Active and Involuntary Tobacco Smoking and Upper Aerodigestive Tract Cancer Risks in a Multicenter Case-Control Study

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Abstract

Introduction: **Several important issues for the established association between tobacco smoking and upper aerodigestive tract (UADT) cancer risks include the associations with smoking by cancer subsite, by type of tobacco, and among never alcohol drinkers and the associations with involuntary smoking among nonsmokers. Our aim was to examine these specific issues in a large-scale case-control study in Europe.**

Methods: **Analysis was done on 2,103 UADT squamous cell carcinoma cases and 2,221 controls in the Alcohol-Related Cancers and Genetic Susceptibility in Europe project, a multicenter case-control study in 10 European countries. Unconditional logistic regression was done to obtain odds ratios (OR) and 95% confidence intervals (95% CI).**

Results: **Compared with never tobacco smoking, current smoking was associated with UADT cancer risks (OR, 6.72; 95% CI, 5.45-8.30 for overall; OR, 5.83; 95% CI, 4.50-7.54 for oral cavity and oropharynx; OR, 12.19; 95% CI, 8.29-17.92 for hypopharynx and larynx; and OR, 4.17; 95% CI, 2.45-7.10 for esophagus). Among never drinkers, dose-response relationships with tobacco smoking pack-years were observed for hypopharyngeal and laryngeal cancers (P_{trend} = 0.010) but not for oral cavity and oropharyngeal cancers (P_{trend} = 0.282). Among never smokers, ever exposure to involuntary smoking was associated with an increased risk of UADT cancers (OR, 1.60; 95% CI, 1.04-2.46).**

Conclusion: **Our results corroborate that tobacco smoking may play a stronger role in the development of hypopharyngeal and laryngeal cancers than that of oral cavity and oropharyngeal cancers among never drinkers and that involuntary smoking is an important risk factor for UADT cancers. Public health interventions to reduce involuntary smoking exposure could help reduce UADT cancer incidence.** (Cancer Epidemiol Biomarkers Prev 2009;18(12):3353–61)

Introduction

Tobacco smoking has been established as a risk factor for upper aerodigestive tract (UADT; including oral cavity, pharynx, larynx, and esophagus) cancers (1, 2). Dose-response relationships for intensity (daily consumption), duration of smoking, and pack-years have been reported in numerous epidemiologic studies (1). Vineis et al. (3) reported that the effects of ever exposure to tobacco smoking vary by subsite of the UADT (average relative risk, 4.0-5.0 for oral cavity and pharynx, 1.5-5.0 for esophagus, and 10.0 for larynx).

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Because alcohol drinking is also a strong risk factor for UADT cancer development, it is important to investigate the role of tobacco smoking with proper consideration of alcohol drinking as a strong confounding factor and a possible effect modifier. The International Head and Neck Cancer Epidemiology consortium reported the effect of tobacco smoking on head and neck cancer among never alcohol drinkers (4). The association with tobacco smoking was found to be stronger for larynx than for oral cavity and pharynx (odds ratio, 6.84 for larynx, 1.35 for oral cavity, and 2.02 for pharynx). A limitation of the study was that the analyses were based on pooled data with different questionnaires.

Although the relationship between active smoking and UADT cancer risks has been studied extensively, there are few previous studies on involuntary smoking and UADT cancer risks. Involuntary smoking has not been fully investigated due to the strong confounding by active tobacco smoking and the small number of cases who are nonsmokers. 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 were estimated to be ever exposed to involuntary smoking at work in the year 2000 (5-7). Although the excess risk might be moderate, its high prevalence makes it a critical environmental carcinogen. Only two individual studies have investigated the association between involuntary smoking and head and neck cancer risk with limited power to control for confounding by active smoking (8, 9). A recent pooled analysis from six studies has provided evidence for a carcinogenic effect of involuntary smoking on head and neck organs, particularly on the pharynx and the larynx (10).

Because smoking is a modifiable behavior by public health intervention, it is essential to investigate the associations in more detail between active smoking and involuntary smoking exposure and the risk of UADT cancers. We aim to assess the associations with tobacco smoking by cancer subsite among the overall study population and among never alcohol drinkers, to evaluate the associations with different types of tobacco smoking, and to investigate UADT cancer risk with involuntary smoking among never smokers in a large European multicenter study.

Materials and Methods

Study Population. Alcohol-Related Cancers and Genetic Susceptibility in Europe is a multicenter case-control study with recruitment in 14 centers from 10 European countries (Czech Republic, Croatia, France, Germany, Greece, Ireland, Italy, Norway, Spain, and United Kingdom). The study was approved by the ethical review board of IARC as well as the respective local boards in the participating centers. All subjects provided written informed consent for their participation in the study.

