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Smokeless Tobacco Use and the Risk of Head and Neck Cancer: Pooled Analysis of US Studies in the INHANCE Consortium

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Previous studies on smokeless tobacco use and head and neck cancer (HNC) have found inconsistent and often imprecise estimates, with limited control for cigarette smoking. Using pooled data from 11 US case-control studies (1981–2006) of oral, pharyngeal, and laryngeal cancers (6,772 cases and 8,375 controls) in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium, we applied hierarchical logistic regression to estimate odds ratios and 95% confidence intervals for ever use, frequency of use, and duration of use of snuff and chewing tobacco separately for never and ever cigarette smokers. Ever use (versus never use) of snuff was strongly associated with HNC among never cigarette smokers (odds ratio (OR) = 1.71, 95% confidence interval (CI): 1.08, 2.70), particularly for oral cavity cancers (OR = 3.01, 95% CI: 1.63, 5.55). Although ever (versus never) tobacco chewing was weakly associated with HNC among never cigarette smokers (OR = 1.20, 95% CI: 0.81, 1.77), analyses restricted to cancers of the oral cavity showed a stronger association (OR = 1.81, 95% CI: 1.04, 3.17). Few or no associations between each type of smokeless tobacco and HNC were observed among ever cigarette smokers, possibly reflecting residual confounding by smoking. Smokeless tobacco use appears to be associated with HNC, especially oral cancers, with snuff being more strongly associated than chewing tobacco.

chewing tobacco; head and neck neoplasms; snuff; tobacco, smokeless

Abbreviations: CI, confidence interval; HNC, head and neck cancer; ICD-10, *International Classification of Diseases, Tenth Revision*; INHANCE, International Head and Neck Cancer Epidemiology; OR, odds ratio.

Editor's note: *An invited commentary on this article appears on page 717.*

Head and neck cancer (HNC) encompasses tumors of the oral cavity, pharynx, and larynx and accounts for 400,000–600,000 new cancer cases and 200,000–300,000 deaths globally each year (1–4). In the United States, estimates of HNC incidence and mortality for 2015 were 59,340 new cases and 12,290 deaths (5). More than 90% of HNCs are squamous cell carcinomas (2). Associations between smoking tobacco products (cigarettes, cigars, and pipes) and HNC have been previously described in the International Head and Neck Cancer Epidemiology (INHANCE) Consortium, with all 3 smoking tobacco products independently contributing to an elevated risk of HNC (6). While the prevalence of cigarette smoking has declined in the United States in recent years (22.2% in 2005 vs. 19.1% in 2010), use of smokeless tobacco has slightly, though not significantly, increased (prevalence of 2.7% in 2005 vs. 3.0% in 2010) (7). The overall prevalence of smokeless tobacco use in the United States is 10 times the Healthy People 2020 target of 0.3% and therefore remains an important public health concern (7). Like smoking

tobacco products, smokeless tobacco products contain numerous carcinogens, including several tobacco-specific *N*-nitrosamines (8, 9). The International Agency for Research on Cancer has concluded that there is sufficient evidence of carcinogenicity for smokeless tobacco (8).

However, previous epidemiologic studies on smokeless tobacco and HNC in the United States have produced mixed results, with some investigators reporting elevated risk and others near-null estimates (8–10). Given the relatively small sample sizes of previous studies, estimates for ever use of smokeless tobacco products were often imprecise, and frequency and duration of use, as well as exclusive use, of smokeless tobacco products was largely unexplored (8–10). Further, some studies had limited information on other lifestyle factors, particularly cigarette smoking (8–10).

Using data from US studies in the INHANCE Consortium, we were able to more precisely estimate associations between smokeless tobacco products and HNC, including associations for exclusive use of smokeless tobacco products and associations with specific tumor sites.

METHODS

Study design

As of June 2014, the INHANCE Consortium (http://www.inhance.utah.edu/) had pooled data from 35 case-control studies of HNC (data version 1.5). Information about tobacco-chewing and snuff use was available from a study in Puerto Rico (11), from Indian research centers in an international study (12), and from most (12 out of 15) US studies (13–25). European, Asian, and South American studies that participate in the INHANCE Consortium did not ascertain information on smokeless tobacco use, since such behaviors are not common in those areas, except in Nordic countries, which are not currently represented in INHANCE. No individuals reported using snuff in the study from Puerto Rico; use of chewing tobacco was infrequent and therefore was previously analyzed in combination with other noncigarette forms of tobacco (11). Although Indian research centers in the international study (12) collected information on smokeless tobacco use, the products used in those centers (e.g., paan, a preparation containing areca nut and betel leaf) differed from those used in other regions of the world, and an analysis of the data from the Indian centers was previously published (investigators reported an increased risk of HNC among paan chewers (8, 9, 12)). Therefore, we considered only US studies in the present analysis.

We further excluded a study from Tampa, Florida (25), because information on chewing tobacco and snuff use was reported jointly in that study. The study from Boston, Massachusetts (14) only ascertained information on chewing tobacco and was therefore excluded from analyses of snuff. In addition, persons with missing demographic data on sex, age, race/ethnicity, or subtype of cancer (66 cases and 51 controls) or missing behavioral data on frequency of alcohol drinking or duration of cigarette, cigar, or pipe smoking (463 cases and 363 controls) were excluded from all analyses, since the models adjusted for these variables. Therefore, our analysis included 6,772 cases and 8,375 controls from 11 studies conducted in the following locations: Seattle, Washington (1985–1989 (18) and 1990–1995 (15)); the state of Iowa (1993–2006) (19); Los Angeles, California (1999–2004) (20); Houston, Texas (2001–2006) (21); Boston, Massachusetts (1999–2003) (14); Baltimore, Maryland (2000–2005) (22); the state of North Carolina (a hospital-based study (1994–1997) (23) and a population-based study (2002–2006) (13)); New York, New York (Memorial Sloan Kettering Cancer Center (1992–1994) (24)); the state of New York and other locations (a multicenter study of hospital patients in New York State, Illinois, Michigan, and Pennsylvania (1981–1990)) (17)); and nationwide (a multicenter study with centers in Atlanta, Georgia; Los Angeles County, California; the state of New Jersey; and Santa Clara and San Mateo counties, California (1983–1984)) (16).

