin 1984	89	46	-	-	Snuff	M	1.7	0.5-6.0	Age, smoking	
	89	46	-	-	Chew	M	0.4	0.1-2.6		
McLaughlin 1995	-	-	-	-	ST	M+F	1.3	0.6-3.1	Age, smoking, other	
Muscat	524	529	5	14	Chew	M	3.2	1.1-8.7	Age, other	
Williams	1574	50	161	3	ST	M	0.86	0.26-2.78	Age, smoking, other	1
	3088	47	52	1	ST	F	2.10	0.28-15.49		1
Yuan	433	357	27	32	ST	M+F	1.02	0.56-1.85	Age, smoking, other	

[a] ST = smokeless tobacco

[b] Adjustment for smoking includes studies restricted to non-smokers; Refer to table 5.10.1 for full details of adjustment factors. Where study presents multiple RR estimates, adjustment factors relate to all RRs unless otherwise stated

[c] Key to notes:

1 Relative risk estimated from data given
2 Hospital controls
3 Population controls
4 Confidence interval estimated from data given
5 Renal adenoma
6 Number of controls refers to population at risk

Table 5.10.3: Summary of meta-analysis results for kidney cancer studies

Tobacco product	No. of studies	Fixed effects estimate RR	95% CI	Heterogeneity chisquared	p value	Random effects estimate RR	95% CI
Smokeless tobacco/ snuff	12[1]	1.34	0.995-1.81	25.10	< 0.01	1.63	0.995-2.67
Smokeless tobacco/ chewing tobacco	12[2]	1.27	0.94-1.72	26.95	< 0.005	1.50	0.89-2.53

[1] Combines results from all available studies, using results for snuff if results for separate types of smokeless tobacco are presented

[2] Combines results from all available studies, using results for chewing tobacco if results for separate types of smokeless tobacco are presented

5.11 *Lung cancer*

5.11.1 Prospective studies

5.11.1.1 Winn: USA (1982)

See section 3.2.1

5.11.1.2 Bolinder: Sweden (1994)

See section 3.2.2

5.11.1.3 Accortt: USA (2002)

See section 3.2.3

5.11.1.4 Boffetta: Norway/USA (2005)

See section 3.2.4

5.11.1.5 Henley: USA (2005)

See section 3.2.5

5.11.2 Case-control/cross-sectional studies

5.11.2.1 Doll: UK - multicentre (1952)

Cases in the study by Doll & Hill, 1952 comprised 1209 men, aged less than 75 years, with lung cancer who were interviewed in hospital during the period from April 1948 to February 1952. The cases were matched to 1209 general medical and surgical patients, who acted as a control group. Matching was on the basis of sex, age and hospital of interview.

The results of the study were as follows:

Tobacco use	No. of cases	No. of controls	RR	95% CI
Never chewed	1169	1145	-	
Ever chewed	40	64	0.61	0.41-0.92
Occasional users	12	15	0.78	0.37-1.68
Less than 10 years duration	8	6	1.31	0.45-3.78
10+ years duration	4	9	0.44	0.13-1.42
Regular users	28	49	0.56	0.35-0.90
Less than 10 years duration	11	17	0.63	0.30-1.36
10+ years duration	17	32	0.52	0.29-0.94
Never used snuff	1176	1166	-	
Ever used snuff	33	43	0.76	0.48-1.21
Occasional users	15	16	0.93	0.46-1.89
Less than 10 years duration	8	11	0.72	0.29-1.80
10+ years duration	7	5	1.39	0.44-4.39
Regular users	18	27	0.66	0.36-1.21
Less than 10 years duration	10	16	0.62	0.28-1.37
10+ years duration	8	11	0.72	0.29-1.80

The crude relative risks shown were estimated from the data given

Although information on other variables was collected by the authors, no attempt was made to adjust the findings for any potential confounders.

5.11.2.2 Williams: USA (1977)

See section 3.3.1

5.11.2.3 Wynder: USA - 8 cities (1977)

See section 3.3.2

5.11.3 Summary

Data relating to the relationship between lung cancer and the use of smokeless tobacco was available from nine studies, details of which are given in table 5.11.1. Six studies were prospective, while the remaining three were of a case-control design. In five of the nine studies the smokeless tobacco analysis was restricted to lifelong non smokers of any product and in one the restriction was to non smokers of cigarettes. Three studies included smokers of all tobacco products. Only one of these three studies carried out adjustment for smoking, and even then only cigarette smoking was considered. Six of the studies adjusted for age, and five of these also carried out adjustment for various other potential confounders. One study appeared to have adjusted its results, but did not state the factors included.

The results of the studies are summarized in table 5.11.2. Six relative risk estimates were above 1.00, two of them significantly so (9.1, 95% CI 1.1-75.4; 2.00, 95% CI 1.23-3.24). Six reduced relative risks were also presented, with one of these reaching statistical significance (0.56, 95% CI 0.35-0.90) and another being of borderline significance (0.69, 95% CI 0.47-1.00). In addition, one study reported a standardized mortality rate of 60 for lung cancer in smokeless tobacco users compared to non-users, but did not estimate the significance of this result.

The results of meta-analysis are presented in table 5.11.3. Two analyses were carried out, as two of the studies gave results for snuff and chewing tobacco separately. Neither analysis provided evidence of a significant association between smokeless tobacco use and the risk of lung cancer. However, there was significant heterogeneity between the studies included in the analyses ($p < 0.03$ for smokeless tobacco/snuff and $p < 0.003$ for smokeless tobacco/chewing tobacco).

Table 5.11.1: Summary of studies of lung cancer

Study	Study Type	Location	Treatment of smoking in analysis		Other adjustment factors
			Smokers excluded	Smoking variables adjusted for	
Accortt	P	USA	Ever cigarette	-	Age, race, poverty index ratio, region of residence, alcohol intake, recreational physical exercise, fruit/ vegetable intake
Boffetta	P	Norway/ USA	Ever smokers	-	Age
Bolinder	P	Sweden	Ever smokers	-	Age, region of origin
Doll	C-C	UK	None	None	None
Henley-CPS I	P	USA	Ever smokers	-	Age, race, education, BMI, exercise, alcohol intake, fat consumption, fruit/vegetable intake, aspirin use
Henley-CPS II	P	USA	Ever smokers	-	Age, race education, BMI, exercise, alcohol intake, employment status and type, fat consumption, fruit/ vegetable intake, aspirin use
Williams	C-C	USA	None	Cigarette smoking	Age, race
Winn	P	USA	Ever smokers	-	Not stated
Wynder	C-C	USA	None	None	None

Table 5.11.2: Summary of results for lung cancer

Study	Non-users		Smokeless tobacco users		Product[a]	Sex	RR	95% CI	Adjustment factors[b]	Notes[c]
	Controls	Cases	Controls	Cases						
Accortt	-	6	-	0	ST	M	-	-	Age, smoking, other	
	-	-	-	-	ST	F	9.1	1.1-75.4	Age, smoking, other	
Boffetta	6921	271	1999	3	ST	M	0.96	0.26-3.56	Age, smoking	1
Bolinder	13784	5	1672	1	ST	M	1.2	0.2-9.1	Age, smoking, other	1,2
	5642	8	1734	2	ST	M	0.8	0.1-3.9		1,3
Doll	1145	1169	49	28	Chew	M	0.56	0.35-0.90	None	4
	1166	1176	27	18	Snuff	M	0.66	0.36-1.21		4
Henley-CPS I	69662	116	7745	18	ST	M	1.08	0.64-1.83	Age, smoking, other	1
Henley-CPS II	111482	378	2488	18	ST	M	2.00	1.23-3.24	Age, smoking, other	1
Williams	1624	532	164	36	ST	M	0.69	0.47-1.00	Age, smoking, other	4
	3135	154	53	1	ST	F	0.63	0.09-4.62		4
Winn	Total population ~ 300,000				ST	M	0.60	-	Smoking, others not stated	5
Wynder	2327	931	233	117	Chew	M	1.26	0.99-1.59	None	
	2491	1012	69	35	Snuff	M	1.25	0.83-1.89		

[a] ST = smokeless tobacco

[b] Adjustment for smoking includes studies restricted to non-smokers; refer to table 5.11.1 for full details of adjustment factors. Where study presents multiple RR estimates, adjustment factors relate to all RRs unless otherwise stated

[c] Key to notes:

1 Number of controls refers to population at risk
2 Age 35-54 years
3 Age 55-65 years
4 Relative risk estimated from data given
5 Standardized mortality ratio/100

Table 5.11.3: Summary of meta-analysis results for lung cancer studies

Tobacco product	No. of studies	Fixed effects estimate RR	95% CI	Heterogeneity chisquared	p value	Random effects estimate RR	95% CI
Smokeless tobacco/ snuff	10[1]	1.05	0.86-1.28	18.90	< 0.03	1.08	0.76-1.53
Smokeless tobacco/ chewing tobacco	10[2]	1.07	0.91-1.25	25.00	< 0.003	1.05	0.74-1.49

[1] Combines results from all available studies, using results for snuff if results for separate types of smokeless tobacco are presented

[2] Combines results from all available studies, using results for chewing tobacco if results for separate types of smokeless tobacco are presented

5.12 *Male genital organ cancers*

5.12.1 Case-control/cross-sectional studies

5.12.1.1 Williams: USA (1977)

See section 3.3.1

5.12.2 Summary

Only one case-control study investigated the relationship between smokeless tobacco use and cancers of the male genital organs, and the results of this study are summarized in table 5.12.1. Although the study group included smokers of cigarettes, cigars and/or pipes, only adjustment for cigarette smoking was carried out. The results were also adjusted for age and race. Only two cases of cancers of the male genital organs were seen in smokeless tobacco users and no conclusions can be drawn.

Table 5.12.1: Summary of studies of male genital organ cancers

Study	Non-users		Smokeless tobacco users		Product[a]	RR	95% CI	Adjustment factors	Notes[b]
	Controls	Cases	Controls	Cases					
Williams	1582	42	162	2	ST	2.75	0.66-11.45	Age, smoking, race	1

[a] ST = smokeless tobacco
[b] Key to notes:
1 Relative risk estimated from data given

5.13 *Nasal cancer*

5.13.1 Case-control/cross-sectional studies

5.13.1.1 Engzell: Sweden (1978)

The case group in the study by Engzell et al., 1978 consisted of 36 men with adenocarcinoma of the nose and paranasal sinuses identified from the Swedish cancer registry between 1961 and 1971. Surviving subjects completed a questionnaire, and the same questionnaire was sent to close relatives of the deceased. Details of the vital status of the participants were not given. It was reported that the incidence of snuff-taking in the case group did not differ from that found in a general survey. Among the 19 cases who had worked as joiners, two had taken snuff.

5.13.1.2 Brinton: USA - North Carolina/Virginia (1984)

Brinton et al., 1984 included patients, aged at least 18 years, diagnosed with primary malignancies of the nasal cavity and sinuses at four hospitals in North Carolina and Virginia between 1 January 1970 and 31 December 1980. For each case who was alive at the time of interview, two live hospital controls, matched on hospital, year of admission, age, sex, race and state economic area of usual residence, were selected. For deceased cases, one hospital control was identified in the same way, except that the control did not have to be alive. Another control series consisted of deceased individuals identified through state vital statistics offices. Matching criteria included age, sex, race, county of usual residence and year of death. Interviews were successfully completed for 160 patients and 290 controls, of whom 178 were hospital controls and 112 were death certificate controls. Interviews were only obtained directly from study subjects for 32.5% of the cases and 39.3% of the controls. Fifteen cases and 37 controls used chewing tobacco, and 23 cases and 28 controls used snuff. For the purposes of analysis, smokeless tobacco users were compared to all subjects who did not use the product in question as opposed to non-users of any form of tobacco.

The results of the study were as follows:

Tumour type	Chewing tobacco		Snuff	
	No.	RR[1] (95% CI)	No.	RR (95% CI)
Controls	37	-	28	-
All tumours of nasal cavity and sinuses	15	0.74 (0.4-1.5)	23	1.47 (0.8-2.8)
Squamous cell (n=86)	9	0.79	14	1.86
Adenocarcinoma (n=24)	2	0.64	6	3.06
Other (n=50)	4	0.58	3	0.59

[1] Relative risks are adjusted for sex

Although information was collected on other potential confounding factors, such as alcohol intake, no attempt was made to adjust the results of the study for anything other than sex.

