

2. Studies of Cancer in Humans

2.1 Introduction

Studies that have investigated the association between the use of smokeless tobacco and cancer have often faced a problem of small numbers of cases, which has often precluded an analysis of specific and relevant subgroups; alternatively, when such analyses were carried out, they resulted in imprecise relative risk estimates. This is of particular concern in relation to specific cancer sites, and also to an analysis of categories of smokeless tobacco use as well as to stratification for cigarette smoking and alcoholic beverage consumption. As an example, associations with smokeless tobacco use should preferably have been analysed in never smokers. In making its evaluation, the Working Group gave greatest weight to studies that adequately addressed potential confounding by smoking. In addition, of the studies that were reviewed previously (IARC, 1985), only those that addressed such potential confounding have been included and re-evaluated in this monograph.

The Working Group also considered the possibility of confounding by human papillomavirus (HPV), since there is sufficient evidence in humans that HPV 16 causes cancer of the oral cavity and oropharynx (IARC, 2007). In a systematic review of the detection of HPV DNA in squamous-cell carcinoma of the head and neck, the prevalence of HPV was only 24% in oral and 36% in oropharyngeal cancer (Kreimer *et al.*, 2005), which limits the proportion of cases that can be attributed to this virus. Moreover, negative associations between HPV DNA, tobacco smoking and alcoholic beverage consumption (Gillison *et al.*, 2000) and between HPV, tobacco smoking and *pan* chewing (Herrero *et al.*, 2003) have been observed. Therefore, the Working Group concluded that positive confounding by HPV is unlikely to account for a strong association of these cancers with tobacco chewing.

In this section, case series studies are generally included only if no analytical studies were available from that region or when cancer at the site where the smokeless tobacco was placed was considered.

2.2 Oral use

2.2.1 *Cancer of the oral cavity and pharynx*

The characteristics of cohort studies are summarized in Table 69 and results from these studies on oral and pharyngeal cancer are presented in Table 70.

The design and results of case-control studies on use of smokeless tobacco and cancer of the oral cavity and pharynx are summarized in Table 71.

(a) *North and South America*

(i) *Cohort studies*

The US Veterans cohort comprised 293 958 veterans who served in the US Armed Forces during 1917–40, were aged 31–84 years in 1953 and held US government life insurance policies in 1953 (Zahm *et al.*, 1992). Most policy holders were men (99.5%) and nearly all were white. The results on smokeless tobacco were based on 248 046 (84%) veterans who responded to the questionnaire mailed in 1954 or the questionnaire mailed in 1957 to 1954 non-respondents. The cohort was followed up for vital status from 1954 (or 1957) through to 1980, and follow-up was 96% complete; death certificates were available for 97% of the deceased cohort members and identified 129 deaths from oral cancer. The relative risk for oral cancer (ICD-7 140-144) was 3.0 (95% CI, 2.0–4.5) for users of chewing tobacco or snuff and those for infrequent use and frequent use were 1.9 (95% CI, 1.0–3.5) and 3.4 (95% CI, 2.1–5.6), respectively. The corresponding relative risks for the pharynx were 8.7 (95% CI, 4.1–8.3), 4.5 (95% CI, 1.7–11.7) and 11.2 (95% CI, 5.0–25.0), respectively. For early age at first use (≤ 14 years of age), the relative risk was 20.7 (95% CI, 8.0–53.7). [The Working Group noted that the results were not adjusted for tobacco smoking or alcoholic beverage consumption.]

NHANES I was a national probability sample survey of the non-institutionalized US population that oversampled the elderly, poor and women of childbearing age (Accortt *et al.*, 2002). A total of 14 407 adults, aged 25–74 years, underwent health examinations between 1971 and 1975. Of the participants, 13 861 persons (96%) were successfully traced in at least one of the NHANES I Epidemiological Follow-up Studies (NHEFS) in 1982–84, 1986, 1987 or 1992. Death certificates were available for 98% of the decedents. A random sample of 3847 of the cohort was asked about smokeless tobacco use at baseline. In the 1982–84 follow-up, information on smokeless tobacco use was obtained to infer baseline behaviour for study participants who were not part of the original random sample. Participants were considered to be users of smokeless tobacco if they currently used smokeless tobacco at baseline or had ever used it according to the 1982–84 questionnaire. The analysis was restricted to the 6805 black and white subjects, aged 45 years and

Table 69. Descriptions of cohort studies of smokeless tobacco use

Location Reference, name of cohort	Cohort description	Assessment of smokeless tobacco use	Follow-up and outcome	Neoplasms reported (no.)
North America				
Hsing <i>et al.</i> (1990); Kneller <i>et al.</i> (1991); Zheng <i>et al.</i> (1993), Lutheran Brother- hood cohort	26 030 white men aged ≥ 35 years who purchased life insurance from Lutheran Brotherhood Insurance Society, mostly from California, upper Midwest and northeastern USA.	17 818 (68.5%) responded to mailed questionnaire; few differences among responders and non-responders in demographic characteristics.	Vital status follow-up, 1966–86; 4027 (23%) lost to follow-up; death certificates coded to ICD-9	Pancreas (54) (after exclusion of 3 deaths) Stomach (75) Prostate (149)
Hsing <i>et al.</i> (1991); Zahm <i>et al.</i> (1992); Heineman <i>et al.</i> (1995), US Veterans' cohort	283 958 veterans who served in US Armed Forces during 1917–40 and who were aged 31–84 years in 1953 and held US government life insurance policies; 99.5% of policy holders were men, nearly all were white.	248 046 (84%) responded to the 1954 mailed questionnaire or the 1957 questionnaire mailed to 1954 non-respondents on use of chewing tobacco or snuff; 48 304 used smokeless tobacco, 2308 used smokeless tobacco only.	Follow-up 1954–80 (96% complete); death certificates coded according to ICD-7 (97% complete)	Oral cavity and pharynx (129 exposed) Colorectum (838) Prostate (1123) Soft-tissue sarcoma (119)
Putnam <i>et al.</i> (2000), Iowa cohort	1601 controls from a case–control study of cancer in Iowa, ascertained from 1986–89 via RDD and HCFA, resident in Iowa, aged 40–86 years, with no prior cancer; exclusion of 24 subjects with proxy respondents ($n = 1577$)	Mailed questionnaire supplemented by telephone interviews.	Vital status follow-up through to 1995 (3 subjects lost); follow-up for prostate cancer incidence through state cancer registry	Prostate (101), after exclusion of the cases diagnosed prior to return of questionnaire
Accort <i>et al.</i> (2002), NHANES I Follow- up cohort	Survey of the non-institutionalized US population who underwent a physical health examination in 1971–75, oversampling of the elderly, poor and women of childbearing age, aged 25–74 years ($n = 14 407$); analysis restricted to white and black subjects, aged 45–75 years at baseline ($n = 6805$)	In-person interviews of a random sample ($n = 3847$) on smokeless tobacco use at baseline or in first NHANES I epidemiological follow-up study (NHEFS)	13 861 persons (96%) successfully traced in at least one follow-up survey of the NHEFS in 1982–84, 1986, 1987 and 1992; death certificates available for 98% of the decedents; coded according to ICD-9	Oral cavity (19) Digestive system (NA) Lung (NA)

Table 69 (contd)

Location Reference, name of cohort	Cohort description	Assessment of smokeless tobacco use	Follow-up and outcome	Neoplasms reported (no.)
Chao <i>et al.</i> (2002); Henley <i>et al.</i> (2005), CPS-II	508 351 men and 676 306 women, aged ≥ 30 years, residing in a US household in which at least one member was 35 years or older (45 years or older for Chao <i>et al.</i> , 2002); analysis restricted to men without prior cancer (except non-melanoma skin cancer) at enrolment and with information on tobacco (<i>n</i> = 467 788) (Chao <i>et al.</i> , 2002) or restricted to men who never used any other tobacco (Henley <i>et al.</i> , 2005)	Questionnaire at enrolment; only men were asked about smokeless tobacco.	Vital status follow-up, 1982–2000 (1996 for Chao <i>et al.</i> , 2002); 0.2% lost to follow-up; death certificates coded to ICD-9 (98.9% complete)	Oral cavity and pharynx (46) Digestive system (1999) Stomach (996) Lung (418)
Henley <i>et al.</i> (2005), CPS-I and CPS-II	456 487 men and 594 544 women (CPS-I), aged ≥ 30 years, residing in a household in which at least one member was ≥ 35 years old; analysis restricted to men without prior cancer (except non-melanoma skin cancer) at enrolment and who never used any other tobacco.	Questionnaire at enrolment	Vital status follow-up, 1959–72; 6.7% lost to follow-up and 4.9% with follow-up truncated for logistic reasons in 1965; death certificates coded to ICD-7 (97% complete)	Oral cavity and pharynx (13) Digestive system (913) Lung (134)
Europe Heuch <i>et al.</i> (1983); Boffetta <i>et al.</i> (2005), Norwegian cohort	Probability sample of general adult population of Norway from 1960 census and relatives of migrants to the USA, alive on 1 January 1966 (<i>n</i> = 12 431)	Mailed questionnaires on lifestyle habits in 1964 and 1967; information on smokeless tobacco available for 10 136 men	Follow-up for cancer incidence via cancer registries, 1966–2001 (99.85% complete)	Oral cavity and pharynx (34) Oesophagus (27) Stomach (217) Pancreas (105) Lung (343) Kidney (88) Bladder (238)

CPS, Cancer Prevention Study; HCFA, Health Care Financing Administration; NA, not available; NHANES, National Health and Nutrition Examination Survey; RDD, random-digit dialling

Table 70. Results of cohort studies on use of smokeless tobacco and cancer of the oral cavity and pharynx

Location Reference, name of cohort	Use of smokeless tobacco	No. of cases	Relative risk (95% CI)	Adjustment for potential confounders; comments
North and South America				
Zahm <i>et al.</i> (1992), US Veterans cohort	Never used any tobacco products		Oral cavity (ICD-7 140–144) 1.0	
	Used chewing tobacco or snuff	74	3.0 (2.0–4.5)	
	Infrequent use		1.9 (1.0–3.5)	
	Frequent use		3.4 (2.1–5.6)	
	Never used any tobacco products		Pharynx 1.0	
	Used chewing tobacco or snuff	55	8.7 (4.1–18.3)	
	Infrequent use		4.5 (1.7–11.7)	
	Frequent use		11.2 (5.0–25.0)	
	Age at first use ≤ 14 years		20.7 (8.0–53.7)	
Accort <i>et al.</i> (2002), NHANES 1 Follow-up cohort	Ever smokeless tobacco use	2	SMR 107 (10–308)	0.8 expected
	Exclusive smokeless tobacco use	0	0 (0–580)	
Henley <i>et al.</i> (2005), CPS-I and CPS-II	Never used smokeless tobacco	<i>CPS-I</i> 9	Oral cavity and pharynx (ICD-7 140–148) 1.0	Multivariate, adjusted results for men who never used other tobacco products
	Current use of smokeless tobacco	4	2.0 (0.5–7.7)	
	Never used smokeless tobacco	<i>CPS-II</i> 45	Oral cavity and pharynx (ICD-9 140–148) 1.0	
	Current use of smokeless tobacco	1	0.9 (0.1–6.7)	
	Former use of smokeless tobacco	0		
Europe				
Boffetta <i>et al.</i> (2005), Norwegian cohort	Never user	25	Oral cavity and pharynx (ICD-7 141–148) 1.0	
	Ever used smokeless tobacco	9	1.1 (0.5–2.4)	Adjusted for age and smoking
	Current use of smokeless tobacco	6	1.1 (0.5–2.8)	
	Former use of smokeless tobacco	3	1.0 (0.3–3.5)	

CI, confidence interval; CPS, Cancer Prevention Study; NHANES, National Health and Nutrition Examination Survey; SMR, standardized mortality ratio

Table 71. Case-control studies on use of smokeless tobacco and cancer of the oral cavity and pharynx

Reference, study location, period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments		
North and South America											
Williams & Horn (1977), USA, 1969–71		Cancer of the oral cavity from 7518 (57% of randomly selected) incident invasive cancers who participated in the population-based Third National Cancer Survey	Cancer at sites unrelated to tobacco	Personal interview	Smokeless tobacco	<i>Men</i>	<i>Cancer of gum and mouth</i>	Age, race, smoking			
					Moderate use	8	3.9 ($p < 0.01$)				
					Heavy use	3	6.7				
							<i>Cancer of lip and tongue</i>				
					Moderate use	1	0.4				
					Heavy use	2	1.9				
							<i>Cancer of the pharynx</i>				
					Moderate use	2	0.5				
					Heavy use	–	–				
					Winn <i>et al.</i> (1981a,b, 1984); Blot <i>et al.</i> (1983); Winn (1986), North Carolina, USA, 1975–78	ICD-8 141, 143–146, 148	Oral and pharyngeal cancer from hospitals discharge diagnoses (156 women) or death certificates (99 women); response rate, 91%			410 (2 per case) matched by age, race, residence, source (hospital or death certificate); excluding mental disorders, cancer of the oesophagus or larynx and other oral or pharyngeal diseases; response rate, 82%	Self- and next-of-kin interviews
	79	1.5 (0.5–4.8)									
	<i>Black women</i>	12									
Years of snuff use in non-smokers		<i>Cancer of gum and buccal mucosa</i>									
0	2	1.0									
1–24	3	13.8 (1.9–98.0)									
25–49	10	12.6 (2.7–58.3)									
≥ 50	15	47.5 (9.1–249.5)									
		<i>Cancer of other mouth and pharynx</i>									
0	22	1.0									
1–24	3	1.7 (0.4–7.2)									
25–49	14	3.8 (1.5–9.6)									
≥ 50	8	1.3 (0.5–3.2)									

Table 71 (contd)

Reference, study location, period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Stockwell & Lyman (1986), Florida, USA, 1982	ICD-O 140–149	1920 incident cancers of the lip, tongue, salivary glands, gum, floor of mouth, other parts of mouth, oropharynx, hypopharynx, pharynx (unspec.), nasopharynx; from population-based Florida cancer registry; overall response rate in case group, 82%	6457 cancers of the colon or rectum, cutaneous melanoma, endocrine neoplasias from same source during same time period; response rate, 78%	Information on tobacco use was obtained by chart and histopathology review at reporting institutions; only primary type of tobacco used was recorded.	Unspecified		<i>Lip and tongue</i> 2.3 (0.2–12.9) <i>Salivary gland</i> 5.3 (1.2–23.4) <i>Mouth and gum</i> 11.2 (4.1–30.7) <i>Pharynx</i> 4.1 (0.9–18.0) <i>Nasopharynx</i> 5.3 (0.7–41.6)	Age, sex, race, tobacco use	
Blot <i>et al.</i> (1988), New Jersey, Atlanta metropolitan area, Santa Clara and San Mateo counties, Los Angeles, USA, 1984–85	ICD 141–149, excluding 142 and 147	1114 incident, pathologically confirmed from population-based cancer registries; all black and white cases; aged 18–79 years; response rate, 75%	1268; RDD for controls aged 64 and younger, HCFA for controls aged 65 and older; frequency-matched on age, sex, race; response rate, 76%	Structured questionnaire interview in home by trained interviewers; next of kin for 22% of cases and 2% of controls	Use of smokeless tobacco	<i>Men</i> 46 <i>Women</i> 11 <i>Nonsmoking women</i> 6	[0.85] [3.4] 6.2 (1.9–19.8)	Age, race, study location, respondent status	Nearly all male tobacco chewers were smokers. Female nonsmokers primarily used snuff rather than chewing tobacco. All six cases had oral cavity cancer.
Spitz <i>et al.</i> (1988), Houston, TX, USA, 1985–87		185 patients (131 men, 54 women), 19–95 years old, at MD Anderson Hospital; histologically confirmed squamous-cell carcinoma of the tongue (25), floor of mouth (14), other parts of the oral cavity (27), oropharynx (15), larynx (50); white US residents; response rate not stated	185 patients at MD Anderson Hospital during the same period, randomly selected, frequency-matched on age (± 5 years) and sex, excluding patients with squamous-cell carcinoma of any site; response rate not stated	Self-administered questionnaire as part of the registration procedure	Chewing tobacco Snuff use	23 9	[1.0] 3.4 (1.0–10.9)		All nine snuff dipping cases drank alcohol, seven also chewed tobacco, eight smoked cigarettes and one smoked cigars and pipes; three of four snuff dipping controls also smoked cigarettes.

Table 71 (contd)

Reference, study location, period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Franco <i>et al.</i> (1989), São Paulo, Curitiba and Goiânia, Brazil, 1986–88	ICD-9 141, 143–145	232 histologically confirmed, invasive carcinomas of the tongue, gum, floor of mouth and other parts of the oral cavity; from 3 hospitals in Sao Paulo, Curitiba and Goiânia; response rate, 98.3%	464 (2 per case) from same or neighbouring general hospitals; individually matched on sex, 5-year age group and trimester of hospital admission, excluding diagnoses of neoplasms or mental disorder	Cases interviewed using structured questionnaire in hospital, controls privately; no proxy respondents	Unspecified	9	[1.4]		Relative risk independent of tobacco smoking and alcohol drinking (data not shown)
Maden <i>et al.</i> (1992), Washington State, USA, 1985–89	ICD-O 141, 143–146	131 in-situ and invasive squamous-cell cancers of the lip (10), tongue (46), gum, floor of mouth (20), unspecified mouth and oropharynx (33); men aged 18–65 years; response rate, 54.4%	136 identified by RDD, frequency-matched on gender, year of diagnosis and age (5-year groups); response rate, 63%	In-person questionnaire interview at home or elsewhere	Unspecified	19	4.5 (1.5–14.3)	Age	
Marshall <i>et al.</i> (1992), New York counties, USA, 1975–83		290 histologically confirmed oral and pharyngeal cancer (tongue, 28%; floor of mouth, 14%; oropharynx, 22%; hypopharynx, 13%), excluding black race from 20 hospitals in three New York counties; 513 contacted, 290 (56%) participated.	290 individually matched on age (± 5 years), sex and neighbourhood; response rate, 41%	Interview	Snuff and chewing tobacco		'Increased risk (statistically non-significant)'	Matching variables	Data not shown

Table 71 (contd)

Reference, study location, period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Mashberg <i>et al.</i> (1993), New Jersey, USA, 1972–83		359 male black or white in-situ or invasive squamous-cell carcinoma of the oral cavity and oropharynx (histologically diagnosed) admitted to Veterans hospital in New Jersey; 94% of study subjects enrolled between 1977 and 1982; response rate not stated	2280 from same series of patients with biopsied oral lesions without cancer or dysplasia of the oesophagus, pharynx, larynx, lung; response rate not stated	In-hospital questionnaire interview	Smokeless tobacco Chewing tobacco ever Snuff use ever	52	1.0 (0.7–1.4) 0.8 (0.4–1.9)	Age, race, tobacco smoking, alcohol; further adjustments for religion, occupation, origin and interviewer did not 'modify materially' the odds ratio.	No dose-response by duration of use (data not shown)
Spitz <i>et al.</i> (1993), Houston, TX USA, 1987–91		108 white patients from MD Anderson Hospital with histologically confirmed cancers of the oral cavity (44), pharynx (31) and larynx (33); response rate not stated	108 blood and platelet donors; frequency-matched by age (± 5 years), sex, race and with no history of cancer; response rate not stated	Self-administered questionnaire in hospital	Chewing tobacco		1.2 'not statistically significant'		Data not shown
Kabat <i>et al.</i> (1994), USA, 1977–90		1560 cases from 28 hospitals in eight cities with incident, histologically confirmed cancers of the tongue, floor of mouth, gums, gingiva, buccal mucosa, palate, retromolar area, tonsil, other pharynx; response rate not stated	2948 individually matched on hospital, admission within 2 months after case, age, sex, race, with diseases not thought to be associated with tobacco or alcohol and no prior history of tobacco-related cancers; 50% cancers, 7% benign neoplasms, 43% non-neoplastic conditions; response rate not stated	In-hospital questionnaire interview	Chewing tobacco Snuff use	<i>Men</i> 4 <i>Women</i> 4	2.3 (0.7–7.3) 34.5 (8.5–140.1)	Among never smokers Among never smokers	Less than 2% of women chewed. Among never-smoking women, there were no tobacco chewers; less than 2% of men and women used snuff. Among never-smoking men, 0 of 82 cases and 0.9% of 444 controls used snuff.