Details on the study design have been provided previously (11). Briefly, incident cases were identified from participating hospitals and were histologically or cytologically confirmed. Eligible cases were classified under specific *International Classification of Diseases for Oncology* codes (C00, C01, C02, C03, C04, C05, C06, C09, C10, C12, C13, C14.0, C14.8, C15.0, C15.3, C15.4, C15.5, C15.8, C15.9, and C32; ref. 11), including cancer of the oral cavity, pharynx (excluding nasopharynx), larynx, and esophagus. Recruitment was conducted from 2002 to 2005 for all centers, except for the French center, where recruitment was conducted during 1987 to 1992. Cases were identified by participating hospitals within 6 months of diagnosis. Six cases were excluded from the analysis due to missing information on age, sex, or education. Among the 2,286 UADT cancer cases, 92.3% of the cases were squamous cell carcinoma (SCC). We focused our analysis on cases with SCC histology because the etiology of UADT cancer of other histologies may differ. Of the 2,103 UADT SCC cases, 993 were oral cavity/oropharyngeal cancers, 854 were hypopharyngeal/laryngeal cancer cases, 152 were esophageal cancer cases, and 104 were overlapping oral cavity/pharyngeal cancer cases.

In each center, controls were frequency-matched to cases by sex, age, and referral (or residence) area. In the UK centers, population controls were randomly chosen from the same family medical practice list as the corresponding cases. In the remaining centers, however, hospital controls were used to facilitate collection of blood samples. Only controls with a recently diagnosed disease were accepted, and admission diagnoses related to alcohol, tobacco, or dietary practices were excluded. Eligible control admission diagnosis included (*a*) endocrine and metabolic; (*b*) genitourinary; (*c*) skin, s.c. tissue, and musculoskeletal; (*d*) gastrointestinal; (*e*) circulatory; (*f*) ear, eye, and mastoid; and (*g*) nervous system diseases as well as (*h*) plastic surgery cases and (*i*) trauma patients. The proportion of controls within a specific diagnostic group did not exceed 33% of the total. In the UK centers, population controls were recruited from a randomly selected list of 10 controls for every case, matched by age, sex, and same family medical practice. After excluding six controls due to missing information on age, sex, or education, 2,221 controls were included in the analysis. In the Paris center, by center-specific protocol, never smokers were not included among cases or controls (11).

Cases and controls underwent identical interviews during which they completed a lifestyle questionnaire. The questionnaire included information on sociodemographic variables as well as detailed smoking and alcohol drinking histories. Nonsmokers were asked about the duration of exposure to involuntary smoking at home and at work, respectively. The participation rates ranged from 35% to 100% for cases and from 26% to 100% for controls. The UK centers with population-based recruitment had lower participation rates compared with the other centers.

Statistical Analysis. For the assessment of main effects of tobacco smoking (cigarette, cigar, and pipe), all UADT cancer cases were analyzed both together and stratified by cancer subsite. The distribution of cases and controls by age, center, sex, education, and histology was examined. OR and 95% confidence interval (95% CI) for UADT cancers by various tobacco smoking variables, including intensity (drinks per day), duration, pack-years, age at start, and years since quitting, were estimated with unconditional logistic regression, adjusting for age (categories shown in Table 1), sex, education level (categories shown), and alcohol consumption (intensity and duration).

Ever smokers were defined as individuals who ever smoked cigarettes, cigars, pipes, or any tobacco products at least once a week for a year. Former smokers were defined as smokers who had stopped for at least 12 months. The Paris center included only regular smokers who smoked 5 cigarettes or cigars or pipes per day for 5 years. The different types of tobacco smoking were converted to cigarette equivalents (1 cigar = 4 cigarettes and 1 pipe = 3.5 cigarettes; ref. 1). The main effect of tobacco smoking was also evaluated among never alcohol drinkers to see whether the effect of tobacco smoking is independent of alcohol drinking. In addition, interactions between tobacco smoking and alcohol drinking were assessed using stratified analysis and log-likelihood ratio tests. The involuntary smoking variables included ever exposure status and duration of exposure at home or at work and were evaluated among never tobacco smokers only.

Statistics from multinomial logistic regression were obtained to assess heterogeneity across cancer subsites. The potential issue of multiple hypotheses testing was evaluated using the approach described by Wacholder et al. (12). A false-positive report probability was calculated to test under a noteworthiness value of 0.2. Because the causal relationship between tobacco smoking and UADT cancer was biologically plausible (1), the prior probability of the hypotheses was set to be 0.25. Statistical analyses were conducted using the SAS 9 statistical software. All *P* values were two-sided.

Results

The demographic characteristics of the cases and controls in the 14 study centers are reported in Table 1. The proportions of women and participants with higher education were greater among controls than cases (25.30% female controls versus 18.59% female cases; 10.90% highly educated controls versus 6.09% highly educated cases) in the overall population. The distributions were similar between cases and controls among never alcohol drinkers.

