Involuntary Smoking and Head and Neck Cancer Risk: Pooled Analysis in the International Head and Neck Cancer Epidemiology Consortium

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Abstract

Although active tobacco smoking has been identified as a major risk factor for head and neck cancer, involuntary smoking has not been adequately evaluated because of the relatively low statistical power in previous studies. We took advantage of data pooled in the International Head and Neck Cancer Epidemiology Consortium to evaluate the role of involuntary smoking in head and neck carcinogenesis. Involuntary smoking exposure data were pooled across six case-control studies in Central Europe, Latin America, and the United States. Adjusted odds ratios (OR) and 95% confidence interval (95% CI) were estimated for 542 cases and 2,197 controls who reported never using tobacco, and the heterogeneity among the study-specific ORs was assessed. In addition, stratified analyses were done by subsite. No effect of ever involuntary smoking exposure either at home or at work was observed for head and neck cancer overall. However, long duration of involuntary smoking exposure at home and at work was associated with an increased risk (OR for >15 years at home, 1.60; 95% CI, 1.12-2.28; $P_{trend} < 0.01$; OR for >15 years at work, 1.55; 95% CI, 1.04-2.30; $P_{trend} = 0.13$). The effect of duration of involuntary smoking exposure at home was stronger for pharyngeal and laryngeal cancers than for other subsites. An association between involuntary smoking exposure and the risk of head and neck cancer, particularly pharyngeal and laryngeal cancers, was observed for long duration of exposure. These results are consistent with those for active smoking and suggest that elimination of involuntary smoking exposure might reduce head and neck cancer risk among never smokers. (Cancer Epidemiol Biomarkers Prev 2008;17(8):1974–81)

Introduction

Involuntary smoking (involuntary exposure to tobacco or secondhand smoke) entails exposure to human carcinogens, which are present in tobacco smoke. The composition of involuntary smoking includes both mainstream smoke and sidestream smoke. Mainstream smoke is inhaled and exhaled by smokers; sidestream smoke is released between puffs into the air from the burning cone. Metabolites of the tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone were observed in the urine of nonsmokers exposed to involuntary smoking (1). In animal experiments, this carcinogen is thought to induce adenocarcinomas rather than squamous cell carcinomas of lung cancer (2), and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and *N*-nitrosononicotine, which is a metabolite of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, together induce oral cavity tumors (3, 4). The evidence in tobacco smoke carcinogen biomarkers, such as urinary compounds, protein adducts, and DNA adducts, supports that involuntary smoking carcinogens are metabolized by passive smokers and have the potential to increase cancer risk (5).

Because people spend most of their time at home and the workplace, these are more likely to be the places for

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involuntary smoking exposure (6, 7). In the United States, about 60% of children (3-11 years old) and more than 40% of nonsmoking adults are estimated to have ever had involuntary smoking exposure based on serum cotinine measures from the U.S. National Health and Nutrition Examination Survey 1999 to 2002 (8). Approximately 7.5 million workers in 15 European Union countries were estimated to be exposed to involuntary smoking at least 75% of their working time in the early 1990s, and 24.6 million workers in the United States are estimated to be ever exposed to involuntary smoking at work in the year 2000 (9-11). Even if the excess risk is small, its large prevalence makes it an important environmental carcinogen. Because smoking is a modifiable behavior by public health intervention, it is of interest to investigate the association between involuntary smoking exposure and the risk of head and neck cancer.

Both the IARC Monograph and the U.S. Surgeon General's Report concluded that there is sufficient evidence for the causal relationship between involuntary smoking exposure and lung cancer but that there is not enough reliable data to make conclusions for the causal relationship between involuntary smoking exposure and other cancer sites, such as the breast, childhood, cervical, gastrointestinal, nasopharyngeal, and nasal sinus cavity cancers (5, 8). The relationship with head and neck cancer was not discussed due to the limited information available.

Only two studies have examined the possible association between involuntary smoking and head and neck cancer, defined as cancer of the oral cavity, the oropharynx, the hypopharynx, and the larynx. A hospital-based case-control study on 175 cases reported an adjusted odds ratio (OR) of 2.4 [95% confidence interval (95% CI), 0.9-6.8] for ever involuntary smoking exposure (12). Smokers were included in the analysis, while active smoking was adjusted for. A cross-sectional case-control study in nonsmokers suggested a higher prevalence of involuntary smoking exposure among patients compared with the control (OR, 2.8; Fisher's exact $P = 0.006$ for home; OR, 10.16; Fisher's exact $P < 0.001$ for workplace; OR, 5.34; Fisher's exact $P < 0.001$ for either home or workplace; ref. 13), without adjustment for any confounding factors.

