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Cigarette, Cigar, and Pipe Smoking and the Risk of Head and Neck Cancers: Pooled Analysis in the International Head and Neck Cancer Epidemiology Consortium

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Cigar and pipe smoking are considered risk factors for head and neck cancers, but the magnitude of effect estimates for these products has been imprecisely estimated. By using pooled data from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium (comprising 13,935 cases and 18,691 controls in 19 studies from 1981 to 2007), we applied hierarchical logistic regression to more precisely estimate odds ratios and 95% confidence intervals for cigarette, cigar, and pipe smoking separately, compared with reference groups of those who had never smoked each single product. Odds ratios for cigar and pipe smoking were stratified by ever cigarette smoking. We also considered effect estimates of smoking a single product exclusively versus never having smoked any product (reference group). Among never cigarette smokers, the odds ratio for ever cigar smoking was 2.54 (95% confidence interval (CI): 1.93, 3.34), and the odds ratio for ever pipe smoking was 2.08 (95% CI: 1.55, 2.81). These odds ratios increased with increasing frequency and duration of smoking ($P_{trend} \leq 0.0001$). Odds ratios for cigar and pipe smoking were not elevated among ever cigarette smokers. Head and neck cancer risk was elevated for those who reported exclusive cigar smoking (odds ratio = 3.49, 95% CI: 2.58, 4.73) or exclusive pipe smoking (odds ratio = 3.71, 95% CI: 2.59, 5.33). These results suggest that cigar and pipe smoking are independently associated with increased risk of head and neck cancers.

head and neck neoplasms; smoking

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

Head and neck cancers are among the most common cancers worldwide with nearly 600,000 new cases and 300,000 deaths occurring globally each year (1, 2). These cancers include cancers of the oral cavity, pharynx, and larynx (2). Approximately 90% of head and neck cancers are squamous cell carcinomas (2). Associations between cigarette smoking and the incidence and mortality of these cancers are well established (3). Although cigar and pipe smoking are not as common as cigarette smoking, previous research has suggested that cigar and pipe smoke may contain equivalent, or in some instances higher, doses of carcinogens such as benzo[*a*]pyrene compared with cigarette smoke (3). Epidemiologic evidence

supports associations between cigar or pipe smoking and the risk of head and neck cancers; however, previous estimates were frequently based on studies with small sample sizes and sometimes limited information on important covariates (e.g., frequency and duration of cigarette smoking and alcohol drinking) (3). Furthermore, it has been difficult to focus on individuals who smoke cigars or pipes exclusively (3). Therefore, we used pooled data from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium to better characterize the individual and combined associations of cigarette, cigar, and pipe smoking with the risk of head and neck cancers.

MATERIALS AND METHODS

Study design

By using pooled data (data version 1.2) from the INHANCE Consortium, we analyzed the risk of head and neck cancers from smoking cigarettes, cigars, or pipes among 13,935 cases and 18,691 controls from 13 case-control studies conducted in Milan, Italy (1984–1989); Aviano, Italy (1987–1992); Vaud, Switzerland (1991–1997); Seattle, Washington (1985–1995); Iowa (1993–2006); North Carolina (1994–1997); Tampa, Florida (1994–2003); Los Angeles, California (1999–2004); Houston, Texas (2001–2006); Puerto Rico (1992–1995); Rome, Italy (2002–2007); New York, New York (1992–1994); and São Paulo, Brazil (2002–2007) and also included 6 multicenter case-control studies from Italy (1990–1999), Central Europe (1998–2003), New York State (1981–1990), Latin America (2000–2003), and the United States (1983–1984) and an international, multicountry study (1992–1997) (4). For the present analysis, we excluded 1 study from France that participates in the INHANCE Consortium because only smokers were enrolled (5), as well as 1 study from Boston, Massachusetts, because it had not been published at the commencement of this analysis. Individuals from the Sudanese (106 cases and 151 controls) and Indian (576 cases and 582 controls) centers from the International Agency for Research on Cancer's (Lyon, France) international multicountry study were also excluded, because the tobacco products used in these areas differ from those of other regions of the world, and an analysis of the tobacco data from Indian centers was previously published (3, 6).

The individual studies and a complete description of the pooling methods used in the INHANCE Consortium have been previously described (4, 7). Briefly, most studies were hospital based with controls that were frequency matched to cases on the basis of age and sex. Although the exact wording of tobacco-related questions differed across studies, questions were conceptually similar. For example, each study asked about ever having smoked cigarettes, cigars, or pipes, but definitions of ever smoking varied among the individual studies. The exact definitions of ever smoking each product for individual studies are detailed in previous INHANCE Consortium publications (4, 7). Variables on the frequency (number of cigarettes, cigars, or pipes smoked per day), duration (in years), and cumulative duration (in pack-years, cigar-years, or pipe-years) of tobacco smoking were also ascertained in each study. Pack-years were calculated as packs of cigarettes smoked per day multiplied by the years of cigarette smoking, where 20 cigarettes equaled 1 pack. Cigar-years and pipe-years were calculated by multiplying the frequency and duration of smoking that specific product. Levels of frequency, duration, and cumulative use of tobacco were categorized according to previous INHANCE Consortium reports (7) except where sparse strata required collapsing of levels, such as in the frequency of cigar and pipe smoking.