5.13.2 Other epidemiological evidence

5.13.2.1 Acheson: UK - Oxfordshire (1968)

Acheson et al., 1968 reported on two groups of cases of carcinoma of the nasal cavity and accessory sinuses in residents within the Oxford Hospital Region. Group 1 consisted of 83 cases diagnosed during 1956-65, while group 2 was made up of 65 cases diagnosed either before or after this period. The source of cases in group 1 was the Oxford Cancer Register, while cases in group 2 occurring after 1965 were obtained either direct from the hospital or from the register. Earlier cases were ascertained from a search of death registers, a circular letter sent to all London hospitals treating patients for nasal cancer who gave an address in the study area, and a search of the diagnostic index of the Radcliffe Infirmary. In addition, letters were sent to all GPs practising in the area and claims for death benefit were also searched. No control group was selected. The main aim of the study was to examine the association between nasal cancer and employment in the woodworking industry, and so information on smokeless tobacco use was only collected for some of the cases. Among the 11 cases of adenocarcinoma for whom such data were available, three were ever users of snuff. In an updated report [Acheson, 1976], three snuff users were found among 17 cases of adenocarcinoma with data on smokeless tobacco use.

5.13.2.2 Redmond: UK - London (1970)

See section 3.4.1.

5.13.2.3 Acheson: UK - Northamptonshire (1976)

In the study by Acheson, 1976, a survey was set up to identify every case of nasal cancer diagnosed in Northamptonshire residents since 1951. A total of 61 patients were included, 39 men and 22 women. Twenty-six of the cases had worked in the boot and shoe industry at some time. No control group was collected, although incidence rates were compared with Northamptonshire men who were not employed in boot and shoe making, and men in the south of England. Information on smokeless tobacco use was only available for 26 cases, 8 of whom reported using snuff. Of these, five were boot and shoe workers, and three were employed in other industries.

5.13.3 Summary

Following earlier reports, in uncontrolled studies, of cases of nasal cancer in users of snuff, two case-control studies looked at the possible association between smokeless tobacco and this endpoint. One study was conducted in Sweden, and the other in the USA. Neither study excluded smokers from the analysis of smokeless tobacco use and neither carried out any form of adjustment for smoking. One study adjusted for sex, while the other did not adjust for any variables. Only two relative risks were reported, one of which was raised and one of which was below 1.00. Neither estimate reached statistical significance. The other study failed to find any association between nasal cancer and the use of smokeless tobacco.

Table 5.13.1: Summary of results for nasal cancer

Study	Non-users		Smokeless tobacco users		Product	Sex	RR	95% CI	Adjustment factors[a]
	Controls	Cases	Controls	Cases					
Brinton	249	144	37	15	Chew	M+F	0.74	0.4-1.5	Sex
	265	122	28	23	Snuff	M+F	1.47	0.8-2.8	
Engzell	-	-	-	-	Snuff	M	No association		None

[a] Where study presents multiple RR estimates, adjustment factors relate to all RRs unless otherwise stated

5.14 *Nervous system cancers*

5.14.1 Case-control/cross-sectional studies

5.14.1.1 Williams: USA (1977)

See section 3.3.1

5.14.2 Summary

Only one case-control study reported on cancers of the nervous system. Although this study included smokers of all tobacco products, only cigarette smoking was adjusted for during analysis. Other adjustment factors included age and race. The relative risk estimated for men was below 1.00, but that for women was substantially raised (14.99, 95% CI 3.52-63.87). The numbers of cases in smokeless tobacco users are so small in this study, three in men and women combined, that further information is clearly needed before any conclusions can be drawn.

Table 5.14.1: Summary of results for nervous system cancers

Study	Non-users		Smokeless tobacco users		Product[a]	Sex	RR	95% CI	Adjustment factors[b]	Notes[c]
	Controls	Cases	Controls	Cases						
Williams	1571	53	163	1	ST	M	0.45	0.06-3.30	Age, smoking, other	1
	3098	37	51	2	ST	F	14.99	3.52-63.87		1

[a] ST = smokeless tobacco
[b] Where study presents multiple RR estimates, adjustment factors relate to all RRs unless otherwise stated
[c] Key to notes:
[1] Relative risk estimated from data given

5.15 *Prostate cancer*

5.15.1 Prospective studies

5.15.1.1 Accortt: USA (2002)

See section 3.2.3

5.15.1.2 Bjelke: Norway/USA (1982)

Section 5.7.1.1 describes results for digestive cancers from two studies, one based on 12,495 Norwegian men and the other on 16,930 insured American men. In their monograph on tobacco habits other than smoking, International Agency for Research on Cancer, 1985 also give some results for prostate cancer. For the Norwegian men, they state that risk was unrelated to tobacco chewing or snuff use. For the US men, regular snuff use/chewing (but not former or occasional use) was linked to a relative risk of 2.2 for prostatic cancer (91 total deaths, 21 deaths in regular users), which was statistically significant, adjusting for age and urban-rural residence.

5.15.1.3 Hsing: USA (1990)

In this study [Hsing et al., 1990], 26,030 white male policy holders of the Lutheran Brotherhood Insurance Society, who were at least 35 years of age, received a questionnaire in 1966. The cohort was primarily from the upper midwest and north-eastern areas of the US, and approximately 30% of men were of Norwegian or other Scandinavian descent. There was also a higher proportion of rural inhabitants and farmers than for the general population. The cohort was followed-up for mortality for up to 20 years, or a total of 286,731 person-years. Cause of death was ascertained from death certificates. A total of 149 prostate cancer deaths occurred during the study period. No details were available for the numbers of subjects who used smokeless tobacco.

Relative risks for prostate cancer were estimated for various categories of smokeless tobacco use, as follows:

Ever tobacco use	No. of deaths	Person-years	Relative risk[1]	95% CI
Never any tobacco	19	58888	1.0	
Smokeless tobacco only	10	4025	4.5	2.1-9.7
Cigarettes only	22	48823	2.0	1.1-3.7
Cigarettes and smokeless tobacco	8	7613	2.9	1.3-6.5
Smokeless tobacco and pipes and/or cigars	4	2729	1.4	0.5-4.1
Cigarettes and smokeless tobacco and pipes and/or cigars	16	22896	1.6	0.8-3.1
Ever used smokeless tobacco[2]	42	41716	2.1[3]	1.1-4.1
Ex-users	13	14117	1.8	0.8-3.9
Occasional	5	8666	1.4	0.5-3.9
Regular	24	18934	2.4	1.3-4.9

[1] Adjusted for age
[2] Includes some smokeless tobacco users who used cigarettes
[3] Adjusted for cigarette smoking

A review of death certificates revealed a further 58 subjects for whom prostate cancer was not the underlying cause of death. These 58 cases were much older than the 149 fatal cases (median age at death 81 years vs. 73 years). Fourteen of the cases were regular users of smokeless tobacco, giving a relative risk estimate of 2.3 (95% CI 1.0-5.2). Eight of these subjects were exclusive users of smokeless tobacco, and their risk of prostate cancer was also elevated (RR = 2.5, 95% CI 1.0-6.5).

5.15.1.4 Hsing: USA (1991)

The second study by Hsing et al., 1991 was based on 293,916 veterans aged 31-84 years, who served in the US Armed Forces between 1917-1940 and held an active US government life insurance policy at the end of 1953, and who responded to questionnaires in 1954 or 1957 requesting detailed information on tobacco use. The Beneficiary Identification and Record Locator Subsystem of the Veterans Administration was used to determine mortality of the cohort during the 26-year follow-up period. During this time, certificates for 4607 deaths from prostate cancer were obtained. Details of the numbers of men using smokeless tobacco were not given. Among exclusive users of smokeless tobacco, there were 48 prostate cancer deaths, from which an age-adjusted relative risk of 1.17 (95% CI 0.88-1.56) was estimated, using the 1075 deaths in the group who never used any tobacco as a reference group.

5.15.2 Case-control/cross-sectional studies

5.15.2.1 Williams: USA (1977)

See section 3.3.1

5.15.2.2 Hayes: USA - Atlanta/Detroit/New Jersey (1994)

Cases for this study [Hayes et al., 1994] were men aged 40-79 years, newly diagnosed with pathologically confirmed prostate cancer in one of three study areas between 1 August 1986 and 30 April 1989, and were identified as part of a study of cancers of the oesophagus, pancreas, prostate and multiple myeloma. Population controls were selected in the three areas proportional to the expected age, gender and race distribution of the four cancer sites. Controls less than 65 years of age were selected by random digit dialling, while older controls were selected from records of the Health Care Financing Administration. In-person interviews were conducted with 981 prostate cancer cases and 1315 controls. In the case group, there were 174 never users of tobacco, 56 former and 14 current tobacco chewers, and 10 former and 10 current users of snuff. In the controls, never users of tobacco numbered 265, and there were 69 former and 33 current users of chewing tobacco and 17 former and 2 current users of snuff.

Odds ratios estimated for the various forms of smokeless tobacco were as follows:

Tobacco use	Blacks			Whites			Total
	Cases	Controls	OR[1] (95% CI)	Cases	Controls	OR[1] (95% CI)	OR[2] (95% CI)
Never used tobacco	88	116	1.0 (-)	86	149	1.0 (-)	1.0 (-)
Chewing tobacco							
Former	29	44	0.8 (0.4-1.4)	27	25	1.2 (0.6-2.3)	1.0 (0.6-1.5)
Current	8	19	0.4 (0.2-1.1)	6	14	0.5 (0.2-1.5)	0.5 (0.2-1.0)
Snuff							
Former	3	9	0.4 (0.1-1.4)	7	8	0.6 (0.2-2.1)	0.6 (0.3-1.4)
Current	7	2	4.7 (0.9-24.7)	3	0	- (-)	5.5 (1.2-26.2)

[1] Adjusted for age and study site
[2] Adjusted for age, race and study site

Although information on other potential confounders was collected, no attempt was made to adjust the results further for these factors. It was also not clear whether users of smokeless tobacco also used other forms of tobacco.

5.15.3 Summary

Data on prostate cancer risk in users of smokeless tobacco were available from six studies, four prospective and two of case-control design. Details of the studies are given in table 5.15.1. In two of the studies the analysis of smokeless tobacco use was restricted to lifelong non smokers of any product and in one to non smokers of cigarettes. The other three studies included smokers of all tobacco products. Two of these studies adjusted for cigarette smoking only, but the other made no attempt whatsoever to adjust for smoking. All of the studies adjusted for age, and four included various other potential confounders as well.

A summary of results for prostate cancer is given in table 5.15.2. Six of the seven relative risks reported were above 1.00, with three of them reaching statistical significance (5.5, 95% CI 1.2-26.2; 4.5, 95% CI 2.1-9.7; 2.2, 95% CI not estimated). The remaining risk estimate was reduced and of borderline significance (0.5, 95% CI 0.2-1.0). One study reported an association but did not present a relative risk.

Meta-analysis results are presented in table 5.15.3. Two analyses were carried out, one using relative risks for smokeless tobacco and snuff use, and one for smokeless tobacco and chewing tobacco. For smokeless tobacco/snuff, there was a significant relationship with the risk of prostate cancer, for both the fixed effects (1.38, 95% CI 1.13-1.69) and random effects (1.75, 95% CI 1.09-2.81) models. However, there was also significant heterogeneity between the studies included in this analysis ($p < 0.01$). When the analysis was based on risk estimates for smokeless tobacco and chewing tobacco use, only the result for the fixed effects model reached statistical significance (1.27, 95% CI 1.04-1.55). Again, there was a high degree of heterogeneity between the studies ($p < 0.003$).