Descriptions of these studies, including definitions of smokeless tobacco use, are provided in Web Table 1 (available at http://aje.oxfordjournals.org/). Most studies were hospital-based, with cases and controls frequency-matched by age and sex. Information on ever use of chewing tobacco and snuff, frequency of use (number of times per day), and duration of use (in years) was ascertained separately in each study. However, information on frequency of smokeless tobacco use in the Seattle (15, 18) and New York multicenter (17) studies was not available or was not easily standardized with data from other studies; therefore, we excluded these studies from analyses of frequency. Pooling methods have been previously described (26, 27).

Tumor sites were categorized according to the *International Classification of Diseases for Oncology, Second Edition*, the *International Classification of Diseases*, *Ninth Revision*, or the *International Classification of Diseases*, *Tenth Revision* (ICD-10) (26, 28–30). Cancers of the oral cavity, oropharynx, hypopharynx, oral cavity or pharynx overlapping or not otherwise specified, and larynx were included (ICD-10 codes are provided in a footnote to Table 1). Among oral cavity cancers, cancers of the gum, cheek mucosa, and vestibule of the mouth (ICD-10 codes C03 and C06) were also analyzed as a subset. Cancers of the salivary glands, lip, nasopharynx, and esophagus were excluded.

Informed consent and institutional review board approval were obtained at each study center, and all identifying information was removed before data were pooled. In addition, this analysis was approved by the institutional review board at the University of North Carolina.

Statistical analysis

We estimated odds ratios and 95% confidence intervals for ever use of each smokeless tobacco product, with never users of that same product serving as the referent group, using hierarchical logistic regression with study centers as a random effect. In addition, levels of frequency and duration for each smokeless tobacco product were modeled using indicator variables. Linear trends in frequency and duration were assessed through *P* values obtained from modeling the continuous forms of those variables. All

Table 1. Characteristics of Head and Neck Cancer Cases and Controls From 11 US Studies in the INHANCE Consortium, 1981–2006

Characteristic	Cases (n = 6,772)		Controls (n = 8,375)	
	No.	%	No.	%
Study location (reference no.)[a]				
Seattle, Washington (15, 18)[b]	387	5.71	601	7.18
Iowa (19)	532	7.86	749	8.94
Los Angeles, California (20)	415	6.13	999	11.93
Houston, Texas (21)	826	12.20	865	10.33
Boston, Massachusetts (14)	500	7.38	630	7.52
Baltimore, Maryland (22)	203	3.00	197	2.35
North Carolina, 1994–1997 (23)	176	2.60	202	2.41
North Carolina, 2002–2006 (13)	1,317	19.45	1,370	16.36
New York, New York (MSKCC) (24)	99	1.46	134	1.60
New York State (multicenter) (17)	1,237	18.27	1,379	16.47
United States (multicenter) (16)[c]	1,080	15.95	1,249	14.91
Age group, years				
17–39	300	4.43	564	6.73
40–44	363	5.36	513	6.13
45–49	717	10.59	821	9.80
50–54	1,026	15.15	1,270	15.16
55–59	1,241	18.33	1,485	17.73
60–64	1,118	16.51	1,247	14.89
65–69	895	13.22	1,113	13.29
70–74	625	9.23	784	9.36
75–94	487	7.19	578	6.90
Race/ethnicity				
Non-Hispanic white	5,554	82.01	6,998	83.56
Black	892	13.17	834	9.96
Hispanic/Latino	211	3.12	394	4.70
Asian/Pacific Islander	54	0.80	91	1.09
Other	61	0.90	58	0.69
Sex				
Male	4,891	72.22	5,666	67.65
Female	1,881	27.78	2,709	32.35
Educational level[d]				
No formal education	7	0.10	5	0.06
Less than junior high school	455	6.72	376	4.49
Some high school	1,478	21.83	1,142	13.64
High school graduate	1,609	23.76	1,664	19.87
Vocational school, some college	1,927	28.46	2,734	32.64
College graduate/postgraduate	1,294	19.11	2,453	29.29
Missing data	2	0.03	1	0.01
Cigarette smoking				
Never smoker	1,257	18.56	3,333	39.80
Ever smoker	5,515	81.44	5,042	60.20
Cigar smoking				
Never smoker	6,072	89.66	7,540	90.30
Ever smoker	700	10.34	835	9.97
Pipe smoking				
Never smoker	6,095	90.00	7,415	88.54
Ever smoker	677	10.00	960	11.46
Alcohol drinking				
Never drinker	921	13.60	2,113	25.23
Ever drinker	5,851	86.40	6,262	74.77
Tumor site[e]				
Oral cavity	2,034	30.04		
Oropharynx	2,373	35.04		
Hypopharynx	366	5.40		
Oral/pharynx NOS	743	10.97		
Larynx	1,256	18.55		

Abbreviations: INHANCE, International Head and Neck Cancer Epidemiology; MSKCC, Memorial Sloan Kettering Cancer Center; NOS, not otherwise specified.

[a] Studies of smokeless tobacco use comprised primarily US studies in version 1.5 of the INHANCE Consortium data set, and only US studies were analyzed. A study from Tampa, Florida (25), was excluded because information on chewing tobacco and snuff use was reported jointly. The publications referenced are representative of each study and do not necessarily report estimates for smokeless tobacco.

[b] Data for the Seattle study were collected at 2 time points: 1985–1989 (271 cases and 464 controls; men only) (18) and 1990–1995 (116 cases and 137 controls; men and women) (15).

[c] Data for the US multicenter study (16) were collected at 4 study centers: metropolitan Atlanta, Georgia (129 cases and 136 controls); Los Angeles County, California (407 cases and 514 controls); the state of New Jersey (480 cases and 460 controls); and Santa Clara and San Mateo counties, California (64 cases and 139 controls).

[d] Educational information in this table represents actual counts and percentages. However, missing education values for 3 individuals were imputed a single time based on age, sex, race/ethnicity, study center, and case-control status.

[e] *International Classification of Diseases, Tenth Revision*, codes: oral cavity—codes C00.3–C00.9, C02.0–C02.3, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C06.0–C06.2, C06.8, and C06.9; oropharynx—codes C01.9, C02.4, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0–C10.4, C10.8, and C10.9; hypopharynx—codes C12.9, C13.0–C13.2, C13.8, and C13.9; oral cavity or pharynx overlapping or NOS—codes C02.8, C02.9, C05.8, C05.9, C14.0, C14.2, and C14.8; larynx—codes C32.0–C32.3 and C32.8–C32.9.

analyses were performed in SAS, version 9.2 (SAS Institute, Inc., Cary, North Carolina), using the `proc nlmixed` procedure (31).