Table 71 (contd)

Reference, study location, period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Muscat <i>et al.</i> (1996), Illinois, Michigan, New York, Philadelphia, USA, 1981–90	ICD-9 141, 143–146, 148, 149	1009 (687 men, 322 women) hospital patients with incident, histologically confirmed cancers of oral cavity and pharynx; aged 21–80 years; response rate, 91%	923 (619 men, 304 women) hospital patients with conditions unrelated to tobacco use, matched by sex, age (± 5 years), race, date of admission (± 3 months); response rate, 97%	In-hospital questionnaire interview	Chewing tobacco: at least once a week for 1 year or more	Men 38 Women 0	[1.04]		
					Snuff use: at least once a week for 1 or more years	Men 9 Women 2	[0.81]		
							[1.9]		
Schwartz <i>et al.</i> (1998), Seattle area counties, WA, USA, 1990–95		284 (165 men, 119 women) from population-based cancer registry with histologically confirmed incident in-situ or invasive (92%) squamous-cell cancers of the tongue, gum, floor of mouth, unspecified mouth, tonsils, oropharynx; aged 18–65 years; response rate, 63.3%	477 (302 men, 175 women) from random digit dialling, frequency matched on sex and age, 3:2 ratio controls to cases; response rate, 60.9%	In-person questionnaire interview	Unspecified	Men 11	1.0 (0.4–2.3)		Only one female control used smokeless tobacco.
Europe Wynder & Wright (1957), Stockholm, Sweden, 1952–55		477 (265 men, 212 women) patients with squamous-cell cancer of lip (15), gingiva (36), tongue (70), buccal mucosa (18), maxillary sinus (45), nasopharynx (40), hypopharynx (116), oesophagus (74), larynx (63)	333 patients from same hospital with other cancers	Interview	Duration of snuff use		Gingiva, buccal mucosa, –2* (non-significant) Other upper aerodigestive tract, 'no association'	Tobacco smoking similar to that in controls Tobacco smoking higher than in controls	*Ridit analysis Cancers often where quid was placed

Table 71 (contd)

Reference, study location, period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Blomqvist <i>et al.</i> (1991), Sweden		61 (57 men, four women) patients with squamous-cell cancer of the lower lip from one surgery department	61 age- and sex-matched hospital patients without prior diagnosis of cancer	Interview	Use of snuff	2*			*2 cases and 2 controls used snuff only. No details on mixed tobacco users provided
Lewin <i>et al.</i> (1998), Stockholm and southern Sweden, 1988–91		605 men from hospitals and cancer registries with head and neck cancer; oral cavity (128), pharynx (138), larynx (157), oesophagus (123); 40–79 years old; response rate, 90%	756 controls from the population registry; stratified by region and age; response rate, 85%	Personal interviews conducted by two specially trained nurses	Current snuff use Former snuff use > 50 g/week <i>Never smokers</i> Current snuff use Former snuff use Current snuff use Former snuff use > 50 g/week Current snuff use Former snuff use	43 40 38 9 10 15 8 7	<i>Head and neck</i> 1.0 (0.6–1.6) 1.2 (0.7–1.9) 1.6 (0.9–2.6) 3.3 (0.8–12.0) 10.5 (1.4–117.8) <i>Oral cavity</i> 1.0 (0.5–2.2) 1.8 (0.9–3.7) 1.7 (0.8–3.9) <i>Pharynx</i> 0.7 (0.3–1.5) 0.8 (0.3–1.9)	Age, region, smoking, alcoholic beverage consumption	
Schildt <i>et al.</i> (1998), northern Sweden, 1980–89	ICD-7 140, 141, 143–145	418 (175 alive; 235 deceased with relatives) reported to cancer registries with squamous-cell cancer; 354 matched pairs (237 men, 117 women) analysed	From population registry; matched by age, sex, county, vital status and year of death for deceased cases	Postal questionnaire	Ever use of snuff Current snuff use Former snuff use <i>Never smokers</i> Current snuff use Former snuff use Current snuff use Former snuff use	 39 28 19 9 9 7	<i>Oral cancer</i> 0.8 (0.5–1.3) 0.7 (0.4–1.1) 1.5 (0.8–2.9) 0.7 (0.4–1.2) 1.8 (0.9–3.5) <i>Lip cancer</i> 'Close to unity' 1.8 (0.9–3.7)	Matching variables	'Ever use' also adjusted for smoking and alcoholic beverage consumption

Table 71 (contd)

Reference, study location, period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
India and Pakistan									
Chandra (1962), India, 1955–59		450 cancers of the buccal mucosa registered in a hospital in Calcutta	500 friends or relatives who came to hospital with the patients, approximately age-matched	[Not reported]	Tobacco chewing No Yes No Yes	<i>Men</i> 18 <i>Women</i> 5	[2.7] [2.5]		Not specified if tobacco product chewed was tobacco only or tobacco with lime
Wahi <i>et al.</i> (1968), India, 1964–66		346 oral and oro-pharyngeal cancers reported to temporary cancer registry in Uttar Pradesh	10% cluster sample of the district population	Interview	Non-chewers of tobacco <i>Pattiwala*</i> chewer	84	Period prevalence rate 0.36/1000 1.17/1000		*Sun-cured tobacco leaf used with or without lime
Jafarey <i>et al.</i> (1977), Pakistan, 1967–72		1192 histologically diagnosed cancers of oral cavity or oropharynx	3562 controls matched for age, sex, place of birth	[Not reported]	Tobacco chewing No Yes No Yes	<i>Men</i> 27 <i>Women</i> 39	[10.4] 13.7		
Goud <i>et al.</i> (1990), India, 1972–75		102 oral cancers from one hospital in Varanasi	102 age- and sex-matched patients from surgical and general wards of same hospital	Questionnaire	Chewing tobacco <i>Khaini</i> <i>Zarda</i> <i>Khaini and zarda</i>	35 36 8	[2.1] [3.7] [2.8]		Not clear whether <i>khaini</i> and <i>zarda</i> were chewed with or without betel quid
Wasnik <i>et al.</i> (1998), India [years of study not reported]		123 (73 men, 50 women) histologically confirmed 'oro-pharyngeal' cancers from three hospitals in Nagpur	246 pair-matched controls; 123 non-cancer patients and 123 patients with cancer at other sites; matched for age, sex	[Not reported]	Tobacco chewing Use of tobacco-containing material for cleaning teeth	24 33	11.4 (4.4–29.6) 4.1 (2.0–8.7)		Results refer to control group 1; in multivariate analysis, all types of tobacco chewing were combined.

Table 71 (contd)

Reference, study location, period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Merchant <i>et al.</i> (2000), Pakistan, 1996–98		79 (54 men and 25 women) histologically confirmed oral squamous-cell cancers (buccal, gingiva, floor of mouth, tongue, palate; fauces and others) from three hospitals	149 (94 men, 55 women) from orthopaedic and general surgical wards, with no past or present malignancy; individually matched on age, sex, hospital	Structured questionnaire, trained interviewer	Ever use of <i>naswar</i>	13	9.5 (1.7–53.5)	Cigarette smoking, alcoholic beverage consumption	
Africa									
Idris <i>et al.</i> (1995b), Sudan, 1970–85	ICD-0 141.5, 143.8, 144.9, 145.0, 141.9, 145.5	(1) 375 squamous-cell cancer of the lip, buccal cavity, floor of mouth (sites of preference for placement of quid); (2) 271 squamous-cell cancer of the tongue, palate, maxillary sinus (sites with little or no contact with quid); both groups admitted to the Radiation and Isotope Center, Khartoum, Sudan	(1) 204 non-squamous-cell oral cancer and cancer of non-oral sites unrelated to tobacco, admitted to the same hospital during the same period; (2) 2820 volunteers attending oral health education programmes in various regions of Sudan	Questionnaire at registration in hospital; similar questionnaire administered by trained interviewers to volunteers	<i>Toombak</i> Never User < 10 years > 11 years Never User < 10 years > 11 years	157 218 10 120	Hospital controls 1.0 7.3 (4.3–12.4) 0.7 (0.3–1.8) 11.0 (4.8–25.1) Population controls 1.0 3.9 (2.9–5.3) 0.2 (0.1–0.4) 4.3 (2.9–6.3)	Age, sex, tribe, residence	

CI, confidence interval; HCFA, Health Care Financing Administration; RDD, random-digit dialling

above for whom data on tobacco were available. Two oral cancers were observed in ever users of smokeless tobacco and 1.9 was expected based on US rates. No oral cancers were observed among exclusive users of smokeless tobacco, but only 0.8 were expected. [The Working Group noted that this study had limited power to examine use of smokeless tobacco and the risk for oral cancer.]

The cohorts of the American Cancer Society comprised volunteers, aged 30 years or above, who responded to a mailed questionnaire and resided in a household in which at least one member was aged 35 years or more (Chao *et al.*, 2002; Henley *et al.*, 2005). The CPS-I cohort included 456 487 men and 594 544 women, and the CPS-II cohort included 508 351 men and 676 306 women. At enrolment in 1959 (CPS-I) or 1982 (CPS-II), cohort members were questioned on use of smokeless tobacco. For CPS-I, vital status was followed-up through to 1972; 6.7% were lost to follow-up and follow-up was truncated for logistic reasons in 1965 for another 4.9%. Death certificates were 97% complete and were coded to ICD-7. For CPS-II, vital status was followed-up through to 1996 (Chao *et al.*, 2002) or 2000 (Henley *et al.*, 2005). Death certificates were 99.8% complete and were coded to ICD-9. Analyses were restricted to men who had had no previous cancer (except for non-melanoma skin cancer) at enrolment. Chao *et al.* (2002) further restricted the analysis to men for whom information on tobacco was available ($n = 467\ 788$) and Henley *et al.* (2005) restricted the analysis to men who had never used any other tobacco. In the CPS-I cohort, the hazard ratio for oral and pharyngeal cancers (ICD-7 140-148) for current users of smokeless tobacco was 2.02 (four deaths; 95% CI, 0.53–7.74), adjusted for potential confounders such as alcoholic beverage consumption and dietary intake. In the CPS-II cohort, the multivariate-adjusted hazard ratio for oral and pharyngeal cancers (ICD-9 140-148) was 0.9 (one death; 95% CI, 0.12–6.71) for current users of smokeless tobacco. No deaths occurred among former users of smokeless tobacco.

(ii) *Case-control studies*

A hospital-based case-control study in Atlanta, GA, USA (Vogler *et al.*, 1962), included four groups who were enrolled over a 19-month period (1956–57): 333 white patients (235 men, 98 women) who had cancers of the oral cavity, pharynx or larynx, 214 patients who had other diseases of the mouth including leukoplakia, 584 patients who had other cancers and 787 patients who had no cancer and whose mouths were not examined. Use of smokeless tobacco was assessed by interview or questionnaire. Among 642 urban women, 40% of the 38 who had oral cavity cancers, but only 2%, 3% and 1% of the 57 who had other mouth diseases, 170 who had other cancers and 377 non-cancer controls, respectively, had used snuff. Similar findings were observed for the 371 rural women: 75% of the 55 cases of oral cavity cancer had used snuff orally in contrast to 11% of 37 who had other mouth diseases, 20% of 129 who had other cancers, and 11% of 150 non-cancer patients. Only 7% of female rural cases smoked. About 30–40% of urban women smoked cigarettes, but smoking habits were similar in each study group. The differences in snuff use between cases and controls were statistically significant for most of the age strata studied. In contrast to 53 (74%) women who had oral cavity cancer, one

of three female lip cancer patients and two (11%) women who had pharyngeal or laryngeal cancer had used snuff. [The Working Group noted that the reportedly similar proportions of smoking habits among urban women and the low proportion of smokers in the rural women indicate that the association between the use of snuff and cancer of the oral cavity was not confounded by smoking. Confounding by smoking could not be ruled out in men and results are not reported here.]

Williams and Horm (1977) conducted a population-based case-control study of the etiology of cancer at many different sites based on the interview responses of randomly selected incident cases of invasive cancer ($n = 7518$; 57% of those selected) from the Third National Cancer Survey (1969–71). Controls for smoking-related cancer case groups comprised men and women who had cancers that were unrelated to smoking. Among men, use of chewing tobacco and snuff was strongly associated with cancer of the gum or mouth, but not with cancer of the lip and tongue or pharynx; after controlling for age, race and smoking habits, relative risks were 3.9 (eight cases; $p < 0.01$) for moderate and 6.7 (three cases; non-significant) for heavy use of chewing tobacco or snuff. Among women, the relative risk for use of chewing tobacco or snuff for cancer of the gum or mouth was 4.9 (two cases; non-significant).

Winn *et al.* (1981a) conducted a case-control study of cancers of the oral cavity and pharynx among women in North Carolina, USA in 1975–78 to examine reasons for the exceptionally high rates of mortality from these cancers among white women throughout the southeastern USA. A total of 232 women (91% of eligible cases) who had been hospitalized with or who had died from cancers of the tongue (ICD-8 141), gum (ICD-8 143), floor of mouth (ICD-8 144), other mouth (ICD-8 145), oropharynx (ICD-8 146), hypopharynx (ICD-8 148) and pharynx unspecified (ICD-8 149) were included in the case group. Two age-, race- and region of residence-matched controls were obtained for each case; an interview was completed for 410 of the 502 eligible controls, excluding subjects with mental disorders or cancer of the oesophagus, larynx or other oral or pharyngeal diseases. Subjects or their next of kin were interviewed in their homes. Tobacco-related risks were estimated by using a common reference group: women who did not use tobacco. The relative risk for white women who used only oral snuff was 4.2 (79 cases; 95% CI, 2.6–6.7), while the relative risk associated with cigarette smoking among non-users of snuff was 2.9 (70 cases; 95% CI, 1.8–4.7). Among white women, the relative risk for those who both used oral snuff and smoked was 3.3 (11 cases; 95% CI, 1.4–7.8); these women had smoked fewer cigarettes and used snuff for fewer years than women who only smoked or used snuff. Risks for black women were somewhat lower, but they had used snuff for fewer years and had used fewer tins per week. Although 37 women had chewed tobacco, all but three were also oral snuff users. One-third of all oral snuff users had started the practice by the age of 10 years, and the average duration of use among white women was 48 years. For cancers of the gum and buccal mucosa, oral snuff use among nonsmokers was related to years of use, with relative risks of 13.8 (three cases; 95% CI, 1.9–98.0) for 1–24 years, 12.6 (10 cases; 95% CI, 2.7–58.3) for 25–49 years and 47.5 (15 cases; 95% CI, 9.1–249.5) for 50 or more years of use. For cancer at other sites

of the mouse and of the pharynx, the corresponding relative risks were 1.7, 3.8 and 1.3. The findings relating to oral snuff use could not be explained by poor dentition (Winn *et al.*, 1981b) or by use of mouthwashes (Blot *et al.*, 1983). The consumption of fruit and vegetables was associated with a reduction in risk in the study population, and was primarily evident in cigarette smokers but not among oral snuff users (Winn *et al.*, 1984). A subsequent additional analysis compared the findings on snuff use and oral and pharyngeal cancer among study subjects who responded for themselves and those for whom next of kin responded to the questions on tobacco use (Winn 1986). Odds ratios by cancer site and race tended to be higher for self-interview versus next-of-kin data. Among non-smokers and non-alcoholic beverage drinkers, the odds ratio for oral and pharyngeal cancer was 3.8 (81 cases; 95% CI, 2.3–6.3) for snuff use.

Stockwell and Lyman (1986) ascertained cases and controls from the population-based cancer registry in the state of Florida, USA, over a 1-year period in 1982. Cases were persons who had incident cancers of the lip, tongue, salivary glands, gum, floor of mouth, other parts of mouth, oropharynx, hypopharynx, pharynx (unspecified) and nasopharynx (ICD-O 140-149). All cases of cancer of the colon and rectum, cutaneous melanoma and endocrine neoplasia from the same source during same period formed the control group. Data on tobacco use were obtained from clinical and registry records, and were available for 79% of the 2351 study subjects data (82% of cases, 78% of controls). Odds ratios, adjusted for age, sex, race and tobacco use by anatomical site were: tongue, 2.3 (95% CI, 0.2–12.9); salivary gland, 5.3 (95% CI, 1.2–23.4); mouth and gum, 11.2 (95% CI, 4.1–30.7); pharynx, 4.1 (95% CI, 0.9–18.0); and nasopharynx, 5.3 (95% CI, 0.7–41.6). [A limitation of this study is that information on tobacco use was obtained from medical records. It seems improbable that all hospitals in Florida captured this information uniformly and it is possible that clinicians may have been more careful in obtaining medical record information from persons who had these head and neck cancers compared with patients who had other forms of cancer.]

In a case-control study in the USA, 623 patients with head and neck cancer were recruited. Cancers of the oral cavity, the oropharynx and the hypopharynx were used as cases and controls were patients with cancer of the salivary gland, nasopharynx and paranasal sinuses. Among men, 3.5% had ever used snuff or chewed tobacco regularly. The authors reported that “there were no statistically significant differences between cancer site groups on these users of tobacco” (Young *et al.*, 1986) [data not shown].

The population-based case-control study of Blot *et al.* (1988) enrolled subjects from cancer registries in New Jersey, Atlanta metropolitan area, Santa Clara and San Mateo counties, and Los Angeles, USA. Cases included all black and white persons aged 18–79 years with incident, pathologically confirmed cancer (coded ICD-9 141–149), excluding cancer of the salivary gland (ICD-9 142) and cancer of the nasopharynx (ICD-9 147) from 1 January 1984 through to 31 March 1985. Random-digit dialling was used to ascertain controls aged 64 years or younger and Health Care Financing Administration (HCFA) was used for controls aged 65 years and older; controls were frequency-matched on age, sex and race to the cases. Structured questionnaires were administered by trained

interviewers in homes and next of kin responded for 22% of cases and 2% of controls. The response rate was 75 and 76% for cases and controls, respectively, and a total of 1114 cases and 1268 controls were included in the analysis. Among men, 6% of 762 cases and 7% of 837 controls used smokeless tobacco, mostly chewing tobacco. Nearly all tobacco chewers were smokers. Among women, 3% of 352 cases and 1% of 431 controls used snuff [odds ratio, 3.44]. Among nonsmoking women, the odds ratio for snuff was 6.2 (95% CI, 1.9–19.8), based on six cases and four controls who used snuff. Nonsmoking women primarily used snuff rather than chewing tobacco. All six cases had oral cavity cancer.

Spitz *et al.* (1988) identified cases who had histologically confirmed squamous-cell carcinoma of the tongue, floor of the mouth, oral cavity, oropharynx and larynx in white US residents, at the MD Anderson Hospital, Houston, TX, USA, from January 1985 through to February 1987. Laryngeal cancer accounted for 38% of the 131 male cases. Controls were patients at MD Anderson Hospital during the same period, were randomly selected and were frequency-matched on age (± 5 years) and sex; patients who had squamous-cell carcinoma of any site were excluded. The study included 185 cases (131 men and 54 women) and 185 controls aged 29–95 years. Self-administered questionnaires were part of the registration procedure. The authors reported that there was ‘no difference in distribution of sites of malignancy for snuff users compared to all other cases’. Among men, the crude odds ratio for chewing tobacco was [1.0]. For women, the odds ratio for snuff use was 3.4 (95% CI, 1.0–10.9). There was no adjustment for smoking. All nine snuff dipping cases drank alcoholic beverages, seven also chewed tobacco, eight smoked cigarettes and one smoked cigars and pipes. Three of four snuff dipping controls also smoked cigarettes.

Newly diagnosed cases were identified from three hospitals in São Paulo, Curitiba and Goiânia, Brazil, and comprised carcinomas of the tongue, gum, floor of the mouth and other oral cavity (ICD-9 141, 143-145) diagnosed from 1 February 1986 to 30 June 1988 (Franco *et al.*, 1989). Two controls per case were identified from same or neighbouring general hospitals, were individually matched on sex, 5-year age group and trimester of hospital admission and excluded diagnoses of neoplasms or mental disorder. Cases were interviewed using a structured questionnaire in hospital and controls were interviewed privately. Four per cent of 232 cases and 3% of 464 controls used smokeless tobacco. The authors reported that use of smokeless tobacco and oral cancer were ‘not associated’. The crude odds ratio was [1.4]. They noted that the relative risk estimates were independent of tobacco smoking or alcoholic beverage drinking, sex or anatomical site. [The Working Group noted that data on the manner in which adjustment was carried out for these factors were not shown and that confidence intervals or statistical significance were not reported.]

A population-based case-control study by Maden *et al.* (1992) enrolled subjects from three urban counties of western Washington State, USA. Cases were men aged 18–65 years with in-situ and invasive squamous-cell cancers of the lip, tongue, gum, floor of the mouth, unspecified mouth and oropharynx diagnosed during 1985–89. Controls ascertained by random-digit dialling were frequency-matched to cases on age (5-year groups),

sex and year of diagnosis; 131 cases (54.4%) and 136 controls (63%) completed in-person questionnaire interviews at home or elsewhere. Of 131 cases, 15% used smokeless tobacco in contrast to 4% of 136 controls, which yielded an age-adjusted odds ratio of 4.5 (95% CI, 1.5–14.3). [The Working Group noted that smoking was not controlled for.]