Table 5.15.1: Summary of studies of prostate cancer

Study	Study Type	Location	Treatment of smoking in analysis		Other adjustment factors
			Smokers excluded	Smoking variables adjusted for	
Accortt	P	USA	Ever cigarette	-	Age, race, poverty index ratio
Bjelke	P	Norway/ USA	None	Cigarette smoking	Age, residence
Hayes	C-C	USA	None	None	Age, race, study site
Hsing 1990	P	USA	Ever smokers	-	Age
Hsing 1991	P	USA	Ever smokers	-	Age
Williams	C-C	USA	None	Cigarette smoking	Age, race

Table 5.15.2: Summary of results for prostate cancer

Study	Non-users		Smokeless tobacco users		Product[a]	RR	95% CI	Adjustment factors[b]	Notes[c]
	Controls	Cases	Controls	Cases					
Accortt	-	-	-	19	ST	1.2	0.5-3.4	Age, smoking, other	1
Bjelke								Age,	
- Norway	Total population 12945				ST	No association		smoking	
- USA	Total population 16930				ST	2.2	Significant	other	
Hayes	265	174	33	14	Chew	0.5	0.2-1.0	Age, other	
	265	174	2	10	Snuff	5.5	1.2-26.2		
Hsing 1990	58888	19	4025	10	ST	4.5	2.1-9.7	Age, smoking	2
Hsing 1991	-	1075	-	48	ST	1.17	0.88-1.56	Age, smoking	
Williams	1224	400	99	65	ST	1.32	0.94-1.84	Age, smoking, other	3

[a] ST = smokeless tobacco
[b] Adjustment for smoking includes studies restricted to non-smokers; refer to table 5.11.1 for full details of adjustment factors. Where study presents multiple RR estimates, adjustment factors relate to all RRs unless otherwise stated
[c] Key to notes:
1 Data came from Accortt et al., 2005
2 Person-years at risk
3 Relative risk estimated from data given

Table 5.15.3: Summary of meta-analysis results for prostate cancer studies

Tobacco product	No. of studies	Fixed effects estimate		Heterogeneity		Random effects estimate	
		RR	95% CI	chisquared	p value	RR	95% CI
Smokeless tobacco and snuff	5[1]	1.38	1.13-1.69	13.69	< 0.01	1.75	1.09-2.81
Smokeless tobacco and chewing tobacco	5[2]	1.27	1.04-1.55	16.04	< 0.003	1.33	0.83-2.13

[1] Combines results from all available studies, using results for snuff if results for separate types of smokeless tobacco are presented
[2] Combines results from all available studies, using results for chewing tobacco if results for separate types of smokeless tobacco are presented

5.16 *Skin cancer*

5.16.1 Prospective studies

5.16.1.1 Odenbro: Sweden (2005)

In the study by Odenbro et al., 2005 information was collected on construction workers through the industry's organization for health and safety, which provides outpatient health services. Entry into the cohort was defined as the first visit to the clinic, if it occurred during the years 1971-1975 or 1978-1992. A total of 337311 men were enrolled into the study, and completed a self-administered questionnaire. Follow-up lasted until 31 December 2000. A total of 756 incident cases of cutaneous squamous cell carcinoma occurred during this time. The proportion of subjects who had ever used snuff was 28%, while 13% were exclusive snuff users. A further 12% of the cohort used cigarettes and snuff.

Incidence rate ratios for cutaneous squamous cell carcinoma for various categories of snuff use were estimated as follows:

Tobacco variable	No. of cases	Person-years accumulated	Incidence rate ratio[1]	95% CI
Non-tobacco users	209	1920810	1.00	-
Snuff users	29	661150	0.64[2]	0.44-0.95
Years of snuff use:				
< 30	14	610320	0.79	0.46-1.38
30 +	15	44660	0.58	0.34-0.99
Mixed users	235	1607340	1.08[2]	0.90-1.30
Cigarette smokers	194	1947400	1.04[2]	0.85-1.26
Cigar smokers	9	42000	0.88[2]	0.45-1.71
Pipe smokers	80	358200	0.81[2]	0.62-1.05

[1] Adjusted for age
[2] Adjusted for all other tobacco categories

No attempt was made to adjust the results for other potential risk factors for cutaneous squamous cell carcinoma, including occupational exposure to sunlight.

5.16.2 Case-control/cross-sectional studies

5.16.2.1 Williams: USA (1977)

See section 3.3.1

5.16.3 Other epidemiological evidence

5.16.3.1 Root: USA - Minneapolis (1960)

Root et al., 1960 described the case history of a 58 year old man who had used snuff in the left ear daily to weekly since the age of 16. He subsequently presented with a squamous cell carcinoma in this ear, which occurred at the site where the snuff had been placed.

5.16.3.2 Sassolas: France (1989)

Sassolas et al., 1989 reported a case of basal cell carcinoma of the scalp in an 83 year old man who had used smokeless tobacco for over 40 years. The tumour arose in the location where the patient habitually kept his tobacco, under his hat. The tumour was removed, and the patient died a year later from heart disease, without the tumour re-appearing.

5.16.4 Summary

Two studies, one prospective and one case-control, provided information on the possible association between smokeless tobacco use and skin cancer. One study was conducted in Sweden, and the other in the USA. Although the analysis of smokeless tobacco use in the study by Odenbro et al., 2005 appeared to be restricted to lifelong non-smokers, adjustment for smoking of all tobacco products was still reported to be carried out. The other study [Williams & Horm, 1977] included smokers of cigarettes, cigars and pipes in the study group, but only adjusted for cigarette smoking during analysis. Both studies adjusted for age, and one also adjusted for race.

The results of the studies are summarized in table 5.16.1. The prospective study [Odenbro et al., 2005], based on 29 cases in smokeless tobacco users, reported a statistically significant reduced risk (0.64, 95% CI 0.44-0.95). The case-control study only included one case in smokeless tobacco users and adds little to the evidence.

Table 5.16.1: Summary of results for skin cancer

Study	Non-users		Smokeless tobacco users		Product[a]	Sex	RR	95% CI	Adjustment factors[b]	Notes[c]
	Controls	Cases	Controls	Cases						
Odenbro	1920810	209	661150	29	Snuff	M	0.64	0.44-0.95	Age, smoking	1,2
Williams	1591	33	163	1	ST	M	0.73	0.10-5.41	Age, smoking, race	3,4
	3080	55	53	0	ST	F	-	-		3,4,5

[a] ST = smokeless tobacco
[b] Where study presents multiple RR estimates, adjustment factors relate to all RRs unless otherwise stated
[c] Key to notes:
1 Person-years at risk
2 Data are for cutaneous squamous cell carcinoma
3 Relative risk estimated from data given
4 Data are for melanoma
5 Not estimated as no cases in smokeless tobacco users

5.17 *Thyroid gland cancer*

5.17.1 Case-control/cross-sectional studies

5.17.1.1 Williams: USA (1977)

See section 3.3.1

5.17.2 Summary

Only one case-control study examined the relationship between smokeless tobacco use and cancer of the thyroid gland. The study group contained smokers of cigarettes, cigars and pipes, but only cigarette smoking was adjusted for during analysis. Adjustment was also made for age and race. Only two cases of thyroid cancer were seen in smokeless tobacco users and no conclusions can be drawn.

Table 5.17.1: Summary of results for thyroid gland cancer

Study	Non-users		Smokeless tobacco users		Product[a]	Sex	RR	95% CI	Adjustment factors[b]	Notes[c]
	Controls	Cases	Controls	Cases						
Williams	1597	27	163	1	ST	M	0.57	0.08-4.21	Age, smoking, race	1
	3055	80	52	1	ST	F	1.64	0.22-12.00		1

[a] ST = smokeless tobacco
[b] Where study presents multiple RR estimates, adjustment factors relate to all RRs unless otherwise stated
[c] Key to notes:
1 Relative risk estimated from data given

5.18 *Other cancers*

5.18.1 Prospective studies

5.18.1.1 Henley: USA – CPS I and CPS II (2005)

See section 3.2.5

5.18.2 Case-control/cross-sectional studies

5.18.2.1 Vogler: USA - Atlanta (1962)

The original aim of the study by Vogler et al., 1962 was to examine risk factors for cancers of the mouth, pharynx and larynx. Therefore, all new adult patients and new and old mouth cancer cases coming to a clinic between January 1956 and July 1957 were either interviewed or completed a questionnaire. Four diagnostic groups were assigned, with the last two comprising all patients with cancers of sites other than mouth, pharynx or larynx, and patients without cancer whose mouth was not examined, who acted as controls. All patients were white and aged over 20 years. In the cancer of other sites group, there were 133 urban and 84 rural men and 210 urban and 144 rural women. In the non-cancer group, there were 141 urban and 44 rural men and 428 urban and 161 rural women. In men, numbers of tobacco chewers were not given, but from the graph presented it could be seen that in both urban and rural residents, the proportion of smokeless tobacco users was higher in the cancer patients than in the controls. There was no attempt to estimate the statistical significance of the differences. Among urban women, 5 cancer patients and 5 controls used smokeless tobacco, while 27 rural cancer patients and 16 rural controls were smokeless tobacco users. From this information, it was possible to estimate an overall relative risk of 2.89 (95% CI 1.63-5.11) for cancer in smokeless tobacco users compared to non-users. Adjustment for age and urban/rural residence reduced this estimate to 1.49 (95% CI 0.80-2.76). Although information was collected on alcohol consumption, it was not possible to adjust the results for this data.

5.18.2.2 Williams: USA (1977)

See section 3.3.1

5.18.3 Summary

Four studies, two prospective and two case-control, provided information on cancers of sites other than those already discussed above for a total of eight study populations. Details of these studies are given in table 5.18.1. Two of the studies were based only on lifelong non-smokers, while the other two included smokers of cigarettes, cigars and pipes. One of these studies adjusted for cigarette smoking only, but the other made no attempt to adjust for any smoking variables. All of the studies adjusted for age, and for at least one other variable.

The results of the studies are summarized in table 5.18.2. Five of the relative risks estimated were above 1.00, with two reaching statistical significance (1.49, 95% CI 1.04-2.14; 3.36, 95% CI 1.03-10.99). In addition, one study reported that smokeless tobacco use was more common in cases, but the significance of this finding was not reported. The remaining two risk estimates were non-significantly reduced. Because of the diverse nature of the endpoints considered by these studies, no attempt was made to meta-analyse these results.

Table 5.18.1: Summary of studies of other cancers

Study	Study Type	Location	Treatment of smoking in analysis		Other adjustment factors
			Smokers excluded	Smoking variables adjusted for	
Henley-CPS I	P	USA	Ever smokers	-	Age, race, education, BMI, exercise, alcohol intake, fat consumption, fruit/vegetable intake, aspirin use
Henley-CPS II	P	USA	Ever smokers	-	Age, race, education, BMI, exercise, alcohol intake, employment status and type, fat consumption, fruit/ vegetable intake, aspirin use
Vogler	C-C	USA	None	None	Age, rural/urban residence
Williams	C-C	USA	None	Cigarette smoking	Age, race

Table 5.18.2: Summary of results for other cancers

Study	Non-users		Smokeless tobacco users		Product[a]	Sex	RR	95% CI	Adjustment factors[b]	Notes[c]
	Controls	Cases	Controls	Cases						
Henley-CPS I	69662	631	7745	85	ST	M	0.90	0.71-1.14	Age, smoking, other	1,2
Henley-CPS II	111482	1022	2488	32	ST	M	1.49	1.04-2.14	Age, smoking, other	1,3
Vogler	Total population 402				ST	M	> 1.00		None	4
	568	322	21	32	ST	F	1.49	0.80-2.76	Age, other	4,5
Williams	1561	63	153	11	ST	M	1.64	0.85-3.18	Age, smoking, other	5,6
	3051	84	50	3	ST	F	3.36	1.03-10.99		5,6
	1569	55	160	4	ST	M	0.68	0.24-1.89		5,7
	3073	62	52	1	ST	F	1.77	0.24-12.97		5,7

[a] ST = smokeless tobacco

[b] Adjustment for smoking includes studies restricted to non-smokers; refer to table 5.18.1 for full details of adjustment factors. Where study presents multiple RR estimates, adjustment factors relate to all RRs unless otherwise stated

[c] Key to notes:

1 Number of controls refers to population at risk
2 Cancers of sites other than lung, digestive and genitourinary system
3 Cancers of sites other than lung, digestive and genitourinary system and haematopoietic cancers
4 Cancers of sites other than mouth, pharynx and larynx
5 Relative risk estimated from data given
6 Other primary cancers (see section 3.3.1 for full list of cancers not included among other primary cancers)
7 Primary cancers of unknown sites

5.19 *Summary for cancers*

The results for all cancers, and 16 separate types of cancer are summarized in table 5.19. Just over half of the 177 relative risks reported by the studies were raised, with 22 reaching statistical significance. Only six significantly reduced relative risks were estimated. For several endpoints, the majority of studies were based on extremely small numbers of cases who were also smokeless tobacco users.