Involuntary smoking has not been studied adequately for head and neck cancer because of the difficulties in assembling large enough series of cases who are never tobacco users. The pooled data in the International Head and Neck Cancer Epidemiology consortium (http://inhance.iarc.fr) provided an opportunity to investigate the effect of involuntary smoking among never tobacco users.

Materials and Methods

Within the version 1.1 of the International Head and Neck Cancer Epidemiology consortium pooled data set, six case-control studies from Europe, Latin America, and the United States with information on involuntary smoking exposure included 4,786 head and neck cancer cases and 5,938 controls (14-18). Subjects with missing data on age, sex, or race/ethnicity and cases with missing information on the site of origin of their cancer were excluded (29 cases and 37 controls). After ever tobacco users who had used cigarettes, cigars, pipes, snuff, or chewing products during their lifetimes were excluded, the data for this analysis included 542 never-smoking head and neck cancer cases and 2,197 controls. The analysis of never tobacco and alcohol users included 257 cases and 1,013 controls. To define never tobacco users and never tobacco and alcohol users for analyses, the exclusion of ever tobacco users and ever alcohol users was based on the definitions used in the studies as described in detail previously (19).

Cases included patients with invasive tumors of the oral cavity, oropharynx, hypopharynx, oral cavity, or pharynx not otherwise specified, larynx, or head and neck cancer unspecified as defined previously (19). Cancers of the salivary gland (*International Classification of Diseases for Oncology* version 2 C07-C08) were excluded from our analysis due to the different etiologic pattern from other head and neck cancers (20). Studies provided tumor site data using either the *International Classification of Diseases for Oncology* version 2 or *International Classification of Diseases, Ninth or Tenth Edition*. Among never tobacco users, there was a total of 146 oral cavity cancer cases, 225 pharyngeal cancer cases (206 oropharynx and 19 hypopharynx), 98 oral cavity/pharynx not specified cases, 71 laryngeal cancer cases, and 2 unspecified head and neck cancer cases. Among never tobacco and alcohol users, there were a total of 92 oral cavity cancer cases, 92 pharyngeal cancer cases (85 oropharynx and 7 hypopharynx), 47 oral cavity/pharynx not specified cases, and 26 laryngeal cancer cases. Some studies restricted case eligibility to squamous cell carcinomas (Tampa and Houston), whereas others provided information on histologic type. Of the 531 head and neck cancer cases for which histologic information was available, 515 were squamous cell carcinomas (97.0%).

Characteristics of the individual studies included in the pooled data are shown in Table 1. Most were hospital-based case-control studies, and in most studies, the control subjects were frequency matched to the case subjects on age, sex, and additional factors (such as study center, hospital, and race/ethnicity).

Interviews in all studies were conducted face-to-face. Written informed consent was obtained from study subjects, and the investigations were approved by institutional review boards at each of the institutes involved. Questionnaires were collected from all the individual studies to assess the comparability of the data and wording of interview questions. Data from individual studies were received at IARC with personal identifiers removed. Each data item was checked for illogical or missing values. Queries were sent to investigators, and inconsistencies were resolved.

In the individual studies, each study subject was asked whether he or she was exposed to involuntary smoking at home or at work. The definitions for ever involuntary smoking exposure at home or at work were: husband/wife/partner and/or anyone at work smoked for $\geq$1 hour a day and $\geq$1 year (Central Europe study), anyone in household and/or anyone at work in enclosed areas smoked (Tampa study), married (or living as married) with a smoker and/or anyone smoked at work in an indoor setting (Latin America study), anyone in the

household smoked regularly at home for ≥1 year and/or anyone at work smoked in an enclosed area for ≥1 year (Los Angeles study), anyone smoked regularly in household and/or at work (Houston study). Ever involuntary smoking exposure at home and/or at work combined could not be determined for the Puerto Rico study because information was reported on only exposure to the smoke of the spouse or the significant other, with whom he/she has lived the longest.