Odds ratios were stratified by ever cigarette smoking and were adjusted for sex, age, race/ethnicity, education, frequency of alcohol use, duration of cigarette smoking,

duration of cigar smoking, and duration of pipe smoking, as specified in the table footnotes. Since the study from Boston (14) did not ascertain information on snuff use, odds ratios for chewing tobacco were not adjusted for snuff use. Likewise, odds ratios for snuff use were not adjusted for chewing tobacco. Finally, we conducted analyses stratified by tumor site, sex, age, and race/ethnicity.

Associations with exclusive use of each smokeless tobacco product, as well as joint use with smoking tobacco products, were also modeled. Exclusive and joint use of product(s) was defined as ever use of the specified tobacco product(s) and never use of all other tobacco product(s).

RESULTS

Study participants were predominantly from the US multicenter study (16) (16.0% of cases and 14.9% of controls), the New York multicenter study (17) (18.3% of cases and 16.5% of controls), and the North Carolina 2002–2006 study (13) (19.5% of cases and 16.4% of controls) (Table 1). Half of the cases (50.0%) and controls (47.8%) were between the ages of 50 and 65 years, and the majority of participants were non-Hispanic white (82.0% of cases and 83.6% of controls). Over two-thirds of the cases (72.2%) and controls (67.7%) were male.

Among never cigarette smokers, odds ratios for smokeless tobacco use and HNC were 1.71 (95% confidence interval (CI): 1.08, 2.70) for ever users of snuff compared with never users and 1.20 (95% CI: 0.81, 1.77) for ever tobacco chewers compared with never chewers (Tables 2 and 3). When duration and frequency of smokeless tobacco use were considered, HNC risk increased with increasing duration of snuff use (P_{trend} = 0.007), though no other monotonic trends were noted among never cigarette smokers. Among ever cigarette smokers, odds ratios were 0.83 (95% CI: 0.63, 1.08) for ever using snuff and 0.96 (95% CI: 0.79, 1.17) for ever chewing tobacco (Tables 2 and 3). Estimates were near null across strata of frequency and duration of snuff use and chewing tobacco use among ever cigarette smokers. When we stratified ever cigarette smokers into former and current smokers, estimates were similar to each other and remained near null (Web Tables 2 and 3).

Table 2. Odds Ratios for Head and Neck Cancer According to Snuff Use and Cigarette Smoking Among US Studies in the INHANCE Consortium, 1981–2006[a]

Snuff Use Variable	Never Cigarette Smokers				Ever Cigarette Smokers			
	No. of Cases	No. of Controls	OR[b]	95% CI	No. of Cases	No. of Controls	OR[c]	95% CI
Snuff use status								
Never user	1,128	3,056	1.00	Referent	4,930	4,462	1.00	Referent
Ever user	44	62	1.71	1.08, 2.70	167	164	0.83	0.63, 1.08
Missing data	0	0			3	1		
Frequency of use, times/day[d]								
Never user	865	2,365	1.00	Referent	3,594	3,198	1.00	Referent
>0–≤2[e]	28	45	1.47	0.82, 2.62	95	104	0.69	0.48, 1.00
>2	9	10	1.40	0.48, 4.06	38	37	0.75	0.42, 1.34
Missing data	4	2			15	4		
P_{trend}[f]			0.31				0.20	
Duration of use, years								
Never user	1,128	3,056	1.00	Referent	4,930	4,462	1.00	Referent
>0–≤20	20	28	1.50	0.77, 2.91	134	140	0.79	0.59, 1.06
>20	22	33	1.78	0.95, 3.36	31	22	1.06	0.54, 2.09
Missing data	2	1			5	3		
P_{trend}[f]			0.007				0.31	

Abbreviations: INHANCE, International Head and Neck Cancer Epidemiology; CI, confidence interval; OR, odds ratio.

[a] The Boston study (14) (500 cases and 630 controls) was excluded from analyses of snuff use because information on snuff use was not available.

[b] Adjusted for sex, age (years), race/ethnicity (white, black, Hispanic, Asian and Pacific Islander, or other race/ethnicity), education (junior high school or less, some high school, high school graduation, technical school or some college, and college graduation or more), frequency of alcohol use (mL/day, truncated at the 95th percentile among alcohol drinkers to account for extreme values), duration of cigar smoking (years), and duration of pipe smoking (years).

[c] Adjusted for the same variables as those for never cigarette smokers, plus duration of cigarette smoking (years).

[d] The New York multicenter (17) and Seattle (15, 18) studies (1,624 cases and 1,980 controls) were excluded from analyses of snuff use frequency because information on frequency was not available or was not easily standardized with data from other studies.

[e] The majority of cases and controls in the >0–≤2 times/day category used snuff once or fewer times per day.

[f] *P* for linear trend obtained from modeling the continuous form of the frequency or duration variable.

Table 3. Odds Ratios for Head and Neck Cancer According to Tobacco Chewing and Cigarette Smoking Among US Studies in the INHANCE Consortium, 1981–2006

Tobacco Chewing Variable	Never Cigarette Smokers				Ever Cigarette Smokers			
	No. of Cases	No. of Controls	OR[a]	95% CI	No. of Cases	No. of Controls	OR[b]	95% CI
Tobacco chewing status								
Never user	1,196	3,237	1.00	Referent	5,130	4,719	1.00	Referent
Ever user	61	96	1.20	0.81, 1.77	382	322	0.96	0.79, 1.17
Missing data	0	0			3	1		
Frequency of use, times/day[c]								
Never user	938	2,554	1.00	Referent	3,818	3,486	1.00	Referent
>0–≤2[d]	37	68	1.03	0.63, 1.70	272	226	0.90	0.71, 1.15
>2	13	12	1.53	0.60, 3.88	43	33	0.99	0.56, 1.75
Missing data	3	3			24	13		
P_{trend}[e]			0.44				0.60	
Duration of use, years								
Never user	1,196	3,237	1.00	Referent	5,130	4,719	1.00	Referent
>0–≤20	29	46	1.23	0.72, 2.13	272	226	0.96	0.76, 1.20
>20	25	40	1.06	0.58, 1.92	73	67	0.88	0.58, 1.35
Missing data	7	10			40	30		
P_{trend}[e]			0.56				0.38	

Abbrevations: CI, confidence interval; INHANCE, International Head and Neck Cancer Epidemiology; OR, odds ratio.

