

**Table 2.2. Case-control studies of smokeless tobacco and cancers of the oral cavity and pharynx, adjusting for tobacco smoking or among non-smokers**

Reference, study location and period	Organ site (ICD code)	Characteristics of cases	Characteristics of controls	Exposure assessment	Exposure categories	No. of cases/controls	Relative risk (95% CI)*	Adjustment for potential confounders	Comments													
Africa																						
Idris, et al., (1995b) Sudan, 1970–85	ICD version not clear) 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. Response rate not stated. Presumed 100% histologically confirmed because all cases were squamous cell cancer.	(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) 2 820 volunteers attending oral health education programmes in various regions of Sudan	Questionnaire at registration in hospital; similar questionnaire administered by trained interviewers to volunteers	<b>Toombak</b>	Never <i>User</i> < 10 years > 11 years	157 218 10 120	<i>Case group 1 versus Hospital controls</i> 1.0 7.3 (4.3–12.4) 0.7 (0.3–1.8) 11.0 (4.8–25.1)	Age, sex, tribe, residence	10–12% of hospital cases and controls smoked. 21.2% of population controls smoked.												
											<b>Toombak</b>	Never <i>User</i> < 10 years > 11 years	1.0 3.9 (2.9–5.3) 0.2 (0.1–0.4) 4.3 (2.9–6.3)	<i>Population controls</i>								
															<b>Toombak</b>	Never <i>User</i> < 10 years > 11 years	1.0 1.4 (0.8–2.5) 0.5 (0.7–0.4) 1.9 (0.7–4.7)	<i>Case group 2 versus Hospital controls</i>				
																			<b>Toombak</b>	Never <i>User</i> < 10 years > 11 years	0.7 (0.5–1.0) 0.2 (0.2–0.1) 0.8 (0.5–1.6)	<i>Population controls</i>

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Europe									
Lewin et al., (1998) Stockholm and southern Sweden, 1988–91	Oral cavity, pharynx, oesophagus	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%. Percent histologically confirmed not stated.	756 controls from the population registry; stratified by region and age; response rate, 85%	Personal interviews conducted by two specially trained nurses Cases interviewed in hospital about one month after diagnosis. No mention of whether any next-of-kin interviews.	<i>Overall</i> Ever Current snuff use Former snuff use <i>Age started</i> < 25 years > = 25 years <i>Duration of use</i> < 30 years > = 30 years <i>Total consumption</i> < 125 kg > = 125 kg <i>Intensity per week</i> < = 50 g/week > 50 g/week Ever Current snuff use Former snuff use > 50 g/week  Ever Current snuff use Former snuff use  <i>Never smokers</i> Ever Current snuff use Former snuff use		<i>Head and neck</i> 1.1(0.7–1.5) 1.0 (0.6–1.6) 1.2 (0.7–1.9)  1.0 (0.6–1.6) 1.1 (0.7–1.8)  1.0 (0.7–1.6) 1.1 (0.6–2.0)  1.0 (0.7–1.6) 1.1 (0.6–2.0)  0.8 (0.5–1.3) 1.6 (0.9–2.6) <i>Oral cavity</i> 1.4 (0.8–2.4) 1.0 (0.5–2.2) 1.8 (0.9–3.7) 1.7 (0.8–3.9) <i>Pharynx</i> 0.7 (0.4–1.3) 0.7 (0.3–1.5) 0.8 (0.3–1.9)  <i>Head and neck</i> 4.7 (1.6–13.8) 3.3 (0.8–12.0) 10.5 (1.4–117.8)	Age, region, smoking, alcoholic beverage consumption	In Boffetta et al (2008) meta-analysis. In Lee and Hamling (2009) meta-analysis

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Schildt et al., (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. Response rate 96%. 100% histologically confirmed	From population registry; matched by age, sex, county, vital status and year of death for deceased cases. Response rate 91%	Postal questionnaire supplemented by telephone call as needed. Next-of-kin interviews for at least 57% of cases and controls	Never 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		<i>Oral cancer</i> 1.0 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 in meta-analysis In Boffetta et al (2008) meta-analysis. In Lee and Hamling (2009)