Variables on frequency (hours per day) of involuntary smoking exposure at home were available in three studies (Central Europe, Tampa, and Latin America studies); variables on frequency (hours per day) of involuntary smoking exposure at work were available in two studies (Central Europe and Latin America studies). Subjects in the Central Europe study were asked about overall lifetime frequency average per week, whereas those in the Latin America and Tampa studies were asked about frequency over different time periods when exposed. Variables on duration (years) of involuntary smoking exposure at home were available in five studies (Central Europe, Tampa, Puerto Rico, Latin America, and Los Angeles studies); variables on duration (years) of involuntary smoking exposure at work were available in four studies (Central Europe, Tampa, Latin America, and Los Angeles studies). The overall frequency and duration variables were calculated, taking into account any overlapping of periods.

In addition, combined duration of involuntary smoking exposure at home and at work were calculated with consideration of periods overlapping for Central Europe, Latin America, and Los Angeles studies. Combined frequency of involuntary smoking exposure at home and at work was also calculated with overlapping periods considered. However, only the Tampa and Latin America studies had the information, and the numbers of subjects became smaller than five for some strata.

Statistical Methods. The association between head and neck cancer risk and involuntary smoking exposure was assessed by estimating OR and 95% CI with unconditional logistic regression models for each case-control study. The models included age (categories shown in Table 2), sex, education (categories shown), race/ethnicity (categories shown), and study center to adjust for potential confounders. To calculate the summary estimates of association, the study-specific estimates were included in a two-stage random-effects logistic regression model with the maximum likelihood method, which allows for unexplained sources of heterogeneity between studies (21). Pooled ORs were also estimated with a fixed-effects logistic regression model adjusting for age, sex, education, race/ethnicity, and study center.

For subjects missing information on education level (12 cases and 70 controls), we applied multiple imputation with the PROC MI procedure in SAS. We assumed that the education data were missing at random (whether education was missing or not did not depend on any other unobserved or missing values; ref. 22). We used the logistic regression model (23) to predict education level with age, sex, race/ethnicity, study, and case/control

Table 1. Summary of individual studies with information on involuntary smoking in International Head and Neck Cancer Epidemiology consortium pooled data version 1.1

Reference*	Study location	Recruitment period	Cases				Controls†			
			Source	Participation rate (%)	No	Never tobacco users	Source	Participation rate (%)	No	Never tobacco users
14	Central Europe (Banská Bystrica, Bucharest, Budapest, Lodz, and Moscow)‡	1998-2003	Hospital	96	762	49	Hospital, unhealthy	97	907	308
15	Puerto Rico	1992-1995	Cancer registry	71	350	32	Residential records	83	521	211
NA	Latin America (Buenos Aires, Havana, Goiânia, Pelotas, Porto Alegre, Rio de Janeiro, and São Paulo)‡	2000-2003	Hospital	95	2,191	123	Hospital, unhealthy	86	1,706	506
16	Tampa, FL	1994-2003	Hospital	98	207	37	Cancer screening clinic, healthy	90	897	345
17	Los Angeles, CA	1999-2004	Cancer registry	49	417	115	Neighborhood	67.5	1,005	453
18	Houston, TX	2001-2006	Hospital	95	829	186	Hospital visitors	>80	865	374
				Total	4,756	542			5,901	2,197

*Representative publication in which study methods are available.
†All studies frequency matched controls to cases, minimally on age and sex. Additional frequency matching factors included center (Central Europe and Latin America studies), ethnicity (Tampa study), and neighborhood (Los Angeles study).
‡Multicenter study.