[a] Adjusted for sex, age (years), race/ethnicity (white, black, Hispanic, Asian and Pacific Islander, or other race/ethnicity), education (junior high school or less, some high school, high school graduation, technical school or some college, and college graduation or more), frequency of alcohol use (mL/day, truncated at the 95th percentile among alcohol drinkers to account for extreme values), duration of cigar smoking (years), and duration of pipe smoking (years).

[b] Adjusted for the same variables as those for never cigarette smokers, plus duration of cigarette smoking (years).

[c] The New York multicenter (17) and Seattle (15, 18) studies (1,624 cases and 1,980 controls) were excluded from analyses of chewing tobacco frequency because information on frequency was not available or was not easily standardized with data from other studies.

[d] The majority of cases and controls in the >0–≤2 times/day category used chewing tobacco once or fewer times per day.

[e] *P* for linear trend obtained from modeling the continuous form of the frequency or duration variable.

When associations between smokeless tobacco use and specific HNC tumor sites among never cigarette smokers were considered, the highest-magnitude odds ratios were observed for tumors of the oral cavity (Tables 4 and 5). Specifically, the odds ratios for ever snuff use and ever tobacco chewing and cancers of the oral cavity were 3.01 (95% CI: 1.63, 5.55) and 1.81 (95% CI: 1.04, 3.17), respectively. When tumors were further restricted to cancers of the gum, the magnitude of odds ratios among never cigarette smokers increased, but estimates were very imprecise due to small cell counts (for snuff use, OR = 12.7, 95% CI: 4.76, 33.7; for tobacco chewing, OR = 3.07, 95% CI: 1.10, 8.59). Among ever cigarette smokers, we observed little association between snuff use or tobacco chewing and risk of oral cavity cancer (Tables 4 and 5). When we considered only HNC with squamous cell carcinoma histology, odds ratios were similar to the overall HNC estimates for each smokeless tobacco product (Tables 4 and 5). Smokeless tobacco–HNC odds ratios stratified by age, sex, and race/ethnicity were imprecise, though estimates among never cigarette smokers appeared elevated in both age groups, in whites and nonwhites, and among females but not males (Tables 4 and 5).

Since analyses stratified by cigarette smoking were adjusted for, but not restricted by, use of other smoking tobacco products, we also estimated odds ratios for exclusive tobacco chewing and exclusive snuff use compared with never tobacco use. Odds ratios for exclusive snuff users and exclusive tobacco chewers were 1.58 (95% CI: 0.86, 2.89) and 0.80 (95% CI: 0.40, 1.60), respectively (Table 6). The odds ratio for joint users of chewing tobacco and snuff was 2.08 (95% CI: 0.97, 4.45) (Table 6). Likewise, odds ratios for joint users of smokeless and smoking tobacco products were elevated (Table 6).

In sensitivity analyses of ever use of each smokeless tobacco product, we investigated the influence of each study center on the overall estimates by omitting one study center at a time and reanalyzing the data. No single study center appeared to substantially influence the odds ratios for either ever snuff use or ever tobacco chewing (Web Table 4). We also evaluated changes in odds ratios for ever snuff use and ever tobacco chewing across different sets of adjustment variables. In addition to the main models described above, we considered 1) a reduced model that did not adjust for duration of cigar smoking or duration of

Table 4. Odds Ratios for Head and Neck Cancer According to Snuff Use and Cigarette Smoking, by Tumor Site, Sex, and Age, Among US Studies in the INHANCE Consortium, 1981–2006[a]

Variable and Snuff Use	Smoking Status							
	Never Cigarette Smoking				Ever Cigarette Smoking			
	No. of Cases	No. of Controls	OR[b]	95% CI	No. of Cases	No. of Controls	OR[c]	95% CI
Tumor Site								
Oral cavity								
Never user	379	3,056	1	Referent	1,479	4,462	1	Referent
Ever user	20	62	3.01	1.63, 5.55	43	164	0.86	0.57, 1.30
Missing data	0	0			0	1		
Gum								
Never user	52	3,056	1	Referent	241	4,462	1	Referent
Ever user	10	62	12.70	4.76, 33.7	8	164	1.15	0.45, 2.90
Missing data	0	0			0	1		
Pharynx								
Never user	499	3,056	1	Referent	1,888	4,462	1	Referent
Ever user	18	62	1.22	0.65, 2.27	74	164	0.94	0.67, 1.31
Missing data	0	0			1	1		
Hypopharynx[d]								
Never user	33	2,845	1	Referent	282	4,081	1	Referent
Ever user	3	59	3.00	0.66, 13.6	10	158	0.90	0.40, 2.03
Missing data	0	0			0	1		
Oropharynx								
Never user	466	3,056	1	Referent	1,606	4,462	1	Referent
Ever user	15	62	1.07	0.55, 2.08	64	164	0.94	0.67, 1.31
Missing data	0	0			1	1		
Oral cavity/pharynx NOS								
Never user	181	3,056	1	Referent	505	4,462	1	Referent
Ever user	4	62	0.90	0.27, 2.96	16	164	0.92	0.47, 1.82
Missing data	0	0			2	1		
Larynx[d]								
Never user	69	2,146	1	Referent	1,058	2,786	1	Referent
Ever user	2	50	—[e]	—	34	136	0.65	0.52, 1.10
Missing data	0	0			0	1		
SCC (all sites)								
Never user	921	3,056	1	Referent	4,173	4,462	1	Referent
Ever user	39	62	1.60	1.00, 2.57	154	164	0.87	0.66, 1.16
Missing data	0	0			2	1		
Demographic Factors								
Sex								
Female								
Never user	391	1,344	1	Referent	1,301	1,161	1	Referent
Ever user	20	12	8.89	3.59, 22.0	23	9	0.92	0.35, 2.43
Missing data	0	0			2	0		
Male								
Never user	737	1,712	1	Referent	3,629	3,301	1	Referent
Ever user	24	50	0.86	0.49, 1.51	144	155	0.81	0.61, 1.07
Missing data	0	0			1	1		