Cases of invasive head and neck cancers were categorized by tumor site according to the *International Classification of Diseases for Oncology, Second Edition,* or the *International Classification of Diseases, Ninth* or *Tenth Edition* (7–10). We included cancers of the 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 not otherwise specified (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), or head and neck cancers that were overlapping or unspecified (7). Cancers of the salivary glands, lip, nasopharynx, and esophagus were excluded (7). Head and neck cancers, regardless of site and histology, were the primary outcome of interest. However, analyses with site-specific outcomes (oral cavity, pharynx, oropharynx, hypopharynx, larynx, or not otherwise specified) and restricted to squamous cell carcinomas of the head and neck were also considered.

Individuals with missing data on sex, age, race/ethnicity, or subtype of cancer (140 cases and 82 controls) were excluded from all analyses; because this was a small proportion of individuals in this pooled analysis (1.0% of cases and 0.4% of controls), these exclusions did not likely materially affect the results. Subjects from the Central European and Latin American multicenter studies were classified as non-Hispanic white and Latin American, respectively, because information on race and ethnicity was not collected in these studies. Information on educational level was not collected in the Rome, Italy, study and was frequently missing in the Latin American multicenter study. For study participants with missing information on educational level, we used single imputation (MI procedure) in SAS, version 9.2, software (SAS Institute, Inc., Cary, North Carolina) to predict educational level within geographical regions on the basis of age, sex, race/ethnicity, study center, and case or control status (7).

Statistical analysis

We estimated odds ratios and 95% confidence intervals for ever tobacco users and levels of the frequency, duration, and cumulative use for each tobacco product compared with never users of that same product by using hierarchical logistic regression with study center as a random effect. Levels of frequency, duration, and cumulative tobacco use were modeled by using disjoint indicator variables except for linear trends, which were assessed through P values obtained from modeling the continuous forms of those variables. We incorporated a random intercept for study center into the model to account for clustering of data by study center and because we detected

significant heterogeneity across studies. Because we included a random intercept for study center, we excluded from the analyses of cigar smoking 811 cases and 1,095 controls from centers in the Latin American, Central European, and international multicenter studies that did not report any cases or any controls who smoked cigars (study centers in Pelotas, Brazil; Bucharest, Romania; Budapest, Hungary; Lodz, Poland; Banska Bystrica, Slovakia; Aviano, Italy; Udine, Italy; Milan, Italy; Poland; and Australia). Likewise, we excluded 625 cases and 735 controls from the analyses of pipe smoking from centers that did not report any cases or controls who smoked pipes (Pelotas, Brazil; Budapest, Hungary; Lodz, Poland; Udine, Italy; Granada, Spain; and Poland). These exclusions did not materially change the magnitude of the odds ratios. All analyses were performed in SAS software (SAS Institute, Inc.) by using the NLMIXED procedure (initial parameter values for the NLMIXED procedure models were based on parameter estimates from logistic procedure models, and an initial variance value of 2.0 was used; varying this starting point did not sustainably change final estimates) (11).

Odds ratios were adjusted for sex, age (continuous years), race (categorical indicator for white, black, Hispanic, Asian or Pacific Islander, Latin American, or other), educational level (categorical indicator for no education or junior high school or less, some high school, high school graduate, technical school or some college, or college graduate or more), and frequency of alcohol use (mL of ethanol per day truncated at the 95th percentile among alcohol drinkers to account for extreme values) (7). Because the reference category for initial analyses was never smokers of only the product of interest, cigarette smoking odds ratios were also adjusted for the duration of cigar smoking and the duration of pipe smoking (both in years); cigar smoking odds ratios were also adjusted for the duration of pipe smoking and the duration of cigarette smoking (both in years); and pipe smoking odds ratios were also adjusted for the duration cigar smoking and the duration of cigarette smoking (both in years). Additionally, cigar and pipe analyses were stratified by ever cigarette smoking to further control for the confounding effect of cigarette smoking (duration of cigarette smoking was removed from the adjustment set for odds ratios among never cigarette smokers). Cigarette, cigar, and pipe smoking odds ratios were not adjusted for smokeless tobacco use because information on smokeless tobacco use was available only for US studies; adjustment for smokeless tobacco use in the analyses restricted to US studies did not substantially change estimates for smoking tobacco products. Likewise, models were not adjusted for marijuana use because few studies collected information on this variable (12). We also considered analyses stratified by region (Europe, North America, or Latin and South America), sex (male or female with sex removed from the adjustment set), and age (<45 years or ≥45 years with continuous age removed from the adjustment set).