Meta-analyses were carried out for a total of 26 endpoint/tobacco product combinations. Of these, 20 showed an increased risk of cancer in users of smokeless tobacco. However, the difference was significant only for oesophageal cancer in users of both smokeless tobacco and chewing tobacco, and for oesophageal and prostate cancers in users of smokeless tobacco and snuff. None of the reduced relative risks estimated was statistically significant. It should be noted that for many meta-analyses, the available data were very limited.

Apart from the significant increases seen for oesophageal cancer and prostate cancer in the meta-analyses, there were also a number of other sites where meta-analysis had not been performed due to too few studies being conducted, but where significant increases had been reported. These include the increases in connective tissue cancer [Zahm et al., 1989], bile duct cancer [Chow et al., 1994], cervical cancer and nervous system cancer [Williams & Horm, 1977]. None of these associations provide convincing evidence of a true effect of smokeless tobacco use bearing in mind the multiple endpoints considered, the relatively marginal significances seen, the weaknesses present in many of the epidemiological studies and the possibility of publication bias. Even if a true effect of smokeless tobacco emerges from further studies, it seems already clear that the association of cancer of sites other than the oral cavity with smokeless tobacco is much less than the association with tobacco smoking.

Table 5.19: Summary of results for cancer

Endpoint	No. of studies	Relative risk estimates S +	NS +	1.00	NS -	S -	Overall RR1	95% CI
All cancers	6	1	3	1[2]	0	1	1.01[3]	0.83-1.21
Bladder cancer	15	2	10[4]	0	12	0	0.99[5]	0.82-1.18
							0.75[6]	0.54-1.04
							1.02[3,7]	0.86-1.22
							0.97[8]	0.85-1.11
Brain cancer	1	0	0	4	0	0	Not performed	
Breast cancer	3	0	3	0	1	0	0.80[9]	0.46-1.40
Connective tissue cancer	3	1	0	0	1	0	Not performed	
All digestive cancers	5	1	2[2]	0	2	1	0.92[3]	0.65-1.30
Bile duct cancer	1	1	0	1	0	0	Not performed	
Colon cancer	3	0	3	2	0	0	1.24	0.996-1.53
Gall bladder cancer	1	0	1	0	0	0	Not performed	
Liver cancer	2	0	2[2]	0	0	0	Not performed	
Oesophageal cancer	12	1	10[2,4]	1	2[10]	0	1.37[7]	1.10-1.71
							1.43[8]	1.13-1.81
Pancreatic cancer	8	0	6[2]	0	2	1	1.13[3,7]	0.55-2.36
							1.12[8]	0.73-1.74
Rectal cancer	3	1	0	2	2	0	1.15[3]	0.56-2.37
Small intestine cancer	1	0	1	0	0	0	Not performed	
Stomach cancer	9	0	8[2]	5	1	0	1.19[7]	0.96-1.48
							1.09[8]	0.90-1.31
Female genital organ cancers	1	1	3	0	0	0	Not performed	
All haematopoietic cancers	1	0	0	0	1	0	Not performed	
All leukaemias	2	0	2	0	0	0	1.45	0.89-2.36
Acute lymphocyctic leukaemia	2	0	1	0	0	0	Not performed	
Chronic lymphocytic leukaemia	2	1	1	0	1	0	1.83	0.99-3.44
Acute granulocytic leukaemia	2	0	1	0	1	0	Not performed	
Chronic granulocytic leukaemia	2	0	1	0	0	0	Not performed	
Myelodysplasia	1	0	1	0	0	0	Not performed	
Other leukaemias	1	0	1	0	0	0	Not performed	
Hodgkin's lymphoma	2	0	1	0	1	0	0.93[3]	0.54-1.60
Non-Hodgkin's lymphoma	5	1	2	0	2	0	1.25[3]	0.73-2.14
Other lymphomas	1	0	1	0	0	0	Not performed	
Multiple myeloma	3	0	2	1	1	0	1.19	0.66-2.15
Kidney cancer	11	4	5	1	3	1	1.50[3,7]	0.89-2.53
							1.63[3,8]	0.995-2.67
Lung cancer	9	2	4	0	7[2]	1	1.05[3,7]	0.74-1.49
							1.08[3,8]	0.76-1.53
Male genital organ cancers	1	0	1	0	0	0	Not performed	
Nasal cancer	2	0	1	1	1	0	Not performed	
Nervous system cancers	1	1	0	0	1	0	Not performed	
Prostate cancer	5	2	3	0	1	0	1.33[3,7]	0.83-2.13
							1.75[3,8]	1.09-2.81
Skin cancer	2	0	0	0	1	1	Not performed	
Thyroid gland cancer	1	0	1	0	1	0	Not performed	
Other cancers	4	2	4[4]	0	2	0	Not performed	

NS = Non-significant; S = Significant

[1] Obtained from meta-analysis using fixed effects model
[2] Includes standardized mortality rate
[3] Significant heterogeneity between studies, therefore results from random effects model shown
[4] Includes observed higher prevalence in cases
[5] Chewing tobacco only
[6] Snuff only
[7] Smokeless tobacco and chewing tobacco
[8] Smokeless tobacco and snuff
[9] Female patients only
[10] Includes observed higher prevalence in controls

6. **Non-neoplastic diseases**

6.1 *Introduction*

In the sections that follow, for all non-neoplastic diseases other than oral and cardiovascular and for eight classifications of other diseases, studies providing relevant data are described and results summarized.

Table 6.1: Number of studies for non-neoplastic diseases

Section	Disease	Number of studies: Prospective	Number of studies: Case-control/ cross-sectional	Total
6.2	Diseases other than cancer or cardio-vascular disease	2	0	2
6.3	Endocrine, nutritional and metabolic diseases	4	4	8
6.4	Diseases of the nervous system and sense organs	2	1	3
6.5	Diseases of the musculoskeletal system	0	1	1
6.6	Diseases of the respiratory system	4	1	5
6.7	Diseases of the digestive system	4	2	6
6.8	Diseases of the genitourinary system	2	0	2
6.9	Adverse pregnancy outcomes	0	1	1
6.10	Sleep disturbances and anxiety symptoms	0	1	0

Finally, in section 6.11, the overall results are summarized.

6.2 *Diseases other than cancer or cardiovascular disease*

6.2.1 Prospective studies

6.2.1.1 Henley: USA (2005)

See section 3.2.5

6.2.2 Summary

Two prospective studies, both of which were conducted in the USA, investigated the relationship between smokeless tobacco use and all diseases other than cancer or cardiovascular disease combined. (Although this category will include some non-neoplastic oral diseases which are beyond the scope of this review, these results are considered here as non-oral diseases will form the great majority of the diseases considered.) Both studies were restricted to lifelong non-smokers, and both adjusted for age along with numerous other potentially confounding variables.

The results of the studies are summarized in table 6.2.1. In both studies, the relative risks estimated were above 1.00, and one of them reached statistical significance (1.17, 95% CI 1.06-1.30). Meta-analysis of these two results produced an overall risk estimate of 1.15 for both the fixed effects and random effects models, which was statistically significant (95% CI 1.06-1.24). There was no evidence of heterogeneity between the studies (heterogeneity chisquared = 0.402 on 1 d.f., p>0.1).

Table 6.2.1: Summary of results for diseases other than cancer or cardiovascular disease

Study	Non-users		Smokeless tobacco users		Product[a]	Sex	RR	95% CI	Adjustment factors[b]
	At risk	Cases	At risk	Cases					
Henley-CPS I	69662	2290	7745	507	ST	M	1.17	1.06-1.30	Age, smoking, other[1]
Henley-CPS II	111482	8712	2488	262	ST	M	1.11	0.97-1.25	Age, smoking, other[2]

[a] ST = smokeless tobacco
[b] Adjustment for smoking includes studies restricted to non-smokers; refer to footnotes for full details of adjustment factors.
[1] Race, education, BMI, exercise, alcohol intake, fat consumption, fruit/vegetable intake, aspirin use
[2] Race, education, BMI, exercise, alcohol intake, employment status and type, fat consumption, fruit/ vegetable intake, aspirin use

6.3 *Endocrine, nutritional and metabolic diseases and immunity disorders*

6.3.1 Prospective studies

6.3.1.1 Accortt/USA (2002)

See section 3.2.3

6.3.1.2 Eliasson: Sweden - Norbotten/Vasterbotten (2004)

In this study [Eliasson et al., 2004], information was collected during four population-based surveys of the MONICA study, in 1986, 1990, 1994 and 1999. Follow-up information on the first three cohorts was also obtained in 1999, giving follow-up periods of 5, 9 and 13 years, respectively. Subjects were randomly selected, stratified for age (25-64 years in first two surveys, 25-74 years in last two surveys) and sex, in two counties of Northern Sweden. The prevalence of self-reported clinically diagnosed diabetes was recorded and a randomly selected subset of subjects underwent a 75g oral glucose tolerance test after an overnight fast. Venous plasma glucose samples were also analysed. Analyses were restricted to men, and a total of 3384 took part in the study. There were 1203 never users of tobacco and 314 exclusive snus users.

The results of the study were as follows:

Tobacco use	No.	Known diabetes mellitus		Pathological glucose tolerance[1]	
		No.	Prevalence % (95% CI)	No.	Prevalence % (95% CI)
Never users	1203	29	2.4 (1.7-3.4)	35	8.2 (5.9-11.1)
Exclusive snus users	314	6	1.9 (0.9-4.1)	5	5.0 (2.2-11.2)
Exclusive smokers	414	17	4.1 (2.6-6.5)	11	7.9 (4.5-13.6)
Combined users	129	1	0.8 (0.1-4.3)	1	1.9 (0.3-10.1)
Smokers with history of snus use	106	5	4.8 (2.1-10.7)	1	3.4 (0.6-17.2)
Snus users with history of smoking	348	18	5.2 (3.3-8.0)	10	9.8 (5.4-17.1)
Ex-snus user, never smoked	161	5	3.1 (1.3-7.1)	6	10.2 (4.7-20.5)
Ex-smokers, ex-snus users	244	16	6.6 (4.1-10.4)	5	6.0 (2.6-13.3)
Ex-smokers, never used snus	475	30	6.3 (4.5-8.9)	24	14.5 (10.0-20.7)

[1] Based on 1158 men

Odds ratios, adjusted for age and waist circumference, were also estimated for known diabetes mellitus and pathological glucose tolerance:

Tobacco use	Known diabetes mellitus		Pathological glucose tolerance	
	OR[1] (95% CI)	OR[2] (95% CI)	OR[1] (95% CI)	OR[2] (95% CI)
Never users	1.00	1.00	1.00	1.00
Ever used snus exclusively	1.34 (0.65-2.73)	1.21 (0.59-2.49)	1.08 (0.52-2.23)	1.05 (0.51-2.17)
Current snus exclusively	1.18 (0.48-2.90)	1.06 (0.43-2.64)	0.78 (0.29-2.09)	0.78 (0.29-2.09)
Ex-snus user	1.58 (0.59-4.21)	1.45 (0.54-3.87)	1.57 (0.61-4.00)	1.48 (0.57-3.80)

1 Adjusted for age
2 Adjusted for age and waist circumference

Results were also available for the incidence of known diabetes mellitus during the follow-up period of the study, which averaged 8.5 years:

Tobacco use	No.	No. cases	% incidence (95% CI)
Consistent no use	585	6	1.0 (0.5-2.2)
Consistent exclusive snus users	103	0	0.0 (0.0-3.6)
Ex-snus users[1]	73	1	1.4 (0.2-7.4)
Smokers who switched to snus[2]	123	3	2.4 (0.8-6.9)
Consistent exclusive smokers	112	5	4.5 (1.9-10.0)

1 Snus users with no history of smoking who quit before baseline or during follow-up
2 Snus users with history of smoking either before or after baseline

Odds ratios, adjusted for various factors, were estimated for the incidence of diabetes mellitus during follow-up. No odds ratios could be calculated for exclusive snus users, due to a lack of cases:

Tobacco use	Odds ratios (95% CI)			
	1	2	3	4
Consistent no use	1.00	1.00	1.00	1.00
Ex-snus users	1.34 (0.16-11.3)	1.75 (0.20-15.1)	1.66 (0.19-14.7)	1.72 (0.20-14.8)
Smokers who switched to snus	2.41 (0.59-9.8)	3.24 (0.78-13.5)	3.08 (0.71-13.0)	3.25 (0.78-13.6)
Consistent exclusive smokers	4.51 (1.35-15.0)	4.63 (1.37-15.6)	5.37 (1.52-19.0)	4.61 (1.37-15.5)

[1] Adjusted for age
[2] Adjusted for age and follow-up
[3] Adjusted for age, follow-up and waist
[4] Adjusted for age, follow-up and annual percentage weight gain between baseline and follow-up

Odds ratios were also estimated for the incidence of impaired glucose tolerance, diabetes and pathological glucose tolerance, from the results of the oral glucose tolerance test:

Tobacco use	Normal GT	IGT		Diabetes		PGT	
		n	OR[1] (95% CI)	n	OR (95% CI)	n	OR (95% CI)
Consistent no use	217	32	1.00	6	1.00	38	1.00
Consistent exclusive snus users	38	1	0.23(0.03-1.80)	1	0.91(0.10-8.01)	2	0.45(0.10-2.04)
Ex-snus users	20	2	0.75(0.16-3.57)	3	3.97(0.86-18.33)	5	1.85(0.60-5.70)
Smokers who switched to snus	47	9	1.18(0.51-2.74)	0	0	9	1.05(0.46-2.44)
Consistent exclusive smokers	25	3	0.68(0.19-2.44)	1	0.66(0.08-5.58)	4	0.77(0.25-2.41)

GT = glucose tolerance; IGT = Impaired glucose tolerance; PGT = Pathological glucose tolerance
[1] Odds ratios adjusted for age, waist and length of the follow-up period

Further adjustment, for leisure time physical activity and alcohol consumption did not change the direction of the estimates or the significance of the odds ratios for either clinically diagnosed diabetes mellitus or pathological glucose tolerance.