Table continues

Table 4. Continued

Variable and Snuff Use	Smoking Status							
	Never Cigarette Smoking				Ever Cigarette Smoking			
	No. of Cases	No. of Controls	OR[b]	95% CI	No. of Cases	No. of Controls	OR[c]	95% CI
Age group, years								
<45								
Never user	214	520	1	Referent	380	465	1	Referent
Ever user	11	19	1.21	0.51, 2.87	24	28	0.96	0.48, 1.95
Missing data	0	0			1	0		
≥45								
Never user	914	2,536	1	Referent	4,550	3,997	1	Referent
Ever user	33	43	1.88	1.10, 3.21	143	136	0.82	0.61, 1.10
Missing data	0	0			2	1		
Race/ethnicity								
White								
Never user	975	2,512	1	Referent	3,976	3,718	1	Referent
Ever user	33	47	1.48	0.88, 2.48	125	148	0.79	0.58, 1.05
Missing data	0	0			2	1		
Nonwhite								
Never user	153	544	1	Referent	954	744	1	Referent
Ever user	11	15	2.82	1.05, 7.57	42	16	1.23	0.59, 2.59
Missing data	0	0			1	0		

Abbrevations: CI, confidence interval; INHANCE, International Head and Neck Cancer Epidemiology; NOS, not otherwise specified; OR, odds ratio; SCC, squamous cell carcinoma.

[a] The Boston study (14) (500 cases and 630 controls) was excluded from analyses of snuff use because information on snuff use was not available.

[b] Adjusted for sex, age (years), race/ethnicity (white, nonwhite), educational level (less than high school, high school or more), frequency of alcohol use (mL/day, truncated at the 95th percentile among alcohol drinkers to account for extreme values), duration of cigar smoking use (years), and duration of pipe smoking (years). ORs stratified by sex were not adjusted for sex. ORs stratified by race/ethnicity were not adjusted for race/ethnicity.

[c] Adjusted for the same variables as those for never cigarette smokers, plus duration of cigarette smoking (years).

[d] Hypopharynx analyses did not include the Seattle study (15, 18) because information on tumors of the hypopharynx was not reported in that study. Larynx analyses did not include the Seattle and US multicenter (16) studies because information on tumors of the larynx was not reported in those studies.

[e] Unstable estimate.

pipe smoking and 2) a full model that further adjusted chewing tobacco odds ratios for duration of snuff use and vice versa. For the full model, the study from Boston (14) was omitted since information on snuff use was not available. Among never cigarette smokers, estimates for snuff use and HNC remained similarly elevated across models (Web Table 5). However, the odds ratio for ever chewing tobacco and HNC among never cigarette smokers varied across models, ranging from 1.38 (95% CI: 0.94, 2.01) for the reduced model to 1.00 (95% CI: 0.66, 1.52) for the full model, which included duration of snuff use (Web Table 6).

DISCUSSION

Previous estimates of the risk of HNC among smokeless tobacco users in the United States have been varied and hard to interpret due to low frequencies of use, inconsistent definitions of exposures and outcomes, and insufficient control for important confounders, such as cigarette smoking (8–10). Two meta-analyses on smokeless tobacco use and HNC in the United States have been published. In 2008, Boffetta et al. (32) conducted a meta-analysis of 9 estimates from 6 US studies (5 case-control studies on oral cancer risk and 1 cohort study on oral cancer mortality), reporting a summary relative risk of 2.6 (95% CI: 1.3, 5.2). In 2009, Lee and Hamling (33) published meta-analysis results showing a summary relative risk of 2.16 (95% CI: 1.55, 3.02), based on 31 estimates from 25 US studies (23 case-control studies on oropharyngeal cancer risk and 2 cohort studies on oropharyngeal cancer mortality). Both Boffetta et al. and Lee and Hamling noted significant heterogeneity across estimates, likely reflecting the array of methods used by individual studies to account for cigarette smoking, among other differences (32, 33). In a subset of 5

Table 5. Odds Ratios for Head and Neck Cancer According to Chewing Tobacco Use and Cigarette Smoking Status, by Tumor Site, Sex, and Age, Among US Studies in the INHANCE Consortium, 1981–2006

Variable and Chewing Tobacco Use	Smoking Status							
	Never Cigarette Smoking				Ever Cigarette Smoking			
	No. of Cases	No. of Controls	OR[a]	95% CI	No. of Cases	No. of Controls	OR[b]	95% CI
Tumor Site								
Oral cavity								
Never user	398	3,237	1	Referent	1,533	4,719	1	Referent
Ever user	23	96	1.81	1.04, 3.17	80	322	0.87	0.64, 1.19
Missing data	0	0			0	1		
Gum								
Never user	59	3,237	1	Referent	267	4,719	1	Referent
Ever user	7	96	3.07	1.10, 8.59	16	322	0.85	0.45, 1.60
Missing data	0	0			0	1		
Pharynx								
Never user	536	3,237	1	Referent	2,034	4,719	1	Referent
Ever user	29	96	1.04	0.62, 1.73	138	322	0.93	0.72, 1.20
Missing data	0	0			2	1		
Hypopharynx[c]								
Never user	36	3,027	1	Referent	303	4,341	1	Referent
Ever user	5	92	1.71	0.45, 6.47	22	313	0.88	0.50, 1.54
Missing data	0	0			0	1		
Oropharynx								
Never user	500	3,237	1	Referent	1,731	4,719	1	Referent
Ever user	24	96	0.98	0.57, 1.68	116	322	0.94	0.72, 1.22
Missing data	0	0			2	1		
Oral cavity/pharynx NOS								
Never user	189	3,237	1	Referent	499	4,719	1	Referent
Ever user	5	96	0.75	0.26, 2.13	50	322	1.28	0.85, 1.92
Missing data	0	0			0	1		
Larynx[c]								
Never user	73	2,339	1	Referent	1,064	3,091	1	Referent
Ever user	4	72	—[d]	—	114	246	1.11	0.79, 1.55
Missing data	0	0			1	1		
SCC (all sites)								
Never user	992	3,237	1	Referent	4,397	4,719	1	Referent
Ever user	53	96	1.17	0.78, 1.76	345	322	0.96	0.79, 1.18
Missing data	0	0			2	1		
Demographic Factors								
Sex								
Female								
Never user	444	1,430	1	Referent	1,410	1,264	1	Referent
Ever user	7	9	2.74	0.81, 9.23	20	6	2.03	0.63, 6.54
Missing data	0	0			0	0		
Male								
Never user	752	1,807	1	Referent	3,720	3,455	1	Referent
Ever user	54	87	1.07	0.71, 1.62	362	316	0.96	0.79, 1.17
Missing data	0	0			3	1		