Joint and exclusive smoking of tobacco products was also modeled. For this set of analyses, joint and exclusive smoking of products was defined as ever having smoked the specified tobacco product(s) and never having smoked all other tobacco products. The reference group comprised never smokers of any product. For example, smoking of only cigars was defined as ever having smoked cigars and never having smoked cigarettes or pipes with a reference group of never smokers of cigarettes, cigars, or pipes. In addition, we modeled dominant and predominant lifetime consumption of individual smoking products. To standardize consumption across products, we calculated product-specific lifetime consumption (in grams of tobacco) on the basis of International Agency for Research on Cancer estimates of average unit weights as follows (3): frequency of cigarette smoking (number of cigarettes per day) × duration of cigarette smoking (years) × 1 (assuming the average weight of tobacco in a cigarette was 1 g); frequency of cigar smoking (number of cigars per day) × duration of cigar smoking (years) × 4 (assuming the average weight of tobacco in a cigar was 4 g); and frequency of pipe smoking (number of pipes per day) × duration of pipe smoking (years) × 3.5 (assuming the average weight of tobacco in a pipe fill was 3.5 g). Total lifetime consumption of smoking tobacco equaled the sum of product-specific lifetime consumptions for cigarettes, cigars, and pipes. Product-specific lifetime consumptions of cigarettes, cigars, and pipes were then divided by the total lifetime consumption of smoking products. Dominant smoking behaviors for each product were defined as 100% lifetime consumption of only that 1 product. For example, if lifetime consumption of cigars divided by total lifetime consumption of smoking tobacco equaled 1, then the tobacco user was a dominant cigar smoker. Predominant smoking behaviors for each product were defined as 66.6%–99.9% of lifetime consumption of only that 1 product. For example, if lifetime consumption of cigars divided by total lifetime consumption of smoking tobacco equaled 0.66–0.99, then the tobacco user was a predominant cigar smoker. The reference group for dominant/predominant smokers was never smokers, who were those with lifetime consumption of 0 g of cigarettes, cigars, and pipes. Odds ratios for exclusive/joint and dominant/predominant use were adjusted for sex, age, race, education, and frequency of alcohol use as previously described.

Institutional review board approval was obtained at each study center, and all identifying information was removed before data were received for pooling. In addition, institutional review board approval was obtained for this analysis from the University of North Carolina at Chapel Hill (Chapel Hill, North Carolina).

RESULTS

Characteristics of cases and controls in this pooled analysis are presented in Table 1. Briefly, one-third of all subjects were from the United States (35% of cases and 36% of controls), and most of the remaining subjects were from Latin America (28% of cases and 17% of controls) or Italy (18% of cases and 29% of controls). Approximately half of the cases (50.6%) and controls (46.7%) were between the ages of 50 and 65 years, and the majority were non-Hispanic white (64.7% of cases and 75.6% of controls). Consistent with the literature, there were more male cases (79.7%) than female cases (20.3%) (2, 13).

The overall odds ratio of head and neck cancers was elevated among ever cigarette smokers compared with never cigarette smokers, even after adjustment for smoking of other products (odds ratio (OR) = 3.46, 95% confidence interval (CI): 3.24, 3.70) (Table 2). We also observed increasing risk

Table 1. Characteristics of Head and Neck Cancer Cases and Controls in the International Head and Neck Cancer Epidemiology Consortium, 1981–2007[a]

Characteristic	No. of Cases	%	No. of Controls	%
Total	13,935		18,691	
Study location				
Aviano, Italy	482	3.5	855	4.6
Central Europe (multicenter)	762	5.5	907	4.9
Houston, Texas	829	5.9	865	4.6
IARC (international multicenter)	881	6.3	992	5.3
Iowa	546	3.9	759	4.1
Italy (multicenter)	1,261	9.0	2,716	14.5
Latin America (multicenter)	2,191	15.7	1,706	9.1
Los Angeles, California	417	3.0	1,004	5.4
Milan, Italy	416	3.0	1,531	8.2
New York State (multicenter)	1,118	8.0	906	4.8
New York, New York (MSKCC)	133	1.0	168	0.9
North Carolina	180	1.3	202	1.1
Puerto Rico	350	2.5	521	2.8
Rome, Italy	361	2.6	396	2.1
São Paulo, Brazil	1,764	12.7	1,508	8.1
Seattle, Washington	407	2.9	607	3.2
Switzerland	516	3.7	883	4.7
Tampa, Florida	207	1.5	897	4.8
United States (multicenter)	1,114	8.0	1,268	6.8
Race/ethnicity[b]				
Asian/Pacific Islander	49	0.4	84	0.4
Black	581	4.2	674	3.6
Hispanic/Latino	213	1.5	429	2.3
Latin American	3,955	28.4	3,214	17.2
Non-Hispanic white	9,014	64.7	14,124	75.6
Other	123	0.9	166	0.9
Age, years				
17–39	502	3.6	1,356	7.3
40–44	766	5.5	1,345	7.2
45–49	1,508	10.8	2,042	10.9
50–54	2,169	15.6	2,808	15.0
55–59	2,537	18.2	3,108	16.6
60–64	2,340	16.8	2,827	15.1
65–69	1,936	13.9	2,408	12.9
70–74	1,341	9.6	1,774	9.5
75–96	836	6.0	1,023	5.5