6.3.1.3 Henley: USA (2005)

See section 3.2.5

6.3.2 Case-control/cross-sectional studies

6.3.2.1 Eliasson: Sweden (1991)

In the study by Eliasson et al., 1991, male volunteers, aged 31 years or less, were recruited from populations of university students and teachers, and also from newspaper advertisements. There were 18 non-tobacco users and 21 snuff users, five of whom were ex-smokers. All subjects underwent a physical examination and completed a lifestyle questionnaire. Blood glucose levels were almost identical in snuff users (4.3 mmol/l) and non-tobacco users (4.4 mmol/l). However, serum insulin was significantly higher in the snuff users (5.5 mU/l) than in the non-users (3.6 mU/l, $p < 0.01$). These results did not appear to have been adjusted for any potentially confounding variables.

6.3.2.2 Eliasson: Sweden (1995)

Participants in the study by Eliasson et al., 1995 were drawn from the Northern Sweden MONICA Project, and may have been included in the study by Eliasson et al., 2004 described above. In January-April 1990 a total of 2000 subjects, aged 25-64 years, were invited to undergo screening for cardiovascular risk factors. Of those who chose to participate, 754 underwent a 75g oral glucose tolerance test after an overnight fast. Data on insulin values were available for 125 male non-tobacco users and 42 snuff users. Although there were also 12 women who used snuff, they were excluded from further analysis. It was reported that, in men, fasting and post-load glucose levels were not related to smoking habits, but detailed information was not given. The mean fasting insulin level was 6.2 mU/l (95% CI 5.6-6.7) in men who were non-tobacco users, compared to 5.8 mU/l (95% CI 4.9-7.0) in male snuff users. This difference did not reach statistical significance. Post-load insulin levels

were 25.0 mU/l (95% CI 21.5-29.0) and 20.6 mU/l (95% CI 15.9-26.8) in non-tobacco and snuff users, respectively. Again, this difference was not significant.

6.3.2.3 Persson: Sweden - Stockholm (2000)

The study by Persson et al., 2000 was carried out in men aged 35-56 years who were resident in four suburban municipalities of Stockholm. A selection procedure was used which ensured that about 50% of the participants had a strong family history of diabetes. Subjects were invited to take part in a health examination, during which an oral glucose tolerance test was performed, and to complete a questionnaire. A total of 3128 men completed the study. Type 2 diabetes and impaired glucose tolerance were diagnosed in 55 and 172 men, respectively.

Results for the study were as follows:

Tobacco use	Normal glucose tolerance	Impaired glucose tolerance			Type 2 diabetes		
	No.	No.	OR[1]	95% CI	No.	OR[1]	95% CI
Never used snuff	1915	121	1.0	-	34	1.0	-
Former snuff user	376	19	0.7	0.4-1.2	5	0.8	0.3-2.0
Current snuff user	492	26	0.8	0.5-1.3	13	1.5	0.8-3.0
≤ 2 boxes per week	235	10	0.7	0.4-1.4	1	0.2	0.0-2.0
3+ boxes per week	256	15	0.8	0.4-1.4	12	2.7	1.3-5.5
Current snuff only user	121	6	0.9	0.4-2.1	4	3.9	1.1-14.3

[1] Adjusted for age, body mass index, family history of diabetes, physical activity and alcohol consumption

Results were also available for insulin resistance and two-hour insulin response, although these analyses were restricted to men with impaired glucose tolerance:

Tobacco use	Normal glucose tolerance	Highest tertile of insulin resistance[1]			Lowest tertile of 2hr insulin response[2]		
	No.	No.	OR[3]	95% CI	No.	OR[1]	95% CI
Never used snuff	1915	37	1.0	-	28	1.0	-
Former snuff user	376	3	0.4	0.1-1.3	12	2.2	1.1-4.4
Current snuff user	492	9	0.9	0.4-2.0	8	1.2	0.5-2.8
≤ 2 boxes per week	471	4	0.5	0.2-1.6	13	2.1	1.1-4.1
3+ boxes per week	388	7	0.7	0.3-1.7	7	1.2	0.5-2.9

[1] ≥161.1
[2] ≤71.9 m U L^{-1}
[3] Adjusted for age, body mass index, family history of diabetes, physical activity and alcohol consumption

6.3.2.4 Wallenfeldt: Sweden (2001)

Participants in the study by Wallenfeldt et al., 2001 consisted of 58-year old men of Swedish ancestry, who were randomly selected from the general population and invited to a screening examination. All of the men with low and high insulin sensitivity, and every fifth man with intermediate sensitivity, were included in further examinations, during which a blood sample was taken and a self-administered questionnaire was completed. A total of 391 men took part in the study. Within this group, there were 310 never users of snuff, 33 ex-users and 48 current snuff users.

Relative risks were not estimated, but mean levels of fasting blood glucose and plasma insulin were reported as follows:

	Never users		Ex-users		Current users		p-value
	Mean	SD	Mean	SD	Mean	SD	
Fasting blood glucose (mmol/l)	4.88	1.08	4.70	0.47	5.22	1.96	NS
Plasma insulin (μU/ml)	9.70	6.13	11.10	6.68	11.09	6.93	NS

Fourteen of the current snuff users were also current smokers. Re-analysis of the data with these 14 subjects excluded did not alter the results above. There was no correlation between snuff-years and either fasting blood glucose or plasma insulin levels.

6.3.3 Summary

Details of the eight studies that considered this endpoint are given in table 6.3.1. Four of the studies were prospective, and four were cross-sectional in design. For two of the studies the analysis of smokeless tobacco use was restricted to never smokers of any product and in one the restriction was to those who had never smoked cigarettes. The other five studies excluded current but not former smokers. No study carried out any form of adjustment for smoking during analysis. Five of the studies adjusted their results for age, and for various other potential confounders.

A summary of the results from the individual studies is given in table 6.3.2. Results for each endpoint are discussed below.

6.3.3.1 All endocrine, nutritional, metabolic and immunity diseases

Only one prospective study [Accortt et al., 2002} provided data on this endpoint in relation to smokeless tobacco use. For both men and women, a non-significantly raised relative risk was estimated.

The combined relative risk for this endpoint was estimated at 2.14 (95% CI 0.70-6.60) for both the fixed and random effects models, and there was no evidence of heterogeneity between the risk estimates included in this analysis (heterogeneity chisquared = 0.15 on 1 d.f., p>0.1).

6.3.3.2 Diabetes mellitus

Four studies, three prospective and one cross-sectional, investigated the incidence of diabetes mellitus in relation to usage of smokeless tobacco, with one prospective study giving results both for the prevalence of diabetes mellitus at baseline, and for the incidence of new cases during follow-up. Three of the relative risks presented were above 1.00, although only one reached statistical significance (3.9, 95% CI 1.1-14.3). The remaining risk estimate was non-significantly reduced.

Using a fixed effects model, meta-analysis of the available relative risks produced an overall risk estimate of 1.09 (95% CI 0.76-1.56). A random effects model gave a result of 1.16 (95% CI 0.72-1.87). There was no evidence of significant heterogeneity between the studies included in this analysis (heterogeneity chisquared = 4.48 on 3 d.f., p>0.1).

6.3.3.3 Insulin levels

Three cross-sectional studies reported insulin levels in users and non-users of smokeless tobacco. Two of the studies found that insulin levels were higher in snuff users than in non-users, and in one of the studies, the difference reached statistical significance. In the other study, levels were lower in subjects who used smokeless tobacco.

Table 6.3.1: Summary of studies of endocrine, nutritional and metabolic diseases and immunity disorders

Study	Study Type	Location	Treatment of smoking in analysis		Other adjustment factors
			Smokers excluded	Smoking variables adjusted for	
Accortt	P	USA	Ever cigarette	-	Age, race, poverty index ratio
Eliasson 1991	C-S	Sweden	Current smokers	None	None
Eliasson 1995	C-S	Sweden	Current smokers	None	None
Eliasson 2004	P	Sweden	Current smokers	None	Age, waist circumference
Henley-CPS I	P	USA	Ever smokers	-	Age, race, education, BMI, exercise, alcohol intake, fat consumption, fruit/vegetable intake, aspirin use
Henley-CPS II	P	USA	Ever smokers	-	Age, race education, BMI, exercise, alcohol intake, employment status and type, fat consumption, fruit/ vegetable intake, aspirin use
Persson	C-S	Sweden	Current smokers	None	Age, BMI, family history of diabetes, physical activity, alcohol intake
Wallenfeldt	C-S	Sweden	Current smokers	None	None

Table 6.3.2: Summary of results for endocrine, nutritional and metabolic diseases and immunity disorders

Study	Non-users		Smokeless tobacco users		Product[a]	Sex	RR	95% CI	Adjustment factors[b]	Notes[c]
	Controls	Cases	Controls	Cases						
All endocrine, nutritional, metabolic and immunity diseases:										
Accortt	-	-	-	-	ST	M	2.4	0.7-8.8	Age, smoking, other	
	-	-	-	-	ST	F	1.4	0.1-13.5		
Diabetes mellitus:										
Eliasson 2004	-	-	-	-	Snuff	M	1.06	0.43-2.64	Age, smoking, other	1
	585	6	103	0	Snuff	M	-	-	Smoking	2,3,4
Henley-CPS I	69662	97	7745	20	ST	M	0.88	0.53-1.47	Age, smoking, other	2
Henley-CPS II	111482	250	2488	8	ST	M	1.12	0.55-2.29	Age, smoking, other	2
Persson	1915	34	121	4	Snuff	M	3.9	1.1-14.3	Age, smoking, other	
Insulin levels:										
Eliasson 1991	18	-	21	-	Snuff	M	Serum insulin significantly higher in snuff users		None	
Eliasson 1995	125	-	42	-	Snuff	M	Fasting and post-load insulin levels non significantly higher in non-tobacco users		None	
Wallenfeldt	310	-	48	-	Snuff	M	Plasma insulin levels non significantly higher in current snuff users		Smoking	

[a] ST = smokeless tobacco

[b] Adjustment for smoking includes studies restricted to non-smokers; refer to table 5.11.1 for full details of adjustment factors. Where study presents multiple RR estimates, adjustment factors relate to all RRs unless otherwise stated

[c] Key to notes:

1 Known diabetes mellitus at baseline

2 Number of controls refers to population at risk

3 Incident cases of diabetes mellitus during follow-up

4 Not estimated as no cases in smokeless tobacco users

6.4 *Diseases of the nervous system and sense organs*

6.4.1 Prospective studies

6.41.1 Accortt: USA (2002)

See section 3.2.3

6.4.1.2 O'Reilly: USA – CPS II (2005)

The study by O'Reilly et al., 2005 was based on 95,981 never-smoking men who were participants in the second Cancer Prevention Study (CPS II). Subjects with a history of stroke or any other serious illness at baseline were excluded. Information on smokeless tobacco use was collected at enrolment, and was not updated during follow-up. The study ran from 1 January 1989 until 31 December 1998. A total of 459 men had Parkinson's Disease listed in their death certificates as an underlying or contributing cause of death. Of these, 452 were never users of smokeless tobacco, 4 were former users, and 3 were current users.