Table continues

Table 5. Continued

Variable and Chewing Tobacco Use	Smoking Status							
	Never Cigarette Smoking				Ever Cigarette Smoking			
	No. of Cases	No. of Controls	OR[a]	95% CI	No. of Cases	No. of Controls	OR[b]	95% CI
Age group, years								
<45								
Never user	224	548	1	Referent	400	486	1	Referent
Ever user	11	18	1.38	0.58, 3.29	27	25	1.18	0.59, 2.38
Missing data	0	0			1	0		
≥45								
Never user	972	2,689	1	Referent	4,730	4,233	1	Referent
Ever user	50	78	1.12	0.73, 1.73	355	297	0.98	0.80, 1.21
Missing data	0	0			2	1		
Race/ethnicity								
White								
Never user	1,033	2,674	1	Referent	4,176	3,966	1	Referent
Ever user	51	79	1.20	0.79, 1.82	293	278	0.98	0.79, 1.21
Missing data	0	0			1	1		
Nonwhite								
Never user	163	563	1	Referent	954	753	1	Referent
Ever user	10	17	1.20	0.43, 3.37	89	44	1.01	0.62, 1.63
Missing data	0	0			2	0		

Abbreviations: CI, confidence interval; INHANCE, International Head and Neck Cancer Epidemiology; NOS, not otherwise specified; OR, odds ratio; SCC, squamous cell carcinoma.

[a] Adjusted for sex, age (years), race/ethnicity (white, nonwhite), educational level (less than high school, high school or more), frequency of alcohol use (mL/day, truncated at the 95th percentile among alcohol drinkers to account for extreme values), duration of cigar smoking use (years), and duration of pipe smoking (years). ORs stratified by sex were not adjusted for sex. ORs stratified by race/ethnicity were not adjusted for race/ethnicity.

[b] Adjusted for same variables as those for never cigarette smokers, plus duration of cigarette smoking (years).

[c] Hypopharynx analyses did not include the Seattle study (15, 18) because information on tumors of the hypopharynx was not reported in that study. Larynx analyses did not include the Seattle and US multicenter (16) studies because information on tumors of the larynx was not reported in those studies.

[d] Unstable estimate.

smokeless tobacco estimates restricted to never cigarette smokers, Lee and Hamling reported a relative risk of 3.33 (95% CI: 1.76, 6.32) (33).

The 2007 International Agency for Research on Cancer monograph on smokeless tobacco (8) and the 2012 update of this report (9) discuss the methods and results of 25 US studies which considered the relationship between smokeless tobacco and HNC (21 case-control studies and 1 cohort study on HNC incidence and 3 cohort studies on HNC mortality). Many of these studies were included in the 2 previous meta-analyses (32, 33). Recently, 2 additional US studies on smokeless tobacco and HNC have been published (13, 14). Of the 24 previous US studies on smokeless tobacco use and HNC incidence, 1 study considered lip cancers (34) and 7 studies, published mostly before 1970, considered the proportions of participants who used smokeless tobacco products (35–41), with many finding a significantly higher proportion of cases who used smokeless tobacco than controls (35, 37, 38, 41). We will specifically discuss the results obtained from our pooled analysis within the context of the similarities with and differences from the remaining 16 US studies (13–18, 42–51). Ten of these previous studies are not represented in the INHANCE Consortium (42–51), while 6 are represented (13–18).

Given the strong association between cigarette smoking and HNC and the large proportions of cases and controls who smoked cigarettes, we stratified smokeless tobacco estimates by cigarette smoking to obtain odds ratios for smokeless tobacco use among persons not influenced by active cigarette smoking. We also adjusted for other important behaviors that may confound the relationship between smokeless tobacco use and HNC (e.g., frequency of alcohol drinking and duration of cigar and pipe smoking). Among never cigarette smokers, snuff use was strongly associated with HNC, while chewing tobacco was weakly associated with HNC.

Ideally, our chewing tobacco models would have adjusted for duration of snuff use and the snuff models for duration

Table 6. Odd Ratios for Head and Neck Cancer According to Exclusive and Joint Use[a] of Smokeless Tobacco Products (Chewing Tobacco and Snuff) and Smoking Tobacco Products (Cigarettes, Cigars, and Pipes) Among US Studies in the INHANCE Consortium, 1981–2006[b]

Tobacco Use	No. of Cases[c]	No. of Controls[d]	OR[e]	95% CI
Never use of tobacco[f]	916	2,767	1.00	Referent
Only smoking products[g]	4,812	4,443	2.47	2.23, 2.74
Only chewing tobacco	14	43	0.80	0.40, 1.60
Only snuff	24	32	1.58	0.86, 2.89
Chewing tobacco and snuff	16	18	2.08	0.97, 4.45
Chewing tobacco and smoking products	315	265	2.23	1.80, 2.77
Snuff and smoking products	89	98	1.78	1.26, 2.52
Chewing tobacco, snuff, and smoking products	82	78	1.77	1.22, 2.58
Missing data	4	1		

Abbrevations: CI, confidence interval; INHANCE, International Head and Neck Cancer Epidemiology; OR, odds ratio.

[a] Exclusive and joint use of tobacco product(s) was defined as ever smoking/using the specified tobacco product(s) and never smoking/using all other tobacco products.

[b] The Boston study (14) (500 cases and 630 controls) was excluded from analyses of exclusive and joint smokeless tobacco use because information on snuff use was not available.