For tobacco smoking, dose-response trends were consistently observed with the risk of UADT SCC for intensity, duration, pack-years (Table 2), and lifetime exposure (data not shown) for all of the UADT cancer subsites. The risk of hypopharyngeal and laryngeal SCC associated with tobacco smoking was higher than that of oral cavity/oropharyngeal and esophageal SCCs regardless of the tobacco measurement considered. After adjustment for

Table 1. Demographic characteristics among UADT SCC cases and controls

Total	Overall		Never alcohol drinkers	
	Cases, *n* (%)	Controls, *n* (%)	Cases, *n* (%)	Controls, *n* (%)
	n = 2,103	*n* = 2,221	*n* = 118	*n* = 272
Center				
Czech Republic: Prague	163 (7.75)	187 (8.42)	4 (3.39)	6 (2.21)
Germany: Bremen	277 (13.17)	327 (14.72)	9 (7.63)	26 (9.56)
Greece: Athens	211 (10.03)	194 (8.73)	20 (16.95)	35 (12.87)
Italy: Aviano	145 (6.89)	151 (6.80)	1 (0.85)	11 (4.04)
Italy: Padova	128 (6.09)	130 (5.85)	9 (7.63)	25 (9.19)
Italy: Turin	158 (7.51)	198 (8.91)	17 (14.41)	31 (11.40)
Ireland: Dublin	33 (1.57)	19 (0.86)	2 (1.69)	3 (1.10)
Norway: Oslo	137 (6.51)	184 (8.28)	8 (6.78)	16 (5.88)
UK: Glasgow	90 (4.28)	91 (4.10)	3 (2.54)	1 (0.37)
UK: Manchester	141 (6.70)	186 (8.37)	3 (2.54)	5 (1.84)
UK: Newcastle	67 (3.19)	113 (5.09)	2 (1.69)	4 (1.47)
Spain: Barcelona	184 (8.75)	166 (7.47)	24 (20.34)	84 (30.88)
Croatia: Zagreb	50 (2.38)	46 (2.07)	3 (2.54)	6 (2.21)
France: Paris	319 (15.17)	229 (10.31)	13 (11.02)	19 (6.99)
Age (y)				
<40	48 (2.28)	107 (4.82)	8 (6.78)	21 (7.72)
40-44	95 (4.52)	118 (5.31)	6 (5.08)	15 (5.51)
45-49	212 (10.08)	193 (8.69)	5 (4.24)	22 (8.09)
50-54	318 (15.12)	316 (14.23)	10 (8.47)	37 (13.60)
55-59	444 (21.11)	386 (17.38)	22 (18.64)	36 (13.24)
60-64	352 (16.74)	310 (13.96)	15 (12.71)	27 (9.93)
65-69	306 (14.55)	341 (15.35)	18 (15.25)	35 (12.87)
70-74	192 (9.13)	252 (11.35)	17 (14.41)	33 (12.13)
≥75	136 (6.47)	198 (8.91)	17 (14.41)	46 (16.91)
P	<0.001		0.548	
Sex				
Men	1,712 (81.41)	1,659 (74.70)	40 (33.90)	113 (41.54)
Women	391 (18.59)	562 (25.30)	78 (66.10)	159 (58.46)
P	<0.001		0.155	
Education				
Finished primary school	778 (36.99)	590 (26.56)	55 (46.61)	109 (40.07)
Finished further school	1,197 (56.92)	1,389 (62.54)	52 (44.07)	139 (51.10)
University degree	128 (6.09)	242 (10.90)	11 (9.32)	24 (8.82)
P	<0.001		0.429	
Histology				
Controls		2,221 (100.00)		272 (100.00)
Oral/oropharynx	993 (47.22)		58 (49.15)	
Hypopharynx/larynx	854 (40.61)		45 (38.14)	
Esophagus	152 (7.23)		13 (11.02)	
Overlapping	104 (4.95)		2 (1.69)	

Table 2. Associations between tobacco smoking and UADT cancer risk by cancer subsite