Histologically confirmed oral and pharyngeal cancers (including cancers of the tongue, floor of the mouth, oropharynx and hypopharynx) were identified in one study (Marshall *et al.*, 1992) from 20 hospitals in three New York counties, USA, during the period 1975–83. Cases of black ethnicity were excluded. Cases were individually matched on neighbourhood, age (± 5 years) and sex. Of 513 cases contacted, 290 (56%) participated and 290 controls were included. The authors noted that “there was a risk associated with chewing tobacco, but it was insignificant, with very few people exposed”. [The data to support this statement were not shown.]

Mashberg *et al.* (1993) identified 359 cases among black or white men who had in-situ or invasive squamous-cell carcinoma of the oral cavity or oropharynx in a Veterans hospital in New Jersey, USA, during 1972–83. A total of 2280 patients from the same series of clinical examinations who had no cancer or dysplasia of the pharynx, larynx, lung or oesophagus were recruited and interviewed in hospital between 1977 and 1982 and served as controls; 94% of study subjects participated. Only 52 cases and 255 controls had ever used smokeless tobacco. Chewing tobacco (odds ratio, 1.0; 95% CI, 0.7–1.4) and snuff (odds ratio, 0.8; 95% CI, 0.4–1.9) were not associated with oral cancer. No trend by duration of tobacco chewing was observed [data not shown].

Spitz *et al.* (1993) identified 108 white cases who had histologically confirmed cancers of the oral cavity (44), pharynx (31) and larynx (33) at MD Anderson Hospital, Houston, TX, USA, from June 1987 to June 1991. Controls who had no history of cancer were ascertained from blood and platelet donors and were frequency-matched to cases by age (± 5 years), race and sex. Patients completed a self-administered questionnaire in the hospital. The odds ratio for chewing tobacco was 1.2. Smoking was not controlled for.

Kabat *et al.* (1994) ascertained cases from 28 hospitals in eight cities in the USA. Cases had histologically confirmed cancers of the tongue, floor of the mouth, gums, gingiva, buccal mucosa, palate, retromolar area, tonsil and other pharynx during 1977–90. Controls were individually matched to cases on hospital, admission within 2 months after the case, age, sex and race, and excluded persons with diseases thought to be associated with tobacco or alcoholic beverages or prior history of tobacco-related cancers. The conditions among the controls were: 50% cancers (also including cancer of the stomach, endometrium and leukaemia), 7% benign neoplasms and 43% other diseases. A total of 1560 cases and 2948 controls were included. In-hospital questionnaire interviews were conducted with the study subjects. Among men, 6.1% of 1097 cases and 5.1% of 2075 controls chewed tobacco. Among women, less than 2% of 1336 subjects chewed tobacco. Among never-smoking men, 4.9% of 82 cases were regular chewers as were 2.2% of 448 controls, yielding an odds ratio of 2.3 (95% CI, 0.7–7.3). Among never-smoking women, there were no tobacco chewers. Among never-smoking women, 3.5% of 113 used snuff in contrast to 0% of 470 controls (odds ratio, 34.5; 95% CI, 8.5–140.1). Among never-

smoking men, 0% of 82 cases and 0.9% of 444 controls were snuff users. [The estimate of the odds ratio of 34.5 used 0.5 snuff-using controls.]

Patients aged 21–80 years diagnosed with histologically confirmed cancer of oral cavity and pharynx (ICD-9 141, 143–146, 148, 149) were recruited between 1981 and 1990 from hospitals in Illinois, Michigan, New York and Philadelphia, USA (Muscat *et al.*, 1996). Hospital patients with conditions unrelated to tobacco use were matched to cases by sex, age (± 5 years), race and date of admission (± 3 months). Response rates were 91% for cases and 97% for controls to yield 1009 cases (687 men, 322 women) and 923 controls (619 men, 304 women). A questionnaire interview was conducted with cases and controls. Among men, 5.5% of 687 cases used chewing tobacco at least once a week for 1 year or more as did 5.3% of 619 controls [crude odds ratio, 1.04]. No women used chewing tobacco. Among men, 1.3% of cases and 1.6% of controls used snuff at least once a week for 1 or more years [crude odds ratio, 0.81]. For women, the crude odds ratio for snuff use was [1.9].

Muscat *et al.* (1998) reported a hospital-based case-control study on salivary gland cancer. One hundred and twenty-eight patients with newly diagnosed histologically confirmed salivary gland cancer and 114 age- and gender-matched controls were interviewed. One case reported using snuff, and three cases and three controls were tobacco chewers.

A population-based case-control study was conducted by Schwartz *et al.* (1998) of in-situ and invasive (92%) squamous-cell cancers of the tongue, gum, floor of mouth, unspecified mouth, tonsils and oropharynx in persons aged 18–65 years during 1990–95 in counties of Seattle area, WA, USA. Controls were ascertained by random-digit dialling and were frequency-matched to the cases on sex and age in a 3:2 ratio of controls to cases; 284 cases (165 men, 119 women) and 477 controls (302 men, 175 women) completed an in-person questionnaire interview; response rates among cases and controls were 63.3% and 60.9%, respectively. Among men, 6.7% of 165 cases and 5.6% of 302 controls used smokeless tobacco (odds ratio, 1.0; 95% CI, 0.4–2.3). Only one female control used smokeless tobacco. [The Working Group noted that smoking was not controlled for.]

(iii) *Cross-sectional study*

A cross-sectional study (Sterling *et al.*, 1992) used two nationally representative surveys to examine the relationship between smokeless tobacco use and cancer of the oral cavity and digestive organs: the 1986 National Mortality Follow-back Survey and the 1987 NHIS. The 1986 National Mortality Follow-back Survey was based on a stratified probability sample of 18 733 decedents in 1986 who were 25 years or older at time of death. A questionnaire sent to their next of kin also included questions on use of smokeless tobacco. Information was obtained for 16 598 decedents. The NHIS annually surveys samples of the non-institutionalized civilian population using a multistage, probability sampling design. Interviewers administered a questionnaire to sample persons in the household. The 1987 NHIS obtained data on the use of smokeless tobacco. Using a reference category of less than 100 times lifetime use of smokeless tobacco, the relative risks for cancers of the oral cavity and pharynx (ICD-9 140–149) for 100–9999 and 10 000 or

more lifetime use were 0.9 (95% CI, 0.3–3.4) and 1.2 (95% CI, 0.3–4.6), respectively, adjusted for sex, race, smoking, alcoholic beverage consumption and occupational group. [The Working Group noted concerns due to uncertainty of the comparability of the two surveys.]

(iv) *Characteristics of oral cancer in smokeless tobacco users*

Link *et al.* (1992) studied a series of 874 squamous-cell carcinomas and 129 verrucous carcinomas. Compared with the squamous-cell carcinomas in non-users of smokeless tobacco, those in the 12 users of smokeless tobacco developed later (mean age, 72.6 versus 61.5 years) and occurred in the buccal mucosa vestibule (33.3% versus 7.7%). Compared with the verrucous carcinomas in non-users of smokeless tobacco, those in the 10 users of smokeless tobacco developed later (mean age, 70.5 versus 64.2 years) and were more likely to occur in the buccal mucosa vestibule (80.0% versus 31.2%).

The Tumor Registry of Wake Forest University Medical Center, Winston-Salem, NC, USA, was used to identify all patients with oral cancer seen at this institution between 1977 and 1991 (Wray & McGuirt, 1993). Of 160 cases who used smokeless tobacco (primarily snuff), 128 (119 women, nine men; mean age, 73.3 years) used only snuff. Only 1.6% had used smokeless tobacco for less than 20 years and 78% had used smokeless tobacco for more than 40 years; 80% of the tumours were located where the smokeless tobacco was customarily held — between the cheek and the gum. Only one non-squamous-cell cancer was observed.

(b) *Europe*

(i) *Cohort study*

A Norwegian cohort was comprised of two samples; one was a probability sample of the general adult population of Norway identified from the 1960 census and the other consisted of relatives of Norwegian migrants to the USA. Information on snuff use and smoking was collected through mailed questionnaires in 1964 and 1967; response rates were 79% of the probability sample in 1964 and between 88 and 93% in 1997. Of the cohort, 12 431 men were alive on 1 January 1966 and information on snuff use was available for 10 136. Cohort members were followed until December 2001 for cancer incidence using national cancer registries, date of emigration or date of death. The follow-up was 99.9% complete. Cancer incidence was coded according to ICD-7 (see Table 69). After adjustment for age and smoking, the relative risk associated with ever using snuff was 1.10 (nine cases; 95% CI, 0.5–2.4) for oral and pharyngeal cancer (ICD-7 141–148) (see Table 70). The relative risks for former and current users were of the same order of magnitude but were based on smaller numbers (Heuch *et al.*, 1983; Boffetta *et al.*, 2005).

(ii) *Case-control studies*

In a study from Sweden, 477 patients with cancers of the lip, oral cavity, maxillary sinus, nasopharynx, hypopharynx, oesophagus and larynx were compared with 333 patients with other malignancies seen in a hospital in Stockholm, during 1952–55 (Wynder &

Wright, 1957). Cases and controls were interviewed and their medical records were reviewed. More of the patients who had buccal and gum cancer used snuff than controls. There was suggestive evidence by ridit analyses that snuff use was related to buccal mucosal cancer in men; nearly half of the patients were habitual users of snuff and the majority had tumours in the area of the mouth where the quid was held. Tobacco smoking among the cancer cases was similar to that in controls. Other upper aerodigestive tract cancers were not associated with snuff use. [The response rate and the number of snuff users were not reported.]

Blomqvist *et al.* (1991) investigated the role of different risk factors for squamous-cell carcinoma of the lower lip. Fifty-seven men and four women, all treated at the department of plastic surgery at a hospital in Sweden, were interviewed. Age- and sex-matched controls were selected among non-tumour patients without a prior diagnosis of cancer [no further details on the selection of controls were reported]. Two of the cases and two of the controls reported using snuff only [in all further analyses, all types of tobacco consumption were combined into one exposure factor].

In a population-based case-control study of 161 cases who had intra-oral squamous-cell carcinoma and 400 controls drawn from the Danish Central Population Register, matched on age and sex, eight patients and 14 controls were using or had used chewing tobacco (Bundgaard *et al.*, 1995). [No risk estimate reported.]

Lewin *et al.* (1998) studied squamous-cell carcinoma of the head and neck in Stockholm and the southern regions of Sweden. Cases included cancer of the oral cavity, pharynx, larynx and oesophagus and were identified through the hospital departments that treated the majority of these cases and the regional cancer registries in 1988–91. Controls were selected as a stratified random sample from the population registries that covered the source population. The number of cases identified was 605 and the number of controls selected was 756; the participation rates were 90 and 85%, respectively. Of the 605 cases, 128 were cancers of the oral cavity and 138 were cancers of the pharynx. Exposure data, including snuff use, were collected by personal interviews conducted by two specially trained nurses. The relative risk for the whole case group was 1.0 (43 cases; 95% CI, 0.6–1.6) for current snuff use, 1.2 (40 cases; 95% CI, 0.7–1.9) for former snuff use and 1.6 (38 cases; 95% CI, 0.9–2.6) for use of > 50 g/week, after adjustment for smoking and alcoholic beverage consumption. In the subgroup of never smokers, the relative risk in the whole case group for ever users of smokeless tobacco was 4.7 (nine cases; 95% CI, 1.6–13.8); the relative risk for current use was 3.3 (95% CI, 0.8–12.0) and that for former use was 10.5 (95% CI, 1.4–117.8). When the analysis was restricted to cancer of the oral cavity, the relative risk was 1.0 (10 cases; 95% CI, 0.5–2.2) among current users, 1.8 (15 cases; 95% CI, 0.9–3.7) among former users and 1.7 (95% CI, 0.8–3.9) among users of more than 50 g/week. For cancer of the pharynx, the relative risks for current and former snuff use were 0.7 (eight cases; 95% CI, 0.3–1.5) and 0.8 (seven cases; 95% CI, 0.3–1.9), respectively.

A study in the northern region of Sweden comprised cases of oral cancer (ICD-7 140, 141, 143, 143–145) diagnosed in 1980–89 (Schildt *et al.*, 1998) and identified through

cancer registries. Of the 418 cases, 175 were alive at the time of the study and 235 deceased had relatives. Controls were matched on age, sex, county and vital status. For each living case, one control was selected from the population registry; for each deceased case with relatives, one deceased control was selected from the Cause of Death Registry. Controls were further matched on age, sex, county and, for deceased cases, on year of death. Exposure, including use of snuff, was assessed based on a postal questionnaire sent to the living subjects and to the next of kin for the deceased; 354 matched pairs were analysed. The relative risk was estimated to be 0.7 (39 cases; 95% CI, 0.4–1.1) for current snuff users and 1.5 (28 cases; 95% CI, 0.8–2.9) for former snuff users. After restriction to never-smokers, the corresponding relative risks were 0.7 (19 cases; 95% CI, 0.4–1.2) and 1.8 (nine cases; 95% CI, 0.9–3.5), respectively. For lip cancer, the relative risk was 1.8 (95% CI, 0.9–3.7) for former snuff users and ‘close to unity’ for current snuff users. [The Working Group noted that the odds ratio in former snuff users increased from 1.5 (95% CI, 0.8–2.9) to 3.0 (95% CI, 0.9–9.4) in an analysis restricted to live subjects. Further, there was only a relative weak effect of smoking (relative risk, 1.1; 95% CI, 0.7–1.6) in an analysis with simultaneous adjustment for snuff and alcoholic beverage use.]

(c) *India and Pakistan*

Many studies from South-East Asia combined all smokeless tobacco use into one category, which was frequently termed tobacco chewing. In these studies, tobacco chewing often includes chewing of betel quid with tobacco. All such studies have been included in the monograph on betel-quid and areca-nut chewing (IARC, 2004a) and are not included here. Studies that have reported separate results for tobacco chewing without betel quid are reviewed here.

Chandra (1962) selected 450 cases of cancer of the buccal mucosa registered in a hospital in Calcutta, India, during 1955–59, and used 500 of the friends or relatives who came to the hospital with the patients as controls. Cases and controls were approximately age matched. Tobacco chewing was reported by 6.3% of 287 cases and 4.2% of 410 controls among men and 3.1% of 163 cases and 2.2% of 90 controls among women. Relative risks for tobacco chewing compared with no chewing or smoking were [2.7] for men and [2.5] for women. [The author did not clarify whether the chewing habit was tobacco only or tobacco plus lime.]

A population-based prospective study was reported by Wahi *et al.* (1968) from a temporary cancer registration system established in Uttar Pradesh (Mainpuri district). Over a period of 30 months (1964–66), a total of 346 oral- and oropharyngeal cancer cases were detected and confirmed. Exposure data were obtained by questionnaire, and a house-to-house interview survey was conducted on a 10% cluster sample of the district population. The numbers in various exposure categories were then extrapolated to the population as a whole and used as denominators to calculate oral cancer ‘period prevalence rates’ for different types of tobacco chewing. Prevalence rates among non-chewers of tobacco and chewers of *Pattiwala* (sun-cured tobacco leaf with or without lime) were 0.36/1000 and 1.17/1000 (based on 84 exposed cases), respectively. [The Working Group noted that

differences in age between cancer patients and the population sample do not seem to have been taken into account; and it is possible that the prevalence of chewing within the population was age-dependent.]

Jafarey *et al.* (1977) reported a hospital-based case-control study in Pakistan. The cases were 1192 histologically diagnosed oral cavity and oropharyngeal cancers. The 3562 controls were matched for age, sex and place of birth. Among men, 4% of 683 cases and 3% of 1978 controls and, among women, 7.7% of 509 cases and 3% of 1584 controls chewed tobacco, yielding relative risks of 10.4 and 13.7, respectively, compared with those who neither chewed nor smoked. [The Working Group considered that, although the chewing in this study is reported as 'tobacco' chewing, in view of other publications by the same authors, it was probably chewing of tobacco and lime.] Eighty-four patients and 114 controls used *naswar* (tobacco, slaked lime and indigo) and 88 patients and 1690 controls did not chew. The relative risk associated with *naswar* use was 14.2. [The Working Group noted that potential confounding due to other tobacco-related practices was not adjusted for.]

Goud *et al.* (1990) reported a case-control study of 102 oral cancer cases from a hospital in Varanasi, India, and an equal number of age- and sex-matched controls selected from general and surgical wards. The odds ratios were [2.1] for *khaini* use, 3.7 for *zarda* use and 2.8 for *khaini* plus *zarda*. [It was not clear whether *khaini* and *zarda* were chewed by themselves or in some cases as an ingredient of betel quid. There was no mention of control for smoking.]

Wasnik *et al.* (1998) reported a matched case-control study of 123 cases of histologically confirmed 'oropharyngeal' cancers [ICD codes not specified — probably included oral and pharyngeal cancers] selected from three hospitals in Nagpur, India. Two control groups were used: one of 123 non-cancer patients and another of 123 patients with cancer at other sites [not specified]. Controls were matched for age and sex. Of the cases, 24 were tobacco chewers (excluding those who chewed betel quid) and 33 reported using tobacco-containing material for cleaning teeth [these may include betel-quid chewers]. Unadjusted odds ratios for the two control groups were 11.4 (24 cases; 95% CI, 4.4–29.6) and 23.7 (95% CI, 7.7–72.4) for chewing tobacco without betel quid and 4.1 (33 cases; 95% CI, 2.0–8.7) and 8.7 (95% CI, 3.3–22.9) for using tobacco-containing material for cleaning teeth. In a multivariate analysis, tobacco chewing (19.5% of cases) was combined with betel-quid chewing (63.4% of cases) and the odds ratio was 8.0 (95% CI, 4.9–14.8) when smoking, alcoholic beverage consumption, occupation and the use of tobacco-containing cleaning material were included in an unconditional logistic regression model. In the same model, the odds ratio for using tobacco-containing material for teeth cleaning was 5.2 (95% CI, 2.5–11.8).

Merchant *et al.* (2000) conducted a case-control study of 79 histologically confirmed primary oral squamous-cell carcinomas from three hospitals in Karachi, Pakistan. The 149 controls were selected from orthopaedic and general surgical wards, had no history of malignancy and were individually matched on hospital, sex and age (± 5 years). Ever use of *naswar* was reported by 13 cases and 10 controls to yield an odds ratio (adjusted for

cigarette smoking and alcoholic beverage consumption) of 9.5 (13 cases; 95% CI, 1.7–52.5).

(d) *Other parts of Asia*

One case of oral cancer was reported among 289 *naswar* users in the Kazakh SSR who underwent oral examination; no oral cancer was seen in 243 smokers or in 1480 persons who neither smoked nor used *naswar* (Aleksandrova, 1970).

Nugmanov and Baimakanov (1970) carried out a study in the Kazakh SSR in which the practices of oral cancer patients were compared with those of controls in relation to use of *naswar*. Of 93 oral cancer patients, 30.1% used *naswar* compared with only 6.7% of 247 controls. Further comparisons that involved 28 *naswar* users with oral cancer and 19 *naswar*-using controls revealed that patients with oral cancer used *naswar* more frequently and kept it in the mouth longer than controls. [The Working Group noted that the sources of cases and controls were not reported; confounding due to other tobacco-related practices was not adjusted for; and no adequate statistical analysis was performed.]

In a study from Saudi Arabia (Amer *et al.*, 1985), 49% of 68 patients with oral cancer reported using *shammah*. [The Working Group noted that the actual percentage may be higher, since *shammah* is illegal in Saudi Arabia and there may be some reluctance to admit to its use.]

Ibrahim *et al.* (1986) reported on the association between use of smokeless tobacco products and the risk for squamous-cell carcinoma of the head and neck. Between December 1981 and December 1983, 38 patients who had oral cancer and 26 patients who had pharyngeal or laryngeal cancer were seen at the King Faisal Hospital, Saudi Arabia. Based on information from the patients' files and further questioning during follow-up, all the 38 patients with oral cancer either used *al-shammah* alone (16) or used both *al-shammah* and *alquat* (22). Fourteen of the 26 patients with pharyngeal and laryngeal cancer used *al-shammah* alone.