Table 2. Selected characteristics of head and neck cancer cases and controls

Total	Never tobacco users		Never tobacco/alcohol users	
	Cases (n = 542), n (%)	Controls (n = 2,197), n (%)	Cases (n = 257), n (%)	Controls (n = 1,013), n (%)
Study				
Tampa	37 (6.83)	345 (15.70)	20 (7.78)	209 (20.63)
Los Angeles	115 (21.22)	453 (20.62)	42 (16.34)	169 (16.68)
Houston	186 (34.32)	374 (17.02)	108 (42.02)	238 (23.49)
Puerto Rico	32 (5.90)	211 (9.60)	18 (7.00)	83 (8.19)
Latin America				
Cuba	10 (1.85)	41 (1.87)	6 (2.33)	21 (2.07)
Porto Alegre	7 (1.29)	46 (2.09)	7 (2.72)	27 (2.67)
Rio de Janeiro	23 (4.24)	75 (3.41)	12 (4.67)	43 (4.24)
São Paulo	25 (4.61)	116 (5.28)	9 (3.50)	66 (6.52)
Pelotas	11 (2.03)	88 (4.01)	8 (3.11)	63 (6.22)
Goiânia	12 (2.21)	70 (3.19)	5 (1.95)	27 (2.67)
Buenos Aires	35 (6.46)	70 (3.19)	15 (5.84)	20 (1.97)
Central Europe				
Bucharest	13 (2.40)	95 (4.32)	2 (0.78)	19 (1.88)
Budapest	1 (0.18)	6 (0.27)	0 (0.00)	1 (0.10)
Lodz	2 (0.37)	45 (2.05)	2 (0.78)	4 (0.39)
Moscow	31 (5.72)	123 (5.60)	3 (1.17)	17 (1.68)
Banská Bystrica	2 (0.37)	39 (1.78)	0 (0.00)	6 (0.59)
Age (y)				
<40	59 (10.89)	186 (8.47)	30 (11.67)	89 (8.79)
40-44	48 (8.86)	185 (8.42)	25 (9.73)	89 (8.79)
45-49	73 (13.47)	283 (12.88)	33 (12.84)	117 (11.55)
50-54	81 (14.94)	397 (18.07)	40 (15.56)	168 (16.58)
55-59	81 (14.94)	366 (16.66)	27 (10.51)	165 (16.29)
60-64	54 (9.96)	268 (12.20)	23 (8.95)	136 (13.43)
65-69	39 (7.20)	221 (10.06)	19 (7.39)	103 (10.17)
70-74	55 (10.15)	173 (7.87)	30 (11.67)	80 (7.90)
≥75	52 (9.59)	118 (5.37)	30 (11.67)	66 (6.52)
P for χ^2 test		<0.001		0.004
Sex				
Female	217 (40.04)	936 (42.60)	145 (56.42)	559 (55.18)
Male	325 (59.96)	1,261 (57.40)	112 (43.58)	454 (44.82)
P for χ^2 test		0.278		0.722
Race/ethnicity*				
White	332 (61.25)	1,302 (59.26)	153 (59.53)	505 (49.85)
Black	20 (3.69)	137 (6.24)	10 (3.89)	81 (8.00)
Hispanic	43 (7.93)	166 (7.56)	19 (7.39)	111 (10.96)
Asian and Pacific Islander	19 (3.51)	41 (1.87)	12 (4.67)	30 (2.96)
Others	5 (0.92)	45 (2.05)	1 (0.39)	19 (1.88)
Latin American	123 (22.69)	506 (23.03)	62 (24.12)	267 (26.36)
P for χ^2 test		0.018		0.006
Education				
Junior high school or less	126 (23.77)	516 (24.26)	66 (26.19)	276 (28.51)
Some high school	37 (6.98)	152 (7.15)	14 (5.56)	56 (5.79)
High school graduate	88 (16.60)	342 (16.08)	43 (17.06)	166 (17.15)
Technical school some college	100 (18.87)	392 (18.43)	57 (22.62)	199 (20.56)
College graduate or higher	179 (33.77)	725 (34.09)	72 (28.57)	271 (28.00)
Missing	12 (—)	70 (—)	5 (—)	45 (—)
P for χ^2 test		0.996		0.934

*Information on ethnicity was not collected in the Central Europe and Latin America studies. In the Central Europe study, all subjects were classified as non-Hispanic White because the large majority of these populations are expected to be White. In the Latin America study, we categorized subjects as ''Latin American.'' We adjusted for study center in all logistic regression models as a proxy variable for race/ethnicity because each center has an expected predominant ethnic group distribution.

status as the covariates, for each of the geographic regions (Europe, Latin America, and North America) separately. The logistic regression results to assess summary estimates for involuntary smoking for the five imputations were combined by the PROC MIANALYZE procedure.

We tested for heterogeneity between the study ORs by using the likelihood ratio test, for head and neck cancer combined and for each of the subsites, by testing the difference between the log likelihood of a model with the product terms between study and the variable of interest, and that of a model with no such product terms, based on a χ^2 distribution with a df one less than the number of studies. If any heterogeneity was detected, we reported the random-effects estimates and examined whether the results from the two-stage random-effects model and the fixed-effects logistic regression model were comparable in magnitude of effect. We also conducted influence analysis, where each study was excluded one at a time to assure that the statistical significance and magnitude of the overall summary estimate was not dependent on any one

study. Stratified analyses were conducted by cancer site (oral cavity, pharynx, oral cavity/pharynx not specified, and larynx) and sex.