	UADT			Oral cavity and oropharynx			Hypopharynx and larynx			Esophagus		
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
Tobacco smoking status*												
Never	179	712	1.00	109	712	1.00	34	712	1.00	25	632	1.00
Former	479	741	2.26 (1.82-2.81)	205	741	1.80 (1.37-2.37)	223	741	4.41 (2.98-6.53)	37	587	1.77 (1.00-3.12)
Current	1,390	715	6.72 (5.45-8.30)	660	715	5.83 (4.50-7.54)	568	715	12.19 (8.29-17.92)	85	509	4.17 (2.45-7.10)
Tobacco smoking intensity* (cigarettes/d)												
Never	179	712	1.00	109	712	1.00	34	712	1.00	25	632	1.00
>0-2	27	44	2.67 (1.58-4.52)	14	44	2.44 (1.27-4.69)	9	44	4.04 (1.77-9.24)	1	33	0.97 (0.12-7.97)
3-4	31	49	2.78 (1.69-4.55)	18	49	2.76 (1.51-5.02)	8	49	3.23 (1.39-7.49)	2	43	2.21 (0.48-10.19)
5-10	172	301	2.21 (1.70-2.87)	92	301	1.99 (1.44-2.75)	55	301	3.50 (2.20-5.56)	21	254	2.16 (1.13-4.13)
11-20	808	598	4.95 (3.99-6.13)	384	598	4.24 (3.26-5.52)	315	598	8.38 (5.68-12.35)	67	471	3.59 (2.10-6.14)
>20	822	461	5.91 (4.69-7.45)	352	461	4.85 (3.64-6.47)	400	461	11.28 (7.59-16.77)	31	293	2.58 (1.37-4.88)
P_{trend}			<0.001			<0.001			<0.001			0.313
Tobacco smoking duration* (y)												
Never	179	712	1.00	109	712	1.00	34	712	1.00	25	632	1.00
1-20	153	404	1.49 (1.15-1.94)	80	404	1.31 (0.94-1.83)	49	404	2.13 (1.33-3.41)	17	308	1.88 (0.95-3.74)
21-40	1,040	737	4.50 (3.64-5.56)	488	737	3.76 (2.90-4.87)	436	737	8.01 (5.46-11.75)	65	545	2.70 (1.57-4.64)
>40	669	313	7.67 (6.03-9.75)	293	313	6.81 (5.06-9.16)	303	313	13.38 (8.92-20.09)	40	241	4.05 (2.21-7.42)
P_{trend}			<0.001			<0.001			<0.001			0.024
Tobacco age at start† (y)												
Never	179	712	1.00	109	712	1.00	34	712	1.00	25	632	1.00
≥20	523	423	3.09 (2.44-3.92)	239	423	3.08 (2.31-4.11)	221	423	5.38 (3.57-8.12)	44	305	2.68 (1.49-4.84)
15-19	911	756	2.68 (2.14-3.37)	421	756	2.65 (2.02-3.48)	386	756	4.84 (3.25-7.20)	56	582	1.70 (0.94-3.10)
<15	425	274	2.59 (1.96-3.41)	199	274	2.74 (1.98-3.80)	180	274	4.35 (2.79-6.78)	22	207	1.64 (0.75-3.60)
P_{trend}			0.094			0.333			0.147			0.086
Smoking status and pack-years‡												
Never	179	712	1.00	109	712	1.00	34	712	1.00	25	632	1.00
Former (>0-20 pack-years) since ≥20 y	80	263	1.26 (0.92-1.72)	40	263	1.09 (0.73-1.64)	25	263	1.71 (0.99-2.97)	13	213	1.98 (0.95-4.11)
Former (>20 pack-years) since ≥20 y	42	95	1.59 (1.03-2.43)	19	95	1.49 (0.84-2.63)	23	95	3.12 (1.70-5.71)		75	
Former (>0-20 pack-years) since <20 y	75	132	2.41 (1.72-3.37)	40	132	2.13 (1.40-3.25)	29	132	4.66 (2.70-8.04)	5	110	1.15 (0.40-3.29)
Former (>20 pack-years) since <20 y	284	247	4.24 (3.27-5.49)	106	247	3.05 (2.19-4.25)	148	247	8.69 (5.70-13.23)	19	184	2.63 (1.33-5.21)
Current (>0-20 pack-years)	173	219	3.53 (2.68-4.66)	102	219	3.42 (2.45-4.78)	46	219	4.75 (2.90-7.77)	13	174	2.60 (1.21-5.58)
Current (21-40 pack-years)	527	258	7.89 (6.18-10.07)	257	258	6.65 (4.95-8.93)	197	258	13.80 (9.12-20.89)	48	188	6.13 (3.38-11.11)
Current (>40 pack-years)	688	244	9.93 (7.73-12.77)	298	244	8.46 (6.22-11.50)	325	244	18.32 (12.14-27.63)	24	147	3.21 (1.62-6.38)
P_{trend}			<0.001			<0.001			<0.001			<0.001

NOTE: P_{trend} values were calculated among ever smokers only. Tobacco smoking includes cigarettes, cigar, and pipe in cigarette equivalents.
*Adjusted for age, sex, education, center, and alcohol drinking intensity (continuous) and duration (continuous).
†Adjusted for sex, education, center, alcohol drinking intensity (continuous) and duration (continuous), and pack-years of smoking (continuous).
‡Adjusted for age, sex, education, center, and alcohol drinking intensity (continuous).

pack-years of smoking and without adjustment for age, starting tobacco smoking at a young age (<15 years) did not confer a higher risk of UADT SCCs than starting at a later age (≥20 years). We performed heterogeneity tests by sex (results not shown). However, the data for women became too sparse to provide meaningful comparisons, except for tobacco among the overall participants. The point estimates suggested stronger associations with tobacco smoking among men than those among women, although the 95% CIs overlapped.

In Table 3, UADT SCC risk due to the different types of tobacco smoking products was assessed. The risk of oral cavity/oropharyngeal SCC was increased by ~5-fold for smoking >20 cigarettes per day, 8-fold for smoking >20 cigarette equivalents of cigars, and 4-fold for smoking >20 cigarette equivalents of pipes. For oral cavity/oropharyngeal SCC, the risk estimates with smoking intensity and duration were suggested to be higher for cigar smoking than for cigarette or pipe smoking. On the other hand, for hypopharyngeal and laryngeal SCC, the point estimates with smoking intensity and duration were suggested to be higher for cigar smoking only at low intensity (≤10 cigarettes per day) and short duration (<20 years). Similar evaluations were done for esophageal cancer, but the data were too sparse to provide reliable estimates (results not shown).