Continued

with increasing frequency, duration, and pack-years of cigarette smoking ($P_{trend} < 0.0001$) (Table 2). After stratification by ever cigarette smoking, the adjusted odds ratios for cigar and pipe smokers were increased among never cigarette smokers but not among ever cigarette smokers (Tables 3 and 4). Among never cigarette smokers, the adjusted odds ratios for ever cigar and ever pipe smokers were 2.54 (95% CI: 1.93, 3.34) and 2.08 (95% CI: 1.55, 2.81), respectively. Among ever cigarette smokers, the adjusted odds ratios for ever cigar and ever pipe smokers were 0.90 (95% CI: 0.78, 1.02) and 0.81 (95% CI: 0.70, 0.93), respectively. With respect to frequency, duration, and cumulative use, head and neck cancer risk increased with increasing cigar smoking and pipe smoking among never cigarette smokers ($P_{trend} \leq 0.0001$), but we did

Table 1. Continued

Characteristic	No. of Cases	%	No. of Controls	%
Sex				
Male	11,108	79.7	13,025	69.7
Female	2,827	20.3	5,666	30.3
Educational level[c]				
No formal education	280	2.0	190	1.0
Less than junior high school	5,656	40.6	7,081	37.9
Some high school	2,077	14.9	2,267	12.1
High school graduate	1,849	13.3	2,280	12.2
Vocational school, some college	2,068	14.8	3,456	18.5
College graduate/postgraduate	1,278	9.2	2,768	14.8
Missing	730	5.2	651	3.5
Tumor site				
Head and neck (not otherwise specified)	314	2.3		
Hypopharynx	1,026	7.4		
Larynx	3,461	24.8		
Oral cavity	4,110	29.5		
Oral/pharynx (not otherwise specified)	1,190	8.5		
Oropharynx	3,834	27.5		

Abbreviations: IARC, International Agency for Research on Cancer; MSKCC, Memorial Sloan-Kettering Cancer Center.

[a] All centers in the International Head and Neck Cancer Epidemiology Consortium studies (data version 1.2) were included except those in Boston, Massachusetts; France; Sudan; and India. The French center was not included because it enrolled only smokers. The Boston, Massachusetts, center was not included because its data are currently unpublished. The centers in Sudan and India from the International Agency for Research on Cancer's international multicenter study were not included because of differences in tobacco products in these regions.

[b] Information on race and ethnicity was not collected in the Central European and Latin American multicenter studies. All cases and controls were classified as non-Hispanic white for the Central European study and as Latin American for the Latin American study.

[c] Educational information in this table represents actual counts and percentages; however, because educational information was not collected in the Rome, Italy, study and was frequently missing in the Latin American study, we imputed educational levels during subsequent analyses. Three cases and 2 controls who were originally missing information on educational level were also missing imputed educational level and were therefore excluded from subsequent analyses.

not observe comparable dose-response trends among ever cigarette smokers (Tables 3 and 4).

When we separately considered tumors in the oral cavity, pharynx, hypopharynx, oropharynx, larynx, and oral cavity/pharynx not otherwise specified, associations between cigarette smoking and laryngeal cancer and hypopharyngeal cancer resulted in odds ratios of the largest magnitudes (8.33 and 6.48, respectively) (Web Table 1 available at http://aje.oxfordjournals.org/). When subsite-specific estimates for ever cigar smoking and ever pipe smoking were stratified by ever cigarette smoking, the odds ratios were consistently elevated among never cigarette smokers but not among ever smokers across subsites (though several estimates were imprecise because of low cell counts and should therefore be interpreted with caution) (Web Table 1). Among never cigarette smokers, associations between cigar and pipe smoking and laryngeal cancer again resulted in odds ratios of the largest magnitudes (6.31 and 3.53, respectively). For oropharyngeal cancers, the odds ratios were 2.31 (95% CI: 1.54, 3.45) for ever cigar smoking and 1.65 (95% CI: 1.04, 2.60) for ever pipe smoking among never cigarette smokers. When we restricted analysis to tumors with squamous cell carcinoma histology, the odds ratios were similar to the overall head and neck cancer estimates for each tobacco product (Web Table 1). The odds ratio for cigarette smoking and head and neck squamous cell carcinoma was 3.37 (95% CI: 3.12, 3.64). Likewise, stratification of squamous cell carcinoma–specific estimates for cigar and pipe smoking by cigarette smoking again resulted in elevated odds ratios among never cigarette smokers (OR = 2.77, 95% CI: 2.08, 3.71 and OR = 1.89, 95% CI: 1.36, 2.63, respectively).