Results

Characteristics of cases and controls who were never tobacco users and never tobacco and alcohol users are shown in Table 2. The Houston study contributed the largest number of cases (34.3%), whereas the Latin America study contributed the largest number of controls (23.0%). The distributions of age and race/ethnicity were different between the case and control groups among never tobacco users and never tobacco/alcohol users, whereas the distributions of sex and education level were similar.

An association between ever involuntary smoking exposure and the risk of head and neck cancer among never tobacco users was not observed (OR, 1.07; 95% CI, 0.85-1.34; Table 3). Associations with involuntary smoking exposure of >15 years were detected (OR, 1.60; 95% CI, 1.12-2.28 at home; OR, 1.55; 95% CI, 1.04-2.30 at work). In addition, the association between the combined duration of >15 years of involuntary smoking exposure at home and at work and the risk of head and neck cancer was suggested (OR, 1.38; 95% CI, 0.99-1.91; P_{trend} = 0.06; data not shown). Among never tobacco and alcohol users, associations between the duration of involuntary smoking exposure were observed with OR of 1.75 (95% CI, 1.06-2.90) for >15 years of exposure at home and OR of 2.59 (95% CI, 1.35-4.95) for >15 years of exposure at work compared with never exposure at home or at work, respectively (Table 3).

In the analysis by head and neck subsites, associations between the involuntary smoking exposure and the risk of laryngeal and pharyngeal cancers were suggested with a dose-response relationship for duration of involuntary smoking exposure (Table 4). Associations with frequency (hours of exposure per day) were not observed by site (data not shown). Compared with subjects who were not exposed to involuntary smoking at home, subjects who were exposed for >15 years at home had an increased risk

Table 3. Involuntary smoking among never tobacco users, involuntary smoking among never tobacco users and never alcohol drinkers, and risk of head and neck cancer

	Never tobacco users		Never tobacco/alcohol users	
	Cases/controls	OR* (95% CI)	Cases/controls	OR* (95% CI)
Ever involuntary smoking exposure [†]				
Never	186/794	1.00	87/409	1.00
Ever at home or at work	303/1,078	1.07 (0.85-1.34)	149/487	1.30 (0.94-1.81)
Ever at home only	117/396	1.15 (0.87-1.53)	68/217	1.37 (0.93-2.03)
Ever at work only	93/375	0.97 (0.72-1.31)	38/144	1.25 (0.78-1.98)
Ever at home and at work	88/283	1.03 (0.75-1.42)	41/115	1.22 (0.76-1.97)
Missing	5/67		3/34	
$P_{heterogeneity}$		0.23		0.78
Duration of involuntary smoking exposure at home [‡] (y)				
Never	184/1,074	1.00	74/477	1.00
1-15	70/294	1.28 (0.91-1.80)	32/103	2.04 (1.21-3.43)
>15	63/251	1.60 (1.12-2.28)	36/130	1.75 (1.06-2.90)
Missing	20/143		7/65	
P_{trend}		<.01		<.01
$P_{heterogeneity}$		0.33		0.07
Frequency of involuntary smoking exposure at home [§] (h/d)				
0-3	116/696	1.00	52/345	1.00
>3	15/81	1.76 (0.83-3.73)	5/20	6.11[‖] (0.03-1449)
Missing	65/343		32/158	
$P_{heterogeneity}$		0.76		0.04
Duration of involuntary smoking exposure at work [¶] (y)				
Never	174/898	1.00	75/446	1.00
1-15	54/309	0.86 (0.60-1.24)	19/105	1.12 (0.61-2.06)
>15	47/185	1.55 (1.04-2.30)	19/56	2.59 (1.35-4.95)
Missing	33/173		18/85	
P_{trend}		0.13		<.01
$P_{heterogeneity}$		0.41		0.29
Frequency of involuntary smoking exposure at work** (h/d)				
Never	107/499	1.00	50/239	1.00
1-3	19/112	1.16[‖] (0.001-6.01)	7/24	2.04 (0.69-6.07)
>3	30/132	1.14[‖] (0.04-32.76)	9/41	1.16 (0.46-2.96)
Missing	3/25		3/10	
P_{trend}		0.68		0.47
$P_{heterogeneity}$		0.04		0.88