Among never alcohol drinkers, dose-response trends were observed for pack-years of smoking for hypopharyngeal and laryngeal SCC (P_{trend} = 0.010; Table 4). On the other hand, the dose-response trends were not detected for oral cavity and oropharyngeal SCC. Under multiplicative models, interactions between measures of tobacco consumption (smoking status, intensity, duration, and pack-years) and alcohol drinking intensity were detected for oral cavity and oropharyngeal cancers (data not shown; P = 0.004 for smoking status, P = 0.031 for smoking intensity, P < 0.001 for smoking duration and accumulative lifetime exposure, and P = 0.024 for pack-years of smoking). Such interactions were not observed for the other UADT cancer subsites. The data became too sparse to examine the relationship with any specific tobacco type other than cigarettes or for esophageal SCC.

Among never tobacco smokers, ever exposure to involuntary smoking at home or at work was associated with

Table 3. Associations between tobacco smoking and UADT cancer risk by subsite for different types of tobacco products

	UADT			Oral cavity and oropharynx			Hypopharynx and larynx		
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
Cigarette smoking frequency* (cigarettes/d)									
Never	179	712	1.00	109	712	1.00	34	712	1.00
>0-10	238	402	2.35 (1.84-2.99)	131	402	2.20 (1.63-2.96)	74	402	3.50 (2.26-5.43)
11-20	827	612	4.95 (4.00-6.13)	390	612	4.19 (3.22-5.46)	327	612	8.40 (5.70-12.37)
>20	779	408	6.23 (4.93-7.88)	332	408	5.05 (3.78-6.76)	378	408	11.91 (8.00-17.74)
P_{trend}			<0.001			<0.001			<0.001
Cigarette smoking duration* (y)									
Never	179	712	1.00	109	712	1.00	34	712	1.00
>1-9	54	141	1.60 (1.11-2.30)	30	141	1.52 (0.96-2.40)	14	141	1.87 (0.96-3.64)
10-19	114	225	2.01 (1.50-2.70)	58	225	1.75 (1.20-2.54)	42	225	3.30 (2.01-5.41)
20-39	975	724	4.28 (3.46-5.29)	459	724	3.58 (2.76-4.65)	406	724	7.68 (5.23-11.28)
≥40	703	333	7.20 (5.68-9.12)	307	333	6.30 (4.71-8.42)	318	333	12.93 (8.64-19.34)
P_{trend}			<0.001			<0.001			<0.001
Cigar smoking frequency† (cigarette equivalents/d)									
Never	179	712	1.00	109	712	1.00	34	712	1.00
>0-10	61	41	6.24 (2.80-13.89)	23	41	5.14 (1.81-14.56)	33	41	8.36 (2.87-24.37)
11-20	32	26	5.03 (2.06-12.30)	16	26	6.26 (2.01-19.47)	15	26	4.53 (1.33-15.45)
>20	37	38	6.02 (2.52-14.37)	21	38	7.66 (2.71-21.62)	14	38	3.93 (1.12-13.73)
P_{trend}			0.863			0.358			0.083
Cigar smoking duration† (y)									
Never	179	712	1.00	109	712	1.00	34	712	1.00
>1-9	63	56	4.98 (2.23-11.12)	32	56	6.23 (2.30-16.85)	27	56	5.64 (1.89-16.79)
10-19	23	21	5.31 (2.07-13.64)	8	21	4.14 (1.22-14.09)	14	21	7.52 (2.17-26.01)
20-39	35	25	8.22 (3.42-19.74)	18	25	10.61 (3.40-33.06)	15	25	6.79 (2.02-22.86)
≥40	11	6	11.18 (2.67-46.80)	3	6	11.90 (1.55-91.67)	7	6	10.36 (1.80-59.54)
P_{trend}			0.093			0.247			0.450
Pipe smoking frequency† (cigarette equivalents/d)									
Never	179	712	1.00	109	712	1.00	34	712	1.00
>0-10	50	52	5.47 (2.53-11.84)	30	52	6.54 (2.54-16.82)	15	52	4.14 (1.29-13.33)
11-20	22	39	3.02 (1.24-7.36)	9	39	2.65 (0.80-8.75)	10	39	3.44 (1.01-11.66)
>20	40	54	5.02 (2.11-11.95)	16	54	4.15 (1.34-12.88)	17	54	6.19 (1.76-21.81)
P_{trend}			0.721			0.231			0.449
Pipe smoking duration† (y)									
Never	179	712	1.00	109	712	1.00	34	712	1.00
>1-9	65	101	3.21 (1.47-7.02)	31	101	3.56 (1.34-9.49)	27	101	3.81 (1.25-11.57)
10-19	16	20	5.37 (2.00-14.41)	6	20	4.19 (1.15-15.21)	5	20	4.19 (0.94-18.79)
20-39	29	20	9.57 (4.00-22.88)	18	20	15.90 (5.43-46.56)	8	20	6.11 (1.63-22.95)
≥40	5	6	5.68 (1.32-24.40)	1	6	3.61 (0.32-40.45)	4	6	10.35 (1.86-57.72)
P_{trend}			0.005			0.004			0.157