From February 1982 to December 1989, a total of 65 patients who had squamous-cell carcinoma of head and neck (21 cancers of the oral cavity, 35 cancers of the pharynx including 28 cancers of the nasopharynx and nine cancers of the larynx) were seen at the King Faisal Hospital (Al-Idrissi, 1990); 17 of the 65 cases (26.2%) had chewed a mixture of tobacco, pepper and oil (*al-shammah*) for an average of about 10 years. [The Working Group noted that this case series probably overlapped with that reported by Ibrahim *et al.* (1986).]

The records from the Tumour Registry of the King Faisal Specialist Hospital and Research Center, Saudi Arabia, from 1976 to 1995 were reviewed (Allard *et al.*, 1999). Among a total of 26 510 cancer patients, the frequency of oral cancer was investigated, specifically for those primary sites located near the habitual placement of *shammah* (mucosa of the lower lip, lower gum, tongue, floor of the mouth, cheek mucosa, vestibule of mouth and retromolar area). Of the 794 such oral cancers, 35.4% were referred from the province of Jizan. The percentage of such oral cancer cases from this province was substantially higher than that of other oral cancers (6.2%), total malignant cases referred

to the hospital from that province (5.6%) and the population of that province (6.0%) when compared with the whole of Saudi Arabia. [The Working Group noted that no information about the frequency of smokeless tobacco use in the province of Jizan was provided.]

(e) *Africa*

Elbeshir *et al.* (1989) interviewed 62 of 78 consecutive cases of oral cancer seen at the Department of Oral Surgery, Dental School, Khartoum, Sudan. Fifty (81%) patients (30 men, 20 women) who used oral snuff (*saffa*), five smoked cigarettes and a pipe, four only smoked cigarettes and eight patients reported no use of tobacco in any form. The mean duration of *saffa* use was 30 years (range, 10–45 years); 82% of the cases had used *saffa* for 20 years or more and one patient (aged 17 years) started using *saffa* at the age of 7 years.

During the period 1970–85, 850 cases of oral cancer (ICD 140–145), including 646 squamous-cell carcinomas and 204 tumours of other histology, were referred to the Radiation and Isotope Centre Khartoum, the only centre in Sudan that offered radiotherapy and chemotherapy to cancer patients (Idris *et al.*, 1995a). The squamous cell-carcinomas were classified into sites that had direct contact with the *toombak* quid (lip, buccal mucosa, floor of the mouth) ($n = 375$) and sites with less or no contact (tongue, palate, maxillary sinus) ($n = 271$). Information on *toombak* use or cigarette smoking, age, sex, area of residence and tribal origin was obtained from the cases and controls through questionnaires routinely administered to all patients admitted to the Centre. Among the three groups who had squamous-cell carcinomas with direct contact, with less or no contact and tumours of other histologies, 218 (58%), 52 (19%) and 23 (11%) used *toombak*, respectively. The corresponding numbers for cigarette smokers were 46 (12%), 29 (11%) and 21 (10%).

Using the same data, Idris *et al.* (1995b) investigated the association between use of *toombak* and carcinoma of the oral cavity in a case–control study. Squamous-cell carcinomas at sites with direct contact or with less or no contact were defined as case group 1 or case group 2, respectively, and the non-squamous-cell cancers served as control group 1. In addition, a second control group of 2820 volunteers who attended oral health education programmes in various regions of Sudan was recruited. For the first case group compared with never users of *toombak*, the odds ratios adjusted for age, sex, tribe and area of residence for *toombak* use were 7.3 (218 cases; 95% CI, 4.3–12.4) and 3.9 (95% CI, 2.9–5.3) for hospital and volunteer controls, respectively. Among users of *toombak* for > 11 years, the corresponding odds ratios were 11.0 (120 cases; 95% CI, 4.8–25.1) and 4.3 (95% CI, 2.9–6.3), respectively. Corresponding odds ratios for the second case group were moderately and statistically non-significantly increased compared with hospital controls and not increased compared with the control group of volunteers.

2.2.2 *Precancerous lesions*

Studies on the natural history of oral cancer suggest that several potentially malignant lesions and conditions precede the development of cancer of the oral cavity. Oral precancerous lesions of relevance are leukoplakia and erythroplakia (Pindborg *et al.*, 1996).

(a) *North America*

(i) *Cross-sectional studies*

A number of cross-sectional studies or case series in the USA have reported prevalences of oral soft-tissue lesions among smokeless tobacco users (Greer & Poulson, 1983; Wolfe & Carlos, 1987; Creath *et al.*, 1988; Cummings *et al.*, 1989; Ernster *et al.*, 1990; Grady *et al.*, 1990; Creath *et al.*, 1991; Greene *et al.*, 1992; Kaugars *et al.*, 1992; Little *et al.*, 1992; Sinusas *et al.*, 1992; Grasser & Childers, 1997; Tomar *et al.*, 1997; Martin *et al.*, 1999) (Table 72).

All studies showed higher prevalences of oral soft-tissue lesions in smokeless tobacco users compared with tobacco non-users; in those studies that distinguished between chewing tobacco and snuff (Ernster *et al.*, 1990; Grady *et al.*, 1990; Greene *et al.*, 1992; Sinusas *et al.*, 1992; Tomar *et al.*, 1997), a higher prevalence was observed both with chewing tobacco and with snuff.

In those studies that controlled for smoking, the relative risks for oral leukoplakia in smokeless tobacco users exceeded those of non-users for smokeless tobacco overall (Ernster *et al.*, 1990; Tomar *et al.*, 1997; Martin *et al.*, 1999), for snuff (Ernster *et al.*, 1990; Tomar *et al.*, 1997; Martin *et al.*, 1999) and for chewing tobacco (Ernster *et al.*, 1990; Tomar *et al.*, 1997).

Strong dose–response relationships were observed between intensity and duration of use of smokeless tobacco, snuff or chewing tobacco. Increasing use of smokeless tobacco was associated with increasing prevalences of mucosal lesions whether measured by hours per day with tobacco in the mouth (Ernster *et al.*, 1990; Greene *et al.*, 1992; Tomar *et al.*, 1997), amounts used (Creath *et al.*, 1988; Ernster *et al.*, 1990; Greene *et al.*, 1992; Martin *et al.*, 1999), shorter time since last used (Ernster *et al.*, 1990; Greene *et al.*, 1992), duration of use in months or years (Creath *et al.*, 1988; Ernster *et al.*, 1990; Greene *et al.*, 1992; Tomar *et al.*, 1997; Martin *et al.*, 1999) or frequency of use in days per month (Tomar *et al.*, 1997). Dose–response relationships were reported separately for chewing tobacco (Ernster *et al.*, 1990; Tomar *et al.*, 1997; Martin *et al.*, 1999) and for snuff (Ernster *et al.*, 1990; Tomar *et al.*, 1997).

Prevalences or prevalence odds ratios for oral lesions were higher in current than in former users, and former users had higher prevalences or prevalence odds ratios than never users (Ernster *et al.*, 1990; Grady *et al.*, 1990; Creath *et al.*, 1991; Greene *et al.*, 1992; Sinusas *et al.*, 1992; Tomar *et al.*, 1997).

Overall prevalence of lesions was higher among snuff users compared with tobacco chewers (Ernster *et al.*, 1990; Grady *et al.*, 1990; Greene *et al.*, 1992; Kaugars *et al.*, 1992; Sinusas *et al.*, 1992; Grasser & Childers, 1997; Tomar *et al.*, 1997; Martin *et al.*,

Table 72. Use of smokeless tobacco and prevalence of precancerous lesions in cross-sectional studies in the USA

Reference, study location, period	Study population	Prevalence of use; type of tobacco product	Type of lesions ^a	Exposure category	Prevalence of lesions (%)	Relative risk (95% CI or <i>p</i> value)	Adjustment for potential confounders; comments
Greer & Poulson (1983) ^b , Denver, CO	1119 adolescents in grades 9–12	10.4% [current] users of smokeless tobacco	Mucosal alterations according to own classification (degree 1–3)	Non-user	0	1.0 8.9 (<i>p</i> = 0.001)	Distribution of lesions among users with lesions (<i>n</i> = 50)
				User	42.7		
				Severity of lesions			
				Degree 1	50		
				Degree 2	36		
				Degree 3	14		
Wolfe & Carlos (1987), New Mexico [not reported]	226 Navajo American adolescents, aged 14–19 years	Use within last 7 months, 64.2%, of which 58.6% used snuff, 4.8% chewing tobacco, 36.6% both	Leukoplakia according to Greer & Poulson (1983) (degree 1–3)	Non-user	3.7	3.6 4.1 10.4 16.9 5.7	34/37 lesions coincided with the reported site of habitual quid placement.
				User	25.5		
				Degree 2 lesion	4.1		
				Degree 3 lesion	8.3		
				<i>Duration (years)</i>			
				≤ 1	13.3		
				2	15		
				3	38.5		
				4	62.5		
				≥ 5	21.1		
<i>Frequency of use</i>							
≤ 1 day/week	11.9						
1–2 days/week	33.3						
3–4 days/week	42.9						
≥ 5 days/week	40.0						
Cummings <i>et al.</i> (1989), Buffalo, NY, 1985	25 professional baseball players, aged 22–44 years; participation rate, 93%	76% ever use; chewing or dipping tobacco	Soft-tissue lesion diagnosed by dental oncologist	Non-user	0		In 4/5 subjects, lesion occurred at the location where tobacco was held
			Ever user	26.3			

Table 72 (contd)

Reference, study location, period	Study population	Prevalence of use; type of tobacco product	Type of lesions ^a	Exposure category	Prevalence of lesions (%)	Relative risk (95% CI or <i>p</i> value)	Adjustment for potential confounders; comments			
Ernster <i>et al.</i> (1990); Grady <i>et al.</i> (1990), Countrywide, 1988	1109 professional baseball players; participation rate, 85%	42% current, 4% occasional, 13% former; among current users, 75% used snuff, 21% chewed tobacco	Oral leukoplakia /erythroplakia, diagnosed by specially trained dentist, graded 1-4 (categories similar to those of Greer & Poulson, 1983)	Non-user	1.4	1.0	Adjustment for age, race, cigarette smoking, alcoholic beverage consumption and dental hygiene did not change results significantly; no chewing tobacco user had a degree 3 or 4 lesion; histology of lesions described in Daniels <i>et al.</i> (1992); 94% of lesions located in the mandibular area, including 42% in the anterior area			
				Former user	1.4	1.0 (0.2-5.0)				
				Occasional	2.5	1.8 (0.2-14.5)				
				Current	46.3	60.0 (27.8-129.5)				
				Chewing	17.2	14.5 (5.7-36.7)				
				Snuff	55.6	86.9 (39.9-189.5)				
				<i>Amount used</i>						
				<i>Snuff (can/week)</i>						
				< 1	36.4	39.8 (17.3-91.7)				
				2-3	69.2	156.2 (66.5-367.1)				
				> 4	83.6	354.1 (129.2-970.2)				
				<i>Chew (pouches/week)</i>						
				< 1	12.5	8.5 (3.0-32.9)				
				2-3	16.7	12.3 (3.8-51.3)				
				> 3	33.3	30.8 (9.4-128.3)				
				<i>Duration of use (years)</i>						
				≤ 3	32.4	33.2 (14.2-77.9)				
				4-6	52.0	75.1 (33.4-169)				
				7-9	52.7	77.4 (32.3-185)				
				≥ 10	50.0	69.4 (29.4-164)				
				<i>Hours in mouth/day</i>						
				0-0.5	24.5	22.6 (9.5-53.7)				
				> 0.5-1.0	42.8	52.1 (22.2-122)				
> 1.0-1.5	53.6	80.1 (32.2-199)								
> 1.5-2.0	67.5	144 (53-391)								
> 2.0-4.0	62.5	115 (46.0-291)								
> 4.0	83.8	361 (107-1215)								
<i>Time since last use (hours)</i>										
> 24	18.6	15.9 (5.9-42.9)								
> 12-24	22.7	20.4 (8.4-49.3)								
> 1-12	55.1	85.2 (37.1-195)								
≤ 1	74.3	201 (84.9-475)								
<i>Type of snuff</i>										
Copenhagen	61.3	111 (50.1-246)								
Skoal	54.0	81 (33-199)								
Hawken	5.3	3.9 (0.5-33.0)								

Table 72 (contd)

Reference, study location, period	Study population	Prevalence of use; type of tobacco product	Type of lesions ^a	Exposure category	Prevalence of lesions (%)	Relative risk (95% CI or <i>p</i> value)	Adjustment for potential confounders; comments
Creath <i>et al.</i> (1988, 1991), Alabama [not reported]	1116 adolescent football players, aged 10–19 years	4.8% current, 30.2% former; among current users, 35 used snuff, 7 used chew and 12 used both.	Oral leukoplakia diagnosed by dentist, according to Axéll <i>et al.</i> (1984)	Non-user	0.5	1.0	Current user = having used for at least 6 months and still using it; former user = stopped at least 1 month before study; 13/15 lesions in the mandibular vestibule retromolar areas
				Ever user	3.0	6.3 (<i>p</i> < 0.005)	
				Skoal Copenhagen		21.1 (<i>p</i> < 0.01)	
				Former user	1.2		
				Current user	13	5.8 (<i>p</i> < 0.001)	
Greene <i>et al.</i> (1992), Countrywide, 1989–90	894 professional baseball players recruited in 1989–90	37% current users (within week of interview)	Oral leukoplakia/erythroplakia, diagnosed by specially trained dentist, graded 1–4 (categories similar to those of Greer & Poulson, 1983)	Non-user	2.9	1.0	Extension of studies by Ernster <i>et al.</i> (1990) and Grady <i>et al.</i> (1990); degree 3–4 lesions found only in current users; prevalence available by seasonality of use for numerous variables
				Former	3.5	36.0	
				Current	51.7		
				Seasonal use	32.1		
				Year-round use	66.7		
				Snuff	61.2		
				Copenhagen	72.3		
				Skoal	42.6		
				Hawken	11.1		
Chewing tobacco	14.8						
Kaugars <i>et al.</i> (1992), Virginia [not reported]	347 users of smokeless tobacco recruited by advertisement; all white men aged 14–77 years	Use for at least 6 months	Epithelial dysplasia, graded 1–4 (focally mild-mild-moderate-severe)	All users	[13]		All lesions at the site of placement of the tobacco in the mouth
				Degree 3–4 lesions	[0.9]		
				Snuff	[14.4]		
				Chewing tobacco	[8.3]		

Table 72 (contd)

Reference, study location, period	Study population	Prevalence of use; type of tobacco product	Type of lesions ^a	Exposure category	Prevalence of lesions (%)	Relative risk (95% CI or <i>p</i> value)	Adjustment for potential confounders; comments	
Little <i>et al.</i> (1992), Oregon, Washington	245 out-patients drawn from Kaiser Permanente Dental Care Program who used smokeless tobacco	100% user (use during the previous week)	Soft-tissue lesions diagnosed by dental hygienist according to Greer & Poulson (1983)	Overall	79	9.35 (3.46–26.21)	85% of lesions at the placement of tobacco *Read from graph	
				<i>Severity of lesions</i>				
				Grade I	28			
				Grade II	27			
				Grade III	23			
				Grade III lesions				
				<i>Frequency of use</i>				
				≤ 2 days/week	7			
				3–6 days/week	7*			
				Daily	33			
				<i>Times/day</i>				
< 2 (<i>n</i> = 24)	0	*Read from graph						
2–5	18							
≥ 6 (<i>n</i> = 59)	37							
<i>Duration (years)</i>								
≤ 2	13							
2–5	18*							
6–10	18*							
≥ 11	47							
Sinusas <i>et al.</i> (1992), 1990	2006 professional baseball players of major and minor leagues		42.7% current use, 16.5% former use; moist snuff, chewing tobacco, plug tobacco, exclusively or in combination	Leukoplakia diagnosed by specially trained doctor, according to modification of the classification system by Greer & Poulson (1983) (degree 1–3)	Never user	6	9.35 (3.46–26.21)	One degree 3 lesion present in a year-round user of chewing tobacco
					Former user	6		
					Seasonal user	8		
		Year-round user			37			
		<i>Type of tobacco</i>						
		Moist snuff			34.2			
Chew or plug	16.7							
Grasser & Childers (1997), North Carolina, 1995	214 soldiers aged 18–47 years	7% current, 7% former; smokeless tobacco undefined	Oral leukoplakia, diagnosed by board-certified oral pathologist	Non-user	1 lesion			
				Chew	0 lesion			
				Snuff	4 lesions			

Table 72 (contd)

Reference, study location, period	Study population	Prevalence of use; type of tobacco product	Type of lesions ^a	Exposure category	Prevalence of lesions (%)	Relative risk (95% CI or <i>p</i> value)	Adjustment for potential confounders; comments
Tomar <i>et al.</i> (1997), Countrywide excluding Alaska, 1986–87	17 027 school children aged 12–17 years; response rate, 78%	3.1% smokeless tobacco (2.0% snuff, 1.5% chewing tobacco)	'Smokeless tobacco lesions' according to Greer & Poulson (1983) criteria, diagnosed by trained dental examiners	All subjects	1.5		Adjusted for age, cigarette smoking (current, former, never) and alcoholic beverage consumption (current, former, never); data on prevalence of lesions of different degrees (1–3) by duration of use, frequency of use and exposure time, for snuff and for chewing tobacco separately; 65% of lesions located in mandibular buccal vestibules, of which 24% in anterior labial vestibule or labial mucosa
				Current	18.4 (8.5–39.8)	<i>Chewing tobacco</i> 2.5 (1.3–5.0)	
				Former	2.4 (1.0–6.1)	1.3 (0.7–2.2)	
				<i>Duration (months)</i>			
				< 1	1.0	1.0	
				1–12	8.1 (3.8–17.4)	2.0 (0.6–6.1)	
				13–24	23.3 (10.5–51.4)	6.6 (1.7–25.2)	
				> 24	58.9 (21.3–162)	13.4 (6.1–29.5)	
				<i>Frequency (days/month)</i>			
				0	1.0	1.0	
				1–14	4.2 (1.6–11.4)	2.9 (1.1–7.9)	
				15–29	7.9 (2.9–21.7)	4.8 (1.3–18.2)	
				30–31	51.4 (19.7–134)	12.1 (5.5–26.5)	
				<i>Min/day in the mouth</i>			
< 1	1.0	1.0					
1–30	9.5 (4.3–20.7)	2.8 (1.1–7.1)					
31–105	14.6 (5.5–39.0)	6.3 (2.7–14.5)					
> 105	26.7 (9.8–72.9)	11.1 (4.3–29.1)					
Martin <i>et al.</i> (1999), Texas, 1996	3051 male US Air Force trainees; participation rate, 99.97%	9.9% current users, of whom 93.4% used snuff, 6.6% chewed	Oral leukoplakia	<i>Duration of use (months)</i>			Percentage of severe lesions according to duration of use and amount used per day available; 97% of lesions found in the mandibular buccal or labial sulcus
				1–12	14.8	11.2 (5.5–22.6)	
				13–24	30.9	28.8 (15.1–54.1)	
				25–48	48.1	59.9 (34.0–105)	
				> 49	70.8	156 (81.0–303)	
				<i>Cans snuff/day</i>			
				< 1/2	29.6	24.0 (14.6–39.2)	
				1/2–1	44.8	46.0 (25.4–83.6)	
				> 1	63.0	108.2 (59.8–196.9)	
				Chewing tobacco	5.0	3.4 (0.08–22.3)	
				<i>Type of snuff</i>			
				Copenhagen	54.7	77.7 (43.4–139.6)	
				Skoal	38.3	40.0 (24.4–65.7)	
Kodiak	36.2	36.5 (17.8–74.9)					

CI, confidence interval

^a Greer and Poulson (1983) established a classification into three degrees of severity (instead of four degrees used previously) to be applied to persons who have used smokeless tobacco four years or less.

1999). In two studies (Ernster *et al.*, 1990; Martin *et al.*, 1999), no chewing tobacco user had a severe lesion.

Among snuff users, the prevalence of lesions and the relative risk varied depending on the brand used (Grady *et al.*, 1990; Greene *et al.*, 1992; Creath *et al.*, 1991; Martin *et al.*, 1999). Relative risks for chewing tobacco were much less variable (odds ratio range, 10–15) (Grady *et al.*, 1990; Greene *et al.*, 1992)

In those studies that noted where the tobacco was placed within the mouth (Greer & Poulson, 1983; Wolfe & Carlos, 1987; Cummings *et al.*, 1989; Creath *et al.*, 1991; Kaugars *et al.*, 1992; Little *et al.*, 1992), most or all lesions were at that site. Several other studies mentioned over 90% of the lesions in the mandibular area (Ernster *et al.*, 1990; Creath *et al.*, 1991; Tomar *et al.*, 1997; Martin *et al.*, 1999).