*Adjusted for centers, age, sex, race/ethnicity, education, and alcohol drinking (in drink-years; for never tobacco users only).
[†]Included Central Europe, Tampa, Latin America, Los Angeles, and Houston studies.
[‡]Included Central Europe, Tampa, Latin America, Los Angeles, and Puerto Rico studies.
[§]Included Central Europe, Tampa, and Latin America studies.
[‖]Estimates from random effect models.
[¶]Included Central Europe, Tampa, Latin America, and Los Angeles studies.
**Included Central Europe and Latin America studies.

Table 4. Involuntary smoking among never tobacco users and risk of head and neck cancer, by cancer subsite

	Oral cavity		Pharynx		Larynx	
	Cases/controls	OR* (95% CI)	Cases/controls	OR*,† (95% CI)	Cases/controls	OR* (95% CI)
Ever involuntary smoking exposure‡						
Never	53/794	1.00	72/794	1.00	23/794	1.00
Ever at home or at work	76/1,078	0.93 (0.61-1.41)	135/1,078	1.30 (0.31-5.34)	45/1,078	1.71 (0.98-3.00)
Missing	2/67		1/67		0/16	
$P_{heterogeneity}$		0.56		<0.01		0.36
Duration of involuntary smoking exposure at home§ (y)						
Never	46/1,074	1.00	53/1,074	1.00	36/938	1.00
1-15	12/294	1.58 (0.73-3.41)	27/294	1.88 (0.42-8.50)	8/278	1.44 (0.59-3.53)
>15	16/251	1.06 (0.53-2.11)	16/251	4.13 (1.43-11.89)	15/221	2.58 (1.20-5.57)
Missing	4/143		5/143		3/68	
P_{trend}		0.78		0.02		0.02
$P_{heterogeneity}$		0.23		0.24		0.77
Duration of involuntary smoking exposure at work‖ (y)						
Never	46/898	1.00	48/898	1.00	34/898	1.00
1-15	9/309	0.65 (0.28-1.51)	19/309	0.81 (0.26-2.50)	9/309	0.98 (0.43-2.23)
>15	10/185	1.31 (0.57-3.00)	13/185	5.16 (0.28-95.95)	17/185	2.07 (1.04-4.11)
Missing	6/173		9/173		1/116	
P_{trend}		0.75		0.37		0.07
$P_{heterogeneity}$		0.97		0.02		0.66

*Adjusted for centers, age, sex, race/ethnicity, education, and alcohol drinking (in drink-years).
†Estimates from random-effects model.
‡Included Central Europe, Tampa, Latin America, Los Angeles, and Houston studies (no Tampa study for larynx).
§Included Central Europe, Tampa, Puerto Rico, Latin America, and Los Angeles studies (no Tampa and Puerto Rico studies for larynx).
‖Included Central Europe, Tampa, Latin America, and Los Angeles studies (no Tampa study for larynx).

of pharyngeal cancer (OR, 4.13; 95% CI, 1.43-11.89; P_{trend} = 0.02) and an increased risk of laryngeal cancer (OR, 2.58; 95% CI, 1.20-5.57; P_{trend} = 0.02). A similar association with laryngeal cancer was observed for the duration of involuntary smoking exposure at work with an adjusted OR of 2.07 (95% CI, 1.04-4.11) for >15 years of exposure (P_{trend} = 0.07). An association between the combined duration for involuntary smoking exposure at home and at work and the risk of laryngeal cancer was also detected (OR, 2.81; 95% CI, 1.42-5.58; for >15 years of exposure; P_{trend} < 0.01; data not shown). Influence analysis suggested that the observed associations for >15 years of duration at home or at work were not due to any particular study.