The odds ratios for cigarette smoking were elevated in each region considered, but appeared to be lower for North American smokers than for smokers in Europe and South America (Web Table 1). Cigarette smokers aged 45 years and older appeared to have a higher risk than cigarette smokers under 45 years of age (Web Table 1). Effect estimates for cigar and

Table 2. Odd Ratios for Cigarette Smoking and Head and Neck Cancer in the International Head and Neck Cancer Epidemiology Consortium, 1981–2007

Variable	Cigarette Smoking			
	No. of Cases	No. of Controls	OR[a]	95% CI
Tobacco smoking[b]				
Never	1,817	7,387	1.00	Referent
Ever	12,052	11,277	3.46	3.24, 3.70
Missing	66	27		
Smoking frequency (cigarettes per day)				
Never	1,817	7,387	1.00	Referent
1–10	1,620	3,158	1.88	1.72, 2.05
11–20	5,127	4,721	3.87	3.59, 4.17
21–30	2,148	1,373	5.30	4.81, 5.85
31–40	2,020	1,173	5.37	4.85, 5.95
>40	996	711	4.02	3.54, 4.58
Missing	207	168		
P_{trend}[c]				<0.0001
Smoking duration, years				
Never	1,817	7,387	1.00	Referent
1–10	382	1,346	1.04	0.90, 1.19
11–20	721	2,021	1.37	1.23, 1.53
21–30	2,258	2,721	2.95	2.71, 3.22
31–40	4,048	2,751	5.02	4.62, 5.45
>40	4,528	2,338	6.55	6.01, 7.15
Missing	181	127		
P_{trend}				<0.0001
Cumulative smoking, pack-years				
Never	1,817	7,387	1.00	Referent
1–10	838	2,525	1.29	1.16, 1.43
11–20	1,213	2,120	2.20	1.99, 2.42
21–30	1,779	1,890	3.53	3.21, 3.88
31–40	2,085	1,538	4.93	4.48, 5.42
41–50	1,743	1,025	5.85	5.26, 6.50
>50	4,205	1,986	6.81	6.24, 7.44
Missing	255	220		
P_{trend}				<0.0001

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Cigarette smoking odds ratios are adjusted for sex, age, race, educational level, study center, frequency of alcohol use (mL of ethanol per day), duration of cigar smoking (in years), and duration of pipe smoking (in years). Individuals missing the main variable or 1 or more covariates were dropped from the models. The most frequently missing variable was frequency of alcohol use. For the model of "ever" cigarette smoking, 1,375 individuals were not included; for the model of frequency of cigarette smoking, 1,593 individuals were not included; for the model of duration of cigarette smoking, 1,553 individuals were not included; and for the model of pack-years, 1,681 individuals were not included.

[b] "Never smoker" was defined as never having smoked the product of interest. For example, a never smoker of cigarettes did not smoke cigarettes but may have smoked cigars or pipes. "Ever smoker" was defined as ever having smoked the product of interest, in a similar manner. For this reason, cigarette smoking odds ratios were adjusted for the duration of cigar smoking and the duration of pipe smoking.

[c] *P* for linear trend was obtained from modeling the continuous forms of the frequency, duration, and cumulative variables.

pipe smoking among never cigarette smokers appeared to follow similar patterns by region and age; however, some estimates were imprecise because of low cell counts (Web Table 1). Among women, odds ratios were elevated, but estimates were based on relatively few female smokers, especially ever cigar and ever pipe smokers who never smoked

Table 3. Odd Ratios for Cigar Smoking and Head and Neck Cancer in the International Head and Neck Cancer Epidemiology Consortium, 1981–2007

Variable	Cigar Smoking							
	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
Tobacco smoking[c]								
Never	1,567	6,824	1.00	Referent	10,525	9,759	1.00	Referent
Ever	171	155	2.54	1.93, 3.34	779	814	0.90	0.78, 1.02
Missing	1	4			15	14		
Smoking frequency (cigars per day)								
Never	1,567	6,824	1.00	Referent	10,525	9,759	1.00	Referent
1–10	130	136	1.99	1.47, 2.71	550	618	0.89	0.77, 1.03
>10	39	14	10.13	4.96, 20.67	184	155	0.99	0.74, 1.32
Missing	3	9			60	55		
P_{trend}[d]			<0.0001				0.62	
Smoking duration, years								
Never	1,567	6,824	1.00	Referent	10,525	9,759	1.00	Referent
1–10	19	52	0.91	0.51, 1.62	331	391	0.77	0.64, 0.92
11–20	18	19	2.42	1.18, 4.95	114	130	1.04	0.77, 1.42
21–30	18	24	1.92	0.95, 3.85	99	113	0.98	0.70, 1.36
31–40	43	29	3.78	2.18, 6.55	91	78	1.20	0.83, 1.72
>40	68	27	5.62	3.29, 9.60	123	87	1.04	0.73, 1.48
Missing	6	8			36	29		
P_{trend}			<0.0001				0.63	
Cumulative cigar-years								
Never	1,567	6,824	1.00	Referent	10,525	9,759	1.00	Referent
1–10	18	44	0.96	0.52, 1.77	162	245	0.71	0.56, 0.90
11–20	20	41	1.15	0.63, 2.11	226	228	0.99	0.79, 1.23
>20	127	64	4.87	3.36, 7.06	337	296	1.01	0.82, 1.25
Missing	7	10			69	59		
P_{trend}			<0.0001				0.05	

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Cigar smoking odds ratios among never cigarette smokers were adjusted for sex, age, race, educational level, frequency of alcohol use (mL of ethanol per day), and duration of pipe smoking (in years). Individuals missing the main variable or 1 or more covariates were dropped from the models. The most frequently missing variable was frequency of alcohol use. For the model of "ever" smoking, 276 individuals were not included; for the model of frequency of smoking, 283 individuals were not included; for the model of duration of smoking, 285 individuals were not included; and for the model of cigar-years, 288 individuals were not included.