(ii) *Severity of lesions*

A few studies conducted analyses that distinguished between lesions of lower severity (degree ≤ 2) and lesions of higher severity (degree 3 and 4). The results of these studies are detailed below.

Wolfe and Carlos (1987) found no consistent relationship between any of the characteristics of smokeless tobacco use and the severity of leukoplakia [data not shown].

In a 3-year study in seven major league baseball teams and their associated minor league teams in the USA conducted in 1988–90, over 1000 players received an oral examination and completed a questionnaire on tobacco use (Ernster *et al.*, 1990; Grady *et al.*, 1990; Daniels *et al.*, 1992; Greene *et al.*, 1992). There was a significant increase in the percentage of more severe leukoplakia lesions (degree 3 and 4) with increasing amount of use, longer duration of use, shorter time since last use and use of snuff; no chewing tobacco user had a severe lesion. Histological examination of 142 lesions showed a prevalence of 4% of basal-cell hyperplasia in snuff users while none occurred in the users of chewing tobacco (Daniels *et al.*, 1992). In the study by Little *et al.* (1992), frequency and duration of smokeless tobacco use were strongly related to the severity of lesions.

In the study of the National Survey of Oral Health of US schoolchildren (Tomar *et al.*, 1997), conducted in 1986–87, schoolchildren in a probability sample of schools were examined and completed a questionnaire with an interviewer. Complete data on tobacco and alcoholic beverage consumption were available for 17 027 children aged 12–17 years. Degree 2 lesions were observed in 14.8% of current snuff users, 3.3% of former users and 0.8% of never users. The corresponding prevalences for degree 3 lesions were 3.0, 0.3 and 0.1%, respectively. The prevalences of degree 2 lesions in tobacco chewers were 7.9%, 2.2% and 1.3%; and those for degree 3 lesions were 2.6, 0.3 and 0.1%, respectively. The prevalence of degree 2 and degree 3 lesions increased with duration of use in months, frequency used per week and exposure time in the mouth for both snuff and chewing tobacco.

Martin *et al.* (1999) calculated the percentage of level I and that of level II or III lesions according to duration of use and amount used per day. They found a significant increase in the percentage of severe lesions with increased length of use and increased

amount used per day. In a logistic regression analysis, length of use was the only predictor of the severity of the lesions (odds ratio, 1.14; 95% CI, 1.01–1.29). The only lesion seen in a tobacco chewer was level I.

(iii) *Reversal of lesions*

Grady *et al.* (1991) examined 1031 male professional baseball players for oral lesions. Of these, 389 were current smokeless tobacco users and 185 had oral lesions. Those with leukoplakia were asked to return for biopsies 1–21 days after the initial examination, and 131 players complied. In the time between examinations, 15% of the lesions resolved and 18% improved by one degree. The lesions most likely to have resolved were smaller lesions in players who decreased or stopped smokeless tobacco use, among users of chewing tobacco compared with those of snuff, among light users and among seasonal users only. Duration of smokeless tobacco use and the number of days between the initial examination and follow-up examination were not associated with the disappearance or regression of lesions.

In a study at a US Air Force camp, male basic trainees were examined upon entry to camp, between 2 and 6 days after they had last used smokeless tobacco (Martin *et al.*, 1999). Of the 302 smokeless tobacco users, 119 had oral leukoplakia. At the end of the 6 weeks of cessation of tobacco use during training, 109 of the 119 were re-examined and 97% of the lesions had completely resolved.

(iv) *Progression of lesions*

Between 1988 and 1991, 70 patients with advanced oral leukoplakia were enrolled in an intervention study to assess the efficacy of various chemopreventive treatments (all patients were treated). The relative risk for developing oral cancer in the one patient who chewed tobacco compared with the 21 who did not chew tobacco was 0.6 (95% CI, 0.2–1.6) (Lee *et al.*, 2000). [No information was given on the assessment of tobacco use or on the etiology of oral leukoplakia.]

(b) *Europe*

(i) *Prevalence of precancerous lesions*

A study of five coal mines in South Lancashire, United Kingdom (Tyldesley, 1971), revealed that, among 1490 miners, 1.7% of surface workers and 34.3% of underground workers chewed tobacco. Of these, 91.2% also smoked cigarettes. In a subanalysis of 280 chewers and 122 non-chewers, none of the non-users had leukoplakia compared with 3.6% of the chewers. In all cases, leukoplakia was observed at multiple sites. All patients with lesions were also smokers.

A randomly selected sample of 918 adults living in a Swedish county was examined for the presence of oral mucosal lesions. None of the women and 79 (17.6%) of the men dipped snuff. Among them, 58 used snuff only, 16 used snuff and smoked cigarettes and five used snuff and smoked a pipe. The prevalence of oral leukoplakia was 2.8% among

men and 1.1% among women; none of the lesions occurred among snuff users (Salonen *et al.*, 1990).

(ii) *Malignant transformation*

Among 450 patients with leukoplakia recorded between 1956 and 1970 at the University Hospital of Copenhagen, Denmark, 32 were snuff users. A 1-year follow-up was conducted for 394 patients. Among them, two of the snuff-induced lesions became malignant or dysplastic, which corresponded to a transformation rate of 6.2%. In contrast, 19.5% of the other leukoplakia patients developed carcinoma or showed dysplasia (Roed-Petersen & Pindborg, 1973).

(c) *India*

Because of the high prevalence of chewing betel quid with or without tobacco in South-East Asia, and particularly in India, many studies that investigated the prevalence of smokeless tobacco use did not dissociate the use of mixtures that included tobacco from those that did not. For this reason, it is difficult to assess precancerous lesions associated with smokeless tobacco only.

A case-control study design was applied to the baseline data of a cross-sectional study in Kerala, India, of a population screened by oral visual inspections that included 927 cases of oral leukoplakia (411 women, 516 men) and 47 773 population-based controls with no oral disease (29 876 women, 17 897 men). Interviews were conducted with structured questionnaires by health workers. Clinical diagnosis of oral precancers was confirmed by dentists and oncologists. For men and women who consumed only chewing tobacco combined, the odds ratio for leukoplakia adjusted for age, sex, education, body mass index, pack-years of smoking and years of alcoholic beverage drinking was 30.9 (eight cases; 95% CI, 13.7–69.7). For both sexes combined in an analysis restricted to nonsmokers and non-drinkers who consumed only chewing tobacco, the odds ratio for leukoplakia adjusted for age, sex, education and body mass index was 263.0 (three cases; 95% CI, 68.5–∞) (Jacob *et al.*, 2004). One tobacco-only chewer had multiple premalignant lesions (Thomas *et al.*, 2003).

(d) *Other parts of Asia*

A cross-sectional study on the prevalence of oral cancer and precancerous lesions among 674 consecutive dental patients carried out in Riyadh, Saudi Arabia, described 13 patients with oral leukoplakia, three of whom used *shammah*. The other lesions occurred among cigarette and *shisha* smokers (Mani, 1985).

A study conducted in Gizan province, Saudi Arabia, included 661 Saudi citizens aged ≥ 15 years. *Shammah* was used by 28% of the study population. Of the surveyed population, 129 (19.5%) had lesions of the oral mucosa diagnosed clinically as leukoplakia. All affected subjects reported the use of *shammah* for more than 5 years (Salem *et al.*, 1984). The lesions were almost always at the site where *shammah* was habitually held.

Male residents of nine villages in one local authority district in the Samarkand Oblast of Uzbekistan were invited to attend a medical examination, which included an interview concerning *naswar* use, smoking and alcoholic beverage consumption (Zaridze *et al.*, 1986). A total of 1569 residents were interviewed and had oral examination, of whom 42% reported using *naswar*. Oral leukoplakia was diagnosed in 127 (8%) individuals, with a total of 144 lesions. The most frequent sites of these lesions were the floor of the mouth, the lower surface of the tongue and the tip of the tongue (38%). [*Naswar* is usually placed under the tongue.] The prevalence of leukoplakia was highest among individuals who both smoked and used *naswar* (21%). Among nonsmokers, the prevalence of leukoplakia was 2.2% among *naswar* non-users, 11.5% among former users and 12% among current users.

A built-in case-control study was carried out to investigate the possible relationship between *naswar* use and practices and the risk for leukoplakia. A total of 191 cases were defined as having oral leukoplakia, while 466 controls were free of leukoplakia. Use of *naswar* was significantly associated with the risk for oral leukoplakia in ever users (3.8; 95% CI, 2.6–5.6), in former users (3.0; 95% CI, 1.1–8.3) and in current users (3.9; 95% CI, 2.6–5.5), adjusted for smoking, alcoholic beverage consumption and age. A significant dose-response relationship was observed with earlier age at start of *naswar* use ($p = 0.027$), duration of use ($p < 0.001$), daily frequency of use ($p < 0.001$) and lifetime intake of *naswar*, calculated as reported daily frequency at the time of interview multiplied by years of use ($p < 0.001$) (Evstifeeva & Zaridze, 1992).

(e) *Africa*

Idris *et al.* (1996) reported on 281 Sudanese subjects (229 men, 50 women and two sex not recorded) with distinctive *toombak*-associated oral lesions that were detected from a random population sample of 5500 persons during a house-to-house survey in northern Sudan. Subjects were interviewed regarding their tobacco habits. *Toombak*-related mucosal lesions were recorded according to a four-point scale proposed by Axéll *et al.* (1984). The majority of the cases had lesions in the anterior lower labial sulcus, the predominant site for snuff dipping among Sudanese. A strong association between the severity of the mucosal lesions and longer lifetime duration (> 10 years) of *toombak* use was found. None of the most severe lesions (degree 4) occurred among subjects with less than 10 years of use.

Ahmed *et al.* (2003) applied exfoliative cytology to 300 volunteers (100 exclusive *toombak* users, 100 exclusive cigarette smokers and 100 non-users of any form of tobacco) to assess the presence and severity of epithelial atypia. Cytological smears were obtained for all subjects from the buccal or labial mucosa, the sites where *toombak* quids are placed. Moderate and severe epithelial atypia was detected in seven of 300 study subjects, in five of 100 *toombak* dippers, in two of 100 cigarettes smokers and in none of the non-users of any form of tobacco.

2.2.3 *Cancer of the oesophagus*

Table 73 summarizes the case-control studies of smokeless tobacco and cancer of the oesophagus.

(a) *America*

The population-based case-control study by Williams and Horm (1977), described in Section 2.2.1, also reported on oesophageal cancer. Among men, the relative risk for moderate use of chewing tobacco or snuff based on two exposed cases was 0.9, adjusting for age, race and smoking.

Cases of oesophageal cancer, primarily (85%) squamous-cell carcinomas, ascertained in 1982–84 in selected hospitals in South Carolina, USA, were matched with two hospital controls per case by hospital, race and age (± 5 years). In addition, oesophageal cancer deaths among men who were residents of eight coastal counties of South Carolina were identified in 1977–81 and matched by race, age, county of residence and year of death to decedents who died from other causes. Controls with a diagnosis at admission or cause of death related to alcoholic beverages or diet were excluded. A total of 207 cases and 422 controls were included in the study. Users of smokeless tobacco were defined as those who had used at least one pouch or plug of chewing tobacco or a small can of snuff per week for at least 1 year. Relative to non-users of tobacco, the odds ratio for users of smokeless tobacco only was 1.7, and 1.2 (95% CI, 0.1–13.3) when adjusted for study series and alcoholic beverages (Brown *et al.*, 1988).

(b) *Europe*

(i) *Cohort study*

In the Norwegian cohort study (Boffetta *et al.*, 2005) described in Section 2.2.1, the relative risk for oesophageal cancer was 1.4 (nine cases; 95% CI, 0.6–3.2) for ever use compared with never use of snuff and adjusted for age and smoking (Table 74).

(ii) *Case-control studies*

The case-control study by Lewin *et al.* (1998) (see Section 2.2.1) reported results separately for oesophageal cancer. The relative risks for current and former versus never use of snuff were 1.1 (10 cases; 95% CI, 0.5–2.4) and 1.3 (nine cases; 95% CI, 0.6–3.1), respectively, after adjustment for age, smoking and alcoholic beverage intake. The relative risk for users of ≥ 50 g/week was 1.9 (95% CI, 0.8–3.9).

All patients with a new diagnosis of adenocarcinoma of the oesophagus or gastric cardia and half of the patients with oesophageal squamous-cell carcinoma were included in a population-based study that comprised the whole population of Sweden (< 80 years) during 1995 through to 1997 (Lagergren *et al.*, 2000). Cases were identified from all clinical departments in Sweden that were involved in the treatment of these diagnoses as well as from local tumour registries. Controls were randomly selected from the study population and frequency-matched for age and sex to the oesophageal adenocarcinoma

Table 73. Case-control studies of smokeless tobacco use and cancer of the oesophagus

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
North America							
Williams & Horm (1977), USA, 1969–71	Cancer of the oesophagus from 7518 (57% of randomly selected) incident invasive cancers who participated in the population-based Third National Cancer Survey	Cancer at sites unrelated to tobacco	Moderate use Heavy use	2	0.9 –	Age, race, smoking	No exposed cases among women
Brown <i>et al.</i> (1988), USA, 1982–84 (cancer cases) 1977–81 (cancer deaths)	207 from selected hospitals in South Carolina; deaths in 8 coastal counties; 74 incident male oesophageal cancer cases (85% squamous-cell carcinoma), ≤ 143 male oesophageal cancer deaths, aged ≤ 79 years; response rate, 85% (incident cases), 94% (deceased cases and controls)	422; 157 hospital patients matched on hospital, race, age ± 5 years; ≤ 285 deaths, matched on race, age, county of residence, year of death; controls with diagnosis at admission or cause of death related to alcoholic beverages or diet excluded; response rate, 95% (hospital controls)	Non-user of tobacco Smokeless tobacco only		1.0 1.2 (0.1–13.3)	Study series and alcoholic beverages	Use defined as at least one pouch or plug of chewing tobacco or a small can of snuff per week for ≥ 1 year
Europe							
Lewin <i>et al.</i> (1998), Stockholm and southern Sweden, 1988–91	605 including 123 cancers of the oesophagus from hospitals and cancer registries, 40–79 years old; overall response rate, 90%	756 from the population registry; stratified by region and age; response rate, 85%	Current snuff use Former snuff use > 50 g/week	10 9	1.1 (0.5–2.4) 1.3 (0.6–3.1) 1.9 (0.8–3.9)	Age, region, smoking, alcoholic beverages	

Table 73 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments	
Lagergren <i>et al.</i> (2000), Sweden, 1995–97	Incident adenocarcinomas of the oesophagus (189), 87% men; gastric cardia cancers (262), 85% men; squamous-cell cancers of the oesophagus (167), 72% men; < 80 years old; response rates, 87%, 83%, 73%, respectively	820 frequency-matched to adenocarcinoma of the oesophagus by age, sex; response rate, 73%	<i>Oesophagus (squamous-cell carcinoma)</i>			Age, sex, tobacco smoking, alcoholic beverages	Additional results by intensity of snuff use reported in text	
			Never use of snuff	134	1.0			
			Ever use of snuff > 25 years of use	33	1.4 (0.9–2.3)			
				14	2.0 (0.9–4.1)			
			<i>Oesophagus (adenocarcinoma)</i>					
			Never use of snuff	154	1.0			
			Ever use of snuff > 25 years of use	35	1.2 (0.7–2.0)			
				15	1.9 (0.9–4.0)			
			<i>Gastric cardia (adenocarcinoma)</i>					
			Never use of snuff	209	1.0			
Ever use of snuff > 25 years of use	53	1.2 (0.8–1.8)						
	15	1.1 (0.6–2.2)						
Asia								
Phukan <i>et al.</i> (2001), India, 1997–98	502 (358 men, 144 women) histologically confirmed cancers of the oesophagus (predominantly squamous-cell cancer) from one hospital; response rate, 94%	Two visitors matched for age, sex	<i>Men</i>			Alcoholic beverage drinking	*Dried tobacco chewed alone	
			Non-chewer/nonsmoker		1.0			
			* <i>Chadha</i> chewer	20	3.2 (1.6–9.5)			
			<i>Women</i>					
			Non-chewer/nonsmoker		1.0			
			* <i>Chadha</i> chewer	8	6.2 (2.4–12.1)			
			<i>Men</i>					Smoking
			Non-chewer/non-alcoholic beverage drinker		1.0			
* <i>Chadha</i> chewer	16	3.8 (1.9–8.5)						
<i>Women</i>								
Non-chewer/non-alcoholic beverage drinker		1.0						
* <i>Chadha</i> chewer	7	5.8 (2.1–12.4)						

CI, confidence interval

Table 74. Results of cohort studies on use of smokeless tobacco and cancer of the oesophagus and pancreas

Reference, name of study	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Adjustment for potential confounders; comments
Oesophagus				
Boffetta <i>et al.</i> (2005), Norwegian Cohort Study	Never user	18	1.0	Adjusted for age, smoking
	Ever user	9	1.40 (0.61–3.24)	
	Current user	4	1.06 (0.35–3.23)	
	Former user	5	1.90 (0.69–5.27)	
Pancreas				
Zheng <i>et al.</i> (1993), Lutheran Brotherhood Study	Ever users of ST	16	1.7 (0.9–3.1)	Adjusted for age, alcoholic beverages, smoking
Boffetta <i>et al.</i> (2005), Norwegian Cohort Study	Never user	60	1.0	Adjusted for age, smoking
	Ever user	45	1.67 (1.12–2.50)	
	Current user	27	1.60 (1.00–2.55)	
	Former user	18	1.80 (1.04–3.09)	

cases. Exposure data were collected through face-to-face interviews by professional interviewers. For oesophageal adenocarcinoma, the participation rate was 87% and the number of cases was 189; for gastric cardia cancer, the rate was 83% and the number of cases was 262; for squamous-cell carcinoma of the oesophagus, the participation rate was 73% and the number of participating cases was 167; 87%, 85% and 72% of the cases were men, respectively. The participation rate among the 820 controls who participated in the study was 73%. For gastric cardia adenocarcinoma, the odds ratio among ever users of snuff was 1.2 (53 cases; 95% CI, 0.8–1.8). For oesophageal adenocarcinoma, snuff users had a relative risk of 1.2 (35 cases; 95% CI, 0.7–2.0) compared with never users. Patients with more than 25 years of use had an adjusted relative risk of 1.9 (15 cases; 95% CI, 0.9–4.0) and those who used 15–35 quids per week had a relative risk of 2.0 (17 cases; 95% CI, 1.0–4.3). For the category of highest use (> 35 quids per week), no excess risk was seen. For oesophageal squamous-cell carcinoma, the relative risk was 1.4 (33 cases; 95% CI, 0.9–2.3) when ever users were compared with never users. Similarly to adenocarcinoma, for those with more than 25 years of use, the relative risk was 2.0 (14 cases; 95% CI, 0.9–4.1); those who used 15–35 quids per week had a relative risk of 2.1 (15 cases; 95% CI, 1.0–4.4) and those with highest intensity of use had no excess risk.

(c) *India*

Many studies from South-East Asia combined all smokeless tobacco use into one category, which was often termed tobacco chewing. In these studies, tobacco chewing

often included chewing of betel quid with tobacco. All such studies have been reviewed in the monograph on betel-quid and areca-nut chewing (IARC, 2004a) and are not included here. Only studies that reported separate results for tobacco chewing without betel quid are reviewed here.

A hospital-based case-control study was carried out in Assam, India, from 1997 to 1998, and recruited 502 (358 men, 144 women) histologically confirmed cases of oesophageal cancer (predominantly squamous-cell carcinomas), and two visitor controls per case group-matched for age and sex. Among nonsmokers compared with non-chewers (after adjusting for alcoholic beverage consumption), the odds ratio for developing oesophageal cancer associated with the use of dried tobacco leaf alone (locally known as *chada*) was 3.2 (20 cases; 95% CI, 1.6–9.5) and 6.2 (8 cases; 95% CI, 2.4–12.1) for men and women, respectively. Similarly, the risk for oesophageal cancer among non-alcoholic beverage drinkers for *chada* users compared with non-chewers (after adjusting for smoking) was 3.8 (16 cases; 95% CI, 1.9–8.5) among men and 5.8 (seven cases; 95% CI, 2.1–12.4) among women (Phukan *et al.*, 2001).

(d) *Africa*

Babekir *et al.* (1989) described the age, sex and geographical distribution of oesophageal cancers seen at the University Hospital of Khartoum, Sudan, in 1979–86. The annual crude incidence rates were 1.19/100 000 in the northern region and 0.17/100 000 or below in any of the other seven regions. Placing tobacco under the tongue or in the labiodental groove was discussed as a potential risk factor. No significant difference in the incidence was observed for the different tribes (Arab and Nuba) of the northern region. Alcoholic beverage drinking was excluded as a potential confounder since a similar difference in incidence rates was observed among women who rarely drink alcoholic beverages.