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Rosenquist et al. (2005), Rosenquist (2005) Southern Health Care Region, Sweden 2000–2004	ICD7 141 (tongue), 143 (floor of mouth), 144 (oral cavity, not otherwise specified), and 145 (oropharynx)	132 (91 men, 41 women) born in Sweden, without a previous cancer diagnosis except skin cancer treated at the two university hospitals were almost all patients with oral cancer are treated; 80% response rate. Percent histologically confirmed not stated.	320 (215 men, 105 women) based on three controls per case born in Sweden with no previous cancer diagnosis except skin cancer living in the Southern Health care Region of Sweden matched on age (+-3 years), sex, county; 81% response rate	Interviewed using a standardized protocol	<i>Moist snuff use</i>			Adjusted for total consumption of alcohol and tobacco smoking	Users of fermented snuff were persons who had been snuff users in 1983 or earlier. 1983 is when the Swedish tobacco manufacturers changed from a fermentation to a heat treatment process. In Lee and Hamling (2009) meta-analysis.
					Never used		1.0		
					<i>Had used</i>		0.7 (0.3–1.3)		
					Ex—users		0.3 (0.1–0.9)		
					Current users		1.1 (0.5–2.5)		
					<i>Fermented snuff</i>				
					Fermented snuff		0.7 (0.3–1.4)		
					Non-fermented snuff		0.6 (0.2–1.9)		
					<i>Duration (years)</i>				
					< = 10		0.6 (0.3–1.3)		
					> 10		0.8 (0.2–2.8)		
					<i>Exposure time (h/day)</i>				
					< = 10		0.7 (0.3–1.5)		
> 10		0.5 (0.2–1.6)							
<i>Consumption (g/day)</i>									
1–14		0.9 (0.3–2.5)							
> 14		1.7 (0.5–5.7)							
<i>Moist snuff use</i>			Adjusted for total consumption of alcohol, tobacco smoking, and high risk HPV subtypes						
Never used		1.0							
<i>Had used</i>		0.6 (0.3–1.4)							
Ex-users		0.4 (0.1–1.1)							
Current users		1.0 (0.4–2.6)							

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Rosenquist et al. (2005), Rosenquist (2005) (contd)					<i>Fermented snuff</i> Fermented Non-fermented snuff <i>Duration (years)</i> < = 10 > 10 <i>Exposure time (h/day)</i> < = 10 > 10  <i>Consumption (g/day)</i> > 14 Cons		0.7 (0.3–1.6) 0.5 (0.1–2.1)  0.6 (0.3–1.3) 0.9 (0.2–3.7)  0.6 (0.3–1.5) 0.7 (0.2–2.1)  0.8 (0.3–2.4) 1.8 (0.4–7.3)		
North America									
Vogler et al., (1962) Atlanta, GA, USA, 1956–57	Oral cavity, pharynx, larynx	333 Whites (235 men, 98 women) with cancers of the oral cavity, pharynx, or larynx at a hospital. Response rate not stated. Percent histologically confirmed not stated	Control group 1: 214 prevalent and incident patients with diseases of the mouth ?including leukoplakia, Control group 2: 584 patients with other cancers, 787 patients with no cancer and whose mouths were not examined. Response rate not stated.	Questionnaire	<b>Cases and control group 1</b> Had not used <i>Urban</i> Had used <i>Rural</i> Had used <b>Cases and control group 2</b> <i>Urban</i> Had used <i>Rural</i> Had used		1.0 [26.5, 4.6–292.8] [24.2, 7.3–80.4] [21.5, 19.3–24.0] [11.6, 5.5–24.4]	Only 7% of rural women smoked and among urban women the proportions of smokers in the groups were similar	No mention of age adjustment/matching. ORs and CIs estimated from data given. In Lee and Hamling (2009) meta-analysis.