NOTE: P_{trend} values were calculated among ever smokers only. 1 cigar = 4 cigarettes and 1 pipe = 3.5 cigarettes for comparison purpose. Esophageal cancer patients were not included due to sparse data.

*Adjusted for age, sex, education, center, and alcohol drinking intensity and duration.

†Adjusted for age, sex, education, center, alcohol drinking intensity and duration, and smoking duration.

Table 4. Associations between tobacco smoking and UADT cancer risk by cancer subsite among never alcohol drinkers

	UADT			Oral cavity and oropharynx			Hypopharynx and larynx		
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
Tobacco smoking status									
Never	45	166	1.00	33	166	1.00	5	166	1.00
Former	18	52	1.55 (0.77-3.10)	5	52	0.62 (0.21-1.82)	12	52	10.32 (2.77-38.47)
Current	55	54	5.15 (2.80-9.45)	20	54	2.26 (1.02-5.03)	28	54	47.32 (12.05-185.80)
P			0.001			0.032			0.002
Tobacco smoking intensity (cigarettes/d)									
Never	45	166	1.00	33	166	1.00	5	166	1.00
>0-10	18	28	2.62 (1.26-5.45)	8	28	1.49 (0.57-3.89)	8	28	16.33 (4.14-64.36)
11-20	29	41	3.49 (1.79-6.80)	10	41	1.25 (0.49-3.16)	14	41	21.27 (5.63-80.40)
>20	25	36	3.44 (1.64-7.22)	7	36	1.60 (0.54-4.73)	17	36	21.99 (5.62-86.02)
P_{trend}			0.574			0.925			0.651
Tobacco smoking duration (y)									
Never	45	166	1.00	33	166	1.00	5	166	1.00
1-20	15	30	1.99 (0.88-4.48)	6	30	0.92 (0.28-3.00)	7	30	11.14 (2.54-48.77)
21-40	31	55	2.76 (1.44-5.30)	8	55	0.92 (0.35-2.40)	19	55	18.57 (5.07-68.04)
>40	26	20	5.48 (2.50-12.01)	11	20	3.30 (1.17-9.32)	13	20	30.45 (7.50-123.70)
P_{trend}			0.050			0.089			0.157
Tobacco smoking lifetime (cigarettes/life)									
Never	45	166	1.00	33	166	1.00	5	166	1.00
>0-50,000	8	19	1.70 (0.64-4.49)	2	19	0.44 (0.09-2.20)	4	19	15.43 (2.91-81.82)
>50,000-100,000	10	9	5.19 (1.80-14.94)	6	9	4.45 (1.19-16.56)	4	9	23.81 (3.96-143.00)
>100,000-500,000	45	72	3.08 (1.72-5.54)	16	72	1.41 (0.63-3.12)	23	72	17.79 (5.08-62.37)
>500,000	9	5	11.51 (3.19-41.57)	1	5	1.70 (0.15-19.05)	8	5	116.10 (18.74-718.90)
P_{trend}			0.084			0.412			0.138
Tobacco smoking pack-years									
Never	45	166	1.00	33	166	1.00	5	166	1.00
>0-20	24	46	2.15 (1.11-4.17)	12	46	1.27 (0.55-2.94)	10	46	13.02 (3.40-49.80)
21-40	18	37	2.55 (1.20-5.40)	5	37	0.85 (0.26-2.83)	8	37	12.84 (3.10-53.18)
>40	30	22	7.75 (3.55-16.93)	8	22	2.75 (0.94-8.03)	21	22	53.11 (13.13-214.90)
P_{trend}			0.004			0.282			0.010

NOTE: Adjusted for center, education, sex, and age. Results on esophagus and cigar or pipe were not included due to sparse data.

an increased risk of UADT SCC (Table 5). The estimates for the associations with involuntary smoking exposure either at home only or at work only were similar with overlapping 95% CIs. Duration of exposure at home and at work combined was observed to be associated with UADT SCC risk overall (OR, 1.84; 95% CI, 1.17-2.89 for >15 years of exposure; P_{trend} = 0.007) and more specifically with oral cavity/oropharyngeal cancers (OR, 2.15; 95% CI, 1.21-3.80 for >15 years of exposure; P_{trend} = 0.007). When stratifying the cancer subsites into finer groups, the OR (95% CI) for ever involuntary smoking status were 2.45 (1.20-5.01) for oral cavity cancer, 1.35 (0.58-3.15) for pharyngeal cancer, and 1.76 (0.64-4.87) for laryngeal cancer (data not shown). Dose-response relations with exposure at home and at work were observed for oral cavity cancer (P_{trend} = 0.002; data not shown) but not for the other cancer subsites. When we removed the adjustment for alcohol drinking, the ORs fluctuated only slightly and 95% CIs remained overlapping (OR, 1.82; 95% CI, 1.17-2.84 for >15 years of exposure in cancers of the UADT; OR, 2.10; 95% CI, 1.19-3.68 for >15 years of exposure in cancers of the oral cavity and oropharynx; data not shown).