2.2.4 *Cancer of the pancreas*

Results of the cohort studies are presented in Table 74 and the case-control studies are summarized in Table 75.

(a) *North America*

(i) *Cohort study*

The Lutheran Brotherhood Insurance Society cohort comprised 17 818 (68.5%) of 26 030 white male policy holders, who responded to a mailed questionnaire in 1966 (Zheng *et al.*, 1993) (see Table 69). Cohort members were 30 years of age or older and lived in California, upper midwest or northeastern USA. After 20 years of follow-up for vital status in 1986, 4027 (23%) persons were lost to follow-up. At 11.5 years of follow-up, respondents, non-respondents and respondents lost to follow-up did not differ significantly with respect to demographic variables. Fifty-seven deaths from pancreatic cancer occurred during the 20-year follow-up period. For dietary reasons, 1656 respondents (including three pancreatic cancer deaths) were excluded from the analysis. The relative

Table 75. Case-control studies of smokeless tobacco use and cancer of the pancreas

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
North America							
Williams & Horn (1977), USA, 1969–71	Cancer of the pancreas from 7518 (57% of randomly selected) incident invasive cancers who participated in the population based Third National Cancer Survey	Cancer at sites unrelated to tobacco	<i>Smokeless tobacco</i>			Age, race, smoking	No exposed cases among women
			Moderate use	2	0.3		
			Heavy use	1	0.3		
Farrow & Davis (1990), Washington, USA, 1982–86	148 married men from population-based cancer registry, aged 20–74 years; 46% histologically confirmed; interview with wife of patient	188 married men from same counties; frequency-matched on age (5-year categories); selected by RDD	Ever chewed tobacco	Prevalence among cases and controls, 6.9%	0.8 (non-significant)	Race, education	Further adjustment for age and dietary factors did not affect the odds ratio.
Muscat <i>et al.</i> (1997), New York, Pennsylvania, Michigan, Illinois, USA, 1985–93	484 incident histologically confirmed from daily hospital admission logs, aged 21–80 years; response rate, 51%	954 individually matched 2:1 on hospital, sex, age (\pm 5 years), race, year of diagnosis; patients without tobacco-related diseases; response rate, 63%	Never smoker and long-term (\geq 20 years) quitter		1.0		Analysis restricted to men as no woman chewed tobacco or used snuff
			Tobacco chewer \geq 1 year and not current cigarette smoker	6	3.6 (1.0–12.8)		
			Use of snuff \geq 1 year	2	[Not reported]		

Table 75 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Alguacil & Silverman (2004), Atlanta, GA, Detroit, MI, New Jersey (USA), 1986–89	154 carcinoma of exocrine pancreas from population-based cancer registries, aged 30–79 years; lifelong non-smokers of cigarettes; of 1153 identified, 46.5% interviewed	844; RDD for cases ≤ 64 years; HCFA for cases aged ≥ 65 years; frequency-matched on age, race, sex, study site; lifelong non-smokers of cigarettes; 78% interviewed	Non-user of tobacco		1.0		
			Chewing tobacco and/or snuff				
			Ever used	7	1.4 (0.5–3.6)	Race, sex, geographic site, cigar smoking, age	Tobacco chewers used more per week (7.2 oz.) than users of snuff (2.4 oz.). 1 can snuff = 1.2 oz.; 1 unit chewing tobacco = 3-oz pouches or 2.33-oz. plugs.
			Only used	5	1.1 (0.4–3.1)		
			<i>Tobacco type</i>				
			Chewing tobacco		1.7 (0.6–4.5)		
			Snuff		1.1 (0.4–3.5)		
			<i>Ounces/week</i>				
			≤ 2.5		0.3 (0.04–2.5)		
			> 2.5		3.5 (1.1–10.6)		
		p for trend = 0.04					
<i>Duration of use</i>							
≤ 20 years		1.1 (0.1–11.0)					
> 20 years		1.5 (0.6–4.0)					
		p for trend = 0.42					

CI, confidence interval; HCFA, Health Care Financing Administration; RDD, random-digit dialling

risk for ever users of smokeless tobacco was 1.7 (16 deaths; 95% CI, 0.9–3.1), adjusted for age, alcoholic beverages and smoking.

(ii) *Case-control studies*

The population-based case-control study by Williams and Horm (1977) reported in Section 2.2.1 also reported on pancreatic cancer. Among men, the relative risks for cancer of the pancreas and for moderate or heavy use of chewing tobacco or snuff were 0.3 (two cases) and 0.3 (one case), respectively, adjusted for age, race and smoking. There were no exposed cases among women.

A population-based study included married men newly diagnosed with pancreatic cancer in the Seattle (USA) area and population-based controls frequency-matched on age (Farrow & Davis, 1990). A telephone interview with the wives was conducted between 2 and 4.5 years after diagnosis. Complete information was available for 148 cases and 188 controls. The odds ratio for chewing tobacco was 0.8 (overall prevalence, 6.9%) with a confidence interval that included 1.0 [smoking was not controlled for].

Muscat *et al.* (1997) conducted a hospital-based study in New York, Pennsylvania, Michigan and Illinois, USA. Of the 949 cases aged 20–81 years ascertained between 1985 and 1993 and the 1526 eligible controls, 484 cases and 949 controls were interviewed in the hospital. The controls did not have tobacco-related diseases, and were individually matched to cases on hospital, sex, age, race and year of diagnosis. The major reasons for non-interviews were that the patient was too ill or unable to communicate. Relative to never smokers and long-term quitters (≥ 20 years), the odds ratio for tobacco chewers who were not current cigarette smokers was 3.6 (95% CI, 1.0–12.8).

In a large population-based case-control study of incident cases of carcinoma of the exocrine pancreas in the Atlanta area, Detroit and New Jersey, USA, lifelong nonsmokers of cigarettes were examined (Alguacil & Silverman, 2004). Forty-one per cent of the cases died before interview, but response rates for the surviving cases and controls were 75% or better. Controls enrolled by random-digit dialling (for cases ≤ 64 years) and HCFA (for cases ≥ 65 years) were frequency-matched to the cases on age, race, sex and study site. Persons were considered to be snuff users if they ever used snuff, whereas tobacco chewers were defined as those who used one pouch or plug per week for at least 6 months. Relative to non-users of tobacco, the odds ratio for ever having used smokeless tobacco was 1.4 (95% CI, 0.5–3.6) and that for having used smokeless tobacco only was 1.1 (95% CI, 0.4–3.1), adjusted for race, sex, geographic site, cigar smoking and age. In a statistical model with cigar smoking, chewing tobacco and snuff and pancreatic cancer as the outcome, the odds ratios were 1.7 (95% CI, 0.6–4.5) for chewing tobacco and 1.1 (95% CI, 0.4–3.5) for using snuff. Dose-response relationships were evaluated and adjusted for age, sex, race, cigar smoking and geographical region. Users of 2.5 oz or less of smokeless tobacco per week had an odds ratio of 0.3 (95% CI, 0.04–2.5) whereas users of more than 2.5 oz had an odds ratio of 3.5 (95% CI, 1.1–10.6; p for trend = 0.04). For 20 years or less of smokeless tobacco use, the odds ratio was 1.1 (95% CI, 0.1–11.0) and that for more than

20 years was 1.5 (95% CI, 0.6–4.0; p trend = 0.42). Tobacco chewers used more ounces of tobacco per week than users of snuff (7.2 versus 2.4 oz).

(b) *Europe*

In the Norwegian Cohort Study (Heuch *et al.*, 1983; Boffetta *et al.*, 2005), the relative risk for pancreatic cancer for ever use of smokeless tobacco was 1.7 (45 cases; 95% CI, 1.1–2.5); similar results were obtained for former and current users. After stratification on smoking status, the relative risks were 1.9 (28 cases, 95% CI, 1.1–3.1) among current smokers and 0.9 (three cases; 95% CI, 0.2–3.7) among never smokers. The results in current smokers were adjusted for amount of smoking. [The Working Group noted that never smokers were too few to give meaningful results and that the absence of an effect for lung cancer speaks against confounding by cigarette smoking.]

2.2.5 *Cancers at other sites*

The characteristics of cohort studies are presented in Table 69 and their results are summarized in Table 76. Case–control studies are summarized in Table 77.

(a) *Cancer of the stomach*

(i) *Cohort studies*

In the Lutheran Brotherhood cohort, white men aged 35 years and above were followed for vital status for 20 years (Kneller *et al.*, 1991). Relative to men who had never used tobacco, the relative risk for smokeless tobacco users was 2.3 (18 deaths; 95% CI, 0.98–5.2). Stratification by pack–years of smoking reduced this relative risk to 1.6 (95% CI, 0.6–4.5). Among nonsmokers who used smokeless tobacco, the relative risk was 3.8 (three deaths; 95% CI, 1.0–14.3).

Among men in the CPS-II cohort, and relative to having never used any type of tobacco, the relative risk for stomach cancer among current users of smokeless tobacco only was 1.6 (8 deaths; 95% CI, 0.8–3.3) adjusted for age, race, education, family history of stomach cancer, consumption of high-fiber grain foods, vegetables, citrus fruits or juices, use of vitamin C, multivitamins and aspirin. For former users of smokeless tobacco only, the relative risk was 1.1 (95% CI, 0.3–4.5) (Chao *et al.*, 2002).

In the cohort study from Norway, the relative risk for stomach cancer and for ever use of snuff was 1.1 (74 cases; 95% CI, 0.8–1.5) compared with never users. Results were similar for current and former users (Boffetta *et al.*, 2005).

(ii) *Case–control studies*

The case–control study by Williams and Horm (1977) described in Section 2.2.1 also reported on stomach cancer. Among men, the relative risks for stomach cancer and for moderate or heavy use of chewing tobacco or snuff were 1.0 (6 cases) and 1.7 (6 cases), respectively, adjusted for age, race and smoking.

Table 76. Results of cohort studies on use of smokeless tobacco and cancer at other sites

Reference, name of study	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Adjustment for potential confounders; comments
Stomach				
Kneller <i>et al.</i> (1991), Lutheran Brotherhood Study	Never used any tobacco		1.0	
	Smokeless tobacco users	18	2.3 (0.98–5.2)	
	Smokeless tobacco users (adjusted*)	18	1.6 (0.6–4.5)	*Stratified by pack-years of smoking
	Smokeless tobacco only users	3	3.8 (1.0–14.3)	
Chao <i>et al.</i> (2002), CPS-II	Never used any tobacco	169	1.0	
	Current smokeless tobacco only	8	1.58 (0.76–3.28)	Adjusted for age, race, education, family history of stomach cancer, aspirin use, dietary factors
	Former smokeless tobacco only	2	1.11 (0.27–4.50)	
Boffetta <i>et al.</i> (2005), Norwegian Cohort Study	Never user	143	1.0	Adjusted for age, smoking
	Ever user	74	1.11 (0.83–1.48)	
	Current user	42	1.00 (0.71–1.42)	
	Former user	32	1.29 (0.87–1.91)	
Colon and rectum				
Heineman <i>et al.</i> (1995), US Veterans Study	Never used any tobacco	782	1.0	
	Smokeless tobacco user			Relative risks for smokeless tobacco users who never smoked cigarettes, pipes or cigars
	Colon	39	1.2 (0.9–1.7)	
	Rectum	17	1.9 (1.2–3.1)	
Digestive tract				
Accort <i>et al.</i> (2002), NHANES 1 Follow-up	No tobacco use		1.0	Adjusted for age, race, poverty index ratio, region of residence, alcoholic beverages, dietary fat intake
	<i>Men</i>			
	Ever smokeless tobacco user/never smoker		0.9 (0.3–2.3)	
	Ever smokeless tobacco user/ever smoker		0.7 (0.3–1.8)	
	<i>Women</i>			
	Ever smokeless tobacco user/never smoker		0.8 (0.3–2.7)	
	Ever smokeless tobacco user/ever smoker		0.2 (0.1–1.1)	

Table 76 (contd)

Reference, name of study	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Adjustment for potential confounders; comments
Henley <i>et al.</i> (2005), CPS-I and CPS-II	<i>CPS-I</i>			Restricted to men who never used other tobacco products; adjusted for age, race, education, body mass index, exercise, aspirin use, alcoholic beverages, dietary factors; CPS-II also adjusted for status, type of employment
	Never use of smokeless tobacco	760	1.0	
	Current use of smokeless tobacco	153	1.26 (1.05–1.52)	
	<i>CPS-II</i>			
	Never use of smokeless tobacco	1932	1.0	
	Current use of smokeless tobacco	48	1.04 (0.77–1.38)	
	Former use of smokeless tobacco	19	0.99 (0.63–1.57)	
Lung				
Accort <i>et al.</i> (2002), NHANES 1 Follow-up	No tobacco use		1.0	Adjusted for age, race, poverty index ratio, region of residence, alcoholic beverages, recreational physical exercise, fruit/vegetable intake
	<i>Men</i>		–	
	Ever smokeless tobacco user/never smoker		22.6 (6.4–80.3)	
	<i>Women</i>		9.1 (1.1–75.4)	
	Ever smokeless tobacco user/never smoker		1.2 (0.2–8.9)	
	Ever smokeless tobacco user/ever smoker			
Boffetta <i>et al.</i> (2005), Norwegian Cohort Study	Never user	39	1.0	Adjusted for age, smoking
	Ever user	72	0.80 (0.61–1.05)	
	Current user	44	0.80 (0.58–1.11)	
	Former user	28	0.80 (0.54–1.19)	
Henley <i>et al.</i> (2005), CPS-I and CPS-II	<i>CPS-I</i>			Restricted to men who never used other tobacco products; adjusted for age, race, education, body mass index, exercise, aspirin use, alcoholic beverages, dietary factors; CPS-II also adjusted for status, type of employment
	Never use of smokeless tobacco	116	1.0	
	Current use of smokeless tobacco	18	1.08 (0.64–1.83)	
	<i>CPS-II</i>			
	Never use of smokeless tobacco	378	1.0	
	Current use of smokeless tobacco	18	2.00 (1.23–3.24)	
	Former use of smokeless tobacco	4	1.17 (0.43–3.14)	

Table 76 (contd)

Reference, name of study	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Adjustment for potential confounders; comments
Soft-tissue sarcoma				
Zahm <i>et al.</i> (1992), US Veterans Study	Never used any tobacco	20	1.0	No smokeless tobacco only users with soft-tissue sarcoma
	Used smokeless tobacco and other tobacco products	20	1.4 (0.8–2.6)	
Prostate				
Hsing <i>et al.</i> (1990), Lutheran Brotherhood Study	Never used any tobacco	19	1.0	Adjusted for cigarette smoking; similar results for 58 subjects for whom prostate cancer was not the underlying cause of death
	Ever used smokeless tobacco	42	2.1 (1.1–4.1)	
	Occasional	5	1.4 (0.5–3.9)	
	Former user	13	1.8 (0.8–3.9)	
	Regular	24	2.4 (1.3–4.9)	
	Smokeless tobacco only	10	4.5 (2.1–9.7)	
Hsing <i>et al.</i> (1991), US Veterans Study	Never used any tobacco	1075	1.0	
	Smokeless tobacco only	48	1.2 (0.9–1.6)	

CI, confidence interval; CPS, Cancer Prevention Study; NHANES, National Health and Nutrition Examination Survey

Table 77. Case-control studies of smokeless tobacco use and cancer at other sites

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Stomach							
Williams & Horm (1977), USA, 1969–71	Cancer of the stomach from 7518 (57% of randomly selected) incident invasive cancers who participated in the population-based Third National Cancer Survey	Cancer at sites unrelated to tobacco	Smokeless tobacco	<i>Men</i>		Age, race, smoking	Personal interview
			Moderate use	6	1.0		
			Heavy use	6	1.7		
Hansson <i>et al.</i> (1994), Sweden, 1989–92	338 incident from population-based national cancer registry, aged 40–79 years; histologically confirmed; response rate, 74%	679, randomly selected from population registries, stratified by age and sex; response rate, 77%	Snuff dipping		0.7 (0.47–1.06)	Age, sex, socio-economic status, vegetable intake	All subjects are also included in Ye <i>et al.</i> (1999).
Ye <i>et al.</i> (1999), Sweden, 1989–95	561 incident from population-based national cancer registry, aged 40–79 years; histologically confirmed; response rate, 62%	1164, randomly selected from population registries, stratified by age and sex; response rate, 75.9%	Snuff dipping			Age, residence area, body-mass index, socio-economic status, smoking	Data available on age at start, duration and intensity of snuff dipping
			<i>Stomach cancer</i>				
			Ever user among never smokers	11	0.5 (0.2–1.2)		
			<i>Cardia</i>				
			Current	9	0.5 (0.2–1.1)		
			Former	6	0.8 (0.3–1.9)		
			<i>Distal intestinal</i>				
			Current	26	0.8 (0.5–1.3)		
Former	18	0.9 (0.5–1.6)					
<i>Distal diffuse</i>							
Current	11	0.6 (0.3–1.2)					
Former	8	0.7 (0.3–1.6)					

Table 77 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Extra-hepatic bile duct							
Chow <i>et al.</i> (1994), Los Angeles county, USA, 1985–89	64 incident cancers of the extrahepatic bile duct (ICD-O 156.1), 41 of the ampulla of Vater (ICD-O 156.2), aged 30–84 years; histologically confirmed, white race; response rate, 76%; for the 58% of deceased cases, information obtained from next-of-kin	255; RDD for cases ≤ 64 years; HCFA for cases ≥ 65 years; matched on age (5-year age groups), sex; no history of cholecystectomy; response rate, 84% (RDD), 87% (HCFA)	Chewing tobacco [current]	Ampulla of Vater 3	18 (1.4–227.7)		Exposed cases also smoked cigarettes and 2 also used cigar/pipes.
Nasal cavities							
Brinton <i>et al.</i> (1984), USA, 1970–80	193 from four hospitals in North Carolina and Virginia, cancers of the nasal cavities and sinuses ICD-8 160.0, 160.2–160.5, 160.8–160.9 (86 squamous-cell carcinomas, 24 adenocarcinomas or adenoid cystic carcinomas, 36 other carcinomas, 14 other histologies), aged ≥ 18 years; response rate, 82.9%	<i>Live cases:</i> two hospital patients per case matched on hospital, year of admission, age, sex, race, excluding controls with admission diagnosis of other cancers or other diseases of the upper aero-digestive tract <i>Deceased cases:</i> one per case with similar criteria as above; one deceased identified from state vital statistics offices; response rate, 78.0%	Use of chewing tobacco Use of snuff	15 23	1.0 (ref.) 0.7 (0.4–1.5) 1.0 (ref.) 1.5 (0.8–2.8)	Sex	Similar results for matched analyses [data not shown]
Stockwell & Lyman (1986), Florida, USA, 1982	92 incident cancers of the nasal cavities and accessory sinuses from population-based Florida cancer registry; overall response rate, 82%	6457; all cancers of the colon or rectum, cutaneous melanoma, endocrine neoplasias from same source during same time period; response rate, 78%	Unspecified	1	3.3 (0.4–25.9)	Age, sex, race, tobacco use	Only primary type of tobacco used was obtained from chart and histopathology reviews.