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Martinez, (1969), Puerto Rico, 1966	Oral and pharyngeal cancer	153 epidermoid carcinomas of the mouth (115 men, 38 women) and 68 of the pharynx (55 men, 13 women) from a cancer registry. 73% histologically confirmed. Of the combined case group of 400 cases of oral, pharyngeal, and oesophageal cancer, 12% proxy interviews. Response rate not stated.	3 controls per case: 1 from the same hospital or clinic as the case and two who had lived in the same community as the case for at least 10 years. 12 percent proxy interviews	Interview by trained persons with a college education	<i>Among never smokers</i> Never chew tobacco Ever chew tobacco  Ever chew tobacco		1.0  <i>Oral</i> [11.9,1.99–71.45]  <i>Pharynx</i> [8.7,1.15–65.96]		The chewing tobacco was usually mixed with molasses. The numbers of tobacco chewers in the sites-specific tables do not add up to the total numbers of chewers in the calculated risks may not be accurate.
Williams and Horm, (1977); Williams et al., (1977) USA, 1969–71	Manual of tumour nomenclature and coding, 1968, lip, tongue, bum and mouth, and pharynx cancer	7518 (57% of randomly selected) incident invasive cancers who participated in the population-based Third National Cancer Survey. Response rate: 57%; 95% histologically confirmed	Cancer at sites unrelated to tobacco. Response rate: 57%	Personal interview by trained personnel, proxies allowed	<i>Among men</i> <i>Smokeless tobacco</i>  Moderate use Heavy use  Moderate use Heavy use  Moderate use Heavy use		<i>Cancer of gum and mouth</i>  3.9 ( $P < 0.01$ ) 6.7 <i>Cancer of lip and tongue</i> 0.4 1.9 <i>Cancer of the pharynx</i> 0.5 –	Age, race, smoking	In Lee and Hamling (2009) meta-analysis

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Winn et al., (1981a, 1981b, 1984); Blot et al. (1983), Winn (1986)	Oral and pharyngeal Cancer (ICD-8 141, 143–146, 148)	Oral and pharyngeal cancer from hospitals discharge diagnoses (156 women) or death certificates (99 women); response rate, 91%. Percent histologically confirmed not stated.	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. Next-of-kin interviews for 51% of cases and 21% of controls.	Never Snuff user, nonsmoker		White women 1.0 4.2 (2.6–6.7)	Poor dentition (Winn et al., 1981b), use of mouthwashes (Blot et al., 1983), fruit and vegetables (Winn et al., 1984), type of respondent (Winn, 1986). Odds ratios higher for self-interviews than for next-of-kin interviews (Winn, 1986)	In Boffetta et al. (2008) meta-analysis. In Lee and Hamling (2009) meta-analysis
					Never Snuff user, nonsmoker		<i>Black Women</i> 1.0 1.5 (0.5–4.8)		
North Carolina, USA, 1975–78					<i>Years of snuff use in nonsmokers</i>		<i>Cancer of gum and buccal mucosa</i>		
					0 1–24 25–49 ≥ 50		1.0 13.8 (1.9–98.0) 12.6 (2.7–58.3) 47.5 (9.1–249.5)		
					0 1–24 25–49 ≥ 50		<i>Cancer of other mouth and pharynx</i> 1.0 1.7 (0.4–7.2) 3.8 (1.5–9.6) 1.3 (0.5–3.2)		
							<i>Among non-smokers who did not use alcohol</i> 3.8 (2.3–6.3)		

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Blot et al., (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%. 100% histologically confirmed.	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	Smokeless tobacco <i>All</i> Never Ever Men Women <i>Non-smoking women</i> Ever		1.0 [0.85] [3.4]       6.2 (1.9–19.8)	Age, race, study location, respondent status.	Female nonsmokers primarily used snuff rather than chewing tobacco; all six female non-smoking cases who used smokeless tobacco had oral cavity cancer. Nearly all male tobacco chewers were smokers. meta-analysis. In Boffetta et al (2008) meta-analysis. In Lee and Hamling (2009).



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Mashberg et al. (1993) New Jersey, USA, 1972–83	Oral and oropharynx cancer	359 male black or white in situ or invasive squamous-cell carcinoma of the oral cavity and oropharynx admitted to Veterans hospital in New Jersey; 94% of study subjects enrolled between 1977 and 1982; response rate not stated. 100% histologically confirmed.	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	<i>Smokeless tobacco</i> Never Ever chewing tobacco ever Ever snuff use ever		1.0 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. [WG: are the smokeless tobacco findings actually crude estimates?]	No dose-response by duration of use (data not shown) In Boffetta et al(2008) meta-analysis. In Lee and Hamling (2009) meta-analysis