[c] Average durations of chewing tobacco use, snuff use, cigarette smoking, cigar smoking, and pipe smoking, respectively, among cases: 0, 0, 0, 0, and 0 years for never use of tobacco; 25.4, 0, 0, 0, and 0 years for only chewing tobacco; 0, 30.1, 0, 0, and 0 years for only snuff; 25.6, 33.2, 0, 0, and 0 years for chewing tobacco and snuff; 0, 0, 34.3, 1.9, and 1.5 years for only smoking products; 12.4, 0, 32.9, 7.6, and 4.1 years for chewing tobacco and smoking products; 0, 12.6, 30.9, 2.5, and 1.6 years for snuff and smoking products; and 15.5, 11.8, 34.7, 7.6, and 4.9 years for chewing tobacco, snuff, and smoking products.

[d] Average durations of chewing tobacco use, snuff use, cigarette smoking, cigar smoking, and pipe smoking, respectively, among controls: 0, 0, 0, 0, and 0 years for never use of tobacco; 20.4, 0, 0, 0, and 0 years for only chewing tobacco; 0, 23.9, 0, 0, and 0 years for only snuff; 22.4, 25.6, 0, 0, and 0 years for chewing tobacco and snuff; 0, 0, 25.4, 2.0, and 1.8 years for only smoking products; 14.0, 0, 25.7, 7.5, and 5.8 years for chewing tobacco and smoking products; 0, 11.5, 23.4, 2.4, and 3.1 years for snuff and smoking products; and 15.8, 14.3, 24.3, 9.2, and 7.8 years for chewing tobacco, snuff, and smoking products.

[e] Adjusted for sex, age (years), race/ethnicity (white, black, Hispanic, Asian and Pacific Islander, or other race/ethnicity), education (junior high school or less, some high school, high school graduation, technical school or some college, and college graduation or more), and frequency of alcohol use (mL/day, truncated at the 95th percentile among alcohol drinkers to account for extreme values).

[f] Never use of tobacco was defined as never smoking cigarettes, cigars, or pipes, never chewing tobacco, and never using snuff.

[g] Use of only smoking products was defined as ever smoking cigarettes, cigars, or pipes and never chewing tobacco or using snuff.

of tobacco chewing, but 1 study included in our analyses did not ascertain information on snuff use. Therefore, our primary models did not mutually adjust for the other smokeless tobacco behavior. However, sensitivity analyses omitting the study from Boston (14), allowing further adjustment, were explored. Snuff use remained strongly associated with HNC when results were adjusted for chewing tobacco, but estimates for chewing tobacco were attenuated towards the null in models adjusting for snuff use.

Similarly to our study, 4 previous studies stratified smokeless tobacco–HNC estimates by cigarette smoking, finding elevated risk among nonsmokers. Winn et al. (45) conducted a study of snuff use among females in North Carolina. Among nonsmokers, odds ratios were elevated in whites (OR = 4.2, 95% CI: 2.6, 6.7) and less so in African Americans (OR = 1.5, 95% CI: 0.5, 4.8) (45). In another study carried out among females in 4 US cities, Blot et al. (16) also reported an elevated odds ratio for smokeless tobacco use among nonsmokers (OR = 6.2, 95% CI: 1.9, 19.8). Among males in 8 US cities, Kabat et al. (46) reported an unadjusted odds ratio of 2.25 (95% CI: 0.69, 7.34) among nonsmokers. Finally, in the Boston study, Zhou et al. (14) reported an odds ratio for smokeless tobacco among never cigarette smokers of 4.21 (95% CI: 1.01, 17.57).

Among ever cigarette smokers, few or no positive associations between chewing tobacco or snuff and HNC were observed in our study. Although we adjusted smokeless tobacco estimates among ever cigarette smokers for duration of cigarette smoking, the null chewing tobacco and snuff results among ever cigarette smokers could have been due to residual confounding attributable to cigarette smoking (6). People who smoke cigarettes and use smokeless tobacco may differ from those who just use smokeless tobacco with respect to the duration and frequency of use of each product. Of the 4 previous studies which stratified smokeless tobacco estimates by cigarette smoking, only Winn et al. commented on smokeless tobacco among ever cigarette smokers, reporting some evidence for elevated HNC risk associated with snuff (45).

Previous studies which adjusted for cigarette smoking without stratifying by cigarette smoking found mixed results for smokeless tobacco use and HNC, with estimates ranging from near 0.5 to over 2.0 (13, 15, 42–44). Among published articles that did not clearly specify adjustment for or stratification by cigarette smoking, 4 studies found elevated associations, with 2 studies reporting an insignificant risk (1 study provided an odds ratio while the other did not) (48, 49) and 2 studies reporting stronger associations

(18, 47). In contrast, in 2 other studies, investigators stated that there was no relationship between smokeless tobacco use and the risk of HNC, though specific estimates were not reported (17, 51). Finally, Accortt et al. (50) reported an age-adjusted standardized incidence ratio for smokeless tobacco and oral cavity cancer of 30 (95% CI: 3, 95), based on only 2 users.

Few of the previous studies have examined HNC risk based on duration and frequency of use of smokeless tobacco. Among never cigarette smokers, Zhou et al. noted a strong positive trend in HNC risk with increasing duration of smokeless tobacco use ($P_{trend} = 0.02$) and a weaker positive trend with increasing frequency ($P_{trend} = 0.14$) (14). Winn et al. also reported a positive trend in the risk of gum cancers with duration of snuff use among nonsmokers; however, similar trends were not noted for other HNC tumor sites (45). Among studies without stratification by cigarette smoking, Mashberg et al. (44) noted that there was no trend in the odds ratios with respect to duration of tobacco chewing.

When we considered tumor site-specific odds ratios among never cigarette smokers, both snuff use and tobacco chewing were associated with elevated risk of cancers of the oral cavity. These associations were especially pronounced for cancers of the gum, though estimates were imprecise. In the United States, it is common practice to place chewing tobacco or snuff between the gums and the cheek; therefore, our finding of elevated risk for these tumor sites is biologically plausible (8, 9). Four previous studies reported oral cancer–specific odds ratios, with 3 studies reporting elevated, though imprecise, estimates. Winn et al. reported gum/buccal mucosa–specific odds ratios of 13.8 (95% CI: 1.9, 98.0) for 1–24 years of snuff use and 47.5 (95% CI: 9.1, 249.5) for over 50 years of snuff use (45). Williams and Horm (42) reported a gum- and mouth-specific relative risk of 3.88 for light users of smokeless tobacco and a relative risk of 6.65 for heavy users. Stockwell and Lyman (43) reported an odds ratio of 11.2 (95% CI: 4.1, 30.7) for ever use of smokeless tobacco and tumors of the gum and mouth. In contrast, Zhou et al. reported an odds ratio of 0.90 (95% CI: 0.38, 2.12) for using smokeless tobacco more than 20 times and oral cavity cancers (14).