Table 5. Involuntary smoking among never tobacco users and never alcohol users and risk of head and neck cancer, by cancer subsite

	Oral cavity		Pharynx		Larynx	
	Cases/controls	OR (95% CI)	Cases/controls	OR (95% CI)	Cases/controls	OR (95% CI)
Ever involuntary smoking exposure*						
Never	32/409	1.00	28/409	1.00	8/409	1.00
Ever at home or at work	51/487	1.17 (0.68-2.01)	57/487	1.33 (0.78-2.26)	18/487	2.90 (1.09-7.73)
Missing	2/34		0/34		0/6	
$P_{heterogeneity}$		0.52		0.67		0.52
Duration of involuntary smoking exposure at home† (y)						
Never	26/477	1.00	14/477	1.00	13/421	1.00
1-15	8/103	2.27 (0.84-6.10)	8/103	2.83 (1.03-7.81)	3/98	2.01 (0.43-9.36)
>15	10/130	1.37 (0.56-3.35)	9/130	4.15 (1.50-11.47)	7/116	1.85 (0.53-6.49)
Missing	2/65		1/65		1/22	
P_{trend}		0.44		<.01		0.28
$P_{heterogeneity}$		0.18		0.92		0.66
Duration of involuntary smoking exposure at work‡ (y)						
Never	25/446	1.00	15/446	1.00	12/446	1.00
1-15	5/105	0.90 (0.26-3.10)	3/105	0.80 (0.21-3.13)	4/105	2.75 (0.71-10.61)
>15	4/56	2.07 (0.49-8.72)	4/56	3.99 (1.06-15.08)	8/56	5.45 (1.69-17.52)
Missing	5/85		3/85		0/53	
P_{trend}		0.49		0.13		<.01
$P_{heterogeneity}$		0.71		0.24		0.40

NOTE: Adjusted for centers, age, sex, race/ethnicity, and education.
*Included Central Europe, Tampa, Latin America, Los Angeles, and Houston studies (no Tampa study for larynx).
†Included Central Europe, Tampa, Puerto Rico, Latin America, and Los Angeles studies (no Tampa and Puerto Rico studies for larynx).
‡Included Central Europe, Tampa, Latin America, and Los Angeles studies (no Tampa study for larynx).

The study-specific ORs were similar in direction but with reduced statistical significance.

For the never tobacco and alcohol users, we detected an association between ever involuntary smoking status and the risk of laryngeal cancer (OR, 2.90; 95% CI, 1.09-7.73; Table 5). In addition, a dose-response relationship was detected for duration of involuntary smoking exposure at work and laryngeal cancer risk ($P < 0.01$). For pharyngeal cancer, a dose-response trend was detected for the duration of involuntary smoking exposure at home ($P < 0.01$).

We examined the association for pharynx and larynx with additional adjustment by duration of involuntary smoking exposure at work when examining exposure at home and by duration of involuntary smoking exposure at home when examining exposure at work and assessed the combined duration of involuntary smoking at home and at work. The results were consistent with those presented in Tables 3 and 4.

After additional adjustment by body mass index, associations with similar magnitude and significance for involuntary smoking exposure at home or at work and the risk of head and neck cancer and its subsites were observed among never tobacco users. Similarly, adjustment by family history of head and neck cancer did not change our results. Influence analysis confirmed that the observed associations were not contributed by any particular study.

Discussion

The results of our pooled analysis suggest long-term involuntary smoking exposure is a risk factor for head and neck cancer, especially pharyngeal and laryngeal cancer, independent of active tobacco smoking and alcohol drinking. The consistency of the results on the effect of duration of involuntary smoking exposure at home or at work and pharyngeal and laryngeal cancer risk adds to the credibility of a causal association with these cancers. To eliminate residual confounding by alcohol, which is a recognized risk factor for head and neck cancer, an analysis was done among never tobacco and alcohol users, and the associations were confirmed.

The pharynx and larynx have a greater opportunity of direct contact with involuntary smoking than the oral cavity, and our results are consistent with this anatomic and physiologic difference. Consistent with our results, active smoking is thought to be a stronger risk factor for laryngeal and pharyngeal cancers than for oral cavity cancer (24). Our results are also consistent with previous evidence from International Head and Neck Cancer Epidemiology consortium studies that active smoking is a stronger risk factor for pharyngeal and laryngeal cancers than for oral cavity cancer among never alcohol drinkers (19).

Information on frequency of involuntary smoking exposure was only available for a subset of subjects. Associations with frequency of involuntary smoking exposure were not observed possibly due to lack of power to detect moderate effects. In addition, the definition of frequency of involuntary smoking exposure was not consistent among studies, which might have resulted in exposure misclassification leading to attenuation of the risk estimates. Because duration of involuntary smoking exposure was more clearly defined, the estimates for duration were more reliable than those for frequency of involuntary smoking exposure.