[b] Cigar smoking odds ratios among ever cigarette smokers were adjusted for sex, age, race, educational level, frequency of alcohol use (mL of ethanol per day), duration of cigarette smoking (in years), and duration of pipe smoking (in years). Individuals missing the main variable or 1 or more covariates were dropped from the models. The most frequently missing variable was frequency of alcohol use. For the model of "ever" smoking, 1,101 individuals were not included; for the model of frequency of smoking, 1,172 individuals were not included; for the model of duration of smoking, 1,127 individuals were not included; and for the model of cigar-years, 1,184 individuals were not included.

[c] "Never smoker" was defined as never having smoked the product of interest. For example, a never smoker of cigars did not smoke cigars but may have smoked pipes. "Ever smoker" was defined as ever having smoked the product of interest, in a similar manner. For this reason, cigar smoking odds ratios were adjusted for the duration of pipe smoking (and the duration of cigarette smoking among ever cigarette smokers).

[d] *P* for linear trend was obtained from modeling the continuous forms of the frequency, duration, and cumulative variables.

cigarettes, as evidenced by confidence intervals that were much wider than those among males, and should therefore be interpreted with caution (Web Table 1).

Analyses of exclusive cigarette, cigar, and pipe smokers yielded elevated odds ratios with similar magnitudes. Compared with never smoking cigarettes, cigars, or pipes, the adjusted odds ratios were 3.93 (95% CI: 3.67, 4.22) for smoking only cigarettes, 3.49 (95% CI: 2.58, 4.73) for smoking only cigars, and 3.71 (95% CI: 2.59, 5.33) for smoking only pipes (Table 5). Likewise, odds ratios were elevated for each type of

Table 4. Odd Ratios for Pipe Smoking and Head and Neck Cancer in the International Head and Neck Cancer Epidemiology Consortium, 1981–2007

Variable	Pipe Smoking							
	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
Tobacco smoking[c]								
Never	1,612	7,022	1.00	Referent	10,888	10,044	1.00	Referent
Ever	138	123	2.08	1.55, 2.81	587	717	0.81	0.70, 0.93
Missing	2	7			17	16		
Smoking frequency (pipes per day)								
Never	1,612	7,022	1.00	Referent	10,888	10,044	1.00	Referent
1–10	118	107	2.11	1.53, 2.90	484	645	0.80	0.69, 0.93
>10	14	11	2.19	0.89, 5.40	69	37	1.00	0.60, 1.69
Missing	8	12			51	51		
P_{trend}[d]			0.0001				0.57	
Smoking duration, years								
Never	1,612	7,022	1.00	Referent	10,888	10,044	1.00	Referent
1–10	28	52	1.27	0.76, 2.14	345	432	0.79	0.66, 0.94
11–20	14	19	1.52	0.71, 3.23	64	120	0.77	0.54, 1.10
21–30	7	17	0.82	0.32, 2.13	59	83	0.70	0.47, 1.05
31–40	21	18	2.34	1.11, 4.91	41	39	1.01	0.61, 1.68
>40	66	17	5.81	3.15, 10.70	62	39	0.98	0.59, 1.63
Missing	4	7			33	20		
P_{trend}			<0.0001				0.16	
Cumulative pipe-years								
Never	1,612	7,022	1.00	Referent	10,888	10,044	1.00	Referent
1–10	20	39	1.31	0.72, 2.40	198	289	0.78	0.63, 0.97
11–20	19	36	0.89	0.47, 1.69	147	208	0.67	0.52, 0.86
>20	93	43	3.76	2.45, 5.76	205	185	1.04	0.81, 1.34
Missing	8	12			54	51		
P_{trend}			<0.0001				0.76	

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Pipe smoking odds ratios among never cigarette smokers were adjusted for sex, age, race, educational level, frequency of alcohol use (mL of ethanol per day), and duration of cigar smoking (in years). Individuals missing the main variable or 1 or more covariates were dropped from the models. The most frequently missing variable was frequency of alcohol use. For the model of "ever" smoking, 283 individuals were not included; for the model of smoking frequency, 294 individuals were not included; for the model of smoking duration, 285 individuals were not included; and for the model of pipe-years, 294 individuals were not included.

[b] Pipe smoking odds ratios among ever cigarette smokers were adjusted for sex, age, race, educational level, frequency of alcohol use (mL of ethanol per day), duration cigarette smoking (in years), and duration cigar smoking (in years). Individuals missing the main variable or 1 or more covariates were dropped from the models. The most frequently missing variable was frequency of alcohol use. For the model of "ever" smoking, 1,122 individuals were not included; for the model of smoking frequency, 1,170 individuals were not included; for the model of smoking duration, 1,131 individuals were not included; and for the model of pipe-years, 1,172 individuals were not included.