Table 77 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Laryngeal cancer							
Stockwell & Lyman (1986), Florida, USA, 1982	797 incident cancers of the larynx from population-based Florida cancer registry; overall response rate, 82%	6457; all cancers of the colon or rectum, cutaneous melanoma, endocrine neoplasias from same source during same time period; response rate, 78%	Unspecified	5	7.3 (2.9–18.3)	Age, sex, race, tobacco use	Only primary type of tobacco used was obtained by chart and histopathology reviews.
Lewin <i>et al.</i> (1998), Stockholm and southern Sweden, 1988–91	605, including 157 cases of cancer of larynx, from hospitals and cancer registries, 40–79 years old; overall response rate, 90%	756 from the population registry; stratified by region, age; response rate, 85%	Current snuff use Former snuff use	15 9	1.0 (0.5–1.9) 0.8 (0.4–1.7)	Age, region, smoking, alcoholic beverages	
Lung							
Williams & Horm (1977), USA, 1969–71	Cancer of the lung from 7518 (57% of randomly selected) incident invasive cancers who participated in the population-based Third National Cancer Survey	Cancer at sites unrelated to tobacco	Smokeless tobacco Moderate use Heavy use	<i>Men</i> 26 10	 0.7 0.8	Age, race, smoking	Personal interview
Sarcoma							
Zahm <i>et al.</i> (1989), Kansas, USA, 1976–82	133 incident soft-tissue sarcomas from population-based registry considered 90% complete, histologically confirmed, white men, aged ≥ 21 years; 50% of interviews with next-of-kin; response rate for cases and controls, 93%	948; for living cases: white men selected through RDD and HCFA, frequency-matched by age (± 2 years); for deceased cases: decedents from Kansas, frequency-matched on age (± 2 years) and year of death, excluding lymphomas, sarcomas, ill-defined malignancies and homicide or suicide; 49% of interviews with next-of-kin	Ever use of smokeless tobacco <i>Location of tumour</i> Upper gastrointestinal Lung, pleura, thorax Head, neck, face Others <i>Cell type</i> Fibromatous Adipose Myomatous Others	28 4 5 3 16 7 3 7 11	1.8 (1.1–2.9) 3.3 (0.8–12.6) 3.1 (0.9–10.5) 2.4 (0.5–10.2) 1.4 (0.7–2.5) 1.8 (0.7–4.7) 1.1 (0.2–4.2) 2.1 (0.8–5.3) 1.9 (0.9–3.9)		

Table 77 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Breast							
Spangler <i>et al.</i> (2001b), Spangler (2002), North Carolina, USA 1990–91	Eight Cherokee women with prevalent breast cancer (ascertained by personal history) from population-based survey in Cherokee tribal lands; age at diagnosis: three, < 55 years; five, ≥ 55 years; response rate, 81% (cases and controls combined)	962 other survey respondents	Ever use of smokeless tobacco Diagnosed at age < 55 years ≥ 55 years	1 2	1.3 (0.12–13.9) 1.2 (0.14–9.52)		Unknown whether smokeless tobacco use preceeded cancer diagnosis
Prostate							
Hayes <i>et al.</i> (1994), Georgia, Michigan, New Jersey, USA, 1986–89	981 men with incident pathologically confirmed prostate cancer from a population-based registry, aged 40–79 years; response rate, 76%	1315; RDD for cases ≤ 64 years, HCFA for cases ≥ 65 years; frequency-matched on age, sex, race; response rate, 74%	Never used tobacco <i>Tobacco chewing</i> Former Current <i>Snuff</i> Former Current	56 14 10 10	1.0 1.0 (0.6–1.5) 0.5 (0.2–1.0) 0.6 (0.3–1.4) 5.5 (1.2–26.2)	Age, race, study site	
Urinary bladder							
Howe <i>et al.</i> (1980), Canada, 1974–76	632 (480 men, 152 women) newly diagnosed bladder cancers identified in three provinces	632 neighbours, individually matched by age (± 5 years), sex	Ever use of chewing tobacco, relative to never use	NR	0.9 (0.5–1.6)	Controlling for cigarette smoking did not affect the risk estimates.	61 discordant pairs

Table 77 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Hartge <i>et al.</i> (1985), 10 areas in USA, 1977–78	2982 from population-based cancer registries, aged 21–84 years; response rate, 75%	2469 RDD and 3313 HCFA, frequency-matched by age, sex, geographic distribution of the cases; response rate, 82% (HCFA), 84% (RDD)	Snuff Chewing tobacco	11 40	0.8 (0.4–1.6) 1.02 (0.7–1.5)	Race, age, residence, pipe, cigars, chewing tobacco/snuff	Analysis restricted to men who never smoked cigarettes.
Slattery <i>et al.</i> (1988), Utah, USA, 1977–83	332 histologically confirmed from population-based Utah cancer registry; white men aged 21–84 years; response rate, 76.3%	686; RDD for cases ≤ 64 years, HCFA for cases ≥ 65 years; matched 2:1 on age, sex; response rate, 81.5%	Snuff Chewing tobacco Snuff Never smoker Smoker Chewing tobacco Never smoker Smoker	16 21	1.0 (0.5–1.9) 1.1 (0.6–1.9) 2.7 (0.5–15.6) 0.7 (0.4–1.4) 2.8 (0.4–20.2) 1.2 (0.7–2.2)	Crude, unmatched	
Burch <i>et al.</i> (1989), Alberta, Ontario, Canada, 1979–82	826 histologically confirmed population-based through cancer institute, tumour registry and hospitals, aged 35–79 years; response rate, 67%	792; randomly selected from province-wide annually updated listings, matched 1:1 on age (± 4 years), sex, area of residence; response rate, 53%	Ever snuff use Ever chewing tobacco	9 26	0.6 (0.3–1.1) 0.5 (0.2–1.1)	Age, lifetime cigarette consumption	Analysis restricted to 627 men

Table 77 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Kidney							
Goodman <i>et al.</i> (1986), USA, 1977–83	267 incident primary adenocarcinomas of kidney, aged 20–80 years, from 18 hospitals in six US cities; response rate, 89%	267, individually matched on hospital, sex, race, age (± 5 years), time of admission; non-tobacco-, non-obesity related disease; response rate, 88%	Ever use* of chewing tobacco Ever versus never use of chewing tobacco, among never users of cigarettes Joint effect for smoking of 30 pack-years of cigarettes and tobacco chewing versus never use of any tobacco	13	4.0 (1.1–14.2) 0.9 (0.2–5.1) 26.00 (4.41–153.00)	Matched analysis Quetelet index, decaffeinated coffee, pack-years, chewing tobacco (ever, never), pack-years \times chewing tobacco.	*At least once a day for 1 year or more Analysis restricted to 189 men
Asal <i>et al.</i> (1988), Oklahoma, USA, 1981–84	315 incident renal cell carcinomas from 29 hospitals; ascertained by tissue diagnosis (95%) or radiological examination (5%); response rate, 91%	313 hospital patients, individually matched by age (± 5 years), sex, race, hospital, time of interview; patients with kidney disease or psychiatric diagnosis excluded; 336 RDD, frequency-matched by age (± 10 years), sex	Use of snuff		3.6 (1.2–13.3)		Among 209 men in matched-pair analysis with hospital controls

Table 77 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
McLaughlin <i>et al.</i> (1995), Australia, Denmark, Germany, Sweden, USA, 1989–92	1732 population-based (hospital-based in Germany) renal-cell adenocarcinomas, aged 20–79 years; histologically or cytologically confirmed; response rate, 72.3%	2309 from population registers, electoral rolls, residential lists, HCFA, RDD; response rate, 74.7%	Smokeless tobacco	11	1.3 (0.6–3.1)	Age, sex, centre, body mass index	Analysis restricted to men because no women used smokeless tobacco.
Muscat <i>et al.</i> (1995), Illinois, Michigan, New York, Pennsylvania, USA, 1977–93	788 renal-cell carcinomas, excluding renal pelvis; histologically confirmed from selected hospitals	779 patients with diseases unrelated to tobacco use, from daily admission lists; frequency-matched on age (± 5 years), sex, race, year of diagnosis	Ever chewing tobacco relative to non-users of smokeless tobacco <i>Chews/week</i> ≤ 10 chews > 10 chews	2.6%	3.2 (1.1–8.7) 2.5 (1.0–6.1) 6.0 (1.9–18.7) <i>p</i> for trend < 0.05		Analysis restricted to men because no women used chewing tobacco. [Snuff was included in questionnaire but not mentioned in results]. Chewing tobacco defined as ever used regularly for at least 1 year
Brain Zheng <i>et al.</i> (2001), Iowa, USA, [not reported]	375 incident gliomas from population-based registry, 40–85 years of age; histologically confirmed; response rate, 91%	2434; drivers' licence records for cases aged ≤ 64 years, HCFA for cases ≥ 65 years; frequency-matched by age (5-year groups), sex; 6.5:1 ratio controls:cases; those with history of cancer excluded; response rate, 82% (licence), 80% (HCFA)	Chewing tobacco or use of snuff	Not reported	“Use of snuff or chewing tobacco was not associated with a significantly increased risk of brain cancer for either men or women.”		

Table 77 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Non-Hodgkin lymphoma							
Brown <i>et al.</i> (1992a), Iowa, Minnesota, USA, 1981–84	622 white men with incident histologically confirmed non-Hodgkin lymphoma, aged ≥ 30 years; population-based, outside of metropolitan areas; 89% interviewed	820 living; RDD for cases ≤ 64 years, HCFA for cases ≥ 65 years; frequency-matched on site, age (± 5 years); response rate, 77% (RDD), 79% (HCFA)	All lymphoma	19	1.3 (0.7–2.5)	Age, state	Same subjects as study by Schroeder <i>et al.</i> (2002)
			Follicular	7	1.7 (0.7–4.3)		
			Diffuse	5	0.8 (0.3–2.3)		
			Small lymphocytic	4	1.7 (0.5–5.4)		
Schroeder <i>et al.</i> (2002), Iowa, Minnesota, 1980–82 (Minnesota), 1981–83 (Iowa)	622; 40% had archival tissue available.	1245 controls; 820 living controls and 425 deceased, from state death certificate files; interviews with next-of-kin of deceased subjects	All cases			Age, state, vital status	Same subjects as in study by Brown <i>et al.</i> (1992a). Ever used if used daily for at least 3 months
			Chewing tobacco	11%	1.3 (0.9–1.8)		
			Snuff	10%	1.0 (0.7–1.4)		
			<i>t(14;18)</i> -positive				
			Chewing	10	1.7 (0.9–3.1)		
			Snuff	7	1.0 (0.5–2.0)		
			<i>Age started chewing</i>				
			> 18 years	59	1.3 (0.6–2.9)		
			≤ 18 years	13	2.5 (1.0–6.0)		
			<i>t(14;18)</i> -negative				
Chewing	9	1.0 (0.6–1.8)					
Snuff	12	0.9 (0.6–1.6)					
<i>Age started chewing</i>							
> 18 years	8	1.2 (0.6–2.2)					
≤ 18 years	16	1.0 (0.3–3.0)					

Table 77 (contd)

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	Comments
Leukaemia							
Brown <i>et al.</i> (1992b), Iowa, Minnesota, USA, 1981–84	578 incident leukaemias, white men aged ≥ 30 years, from cancer registry in Iowa or ‘special surveillance network of hospitals in Minnesota’; histologically confirmed; response rate, 86%; interviews with close relatives for deceased or too ill subjects	820 living; RDD for cases ≤ 64 years; HCFA for cases ≥ 65 years; frequency-matched on age (5-year groups), state; response rate, 77% (RDD), 79% (HCFA)	Non-user of tobacco		1.0	Age, state, alcoholic beverage use	
			Chewing tobacco/snuff only	24	All 1.8 (0.9–3.3)		
				3	Acute non-lymphocytic 0.9 (0.2–3.1)		
				2	Chronic myelogenous 2.1 (0.4–10.7)		
				10	Chronic lymphocytic 1.9 (0.8–4.3)		
				4	Myelodysplasia 2.7 (0.8–9.4)		
	5	Other 3.0 (0.9–9.2)					

CI, confidence interval; HCFA, Health Care Financing Administration; NR, not reported; RDD, random-digit dialling

Two case-control studies on stomach cancer were conducted in selected counties in central and northern Sweden with different rates of stomach cancer incidence (Hansson *et al.*, 1994; Ye *et al.*, 1999) (Table 77). Eligible cases were all patients with newly diagnosed and histologically confirmed stomach cancers between 1989 and 1992 or 1995, and were ascertained via personal contacts at all departments of surgery and pathology, supplemented by record linkages to the regional and national cancer registries. In the early study (Hansson *et al.*, 1994), the odds ratio for snuff dipping adjusted for age, sex, socio-economic status and vegetable intake was 0.7 (95% CI, 0.5–1.1). In the later study (Ye *et al.*, 1999), the stomach cancers were classified as cancer of the cardia or of the distal stomach. About two controls per case were selected from the continuously updated population registry with stratification for age and sex. Face-to-face interviews were performed by specially trained personnel. The participation rates were 62% and 76% for cases and controls, respectively; the majority of the non-participants among the cases had died before the interview. For cardia cancer, the relative risk for current snuff use was 0.5 (95% CI, 0.2–1.1) and that for former users was 0.8 (95% CI, 0.3–1.9). For distal stomach cancer, the relative risks for current use were 0.8 (95% CI, 0.5–1.3) for the intestinal type and 0.6 (95% CI, 0.3–1.2) for the diffuse type. After restriction to never smokers and after combining all sites, the relative risk for ever using snuff was 0.5 (95% CI, 0.2–1.2). [The limitation is small numbers in the subgroups, which precludes e.g. site-specific analysis in never smokers with various categories of snuff use.]

(b) *Cancer of the colon and rectum*

Risk for colorectal cancer was examined in relationship to smokeless tobacco use among members of the US Veterans' cohort (Heineman *et al.*, 1995). Relative to those who had never used tobacco, smokeless tobacco users who had never smoked cigarettes, pipes or cigars had a relative risk of 1.2 (39 deaths; 95% CI, 0.9–1.7) for cancer of the colon and 1.9 (17 deaths; 95% CI, 1.2–3.1) for cancer of the rectum.

(c) *Cancer of the extra-hepatic bile duct*

A population-based case-control study in Los Angeles County, USA, included 64 cases of cancer of extra-hepatic bile duct, 41 cases of cancer of ampulla of Vater, and 255 controls (Chow *et al.*, 1994). In-person questionnaire interviews were conducted with the cases or their next-of-kin. Results obtained for the entire group of cases (personal and surrogate interviews) and for the subgroup with personal interviews only were consistent. An odds ratio of 18 (95% CI, 1.4–227.7) for chewing tobacco was observed for cancers of ampulla of Vater. [All cases of cancer of the ampulla of Vater who chewed tobacco also smoked.]

(d) *Cancer of the digestive system (combined)*

The case-control study by Sterling *et al.* (1992), described in Section 2.2.1, also reported results for cancers of the digestive organs (ICD-9 150–159). Using a reference

category of less than 100 lifetime uses of smokeless tobacco, the relative risks for 100–9999 and 10 000 or more lifetime uses were 0.2 (95% CI, 0.04–0.5) and 0.61 (95% CI, 0.3–1.1), respectively.

Gastrointestinal cancer deaths (ICD-9 150–159) were examined in the NHANES I follow-up study. Relative to non-users of tobacco, the hazard ratios for users of smokeless tobacco only for men and women were 0.9 (95% CI, 0.3–2.3) and 0.8 (95% CI, 0.3–2.7), respectively, adjusted for age, race, poverty index ratio, alcoholic beverage and dietary fat intake (Accortt *et al.*, 2002).

In the CPS-I cohort, men who reported current use of smokeless tobacco and never used other tobacco products had statistically significantly higher death rates than never users (153 deaths; hazard ratio, 1.3; 95% CI, 1.1–1.5) after adjustment for age, race, educational level, body mass index, exercise, alcoholic beverage consumption, fat consumption, fruit and vegetable intake and aspirin use. In the CPS-II cohort, compared with never users, the hazard ratio for men who reported current use of smokeless tobacco but never used any other tobacco products was 1.04 (48 deaths; 95% CI, 0.8–1.4) adjusted for the same variables and status and type of employment (Henley *et al.*, 2005).

(e) *Cancers of the respiratory tract*

(i) *Nasal cavities*

Brinton *et al.* (1984) performed a case–control study of risk factors for cancers of the nasal cavities and sinuses (ICD 8 160.0, 160.2–160.5, 160.8–160.9). Cases were selected from four hospitals in North Carolina and Virginia, USA, between 1 January 1970 and 31 December 1980. Cases were aged 18 years or older and were residents of the state in which the admitting hospital was located. For each case alive at the time of the interview, two hospital controls were selected and matched to the case on hospital, year of admission, age, sex, race and other factors. Controls with a primary diagnosis at admission of other cancers or other diseases of the upper aerodigestive tract were excluded. For deceased controls, two different controls were selected: a hospital control derived in the same manner as above and a deceased control identified through state vital statistics offices. A total of 193 cases, 232 hospital controls and 140 death certificate controls were identified and telephone interviews with study subjects or their next of kin were successfully conducted for 160 of the cases (82.9%) and 290 controls (78.0%). The cancers were 86 squamous-cell carcinomas, 24 adenocarcinomas or adenoid cystic carcinomas, 36 other carcinomas and 14 other histological types. Unmatched stratified analyses and logistic regression analyses for matched data were performed. Since the results were similar for the two analytical approaches [data not shown], only results that ignored the individual matching were presented. Sex-adjusted odds ratios for tobacco chewers or snuff users were 0.7 (15 cases; 95% CI, 0.4–1.5) and 1.5 (23 cases; 95% CI, 0.8–2.8), respectively. The odds ratio for snuff use and squamous-cell tumours was 1.9.

A case–control study in Florida assessed the association with use of smokeless tobacco among 92 cases of cancer of the nasal cavities and 6457 controls (Stockwell &

Lyman, 1986). Tobacco use was determined from medical and cancer registry records and was available for 79% of subjects. The odds ratio for smokeless tobacco was 3.3 (95% CI, 0.4–25.9), adjusted for age, race, sex and tobacco use. [The limitations of this study are presented in Section 2.2.1.]

(ii) *Larynx*

A case–control study in Florida assessed the association with use of smokeless tobacco among 797 cases of cancer of the larynx and 6457 controls (Stockwell & Lyman, 1986). Tobacco use was determined from medical and cancer registry records and was available for 79% of subjects. The odds ratio for smokeless tobacco was 7.3 (95% CI, 2.9–18.3), adjusted for age, race, sex and tobacco use. [The limitations of this study are presented in Section 2.2.1.]

The case–control study by Lewin *et al.* (1998, see Section 2.2.1) reported results separately for cancer of the larynx. Relative risks for current and former use of snuff were 1.0 (95% CI, 0.5–1.9) and 0.8 (95% CI, 0.4–1.7), respectively, after adjustment for age, smoking and alcoholic beverages.

(iii) *Lung*

Lung cancer deaths were examined in the NHANES I follow-up study (Accortt *et al.*, 2002). In the multivariate analysis and relative to non-users of tobacco, the hazard ratio for women who used only smokeless tobacco was 9.1 (95% CI, 1.1–75.4), adjusted for age, race, poverty index ratio, region of residence, alcoholic beverages, recreational physical exercise and fruit/vegetable intake. No deaths from lung cancer occurred among men who used smokeless tobacco only.

In the CPS-I cohort, the hazard ratio for lung cancer for current smokeless tobacco users who never used other tobacco products was 1.1 (18 deaths; 95% CI, 0.6–1.8) after adjustment for age, race, level of education, body mass index, exercise, alcoholic beverage consumption, fat consumption, fruit and vegetable intake and aspirin use (Henley *et al.*, 2005). In the CPS-II cohort, the hazard ratio for men who reported current use of smokeless tobacco but never used any other tobacco products compared with never users was 2.0 (18 deaths; 95% CI, 1.2–3.2) adjusted for the same variables and status and type of employment. The hazard ratios were similar for those who chewed but never used snuff and for those who used snuff but never chewed.

In the Norwegian cohort study, the relative risk for lung cancer was 0.8 (72 cases; 95% CI, 0.6–1.1) in a comparison of ever users of smokeless tobacco with never users and adjusting for age and smoking. Results were similar for ever or current users of smokeless tobacco and when stratified by smoking status (Boffetta *et al.*, 2005).

The case–control study by Williams and Horm (1977) described in Section 2.2.1 also reported on lung cancer. Among men, the relative risks for lung cancer and for moderate or heavy use of chewing tobacco or snuff were 0.7 (26 cases) and 0.8 (10 cases), respectively, adjusted for age, race and smoking.

(f) *Sarcoma*

In the US Veterans' cohort, the relative risk for soft-tissue sarcomas associated with smokeless tobacco use relative to persons who never used tobacco products was 1.5 (95% CI, 0.8–2.7). None of the users of smokeless tobacco who never used other tobacco products developed a soft-tissue sarcoma (Zahm *et al.*, 1992).

A population-based registry in Kansas, USA, provided information on white men aged 21 years or older in 1976–82 who had soft-tissue sarcomas (Zahm *et al.*, 1989). Controls were recruited through RDD and HCFA and were frequency-matched to cases on age (± 2 years). In addition, decedents from Kansas during the same period were selected for deceased cases. Controls with lymphomas, sarcomas or ill-defined malignancies, or who were homicides or suicides were excluded. Telephone interviews were conducted with 133 cases and 948 controls. The odds ratio for ever use of smokeless tobacco was 1.8 (95% CI, 1.1–2.9). Odds ratios for smokeless tobacco use by anatomic site of the soft-tissue sarcoma were: upper gastrointestinal, 3.3 (95% CI, 0.8–12.6); lung, pleura and thorax, 3.1 (95% CI, 0.9–10.5); head, neck and face, 2.4 (95% CI, 0.5–10.2); and others, 1.4 (95% CI, 0.7–2.5). The odds ratios by cell type were: fibromatous, 1.8 (95% CI, 0.7–4.7); adipose, 1.1 (95% CI, 0.2–4.2), myomatous, 2.1 (95% CI, 0.8–5.3), and others, 1.9 (95% CI, 0.9–3.9). The relative risk was highest for those diagnosed at age 80 years or above (relative risk, 3.2; 95% CI, 1.0–10.1).