Discussion

The association with active tobacco smoking was stronger for cancer risk of hypopharynx and larynx than for that of oral cavity and oropharynx and esophagus, consistent with previous findings (3, 4). Tobacco smoking was suggested to have an independent effect from alcohol drinking for laryngeal and hypopharyngeal cancers but not for oral cavity and oropharyngeal cancers. Heterogeneity across cancer subsites was detected for all tobacco smoking variables, except for age at start smoking. Differences in UADT SCC risk associated with cigarettes, cigars, and pipes were suggested by the point estimates. Boffetta et al. (13) suggested that different inhalation pattern may have an impact on the results. The observations that cigar-only smokers seldom inhale into the lung, whereas former cigarette smokers and concurrent cigar and cigarette smokers tend to keep their cigarette inhalation pattern when they smoke cigars (14) supports our results that cigar smoking might have a stronger association with oral cavity and oropharynx. However, we were not able to adjust for inhalation patterns.

The observation that an association with cigar smoking was stronger than that with cigarette or pipe smoking might be due to chance with the sparse data or due to the higher delivered dosages of nicotine, tar, and carbon monoxide in cigars than in cigarettes according to machine-smoking analysis (15). The levels of nicotine, benzo[*a*]pyrene, and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone were found to be higher in the mainstream smoke of premium cigars, even the cigarette-size cigars (15).

Among never alcohol drinkers, an association with tobacco smoking for oral cavity and oropharyngeal cancer was not observed. One possible reason is that there might not be adequate power to detect a moderate effect of smoking on oral cavity and oropharyngeal cancer development. Another possible reason is that a potential smoking effect on the oral cavity may require exposure to alcohol consumption (16), whereas the effect of smoking

Table 5. Association between involuntary smoking and UADT cancer, overall and by cancer subsite

	UADT			Oral cavity and oropharynx			Larynx and hypopharynx			Esophagus		
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
Passive smoking exposure												
Never	39	212	1.00	21	212	1.00	7	212	1.00	9	198	1.00
Ever at home only	54	182	1.49 (0.90-2.48)	36	182	1.72 (0.91-3.22)	9	182	2.01 (0.66-6.14)	6	164	0.68 (0.19-2.46)
Ever at work only	35	122	1.79 (1.03-3.13)	25	122	2.46 (1.24-4.87)	7	122	1.72 (0.55-5.44)	3	111	0.96 (0.21-4.33)
Ever both at home and at work	52	190	1.68 (1.00-2.83)	29	190	1.62 (0.84-3.14)	11	190	2.34 (0.74-7.40)	6	151	0.74 (0.21-2.68)
Ever at home or work	141	494	1.63 (1.06-2.51)	90	494	1.87 (1.08-3.23)	27	494	1.98 (0.77-5.07)	15	426	0.76 (0.27-2.12)
Duration of exposure at home (y)												
Never	75	338	1.00	46	338	1.00	14	338	1.00	13	313	1.00
1-15	26	104	0.98 (0.56-1.69)	14	104	0.80 (0.40-1.62)	7	104	2.00 (0.67-5.96)	1	95	0.15 (0.01-1.68)
>15	66	191	1.50 (0.97-2.32)	44	191	1.50 (0.89-2.53)	9	191	1.68 (0.62-4.52)	10	168	1.28 (0.43-3.78)
P_{trend}			0.073			0.133			0.269			0.661
Duration of exposure at work (y)												
Never	92	392	1.00	56	392	1.00	16	392	1.00	15	360	1.00
1-15	34	137	1.14 (0.70-1.86)	20	137	1.04 (0.56-1.93)	8	137	1.86 (0.70-4.93)	4	116	1.00 (0.27-3.67)
>15	52	174	1.65 (1.06-2.57)	33	174	1.92 (1.12-3.28)	10	174	1.18 (0.47-2.97)	5	145	0.97 (0.28-3.40)
P_{trend}			0.029			0.025			0.624			0.964
Duration of exposure both at home and at work (y)												
Never	39	212	1.00	21	212	1.00	7	212	1.00	9	198	1.00
1-15	35	144	1.31 (0.75-2.28)	22	144	1.38 (0.68-2.78)	9	144	2.38 (0.78-7.30)	1	127	0.15 (0.02-1.44)
>15	101	320	1.84 (1.17-2.89)	64	320	2.15 (1.21-3.80)	17	320	1.82 (0.67-4.92)	14	277	1.11 (0.39-3.14)
P_{trend}			0.007			0.007			0.313			0.635

NOTE: Adjusted by age, sex, education, center, alcohol drinking intensity, and duration (categorical).

on larynx and hypopharynx is independent of alcohol consumption. The findings that the association with active smoking was stronger for laryngeal and pharyngeal cancers than that for oral cavity cancer are consistent with those in the pooled analysis in the International Head and Neck Cancer Epidemiology consortium (4). The interactions detected between tobacco smoking and alcohol drinking further supports the necessary role of alcohol drinking in the mechanism for the relationship between tobacco smoking and the development of oral cavity and oropharyngeal cancers.