When we examined exclusive use, we found a weakly elevated odds ratio for exclusive snuff use and HNC risk but not for exclusive tobacco chewing. Use of both chewing tobacco and snuff was associated with elevated HNC risk, as was use of both smokeless and smoking tobacco products. Since this analysis was restricted by type of tobacco product, some cell counts were small, resulting in imprecise estimates. We were also unable to analyze frequency and duration of use among exclusive users due to small cell counts, and as previously noted, it is possible that exclusive users of a single tobacco product differ from users of more than 1 product with respect to frequency and duration. For example, in our study the mean duration of chewing tobacco use was approximately 25.5 years among exclusive users and among those who used both chewing tobacco and snuff, as compared with 15.5 years among those who used all types of tobacco. Only 1 previous study, which was included in our pooled analysis, examined exclusive use of smokeless tobacco products; in that study, Stingone et al. (13) reported an odds ratio of 0.9 (95% CI: 0.38, 2.07) for exclusive use of chewing tobacco or snuff.

When we stratified analyses by age (<45 years and ≥45 years), estimates for snuff and chewing tobacco and HNC were weakly elevated in both age groups among never cigarette smokers. Estimates also appeared elevated in both white and nonwhite never cigarette smokers, with the strongest associations being observed for snuff use and HNC among nonwhites. Although we found elevated HNC risk among females but not among males, smokeless tobacco estimates stratified by sex were imprecise and should be interpreted with some caution. Winn et al. (45) and Blot et al. (16) also found elevated HNC risk among female smokeless tobacco users who were nonsmokers, and in their meta-analysis Lee and Hamling noted higher estimates among women, though estimates were not statistically significant after adjustment for study period/type (33).

The major strength of our study was the large number of cases and controls, which made it possible to estimate associations between smokeless tobacco and HNC among never smokers with reasonable precision. Pooling data across studies also allowed us to better harmonize variable definitions and uniformly adjust for important confounders, namely duration of cigarette smoking and duration of use of other smoking products. Further adjustment for frequency of cigarette smoking and use of other smoking products did not materially change estimates for ever snuff use or ever tobacco chewing (data not shown). Other important contributions of our study included analyses of the frequency and duration of smokeless tobacco use, analyses of specific tumor sites, and analyses of both exclusive and joint use of chewing tobacco and snuff. Although some estimates were still somewhat imprecise for a few analyses, to our knowledge this was the largest and most comprehensive study to date to estimate associations between smokeless tobacco use and HNC in the United States.

Although response rates were relatively high across studies, many studies selected participants from hospital settings, which may not be as representative as population-based studies. Further, participants were asked to retrospectively recall smokeless tobacco use, which may have led to some exposure misclassification. Although studies indicate that people do accurately report current and past use of tobacco products (52, 53), there remains uncertainty about whether potential misclassification would be differential or nondifferential between cases and controls. The prevalence of smokeless tobacco use reported among controls in our analysis was similar to US national estimates; 5.0% and 2.9% reported using chewing tobacco or snuff, respectively, compared with an estimated 3.0% nationally (7). Another issue related to misclassification is that people may have had difficulty accurately reporting the type of smokeless tobacco product (snuff vs. chewing tobacco) they used. When we analyzed ever use of smokeless tobacco (i.e., ever snuff use or ever tobacco chewing), we found that the risk of HNC was weakly elevated among never cigarette smokers (OR = 1.30, 95% CI: 0.93, 1.81)

but not among ever cigarette smokers (OR = 0.93, 95% CI: 0.78, 1.11). For duration and frequency, we were unable to reliably combine values across products and therefore did not analyze duration and frequency for combined smokeless tobacco variables. Snuff can be used orally or inhaled, though it is common to place it in the mouth in the United States (8, 9). Therefore, we assumed that snuff was used orally across studies in our analysis. In the study from Baltimore (22), participants were asked whether they ever used snuff along with a prompt regarding inhalation. However, sensitivity analyses excluding the Baltimore study, as well as all other study centers one at a time, showed that the estimates for ever snuff use were robust. Other limitations of our study included the following: We were unable to consider current versus former use of smokeless tobacco products, including ages at starting and stopping, as well as type (e.g., brand of chewing tobacco and dry snuff vs. wet snuff) and amount (e.g., grams) of smokeless tobacco used, because many studies included in our analysis did not collect this information; our models did not account for human papillomavirus infection, because many studies also did not contain this information; approximately 3.4% of individuals were missing information on duration of alcohol use and were therefore excluded from analyses; and the main analyses included cases who had tumors with a histological type other than squamous cell carcinoma (15.4%), though odds ratios for ever tobacco chewing and ever snuff use and HNC restricted to squamous cell carcinoma were similar to the estimates from the main analyses.

In the United States, smokeless tobacco is commonly used orally, which directly exposes tissues in the oral cavity, pharynx, and larynx to a number of carcinogens, including tobacco-specific *N*-nitrosamines, *N*-nitrosamino acids, volatile *N*-nitrosamines, and polycyclic aromatic hydrocarbons, which have been shown to disrupt DNA repair, among other molecular processes (9). We found robust evidence of elevated risk of HNC associated with snuff use among never cigarette smokers across various sets of adjustment variables and when analysis was restricted to cancers of the oral cavity. Associations between chewing tobacco and HNC were less consistent. Main analyses among never cigarette smokers showed weak associations which were attenuated towards the null when adjusted for snuff use, while analyses restricted to cancers of the oral cavity showed stronger associations. Additional large studies which examine smokeless tobacco use separately from joint smoking and smokeless tobacco use are needed to more precisely estimate associations with HNC among both types of users. Studies that included a larger number of individuals from minority populations within the United States, as well as studies of international populations, would further contribute to the existing literature. In addition, studies which focus on high-risk groups (e.g., the construction and mining industries, where US prevalence of smokeless tobacco use is 7.9% and 18.8%, respectively (7)), may further elucidate associations between smokeless tobacco use and HNC risk and offer insight into exposure and disease reduction.

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