[c] "Never smoker" was defined as never having smoked the product of interest. For example, a never smoker of pipes did not smoke pipes but may have smoked cigars. "Ever smoker" was defined as ever having smoked the product of interest, in a similar manner. For this reason, pipe smoking odds ratios were adjusted for the duration of cigar smoking (and the duration of cigarette smoking among ever cigarette smokers).

[d] *P* for linear trend was obtained from modeling the continuous forms of the frequency, duration, and cumulative variables.

smoking tobacco when dominant and predominant smoking habits were considered (Table 5). Joint effects from smoking more than 1 type of tobacco were also elevated compared with never smokers (Table 5) but not when compared with only cigarette smokers (data not shown). Because of small counts across strata in many of these analyses, we were unable to consider the duration and frequency of use among exclusive users.

Table 5. Odd Ratios for Exclusive/Joint and Dominant/Predominant Cigarette, Cigar, and Pipe Smoking and Head and Neck Cancer in the International Head and Neck Cancer Epidemiology Consortium, 1981–2007

Variable[a]	No. of Cases	No. of Controls	OR[b]	95% CI
Exclusive/joint tobacco smoking				
Never smoker	1,567	7,154	1.00	Referent
Cigarette, cigar, and pipe	211	277	2.42	1.96, 2.99
Cigarette and cigar	566	541	3.05	2.61, 3.56
Cigarette and pipe	371	445	2.94	2.49, 3.48
Cigar and pipe	61	52	3.44	2.29, 5.17
Cigarette only	10,880	9,996	3.93	3.67, 4.22
Cigar only	110	103	3.49	2.58, 4.73
Pipe only	77	71	3.71	2.59, 5.33
Missing	92	52		
Dominant/predominant tobacco smoking				
Never smoker	1,567	7,154	1.00	Referent
Predominantly cigarette	659	736	2.88	2.51, 3.30
Only cigarette	10,755	9,895	3.94	3.67, 4.23
Predominantly cigar	131	111	3.22	2.38, 4.35
Only cigar	107	97	3.56	2.62, 4.86
Predominantly pipe	48	50	2.93	1.89, 4.55
Only pipe	75	70	3.67	2.55, 5.28
Less than 66.6% for any smoking product	237	261	2.72	2.20, 3.35
Missing	356	317		

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] For the exclusive/joint model, "never smoker" was defined as never having smoked cigarettes, cigars, and pipes; joint and exclusive smokers of tobacco products were defined as ever having smoked the specified tobacco product (s) and never having smoked any other tobacco products. For the dominant/predominant model, "never smoker" was defined as having 0 g of lifetime consumption of cigarettes, cigars, and pipes; predominant smokers of a given product were defined as the lifetime consumption of the specified smoking product (in grams) divided by the sum of lifetime consumption of all smoking products (in grams) of between 66.6% and 99.9%; and dominant (only) smokers of a given product were defined as lifetime consumption of specified smoking product (in grams) divided by the sum of lifetime consumption of all smoking products (in grams) of 100%.

[b] Odds ratios were adjusted for sex, age, race, educational level, and frequency of alcohol use (mL of ethanol per day). A total of 1,319 individuals were not included in the exclusive/joint tobacco smoking model for missing the main variable or 1 or more covariates. A total of 1,788 individuals were not included in the dominant/predominant model for missing the main variable or 1 or more covariates. The most frequently missing covariate was frequency of alcohol use. (Additional footnotes are available in Web material at http://aje.oxfordjournals.org/.)

DISCUSSION

We found that cigarette smokers had elevated odds ratios for head and neck cancers, consistent with extensive literature (3). Given the strong association between cigarette smoking and head and neck cancers and the large proportion of cases and controls who had smoked cigarettes, simply adjusting the cigar and pipe smoking models for the duration of cigarette smoking would not have adequately controlled for the confounding influence of cigarette smoking. Therefore, we stratified estimates by ever cigarette smoking to obtain cigar and pipe smoking odds ratios among individuals not influenced by active cigarette smoking. Among never cigarette smokers, we observed an increased risk associated with ever cigar and ever pipe smoking. The risk of head and neck cancers also increased with increasing levels of frequency and duration of cigar or pipe smoking among never cigarette smokers. Moreover, elevated odds ratios associated with exclusive smoking of cigars or pipes compared with those of a reference group of never smokers of cigarettes, cigars, or pipes suggest that both products independently contribute to head and neck cancer risk. Similarly, analyses considering predominant cigar smokers and predominant pipe smokers also resulted in increased odds ratios compared with those of a reference group of never smokers of any product.