The results of the study were as follows:

Smokeless tobacco use	Person-years	No. of deaths	Age-adjusted RR (95% CI)	Multivariate[1]-adjusted RR (95% CI)
Never	870751	452	-	-
Past	5734	4	0.81 (0.30-2.17)	0.86 (0.32-2.31)
Current	21384	3	0.22 (0.07-0.67)	0.24 (0.08-0.75)

[1] Adjusted for age, coffee and alcohol intake, and education

A limitation of this study is the incompleteness of reporting of Parkinson's disease in death certificates, which is estimated at only 70-75%.

6.4.2 Case-control/cross-sectional studies

6.4.2.1 Benedetti: USA - Olmsted County (2000)

The case group in the study by Benedetti et al., 2000 consisted of all subjects residing in Olmsted County, MN, who developed Parkinson's disease during the period 1976-1995. Each case was individually matched by age and sex to a general population control subject who resided in the study area and was free of all symptoms of Parkinson's disease, other parkinsonism or tremor of any type. A total of 196 cases and an equal number of controls took part in the study. Information on smoking was abstracted from medical records, and the reliability of these data was assessed by interviewing a subsample of cases and controls. Two cases and 11 controls reported ever using smokeless tobacco. The relative risk for Parkinson's disease in ever users of smokeless tobacco compared to never users was estimated at 0.18 (95% CI 0.04-0.82). This estimate accounted for the matching factors, but did not appear to have been adjusted for other factors, despite such information having been collected.

6.4.3 Summary

Three studies, two prospective and one case-control in design, investigated the relationship between smokeless tobacco use and diseases of the nervous system and sense organs. All three of the studies were conducted in the USA. In one of the studies [O'Reilly et al., 2005] the analysis of smokeless tobacco was restricted to non smokers of any product, while for another [Accortt et al., 2002] it was restricted to non smokers of cigarettes. In the remaining study [Benedetti et al., 2000], smokers of cigarettes, cigars and pipes were included, with no form of adjustment for this carried out. All of the studies adjusted for age, and for various other factors.

A summary of the results of these studies is given in table 6.4.1, and results for each endpoint are discussed individually below.

6.4.3.1 All diseases of the nervous system and sense organs

One prospective study investigated the relationship between smokeless tobacco use and this endpoint. While men who used smokeless tobacco had an increased risk of these diseases, in women, the risk was reduced. However, in neither sex did the findings reach statistical significance.

Although the relative risk estimated from meta-analysis of these results was reduced, at 0.81, it too failed to reach statistical significance (95% CI 0.26-2.57), and there was no significant heterogeneity among the risk estimates included in this analysis (heterogeneity chisquared = 0.27 on 1 d.f., $p>0.1$).

6.4.3.2 Parkinson's disease

One prospective and one case-control study presented data on the possible association between smokeless tobacco use and Parkinson's disease. Both of the studies found a markedly significantly reduced risk of the disease in smokeless tobacco users compared to non-users (0.18, 95% CI 0.04-0.82; 0.24, 95% CI 0.08-0.75).

A meta-analysis of these findings gave a risk estimate of 0.22, which was highly statistically significant (95% CI 0.09-0.53). There was no evidence of heterogeneity between the two studies (heterogeneity chisquared = 0.09 on 1 d.f., $p>0.1$).

Table 6.4.1: Summary of results for diseases of the nervous system and sense organs

Study	Non-users		Smokeless tobacco users		Product[a]	Sex	RR	95% CI	Adjustment factors[b]	Notes[c]
	Controls	Cases	Controls	Cases						
All diseases of the nervous system and sense organs:										
Accortt	-	-	-	-	ST	M	1.1	0.2-5.2	Age, smoking, other	1
	-	-	-	-	ST	F	0.6	0.1-2.6		
Parkinson's disease:										
Benedetti	167	176	11	2	ST	M+F	0.18	0.04-0.82	Age, other	2
O'Reilly	870751	452	21384	3	ST	M	0.24	0.08-0.75	Age, smoking, other	3,4

[a] ST = smokeless tobacco

[b] Adjustment for smoking includes studies restricted to non-smokers. Where study presents multiple RR estimates, adjustment factors relate to all RRs unless otherwise stated

[c] Key to notes:

1 Other adjustment factors include race and poverty index

2 Other adjustment factor includes sex

3 Number of controls refers to person-years at risk

4 Other adjustment factors include coffee and alcohol intake and education

6.5 *Diseases of the musculoskeletal system*

6.5.1 Case-control/cross-sectional studies

6.5.1.1 Bolinder: Sweden (1992)

See section 3.3.3.

6.5.2 Summary

Only one cross-sectional study gave information on the relationship between smokeless tobacco use and diseases of the musculoskeletal system. The study was restricted to lifelong non-smokers. The relative risk estimates were either adjusted for age, or results for separate age groups were presented.

A summary of the available results is given in table 6.5.1. All of the relative risks estimated were significantly raised for users of smokeless tobacco compared to non-users (disability pension for musculoskeletal diagnosis, age 46-55 years: 2.8, 95% CI 1.6-4.8; age 56-65 years: 1.5, 95% CI 1.2-1.8), although for low back pain in the previous year, the result was of borderline significance (1.1, 95% CI 1.0-1.2).

Meta-analysis of the results for disability pension for musculoskeletal diagnosis gave an overall risk estimate of 1.62 (95% CI 1.34-1.96) for the fixed effects model, and 1.94 (95% CI 1.06-3.55) for the random effects model. There was a significant degree of heterogeneity between these two risk estimates (heterogeneity chisquared = 4.365 on 2 d.f., $p < 0.05$).

Table 6.5.1: Summary of results for diseases of the musculoskeletal system

Study	Non-users		Smokeless tobacco users		Product[a]	Sex	RR	95% CI	Adjustment factors[b]	Notes[c]
	Controls	Cases	Controls	Cases						
Bolinder	18630	5255	Total 5014		ST	M	1.1	1.0-1.2	Age, smoking	1
	-	43	-	20	ST	M	2.8	1.6-4.8		2,3
	-	318	-	149	ST	M	1.5	1.2-1.8		2,4

[a] ST = smokeless tobacco

[b] Adjustment for smoking includes studies restricted to non-smokers. Where study presents multiple RR estimates, adjustment factors relate to all RRs unless otherwise stated

[c] Key to notes:
1 Low back pain in past year
2 Disability pension for musculoskeletal diagnosis
3 Aged 46-55 years
4 Aged 56-65 years

6.6 *Diseases of the respiratory system*

6.6.1 Prospective studies

6.6.1.1 Winn: USA (1982)

See section 3.2.1

6.6.1.2 Accortt/USA (2002)

See section 3.2.3

6.6.1.3 Henley: USA – CPS I and CPS II (2005)

See section 3.2.5

6.6.2 Case-control/cross-sectional studies

6.6.2.1 Bolinder: Sweden (1992)

See section 3.3.3

6.6.3 Summary

Five studies looked at the possible relationship between smokeless tobacco use and respiratory diseases, and details of them are given in table 6.6.1. Four of the studies were prospective, and one was cross-sectional in design. In four of the studies the analysis of smokeless tobacco use was restricted to lifelong non smokers of any product, and in one it was restricted to non smokers of cigarettes. Four of the studies adjusted their results for age, and three of these also adjusted for various other factors. While the fifth study also appeared to have carried out adjustment, the factors included were not stated.

Results of the individual studies and of meta-analyses are summarized in tables 6.6.2 and 6.6.3 respectively, and are discussed for each endpoint below.

6.6.3.1 All diseases of the respiratory system

Three prospective studies investigated the relationship between smokeless tobacco use and all diseases of the respiratory system combined. Two of the four relative risks presented were above 1.00, one of them significantly so (1.28, 95% CI 1.03-1.59). The remaining risk estimates were non-significantly reduced. Meta-analysis of the relative risks produced an overall risk estimate of 1.19 (95% CI 1.01-1.41), for both the fixed and random effects models.

6.6.3.2 Chronic obstructive pulmonary disease

Two prospective studies reported on the incidence of this endpoint in relation to smokeless tobacco use. Both of the relative risks estimated were raised, and one reached statistical significance (1.86, 95% CI 1.12-3.06). Meta-analysis gave an overall relative risk of 1.59 (95% CI 1.08-2.33), using either a fixed effects or random effects model.

6.6.3.3 Influenza and pneumonia

The incidence of these endpoints in relation to smokeless tobacco use was investigated by two prospective studies. In one study, the risk of influenza and pneumonia was increased in users of smokeless tobacco compared to non-users, while in the other study it was reduced. However, in neither study did the difference reach statistical significance. Meta-analysis of these results provided no evidence of an

association between smokeless tobacco and influenza and pneumonia (1.06, 95% CI 0.84-1.33).

6.6.3.4 Tuberculosis

One prospective study reported a standardized mortality rate of 148 for tuberculosis in users of smokeless tobacco compared to non-users. However, there was no attempt to estimate the significance of this finding.

6.6.3.5 Other respiratory symptoms

One cross-sectional study investigated the prevalence of various respiratory symptoms in relation to smokeless tobacco use. For each of the endpoints considered, a significantly increased relative risk was reported for users of smokeless tobacco compared to non-users (cough in the morning: 2.1, 95% CI 1.8-2.4; more than 3 months cough/year: 1.4, 95% CI 1.1-1.7; breathlessness on slight effort: 1.4, 95% CI 1.3-1.6).

Table 6.6.1: Summary of studies of diseases of the respiratory system

Study	Study Type	Location	Smokers excluded	Other adjustment factors
Accortt	P	USA	Ever cigarette	Age, race, poverty index ratio
Bolinder	C-S	Sweden	Ever smokers	Age
Henley-CPS I	P	USA	Ever smokers	Age, race, education, BMI, exercise, alcohol intake, fat consumption, fruit/vegetable intake, aspirin use
Henley-CPS II	P	USA	Ever smokers	Age, race education, BMI, exercise, alcohol intake, employment status and type, fat consumption, fruit/ vegetable intake, aspirin use
Winn	P	USA	Ever smokers	Not stated

Table 6.6.2: Summary of results for diseases of the respiratory system

Study	Non-users		Smokeless tobacco users		Product[a]	Sex	RR	95% CI	Adjustment factors[b]	Notes[c]
	Controls	Cases	Controls	Cases						
All diseases of the respiratory system:										
Accortt	-	-	-	-	ST	M	0.9	0.3-2.5	Age, smoking, other	
	-	-	-	-	ST	F	0.6	0.1-2.3		
Henley-CPS I	69662	433	7745	123	ST	M	1.28	1.03-1.59	Age, smoking, other	1
Henley-CPS II	111482	1685	2488	56	ST	M	1.11	0.84-1.45	Age, smoking, other	1
Chronic obstructive pulmonary disease:										
Henley-CPS I	69662	65	7745	25	ST	M	1.86	1.12-3.06	Age, smoking, other	1
Henley-CPS II	111482	269	2488	12	ST	M	1.28	0.71-2.32	Age, smoking, other	1
Influenza and pneumonia:										
Henley-CPS I	69662	299	7745	79	ST	M	1.16	0.88-1.51	Age, smoking, other	1
Henley-CPS II	111482	930	2488	24	ST	M	0.85	0.56-1.29	Age, smoking, other	1
Tuberculosis:										
Winn	Total population ~300,000				ST	M	1.48	-	Smoking, others not stated	2
Other respiratory symptoms:										
Bolinder	23168	717	Total 5014		ST	M	2.1	1.8-2.4	Age, smoking	3
	23383	502	Total 5014		ST	M	1.4	1.1-1.7		4
	22906	979	Total 5014		ST	M	1.4	1.3-1.6		5