A potential limitation with regards to pooling data on involuntary smoking is the slight difference of definition of involuntary smoking. Exposure to involuntary smoking from anyone at home was considered in Tampa, Los Angeles, and Houston studies, whereas only exposure to involuntary smoking from the spouse or partner at home was considered in the Central Europe, Puerto Rico, and Latin America studies. For exposure to involuntary smoking at work, three of the five studies specified exposure in enclosed areas. However, the study-specific OR estimates were not consistently higher in the studies with consideration of involuntary smoking from anyone at home compared with those from the spouse or partner only or in enclosed areas at work. Moreover, involuntary smoking exposure for most of adults who have involuntary smoking exposure at home are likely to be mainly from their spouse or partner based on the family structure in the United States (25). We were not able to consider childhood involuntary smoking exposure because only two studies collected such information. If this circumstance of involuntary smoking exposure increases the risk of head and neck cancer, the direction of bias could not be predicted. This potential bias might not be a serious concern because childhood involuntary smoking exposure has not been a clear risk factor even for lung cancer (5).

Similarly, some individuals with very minimal tobacco use may have been categorized as ''never tobacco users'' in the analysis due to the wording of the questions. The studies with higher threshold for the classification were the Tampa study (smoking cigars, pipes, or using snuff or chewing tobacco less than once a day for <1 year as never users of cigars, pipes, chewing tobacco, or snuff) and Latin America study (<1 cigarette per day for 1 year as never cigarette smokers). However, ORs were not consistently higher for these groups across different involuntary smoking variables. Another potential source of bias might come from misclassification of smokers as nonsmokers due to misreporting. The concordance of smoking status within couples might result in bias of the estimates. Although we were not able to assess this issue in this study population, a European validation study has suggested that such bias from smoker misclassification is likely to be insignificant (26).

Recall bias may be another limitation for our pooled analysis because information about exposure was collected after onset of head and neck cancer. However, most of the studies in our analysis were hospital–based, so we may expect the cases and controls to recall similarly depending on the disease in controls. In addition, involuntary smoking is not yet an established risk factor for head and neck cancer, especially in the knowledge of the public at the time of the studies. Therefore, we would expect recall bias to be minimal during the interview for involuntary smoking assessment.

There may be other confounding factors, although we have excluded residual confounding by tobacco and alcohol with investigation among never tobacco users and never tobacco and alcohol users. We examined the associations with additional adjustment by duration at work for home estimates and by duration at home for work estimates and assessing the combined duration of

involuntary smoking at home and at work. We obtained similar estimates suggesting that the observed associations with involuntary smoking exposure at home or at work were not confounded by each other. In addition, because body mass index and family history of head and neck cancer are risk factors for head and neck cancer, confounding by body mass index or family history of head and neck cancer could influence the observed association. However, additional adjustment by body mass index or family history of head and neck cancer did not change the associations observed. Furthermore, other potential confounding factors, such as occupational exposure to carcinogens and human papillomavirus infections, were not adjusted for. Because no association between involuntary smoking exposure and human papillomavirus has been established, human papillomavirus would not be expected to result in major confounding. The effect of occupational exposure to carcinogens will warrant future investigation because no appropriate information was available for such an evaluation.

A caution for interpreting the results is that each estimate has a different set of studies included. The point estimates for the associations with involuntary smoking exposure for laryngeal cancer were generally observed to be positive in each study, although the significance level within each stratum was greatly reduced due to limited sample size. Therefore, we do not believe that the associations detected for laryngeal cancer can be explained by the potential sources of heterogeneity.

Furthermore, although the pooled data provided large sample size for the investigation on involuntary smoking and head and neck cancer risk, the statistical power of analyses stratified by gender, region, or age was limited. Because the incidence of head and neck cancer and the prevalence of involuntary smoking exposure are high in Asia, pooling of potential candidate studies from Asia in International Head and Neck Cancer Epidemiology consortium in the future would be of interest.

The major strengths of our pooled analyses were the detailed assessment of involuntary smoking exposure, the high statistical power for the overall analysis, and the restriction to never tobacco users and never alcohol drinkers.

In conclusion, our pooled study provides evidence for a carcinogenic effect of involuntary smoking on head and neck organs, particularly the pharynx and the larynx. Our results imply that reduction of involuntary smoking exposure via regulation of smoking in public settings and promotion of smoke-free households would reduce the risk of head and neck cancer not only among smokers but also among nonsmokers.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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