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Kabat et al., (1994) USA, 1977–90	Oral cavity and pharynx	1560 cases from 28 hospitals in eight cities with incident, cancers of the tongue, floor of mouth, gums, gingiva, buccal mucosa, palate, retromolar area, tonsil, other pharynx; response rate not stated. 100% histologically confirmed.	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% nonneoplastic conditions; response rate not stated	In-hospital Questionnaire interview	<i>Among non-smokers</i> Chewing tobacco Snuff use		2.3 (0.7–7.3) 34.5 (8.5–140.1)		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. meta-analysis In Boffetta et al (2008) meta-analysis. In Lee and Hamling (2009)
South Asia									
Chandra, (1962) Calcutta, India 1955–59	Buccal mucosa	455 with buccal mucosal cancer (287 men, 163 women) from a hospital	500 friends or relatives (410 men, 90 women) who came the hospital, approximately age-matched	Interview	<i>Among non-smokers</i> Never Ever Men Women		1.0 [2.7] [2.5]		Author did not clarify if chewing habit was tobacco only or tobacco plus lime

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Wasnik et al., (1998) India [years of study not reported]	'oropharyngeal cancer'	123 (73 men, 50 women) 'oro-pharyngeal' cancers from three hospitals in Nagpur. Response rate not stated. 100% histologically confirmed	246 pair-matched controls; 123 non-cancer patients and 123 patients with cancer at other sites; matched for age, sex. Response rate not stated.	[Not reported]	Never Tobacco chewing Use of tobacco containing material for cleaning teeth		1.0 11.4 (4.4–29.6) 5.2 (2.5–11.8)	Unadjusted. All types of tobacco chewing (including with betel quid components were combined) Tobacco chewing, tobacco smoking, alcohol intake, and occupation	Results refer to control group of non-cancer patients
Merchant et al., (2000) Pakistan, 1996–98	Oral cavity	79 (54 men and 25 women) oral squamous-cell cancers (buccal, gingiva, floor of mouth, tongue, palate; fauces and others) from three hospitals. Response rate not stated. 100% histologically confirmed.	149 (94 men, 55 women) from orthopaedic and general surgical wards, with no past or present malignancy; individually matched on age, sex, hospital. Response rate not stated.	Structured questionnaire, trained interviewer at hospital	Never use of naswar Ever		1.0 9.5 (1.7–53.5)	Cigarette smoking, alcoholic beverage consumption	

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Sapkota et al. (2007) Ahmedabad, Bhopal, Kolkata, and Chennai 2001–2004	Hypopharyngeal cancers (ICD0–2 codes C12, C13) laryngeal cancers (ICDO-2 codes 32.0–32.9)	1024 invasive cancer cases from 4 hospitals/cancer centres: 513 hypopharyngeal (430 men and 83 women). Response rate not stated. 100% histologically confirmed. 90% were squamous cell carcinoma.	718 (607 men and 111 women) matched on age (+/- 5 years), sex and geographical area of residency. 19% were hospital-based patients with diseases not related to alcohol or tobacco consumption, 81% were visitors to patients at hospital. Response rate not stated.	Standardized questionnaire administered by trained staff at hospital	<i>Never chew non-tobacco product, never chew tobacco product</i>	1	2.25 (0.99–5.13)	Adjusted for centre, age, sex, SES, alcohol consumption, and tobacco pack years.	For product-specific analysis, if more than one chewing tobacco product was reported, individuals assigned to product they reported using for the longest duration. (This would attenuate ORs). Snuffing is oral or nasal use of tobacco products; the most common in this region is naswar. Cannot distinguish nasal from oral snuffing. Ever chewer (at least once a week for 6 months or more). Khaini is a mixture of tobacco and slaked lime. Zarda is tobacco and slaked lime.
					Never snuffing				
					Ever snuffing	1	2.85 (1.15–7.08)	Adjusted for centre, age, sex, SES, alcohol consumption, tobacco snuffing, and tobacco pack years.	
					<i>Never chew non-tobacco product, never chew tobacco product, and never smokers</i>				
					Never snuffing	1	0.74 (0.39–1.42)	Adjusted for centre, age, sex, SES, alcohol consumption, and tobacco pack years.	
					Ever snuffing				
<i>All individuals</i>	1	2.23 (1.11–4.50)	Adjusted for centre, age, sex, SES, alcohol consumption, and tobacco snuffing.						
Never									
Khaini	1	2.02 (0.81–5.03)	Adjusted for centre, age, sex, SES, alcohol consumption, and tobacco snuffing.						
Zarda									
<i>Never smokers</i>	1	3.58 (1.20–10.68)	Adjusted for centre, age, sex, SES, alcohol consumption, and tobacco snuffing.						
Never									
Khaini	1	2.02 (0.81–5.03)	Adjusted for centre, age, sex, SES, alcohol consumption, and tobacco snuffing.						
Zarda									

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