[a] ST = smokeless tobacco

[b] Adjustment for smoking includes studies restricted to non-smokers; refer to table 6.6.1 for full details of adjustment factors. Where study presents multiple RR estimates, adjustment factors relate to all RRs unless otherwise stated

[c] Key to notes:

1 Number of controls refers to population at risk
2 Standardized mortality ratio/100
3 Cough in the morning
4 More than 3 months cough/year
5 Breathlessness on slight effort

Table 6.6.3: Summary of meta-analysis results for studies of diseases of the respiratory system

Endpoint	No. of studies	Fixed effects estimate RR	95% CI	Heterogeneity chisquared	p value	Random effects estimate RR	95% CI
All respiratory diseases	4	1.19	1.01-1.41	1.68	NS	1.19	1.01-1.41
COPD	2	1.59	1.08-2.33	0.89	NS	1.59	1.08-2.33
Influenza/pneumonia	2	1.06	0.84-1.33	1.50	NS	1.04	0.77-1.39

6.7 *Diseases of the digestive system*

6.7.1 Prospective studies

6.7.1.1 Winn: USA (1982)

See section 3.2.1

6.7.1.2 Accortt/USA (2002)

See section 3.2.3

6.7.1.3 Henley: USA – CPS I and CPS II (2005)

See section 3.2.5

6.7.2 Case-control/cross-sectional studies

6.7.2.1 Bolinder: Sweden (1992)

See section 3.3.3

6.7.2.2 Persson: Sweden - Stockholm (1993)

Cases in this study [Persson et al., 1993] were selected from a central register of all hospital admissions in Stockholm County, and consisted of 60 men with Crohn's disease and 82 men with ulcerative colitis. The control group of 145 men was selected as part of a random sample, stratified by age and sex, from a register of inhabitants of the study area. Each participant received a questionnaire. Oral moist snuff use was reported by 16 men with Crohn's disease, 24 men with ulcerative colitis, and 21 controls.

Relative risks were estimated for Crohn's disease in relation to cigarette smoking and oral snuff use jointly as follows:

Cigarette use	Moist snuff use: Never			Ever			All[1]		
	Cases	Controls	RR (95% CI)	Cases	Controls	RR (95% CI)	Cases	Controls	RR (95% CI)
Never	22	61	1.0	5	11	0.9 (0.3-3.1)	27	72	1.0
Former	6	17	1.1 (0.4-3.3)	3	5	1.8 (0.3-8.9)	9	22	1.2 (0.5-3.1)
Current	16	46	1.1 (0.5-2.3)	8	5	3.7 (1.1-13.1)	24	51	1.3 (0.7-2.7)
All	44	124	1.0	16	21	2.1 (1.0-4.6)			
			1.0			2.1 (1.0-4.6)[2]			

[1] Adjusted for age and snuff use
[2] Adjusted for age and cigarette smoking

Relative risks were also presented for ulcerative colitis:

Cigarette use	Moist snuff use: Never			Ever			All[1]		
	Cases	Controls	RR (95% CI)	Cases	Controls	RR (95% CI)	Cases	Controls	RR (95% CI)
Never	31	61	1.0	9	11	1.1 (0.4-3.1)	40	72	1.0
Former	10	17	1.3 (0.5-3.4)	6	5	2.3 (0.6-8.9)	16	22	1.5 (0.7-3.4)
Current	17	46	0.7 (0.3-1.5)	9	5	3.3 (1.0-10.9)	26	51	0.9 (0.5-1.8)
All	58	124	1.0	24	21	2.3 (1.1-4.5)			
			1.0			2.2 (1.1-4.4)[2]			

[1] Adjusted for age and snuff use
[2] Adjusted for age and cigarette smoking

Although information on other potentially confounding factors was collected, there was no attempt to adjust the results for any of these variables.

6.7.3 Summary

Details of the six studies that provided information on this endpoint are given in table 6.7.1. Four of the studies were prospective, one was cross-sectional and one was a case-control study. In five of the studies the analysis of smokeless tobacco use was restricted to lifelong non smokers of any product and in one it was restricted to non smokers of cigarettes. Four of the studies adjusted their results for age, and three of these studies also carried out adjustment for various other potentially confounding variables. In another study, adjustment appeared to have taken place, but the factors adjusted for were not stated.

Tables 6.7.2 and 6.7.3 present a summary of the results of the individual studies and of meta-analyses respectively. Below, results for each separate endpoint are considered.

6.7.3.1 All diseases of the digestive system

Three prospective studies presented data relating to the possible association between usage of smokeless tobacco and all diseases of the digestive system combined. All three of the relative risks reported were above 1.00, but only one reached statistical significance (1.49, 95% CI 1.14-1.93). Meta-analysis showed that there was a significantly positive relationship between smokeless tobacco use and the risk of all diseases of the digestive system, producing an overall risk estimate of 1.46 (95% CI 1.18-1.82) for both fixed and random effects models.

6.7.3.2 Colitis and other intestinal diseases

Two prospective studies and one case-control study gave information relevant to this endpoint in smokeless tobacco users. All three of the relative risks estimated were above 1.00, but none was significantly so. There was no evidence of a significant association between smokeless tobacco use and colitis when the results were meta-analysed (1.27, 95% CI 0.93-1.72).

6.7.3.3 Heartburn

One cross-sectional study reported a significantly reduced relative risk for the prevalence of heartburn in smokeless tobacco users compared to non-users (0.9, 95% CI 0.8-0.9).

6.7.3.4 Liver cirrhosis

The possible association between liver cirrhosis and smokeless tobacco use was investigated by three prospective studies. Both of the relative risks estimated were raised, but only one was significantly so (3.02, 95% CI 1.60-5.69). In addition, one study reported a standardized mortality rate of 294 for this endpoint in smokeless tobacco users compared to non-users, although no confidence interval or p value was given for this finding. Using a fixed effects model, meta-analysis gave an overall relative risk of 2.00 (95% CI 1.33-3.02). The result for the random effects model was 2.08 (95% CI 1.04-4.15).

6.7.3.5 Peptic ulcer

The single cross-sectional study that investigated this endpoint reported a non-significantly increased relative risk for peptic ulcer in users of smokeless tobacco compared to non-users.

Table 6.7.1: Summary of studies of diseases of the digestive system

Study	Study Type	Location	Smokers excluded	Other adjustment factors
Accortt	P	USA	Ever cigarette	Age, race, poverty index ratio
Bolinder	C-S	Sweden	Ever smokers	Age
Henley-CPS I	P	USA	Ever smokers	Age, race, education, BMI, exercise, alcohol intake, fat consumption, fruit/vegetable intake, aspirin use
Henley-CPS II	P	USA	Ever smokers	Age, race education, BMI, exercise, alcohol intake, employment status and type, fat consumption, fruit/ vegetable intake, aspirin use
Persson	C-C	Sweden	Ever smokers	None
Winn	P	USA	Ever smokers	Not stated

Table 6.7.2: Summary of results for diseases of the digestive system

Study	Non-users		Smokeless tobacco users		Product[a]	Sex	RR	95% CI	Adjustment factors[b]	Notes[c]
	Controls	Cases	Controls	Cases						
All diseases of digestive system:										
Accortt	-	-	-	-	ST	M	1.9	0.4-9.8	Age, smoking, other	
	-	24	-	0	ST	F	Not given			
Henley-CPS I	69662	298	7745	85	ST	M	1.49	1.14-1.93	Age, smoking, other	1
Henley-CPS II	111482	689	2488	25	ST	M	1.38	0.92-2.07	Age, smoking, other	1
Colitis and other intestinal diseases:										
Henley-CPS I	69662	124	7745	35	ST	M	1.42	0.94-2.12	Age, smoking, other	1
Henley-CPS II	111482	467	2488	14	ST	M	1.12	0.65-1.92	Age, smoking, other	1
Persson	61	53	11	14	Snuff	M	1.01	0.41-2.46	Smoking	2,3
Heartburn:										
Bolinder	19251	4634	Total 5014		ST	M	0.9	0.8-0.9	Age, smoking	
Liver cirrhosis:										
Henley-CPS I	69662	81	7745	19	ST	M	1.49	0.87-2.56	Age, smoking, other	1
Henley-CPS II	111482	157	2488	11	ST	M	3.02	1.60-5.69	Age, smoking, other	1
Winn	Total population ~ 300,000				ST	M	2.94	-	Smoking, others not stated	4
Peptic ulcer:										
Bolinder	23025	860	Total 5014		ST	M	1.1	0.9-1.2	Age, smoking	

[a] ST = smokeless tobacco

[b] Adjustment for smoking includes studies restricted to non-smokers; refer to table 6.7.1 for full details of adjustment factors. Where study presents multiple RR estimates, adjustment factors relate to all RRs unless otherwise stated

[c] Key to notes:
1 Number of controls refers to population at risk
2 Estimated from data given
3 Crohn's disease and ulcerative colitis
4 Standardized mortality ratio/100

Table 6.7.3: Summary of meta-analysis results for studies of diseases of the digestive system

Endpoint	No. of studies	Fixed effects estimate		Heterogeneity		Random effects estimate	
		RR	95% CI	chisquared	p value	RR	95% CI
All digestive diseases	3	1.46	1.18-1.82	0.20	NS	1.46	1.18-1.82
Colitis/other intestinal	3	1.27	0.93-1.72	0.75	NS	1.27	0.93-1.72
Liver cirrhosis	2	2.00	1.33-3.02	2.76	NS	2.08	1.04-4.15

6.8 *Diseases of the genitourinary system*

6.8.1 Prospective studies

6.8.1.1 Henley: USA – CPS I and CPS II (2005)

See section 3.2.5

6.8.2 Summary

Two prospective studies gave information relevant to an investigation into the possible association between smokeless tobacco use and diseases of the genitourinary system. Both studies were conducted in the USA, and the analyses were restricted to lifelong non-smokers. In addition to age, both studies adjusted their results for numerous other potential confounders.

A summary of the results of the studies is given in table 6.8.1, and the results for separate endpoints are discussed below.

6.8.2.1 All genitourinary system diseases

Both of the studies that reported on this endpoint presented a relative risk estimate that was above 1.00. However, only one of these reached borderline statistical significance (1.34, 95% CI 1.00-1.80).

Meta-analysis of these results produced an overall risk estimate of 1.25 (95% CI 0.97-1.61) for both the fixed effects and random effects models, and there was no evidence of heterogeneity between the two studies (heterogeneity chisquared = 0.847 on 1 d.f., $p>0.1$).

6.8.2.2 Nephritis and other kidney diseases

Kidney diseases were considered as a separate endpoint by both of the studies. Both of the relative risks estimated were raised, though neither reached statistical significance.

An overall relative risk of 1.28 (95% CI 0.95-1.73) was estimated by meta-analysis, using both a fixed effects and a random effects model, and again there was no significant heterogeneity between the studies (heterogeneity chisquared = 0.579 on 1 d.f., $p>0.1$).

Table 6.8.1: Summary of results for diseases of the genitourinary system

Study	Non-users		Smokeless tobacco users		Product[a]	Sex	RR	95% CI	Adjustment factors[b]	Notes[c]
	At risk	Cases	At risk	Cases						
All genitourinary system diseases:										
Henley-CPS I	69662	222	7745	64	ST	M	1.34	1.00-1.80	Age, smoking, other	1
Henley-CPS II	111482	501	2488	17	ST	M	1.02	0.62-1.69	Age, smoking, other	2
Nephritis and other kidney diseases:										
Henley-CPS I	69662	174	7745	51	ST	M	1.37	0.98-1.92	Age, smoking, other	1
Henley-CPS II	111482	299	2488	10	ST	M	1.01	0.53-1.93	Age, smoking, other	2

[a] ST = smokeless tobacco

[b] Adjustment for smoking includes studies restricted to non-smokers; refer to notes for full details of adjustment factors.

[c] Key to notes:

1 Adjustment factors include race, education, BMI, exercise, alcohol intake, fat consumption, fruit/ vegetable intake and aspirin use

2 Adjustment factors include race, education, BMI, exercise, alcohol intake, employment status and type, fat consumption, fruit/vegetable intake and aspirin use

6.9 *Adverse pregnancy outcomes*

6.9.1 Case-control/cross-sectional studies

6.9.1.1 England: Sweden (2003)

In the study by England et al., 2003, information was collected from women delivered of singleton, live-born infants in Sweden from 1999-2000. Data on current tobacco use at the time of the first ante-natal visit were used to determine exposure groups. All 1322 snuff users identified were included in the study, and for each of these, 10 cigarette smokers and 10 women who used neither product were selected randomly. After exclusions, analyses were based on 789 snuff users and 11,495 non-tobacco users. The 67 women who used both snuff and cigarettes were excluded.