(g) *Breast*

In a study by Spangler *et al.* (2001b) and Spangler (2002), Cherokee Indian women were investigated over a 2-year period, and prevalent breast cancer cases were identified through medical histories from the women themselves, and other female survey respondents formed the control group; the women were interviewed in their homes. The odds ratio for use of smokeless tobacco in the women diagnosed at less than 55 years of age was 1.3 (one case; 95% CI, 0.1–13.9) and that in women diagnosed at more than 55 years was 1.2 (two cases; 95% CI, 0.1–9.5). [There are major limitations to this study. There was no medical verification of breast cancer and the time relationship between use of smokeless tobacco and breast cancer diagnosis was not reported.]

(h) *Cervix uteri*

The population-based case–control study of randomly selected patients from the Third National Cancer Survey (1969–71) also reported results on cervical cancer (Williams & Horm, 1977). Controls for the cervical cancer case group comprised patients with other cancers that were unrelated to smoking. The relative risks controlled for smoking, age and race were 4.7 (six cases; $p < 0.05$) for moderate and 3.6 (four cases; non-significant) for heavy use of chewing tobacco or snuff. [The Working Group noted that multiple comparisons were made of many risk factors and many cancer sites in this study and, therefore, that some positive findings may have been due to chance alone.]

(i) *Prostate*

The 1601 controls from a case-control study of cancer were used to form a historical cohort in Iowa, USA; they were ascertained in 1986-89 via RDD and US HCFA, had Iowa residency, were aged 40-86 years and had no prior cancer. Twenty-four subjects who required proxy respondents were excluded, which left 1577 in the cohort who answered a mailed questionnaire that was supplemented by telephone interviews. The cohort was followed for vital status, and three persons were lost to follow-up; 103 cases of prostate cancer were identified through the state cancer registry. Two cases were subsequently excluded due to diagnosis before the questionnaire was returned. The authors reported that 'no association was seen for [...] snuff and chewing tobacco' (Putnam *et al.*, 2000). [The Working Group noted that data were not presented to support this statement.]

The Lutheran Brotherhood cohort was examined for deaths from prostate cancer (Hsing *et al.*, 1990). Relative to never use of tobacco, the relative risk for users of smokeless tobacco only was 4.5 (10 deaths; 95% CI, 2.1-9.7) adjusted for age. Ever use of smokeless tobacco compared with never use of tobacco yielded a relative risk of 2.1 (42 deaths; 95% CI, 1.1-4.1), adjusted for age and cigarette smoking. Other relative risks were 1.8 (13 deaths; 95% CI, 0.8-3.9) for former users of smokeless tobacco, 1.4 (5 deaths; 95% CI, 0.5-3.9) for occasional users and 2.4 (24 deaths; 95% CI, 1.3-4.9) for regular users, adjusted for age and cigarette smoking. The relative risk for death from prostate cancer listed on the death certificate, but not as the underlying cause, was 2.3 (14 deaths; 95% CI, 1.0-5.2) for regular users of smokeless tobacco and 2.5 (eight deaths; 95% CI, 1.0-6.5) for smokeless tobacco only users.

In the US Veterans' cohort, the relative risk for prostate cancer of smokeless tobacco only users compared with those who never used any tobacco was 1.2 (48 deaths; 95% CI, 0.9-1.6) (Hsing *et al.*, 1991).

In-home interviews were conducted with population-based cases of prostate cancer and RDD and HCFA controls in the Atlanta metropolitan area, in Detroit and in 10 New Jersey counties, USA (Hayes *et al.*, 1994). Controls were frequency-matched on age and race. Interviews were completed for 981 cases and 1315 controls. Relative to those who had never used tobacco, the odds ratios for chewing tobacco were 1.0 (95% CI, 0.6-1.5) for former users and 0.5 (95% CI, 0.2-1.0) for current users. For snuff, the odds ratios were 0.6 (95% CI, 0.3-1.4) for former and 5.5 (95% CI, 1.2-26.2) for current users.

(j) *Penis*

In a case-control study in Chennai, India, in which 505 cases of squamous-cell carcinoma of the penis were identified over a period of 30 years (Harish & Ravi, 1995), the relative risk for snuff users was 4.2 (95% CI, 1.6-11.3) after adjustment for smoking, tobacco chewing and phimosis. [It was not clear whether snuff was used orally or nasally.]

(k) *Urinary bladder*

A population-based case-control study was conducted in three provinces of Canada (Howe *et al.*, 1980). Eligible cases were all patients who had recently been diagnosed with urinary bladder cancer; controls were matched individually for sex, age and neighbourhood. The study included 480 men and 152 women (cases), and the same number of controls. In a matched pair analysis, no association between chewing tobacco and bladder cancer was observed; the estimated relative risk was 0.9, based on 61 discordant pairs, and remained unchanged after controlling for smoking.

The study by Hartge *et al.* (1985) included 2982 patients with urinary bladder cancer who were identified from records of 10 large population-based cancer registries throughout the USA (1977-78) and who were interviewed to obtain information on tobacco use and other factors. A total of 5782 population-based controls were included: controls aged under 65 years were chosen by a RDD and those aged 65 years and older were selected from the HCFA. The analysis was restricted to men. Among men who never smoked cigarettes, the relative risk for bladder cancer was 1.0 for chewing tobacco and 0.8 for use of snuff, after controlling for age, race, residence and other non-cigarette tobacco practices.

In a population-based case-control study, urinary bladder cancer cases were identified from the Utah Cancer Registry between 1970 and 1983 in individuals aged 21-84 years (Slattery *et al.*, 1988). RDD and HCFA controls were frequency-matched to cases on age and sex. After exclusion of women and non-white subjects, 332 cases and 686 controls for whom information on tobacco was obtained through an interview at the participants' homes were analysed. The crude odds ratios for urinary bladder cancer were 1.03 for use of snuff and 0.96 for chewing tobacco. When never smokers and smokers were examined separately, the odds ratios for snuff use were 2.7 (95% CI, 0.5-15.6) among never smokers and 0.8 (95% CI, 0.4-1.4) among smokers. Corresponding estimates for tobacco chewing were 2.8 (95% CI, 0.4-20.2) and 1.2 (95% CI, 0.7-2.2).

A population-based case-control study of urinary bladder cancer was conducted in the Alberta and Ontario populations of Canada (Burch *et al.*, 1989). Province-wide annually updated listings were used to identify randomly selected controls who were matched to cases on age, sex and area of residence, and all participants completed a questionnaire. Response rates were 67% for cases and 53% for controls. The odds ratio for urinary bladder cancer was 0.6 (95% CI, 0.3-1.1) for ever versus never use of snuff, and 0.5 (95% CI, 0.2-1.1) for ever versus never chewing tobacco, adjusted for lifetime cigarette consumption. Analyses that were restricted to subjects who had never smoked cigarettes gave similar results [data not shown].

(l) *Kidney*

A hospital-based case-control study identified cases of renal cancer aged 20-80 years in 18 hospitals in six US cities in 1977-83 (Goodman *et al.*, 1986). A total of 267 controls were identified by RDD and were individually matched 1:1 on hospital, sex, race, age, time of admission and non-tobacco- and non-obesity-related diseases. The matched odds

ratio for chewing tobacco among men was 4.0 (95% CI, 1.1–14.2) compared with never users. The final logistic model included Quetelet index, consumption of decaffeinated coffee, pack-years of cigarette smoking and chewing tobacco (ever, never and an interaction term of pack-years \times chewing tobacco). Based on this model, the odds ratio for chewing tobacco among never users of cigarettes was 0.9 (95% CI, 0.2–5.1).

In a case-control study in 29 hospitals in Oklahoma, USA (Asal *et al.*, 1988), 315 cases and 313 controls were individually matched on age, sex, race, hospital and time of interview. Controls with kidney disease or psychiatric diagnoses were excluded and interviews were conducted during hospitalization. Among men, snuff use was associated with a risk for renal-cell carcinoma to yield an odds ratio of 3.6 (95% CI, 1.2–13.3). [Smoking was not controlled for.]

A case-control study (McLaughlin *et al.*, 1995) that used cases from several countries was carried out in Europe, Australia and the USA. The main source of cases was population-based cancer registries, except in Germany, where cases were identified through hospital networks. Controls were selected from various sources, and interviews were completed for 1732 cases and 2309 controls. The odds ratio for use of smokeless tobacco only versus no use of tobacco was 1.3 (95% CI, 0.6–3.1), adjusted for age, sex, centre and body mass index.

In a case-control study in the USA, cases were ascertained from selected hospitals in the states of New York, Pennsylvania, Illinois and Michigan during 1977–93 (Muscat *et al.*, 1995). Controls who had conditions that were unrelated to tobacco use were selected from the same hospitals and were frequency-matched on age, sex, race, hospital and year of diagnosis. Questionnaires were administered by interviewers in the hospitals. A total of 788 cases and 779 controls were included in the analyses. Relative to men who had never chewed tobacco, the odds ratio for ever use of smokeless tobacco regularly for at least 1 year was 3.2 (95% CI, 1.1–8.7). A dose-response relationship was observed and yielded an odds ratio of 2.5 (95% CI, 1.0–6.1) for chewing 10 times or fewer per week and 6.0 (95% CI, 1.9–18.7) for chewing 11 or more times per week. [Smoking was not controlled for.]

(m) *Brain*

In a population-based case-control study in Iowa, USA, data from 375 brain cancer cases and 2434 controls from drivers licence records and HCFA were analysed (Zheng *et al.*, 2001). Cases were 40–85 years of age and controls were selected at a ratio to cases of 6.5:1. Information on tobacco use was obtained through a mailed questionnaire. Next of kin were used as respondents when the cases were deceased. Response rates were above 80% for both cases and controls. The authors reported that “use of [...] snuff or chewing tobacco was also not associated with a significantly increased risk of brain cancer for either men or women”. [Data to support this statement were not presented.]

(n) *Non-Hodgkin lymphoma*

Iowa and non-metropolitan areas in Minnesota, USA, were the sites of two population-based studies of non-Hodgkin lymphoma in men (Brown *et al.*, 1992a; Schroeder *et al.*,

2002). White male cases aged 30 years and older were identified in 1980–82. Living cases were matched to RDD and HCFA controls; state vital status lists provided controls for deceased cases. Controls were frequency-matched to cases on age, state of residence and vital status. In-person interviews were conducted for 622 cases and 1245 controls or their next of kin. Persons were considered to be smokeless tobacco users if they had used it daily for at least 3 months. In an analysis by lymphoma subtypes using cases and living controls only, odds ratios adjusted for age and state for users of smokeless tobacco only compared with never users of tobacco were: all lymphomas, 1.3 (95% CI, 0.7–2.5); follicular, 1.7 (95% CI, 0.7–4.3); diffuse, 0.8 (95% CI, 0.3–2.3); small lymphocytic, 1.7 (95% CI, 0.5–5.4); high-grade, 1.3 (95% CI, 0.1–10.8); and unclassified, 1.5 (95% CI, 0.3–7.4). For multiple myeloma, the odds ratio was 1.9 (95% CI, 0.5–6.6), adjusted for age. In a further analysis of lymphoma subtypes by t(14;18) positivity (Schroeder *et al.*, 2002), no consistent pattern emerged.

(o) *Leukaemia*

Brown *et al.* (1992b) conducted a case–control study of tobacco use and risk for leukaemia. Personal interviews were conducted with subjects or with close relatives for those who were deceased or too ill. Odds ratios adjusted for age, state and use of alcoholic beverages for users of smokeless tobacco only compared with non-users of tobacco were: all leukemias, 1.8 (95% CI, 0.9–3.3); acute non-lymphocytic, 0.9 (95% CI, 0.2–3.1); chronic myelogenous, 2.1 (95% CI, 0.4–10.7); chronic lymphocytic, 1.9 (95% CI, 0.8–4.3); myelodysplasia, 2.7 (95% CI, 0.8–9.4); other, 3.0 (95% CI, 0.9–9.2).

2.3 Nasal use

2.3.1 *Cancer of the oral cavity*

Three case–control studies from Kerala, India (Sankaranarayanan *et al.*, 1989a,b, 1990a) investigated the association between nasal snuff use and cancer of oral subsites among men (Table 78).

The first part of the study (Sankaranarayanan *et al.*, 1989b) focused on cancer of the anterior two-thirds of tongue and floor of the mouth and comprised 158 cases and 314 controls who were selected from a pool of 546 hospital controls with non-malignant conditions at sites other than the head and neck and were matched for age and religion. For cancer of the tongue and floor of the mouth, the age-adjusted odds ratio was 3.0 (95% CI, 0.9–9.6) for regular snuff users and 4.3 (95% CI, 1.2–14.7) for occasional snuff users. The odds ratio for < 100 unit years was 10.0 (95% CI, 1.2–86.1) and that for ≥ 100 unit years was 1.1 (95% CI, 0.2–6.2).

The second part of the study on cancer of the gingiva (Sankaranarayanan *et al.*, 1989a), comprised 109 cases, and the third part on cancer of buccal and labial mucosa comprised 250 cases (Sankaranarayanan *et al.*, 1990a). All 546 controls from the same pool as that in the first study were used for both the second and third studies. For gingival

Table 78. Case-control studies of nasal use of smokeless tobacco and oral cancer

Reference, study location, period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders	
Sankaranarayanan <i>et al.</i> (1989b), India, 1983–84	Tongue (ICD-9 141.1, 141.2, 141.3, 141.4), floor of mouth (ICD-9, 144)	158 men; biopsy-proved cases of cancer from one hospital	314 male patients with non-malignant conditions at sites other than head and neck; matched by age, religion	<i>Snuff inhalation</i>			Age	
				No	142	1.0		
				Yes	8	3.0 (0.9–9.6)		
				<i>Snuff inhalation</i>				
				Never	142	1.0		
				< 100 unit years	6	10.0 (1.2–86.1)		
				≥ 100 unit years	2	1.1 (0.2–6.2)		
Sankaranarayanan <i>et al.</i> (1989a), India, 1983–84	Gingiva (ICD-9, 143.0, 143.1)	109 men from one hospital	546 male patients with non-malignant conditions at sites other than head and neck	<i>Snuff inhalation</i>			<i>Bidis</i> , alcoholic beverages, betel quid	
				No	100	1.0		
				Yes	4	3.0 (0.7–12.6)		
Sankaranarayanan <i>et al.</i> (1990a), India, 1983–84	Buccal mucosa (ICD-9, 145.0, 145.1, 145.6), labial mucosa (ICD-9, 140.3, 140.4)	250 men from one hospital	546 male patients with non-malignant conditions at sites other than head and neck	<i>Snuff inhalation</i>			<i>Bidis</i> , alcoholic beverages, betel quid	
				No	232	1.0		
				Yes	12	2.9 (0.98–8.8)		
				<i>Snuff inhalation</i>				Age
				Never	232	1.0		
				< 100 unit years	7	15.7 (2.0–125.3)		
				≥ 100 unit years	5	2.0 (0.6–6.6)		

cancer, the age-adjusted odds ratio for daily snuff use was 3.9 (95% CI, 1.2–12.7) and that for occasional use was 3.8 (95% CI, 1.1–13.5). The odds ratio for regular snuff use was 3.0 (95% CI, 0.7–12.7) after adjustment for daily frequency of use of betel quid, *bidi* smoking and alcoholic beverage use. For cancer of the buccal and labial mucosa, the age-adjusted odds ratio was 4.0 (95% CI, 1.5–10.3) for regular snuff users and 2.3 (95% CI, 0.8–7.0) for occasional snuff users. After adjusting for daily frequency of use of betel quid, *bidi* smoking and alcoholic beverage use, the odds ratio was 2.9 (95% CI, 0.98–8.8). The odds ratio for users of < 100 unit years was 15.7 (95% CI, 2.0–125.3) and that for users of ≥ 100 unit years was 2.0 (95% CI, 0.6–6.6).

2.3.2 *Cancer of the oesophagus*

The series of case-control studies from Kerala, India, also reported on 267 male patients with cancer of the oesophagus and the same 546 controls (Sankaranarayanan *et al.*, 1991). The age-adjusted odds ratio for daily snuff use was 2.4 (95% CI, 0.8–7.0) and that for occasional use was 3.6 (95% CI, 1.2–10.7) (Table 79). [The Working Group noted that effect estimates were not adjusted for smoking or betel quid chewing.]

2.3.3 *Cancer of the paranasal sinus*

Shapiro *et al.* (1955) studied 37 Bantu cases of cancer of the paranasal sinus from radiation therapy department records from 1949–51 of a group of hospitals in Johannesburg, South Africa. Cancer of the paranasal sinuses (22 men, five women) accounted for a high proportion of respiratory tract cancer (71% of men, 83% of women) in Bantu Africans. This was in sharp contrast to European cases seen in the Transvaal, where only seven (5%) of the respiratory tract cancers occurred in the nasal sinuses. Most of the cancers were in the maxillary antrum (28/34 studied) and were described typically as well-differentiated ‘squamous epitheliomata’. The authors noted that 80% of the 28 antral cancer cases reported ‘prolonged and heavy’ use of snuff in contrast to only 34% of Bantu men with cancer at other sites. According to Keen *et al.* (1955), the product snuffed by Bantus typically contained powdered tobacco leaves and an ash from aloe plants or other species, with the occasional addition of oil, lemon juice and herbs; typical use was ‘one teaspoonful’ per day. The authors stated that ‘there was no obvious correlation’ between cancer of the maxillary antrum and cigarette, pipe or *dagga* [marijuana] smoking. [The Working Group noted that the source and nature of the control group was not described.]

2.3.4 *Cancer of the larynx*

The series of case-control studies from Kerala, India, also reported on 191 male patients with biopsy-proved cancer of the larynx and used the same 546 controls (Sankaranarayanan *et al.*, 1990b). The age-adjusted odds ratio for daily snuff use was 1.2 (95% CI, 0.3–4.9) and that for occasional use was 2.8 (95% CI, 0.9–8.7) (Table 79). [The Working Group noted that effect estimates were not adjusted for smoking.]

Table 79. Case-control studies of nasal use of smokeless tobacco and cancer at other sites

Reference, study location, period	Characteristics of cases	Characteristics of controls	Exposure categories	No. of exposed cases	Relative risk (95% CI)	Adjustment for potential confounders
Oesophagus						
Sankaranarayanan <i>et al.</i> (1991), India, 1983–84	207 men from one hospital	546 male patients with non-malignant conditions at sites other than head and neck	Snuff inhalation No Yes	192 7	1.0 2.4 (0.8–7.0)	Age
Larynx						
Sankaranarayanan <i>et al.</i> (1990b), India, 1983–84	191 men biopsy-proved from one hospital	546 male patients with non-malignant conditions at sites other than head and neck	Snuff inhalation No Yes	182 3	1.0 1.2 (0.3–4.9)	Age
Lung						
Hsairi <i>et al.</i> (1993), Tunisia, 1988–89	110 (107 men, 3 women) from one hospital in Tunis; 77 histologically confirmed	110 men individually matched on age, sex, cigarettes/day (± 5)	Use of smokeless tobacco	20	2.2 (0.9–5.6)	Age, sex, number of cigarettes/day, water pipe, cannabis

2.3.5 *Cancer of the lung*

A case-control study was conducted by Hsairi *et al.* (1993) on 110 (107 men, three women) bronchial cancer patients and 110 controls individually matched for age, sex and number of cigarettes (± 5) smoked per day (Table 79). Cases were recruited from December 1988 to May 1989 in the Ariana Hospital that covered Tunis City and the suburban area; controls were chosen among residents of the same area. Twenty cases (18.2%) and eight controls (7.3%) had ever inhaled snuff, which yielded a crude odds ratio of 2.8 (95% CI, 1.2–6.8). The Cochrane Mantel-Haenzel method was used to adjust the association for age, sex, cigarette use (0, 1–10, 11–20, ≥ 20 per day), and water pipe and cannabis use. The adjusted odds ratio obtained was 2.2 (95% CI, 0.9–5.6). The authors indicated that no quantitative analyses were appropriated as the amounts used were ‘relatively weak’. [The paper was written in French and the expression ‘tabac à priser’ was used for smokeless tobacco. The Working Group deduced that this represented nasal use of snuff according to the popular meaning of this expression. Nine interviewers were involved in the data collection. The control recruitment was not reported in detail.]