Although we observed strong associations between cigar and pipe smoking and head and neck cancer risk in the absence of cigarette smoking, the added impact of cigar and pipe smoking in the presence of cigarette smoking was not discernible. Specifically, we noted near null odds ratios for cigar and pipe smoking among ever cigarette smokers in stratified analyses. Further, the odds ratios for the joint smoking of

products were not appreciably different from those for the exclusive smoking of single products. One explanation for null cigar and pipe smoking results among ever cigarette smokers may be residual confounding attributed to cigarette smoking. Adjustment by other smoking metrics did not materially change the interpretation. Misclassification bias or unmeasured confounders may also explain the null results for cigar and pipe smoking among ever cigarette smokers. Another explanation may be that smokers of more than 2 products differ from smokers of only 1 product with regard to duration and frequency of use of each product. Among individuals who smoke cigarettes and cigars or pipes, the greater frequency of cigarette smoking may make cigarette smoke the predominant source of carcinogen exposure.

The finding of elevated head and neck cancer risk among pipe and cigar smokers is consistent with those of previous studies, including both individual studies in this pooled analysis (14–18) and non–INHANCE Consortium studies (19–28), as well as studies on mortality (mostly disease-specific mortality) (29–34). Among previous studies that were not included in the INHANCE Consortium, effect estimates for the association between cigar and/or pipe smoking and head and neck cancers ranged from approximately null to more than 5.0 (19–28). Among studies of exclusive cigar and/or pipe smoking, 2 reported elevated odds ratios of magnitudes similar to our estimates (i.e., ORs of approximately 2.5–3.5) (20, 22). Most recently, a study that used data from the European Prospective Investigation into Cancer Nutrition cohort noted elevated risk of upper aerodigestive tract cancers (head and neck cancers and esophageal cancer) associated with exclusive cigar smoking (hazard ratio = 4.0, 95% CI: 1.7, 9.4) and exclusive pipe smoking (hazard ratio = 1.7, 95% CI: 0.6, 4.4), although estimates were based on relatively few cases (7 cases exclusively smoked cigars and 5 exclusively smoked pipes) (28).

As detailed in an International Agency for Research on Cancer monograph, tobacco smoke contains numerous carcinogens (3). Although cigar and pipe smoking are not as common as cigarette smoking, cigar and pipe products contain higher average weights of tobacco than do cigarette products (3). Machine-smoking studies have further suggested that delivered doses of tar, nicotine, carbon monoxide, benzene, benzo[*a*]pyrene, and tobacco-specific nitrosamines from cigar and pipe smoking are comparable to, and in some instances higher than, those from cigarette smoking (3). Given similarities between delivered carcinogens across tobacco smoking products and the direct exposure of the oral cavity, pharynx, and larynx to tobacco smoke, it seems reasonable that associations between cigar or pipe smoking and head and neck cancer risk would be similar in magnitude to those between cigarette smoking and head and neck cancer risk.

The major strength of our study was the evaluation of multiple tobacco products by using a large international data set. The analysis of exclusive and predominant smokers of cigars and pipes was another key contribution. Although we were unable to analyze the frequency and duration of smoking among exclusive pipe and cigar smokers because of small cell counts, it should be noted that this analysis had the largest sample size to date. Most previous studies that evaluated cigar and pipe smoking and head and neck cancer risk (and were not included in the INHANCE Consortium) had sample sizes of approximately 100 to a few thousand cases and controls, with approximately 10–100 cases and controls who ever or exclusively smoked cigars or pipes (19–28).

Another asset of our study was detailed information on important covariates. In addition to stratifying cigar and pipe analyses by cigarette smoking, we adjusted all estimates for the frequency of alcohol drinking. Previous INHANCE Consortium studies reported strong dose-response relationships between the frequency of alcohol drinking and head and neck cancers, especially among never cigarette smokers (7). Further, all models were adjusted and/or stratified by demographic factors including age, gender, race, and educational level. Subsite-specific models were also considered, including estimates specific to oropharyngeal cancers. Information on human papillomavirus status is currently not available in INHANCE Consortium data. Future studies that incorporate longitudinal designs with serial assessment of confounders would further strengthen conclusions regarding cigar and pipe smoking and head and neck cancers.

Because information on grams of smoking tobacco consumed was not available, we had to use conversions based on estimates of the average weight of tobacco in each smoking product for lifetime consumption analyses. It is also important to note that cumulative measures of smoking (i.e., pack-years, cigar-years, and pipe-years) are based on the total duration and average frequency of smoking of the given product and may not reflect fluctuations in the duration and frequency of smoking across the life span. Furthermore, cumulative measures do not account for the amount of delivered carcinogen in each tobacco product nor for unique habits in how products are smoked. Finally, main analyses included head and neck cancers with histologies other than squamous cell carcinomas (approximately 87.6% of cases with reported histology were squamous cell carcinomas, and the remaining 12.4% encompassed other histologies). However, odds ratios for ever smoking each product and head and neck cancers restricted to squamous cell carcinomas were similar to the estimates for the overall analyses.

Our findings of an increased risk of head and neck cancers among cigarette smokers are consistent with those of the previous literature. We also found increased risk of head and neck cancers among cigar smokers and pipe smokers, with the magnitude of the associations for cigar or pipe smoking similar to that for cigarette smoking. The results of the present study provide more precise estimates of the risks of head and neck cancers associated with pipes and cigars, especially among never cigarette smokers, considerably strengthening the evidence that pipe smoking and cigar smoking are risk factors for head and neck cancers.

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