Compared with non-tobacco users, mean adjusted birth weight was significantly reduced in snuff users, by 40g (95% CI 6-72g). After restriction to women whose late pregnancy tobacco exposure was known, the adjusted mean birth weight was also significantly reduced in snuff users, by 93g (95% CI 38-147g). Odds ratios for other birth outcomes were estimated as follows:

Tobacco use	Small-for-gestational-age birth		Pre-term delivery		Pre-eclampsia	
	No.	OR[1] (95% CI)	No.	OR[2] (95% CI)	No.	OR[3] (95% CI)
Non-users	179	1.00	453	1.00	343	1.00
Snuff users	17	1.25 (0.72-2.17)	59	1.98 (1.46-2.68)	37	1.58 (1.09-2.27)

[1] Adjusted for maternal age, BMI, height and parity
[2] Adjusted for maternal age, BMI, height, parity and infant sex
[3] Adjusted for maternal age, BMI and height

After excluding women with pre-eclampsia, the odds ratio for pre-term delivery in snuff users was 1.79 (95% CI 1.27-2.52). Information on alcohol consumption and illicit drug use, both of which may be associated with adverse pregnancy outcomes, was not available from the database.

6.9.2 Summary

Information regarding the relationship between adverse pregnancy outcomes and the use of snuff was available from one cross-sectional study only. This study was conducted in Sweden, and was restricted to lifelong non-smokers. Adjustment was carried out for age, and for a variety of other factors.

A summary of the results of the study is given in table 6.9.1. For each of the outcomes investigated, the relative risk estimated for women who used snuff compared to those who did not use any tobacco was above 1.00, and for pre-term delivery (1.98, 95% CI 1.46-2.68) and pre-eclampsia (1.58, 95% CI 1.09-2.27), the differences reached statistical significance.

Table 6.9.1: Summary of results for adverse pregnancy outcomes

Study	Non-users		Smokeless tobacco users		Product[a]	RR	95% CI	Adjustment factors[b]	Notes[c]
	Controls	Cases	Controls	Cases					
England	11316	179	772	17	Snuff	1.25	0.72-2.17	Age, smoking, other	1,2
	11042	453	730	59	Snuff	1.98	1.46-2.68		3,4
	-	-	-	-	Snuff	1.79	1.27-2.52		3,4,5
	11152	343	752	37	Snuff	1.58	1.09-2.27		6,7

[a] ST = smokeless tobacco

[b] Adjustment for smoking includes studies restricted to non-smokers; refer to notes for full details of adjustment factors. Where study presents multiple RR estimates, adjustment factors relate to all RRs unless otherwise stated

[c] Key to notes:

1 Small-for-gestational-age birth
2 Adjustment factors include BMI, height and parity
3 Pre-term delivery
4 Adjustment factors include BMI, height, parity and infant sex
5 Excluding women with pre-eclampsia
6 Pre-eclampsia
7 Adjustment factors include BMI and height

6.10 *Sleep disturbances and anxiety symptoms*

6.10.1 Case-control/cross-sectional studies

6.10.1.1 Bolinder: Sweden (1992)

See section 3.3.3

6.10.2 Summary

One cross-sectional study examined the possible relationship between symptoms of anxiety and the use of smokeless tobacco. The study was carried out in Sweden, and was restricted to lifelong non-smokers. Adjustment for age was also carried out.

The results of the study are summarized in table 6.10.1. Users of smokeless tobacco had a significantly increased risk of both sleep disturbances and "nervous" problems compared to subjects who had never used any form of tobacco (1.2, 95% CI 1.1-1.4 for both endpoints).

Table 6.10.1: Summary of results for sleep disturbances and anxiety symptoms

Study	Non-users		Smokeless tobacco users		Product[a]	Sex	RR	95% CI	Adjustment factors[b]	Notes[c]
	Controls	Cases	Controls	Cases						
Bolinder	22547	1338	Total 5014		ST	M	1.2	1.1-1.4	Age, smoking	1
	22786	1099	Total 5014		ST	M	1.2	1.1-1.4		2

[a] ST = smokeless tobacco
[b] Adjustment for smoking includes studies restricted to non-smokers. Where study presents multiple RR estimates, adjustment factors relate to all RRs unless otherwise stated
[c] Key to notes:
1 Sleeping disturbances
2 Nervous problems

6.11 *Summary for non-neoplastic diseases other than oral or cardiovascular*

Results of the studies that considered non-neoplastic diseases other than oral or cardiovascular are summarized in table 6.11. Thirty-nine of the 47 relative risks reported were raised, with 15 of these reaching statistical significance. Only three significantly reduced relative risks were estimated.

Meta-analysis was carried out for 14 separate endpoints. Twelve of the overall relative risks estimated were above 1.00, and the difference reached statistical significance for all diseases other than cancer or cardiovascular disease, all diseases of the musculoskeletal system, all diseases of the respiratory system, COPD and, most significantly, all diseases of the digestive system and liver cirrhosis. Meta-analysis also showed a highly significantly negative relationship between Parkinson's disease and the use of smokeless tobacco. It should be noted that all of these analyses were based on a very limited number of studies.

Table 6.11: Summary of results for non-neoplastic diseases other than oral or cardiovascular

Endpoint	No. of studies	Relative risk estimates					Overall	
		S +	NS +	1.00	NS -	S -	RR[1]	95% CI
Diseases other than cancer or cardiovascular disease	2	1	1	0	0	0	1.15	1.06-1.24
All endocrine, nutritional and metabolic diseases	1	0	2	0	0	0	2.14	0.70-6.60
Diabetes mellitus	4	1	2	0	1	0	1.09	0.76-1.56
All diseases of the nervous system and sense organs	1	0	1	0	1	0	0.81	0.26-2.57
Parkinson's disease	2	0	0	0	0	2	0.22	0.09-0.53
Diseases of the musculoskeletal system	1	2	1	0	0	0	1.94[2,3]	1.06-3.55
All diseases of the respiratory system	3	1	1	0	2	0	1.19	1.01-1.41
COPD	2	1	1	0	0	0	1.59	1.08-2.33
Influenza and pneumonia	2	0	1	0	1	0	1.06	0.84-1.33
Tuberculosis	1	0	1[4]	0	0	0	Not performed	
Other respiratory symptoms	1	3	0	0	0	0	Not performed	
All diseases of the digestive system	3	1	2	0	0	0	1.46	1.18-1.82
Colitis/intestinal disease	3	0	3	0	0	0	1.27	0.93-1.72
Heartburn	1	0	0	0	0	1	Not performed	
Liver cirrhosis	3	1	2[4]	0	0	0	2.00	1.33-3.02
Peptic ulcer	1	0	1	0	0	0	Not performed	
All diseases of the genitourinary system	2	0	2	0	0	0	1.25	0.97-1.61
Nephritis/kidney disease	2	0	2	0	0	0	1.28	0.95-1.73
Adverse pregnancy outcomes	1	2	1	0	0	0	Not performed	
Sleep disturbances and anxiety symptoms	1	2	0	0	0	0	Not performed	

NS = Non-significant; S = Significant

[1] Obtained from meta-analysis using fixed effects model

[2] Based on relative risks for disability pension for musculoskeletal diagnosis only

[3] Significant heterogeneity between studies, therefore results from random effects model shown

[4] Includes standardized mortality rate

7. Summary

This review was carried out to investigate in detail the epidemiological evidence relating diseases other than oral and cardiovascular to smokeless tobacco use by Western populations. Evidence relating to India and other parts of Central and South-Eastern Asia, where the usage of smokeless tobacco differs from that in the West, is not considered.

A total of 75 studies that provided relevant information were identified. Of these, 51 were of a case-control design, 18 were prospective studies, and 6 were cross-sectional. Forty-six of the studies were conducted in the USA, 18 were carried out in Sweden, three took place in Norway and the USA, two each were conducted in Canada, Denmark, and the UK, and one study took place in Puerto Rico. One multi-centre study was conducted in Australia, Denmark, Germany, Sweden and the USA.

In 27 of the studies, the analyses for smokeless tobacco were restricted to lifelong non-smokers, although in one of these studies, smokers were only excluded if this was their main form of tobacco usage. Three studies excluded ever smokers of cigarettes only, but only one of these adjusted for other forms of tobacco. Five studies excluded current smokers, but included former smokers, and none adjusted for this during analysis. In 38 studies the smokeless tobacco users could also have smoked, but in one of these studies analysis for two endpoints was restricted to never smokers. Of these 38 studies, six studies carried out proper adjustment for smoking variables, with another five studies carrying out partial adjustment. In two studies, it was not stated whether smoking had been adjusted for, and in the remaining 25 studies, no attempt was made to adjust the results for smoking. In two studies, it was not possible to determine whether the study group included smokers. Forty-two of the studies adjusted for age, while 36 studies carried out adjustment for a variety of other potential confounders. In four studies, no information on adjustment was given.

Various other problems were noted with some of the studies in this review. These included the small number of cases who also used smokeless tobacco, the collection of data from potentially unreliable sources, and a failure to present results in sufficient detail to allow relative risks to be calculated. Generally, there was also a

failure to present results separately for chewing tobacco and snuff. Despite these limitations, various conclusions can be drawn from the available data.

Firstly, smokeless tobacco carried little increased risk of those cancers investigated in this review. Twenty-six meta-analyses were carried out, but significant increases were seen only for oesophageal cancer and prostate cancer. For oesophageal cancer the relative risk was estimated as 1.37 (95% CI 1.10-1.71, number of estimates = 8) where results for chewing tobacco were included for one study providing separate estimates for chewing tobacco and snuff and 1.43 (1.13-1.81) where results for snuff were included. For prostate cancer, corresponding relative risks were 1.75 (1.09-2.81, n = 5) and 1.33 (0.83-2.13). No significantly reduced relative risks were estimated. For many of the endpoints considered, meta-analysis was based on very limited data. There were also isolated reports of significant increases for connective tissue cancer, bile duct cancer, cervical cancer and nervous system cancer, all cancers where the number of studies was too few to justify meta-analysis. Bearing in mind the multiple endpoints considered, the relatively marginal significances seen, the weaknesses present in many of the epidemiological studies and the possibility of publication bias, none of these associations provide convincing evidence of a true effect of smokeless tobacco use. If there is a true association of cancer of those sites investigated in this review with smokeless tobacco use it is clear that this is much less than that with smoking.

The evidence for a relationship between smokeless tobacco and non-neoplastic diseases other than oral or cardiovascular is slightly stronger. Of the 14 endpoints considered in this section, six - all diseases other than cancer or cardiovascular disease (RR = 1.15, 95% CI 1.06-1.24, n = 2), all diseases of the musculoskeletal system (1.94, 1.06-3.55, n = 2), all diseases of the respiratory system (1.19, 1.01-1.41, n = 3), COPD (1.59, 1.08-2.33, n = 2), and particularly all diseases of the digestive system (1.46, 1.18-1.82, n = 3) and liver cirrhosis (2.00, 1.33-3.02, n = 2) - showed a significantly higher risk in users of smokeless tobacco. There was also a highly significant and markedly reduced risk of Parkinson's disease (0.22, 0.09-0.53, n = 2) in smokeless tobacco users. Again, though, most of the meta-analyses were based on a limited number of studies, and indeed for some of the endpoints cited above the two individual estimates were for males and females in the same study.

Therefore, until more data are available, there is little clear evidence of an effect of smokeless tobacco use on the risk of non-neoplastic diseases other than oral or cardiovascular in Western populations.

This report also includes results of a meta-analysis of those four studies, all prospective, that had provided data relating smokeless tobacco to all cause mortality. This showed a significantly increased risk (RR = 1.19, 95% CI 1.12-1.27) in smokeless tobacco users. In view of the small number of studies, the relatively weak association, and the fact that the results included deaths from oral and cardiovascular disease, the increased risk does not provide any clear evidence of an effect of smokeless tobacco on the diseases of primary interest in this review.

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