Among never tobacco smokers, the association with involuntary smoking that we observed for oral cavity and oropharyngeal cancers has not been reported in previous studies (10). This association might be real or might be due to residual confounding of alcohol drinking. Unfortunately, we did not have enough power to investigate the relationship among never alcohol drinkers. The difference between the ORs with and without the adjustment for alcohol drinking was minimal. Thus, the residual confounding by alcohol might be minimal. Associations between involuntary smoking and pharyngeal and laryngeal cancers have been reported in the pooled analysis in the International Head and Neck Cancer Epidemiology consortium (10). However, the associations between involuntary smoking and pharyngeal and laryngeal cancers were suggestive in our analysis because the 95% CIs included the null value and no dose-response relationship was observed with duration of exposure.

There are some limitations in our present analysis. There might be selection bias due to the use of hospital controls for most of the study centers. However, oversampling of long-stay patients or patients within a specific diagnostic group was avoided. Most controls were patients who had been in the hospital for <1 week. We expect selection bias in our study to be minimal. To assess the effect of any potential selection bias due to the control selection, we compared the results stratified by control type (hospital-based and population-based). The point estimates for the population-based controls were higher than those from the hospital-based controls with overlapping 95% CIs, which suggested that our results might be biased toward the null because most of the controls were hospital-based and might result in nondifferential reporting bias. In addition, recall bias might be a concern because the interviews were done after disease diagnosis.

Although our study was large-scale, some analyses were difficult to carry out due to sparse data. For instance, we were not able to examine subjects who only smoked a certain type of tobacco product, because the prevalence of cigar-only smokers ($n = 4$) or pipe-only smokers ($n = 9$) was low among cancer cases in our study population. Furthermore, the number of esophageal SCC cases was fairly small; thus, we focused on the main effects for tobacco and cigarette smoking for the analysis of esophageal SCC cases.

Although we had the statistical power to examine the association of involuntary smoking with the risk of UADT cancers among never tobacco smokers, there was not enough power to assess that among never tobacco and never alcohol users. The association with involuntary smoking exposure both at home and at work was observed to be similar to that with exposure either at home only or at work only probably due to the limitation of no adjustment by exposure intensity.

In addition, confounding by family history of cancer and by human papillomavirus (HPV) infection might be of concern in our investigation. According to a recent pooled analysis in International Head and Neck Cancer Epidemiology consortium, family history of head and neck cancer was found to be associated with an increased risk of head and neck cancer (OR, 2.2; 95% CI, 1.6-3.1 when the affected relative was a sibling; ref. 17). However, we do not have the information on family history of cancer available for further investigation in our study. Negri et al. (17) reported that subjects with family history of head and neck cancer was not associated with an increased risk of head and neck cancer when exposure to tobacco was absent. Furthermore, when we considered the magnitude of the point estimates for the association with family history of cancer, the association with tobacco smoking could not have been fully explained by family history of cancer.

High-risk types of HPV have been associated with a higher risk of a subgroup of head and neck SCC (18). Confounding by HPV status might affect the association between tobacco smoking and UADT cancers. Although we did not have any HPV information available in this study population, we suspected the effect of HPV confounding, if any, to result in bias toward the null value because HPV-positive patients tended to be younger and nonsmokers and nondrinkers (18, 19). Tobacco smoking/alcohol drinking and HPV infection were hypothesized to be two distinct pathogenic mechanisms (18, 19). Despite the above-mentioned potential limitations, this study provides a more homogeneous population within Europe and more adequate power for evaluating the main effect of tobacco smoking among never alcohol drinkers and by cancer subsite.

According to the assessment of false-positive report probability, the detected associations with active tobacco smoking were robust, whereas the observed associations with involuntary smoking warrant further investigation with a larger sample size. In summary, an independent effect of tobacco smoking from alcohol drinking for hypopharyngeal/laryngeal cancer was more substantial than that for oral cavity/oropharyngeal cancers. Our results corroborate that active tobacco smoking may play a stronger role in the development of hypopharyngeal and laryngeal cancers than that of oral cavity and oropharyngeal cancers among never alcohol drinkers. In addition, avoiding exposure to involuntary smoking is important for the prevention of UADT cancers. For future direction, it is important to investigate the effect of tobacco smoking by type of tobacco in a larger study population of cigar-only and/or pipe-only smokers.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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