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Involuntary smoking and the risk of head and neck cancer in an East Asian population

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ABSTRACT

Background: Although tobacco involuntary smoking is an established risk factor for lung cancer, the association with head and neck cancer (HNC) is not established. We aimed to investigate this potential association in an East Asian population.

Methods: We conducted a multicenter case-control study in East Asia including eight centers. We restricted our analysis to never tobacco smokers (303 cases and 459 controls) and to never tobacco smokers/never alcohol drinkers (243 cases and 403 controls).

Results: Among never tobacco smokers, involuntary smoking was associated with a 1.47-fold increase in risk of HNC (95%CI = 1.02, 2.13) and a 1.8-fold increase in the risk of oral cavity cancer (95%CI = 1.14, 2.92). Among never tobacco smokers who were also never alcohol drinkers, increased risks were detected for more than 3 h per day of involuntary smoking exposure and for 15 or more years of exposure. A dose-response relation was suggested for frequency of exposure (p for trend = 0.014) and for years of exposure (p for trend = 0.010) for oral cavity cancer. We did not detect strong increases in the risk of the other HNC subsites.

Conclusions: Our study supports the association between involuntary smoking and the risk of HNC. The association may be stronger for oral cavity cancer than for other HNC subsites.

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1. Introduction

Although involuntary smoking is an established risk factor for lung cancer [1], the association with other tobacco-related cancers, and in particular head and neck cancer, is not established. In an International Head and Neck Cancer Epidemiology (INHANCE) Consortium study, 6 studies from North America, South America and Central Europe were pooled on 542 head and neck cancer cases who were never tobacco users to investigate involuntary smoking. Involuntary smoking for more than 15 years in the home (OR = 1.60, 95%CI = 1.12, 2.28) and for more than 15 years at work (OR = 1.55, 95%CI = 1.04, 2.30) were both associated with increased risks of head and neck cancer among never tobacco users [2].

In a multicenter case-control study in Western Europe, oral cavity and oropharyngeal cancer risk (n = 111) among never tobacco users were increased for involuntary smoking exposure for more than 15 years at work (OR = 1.92, 95%CI = 1.12, 3.28) [3]. A US based study of 184 never smoking head and neck cancer patients reported no association between childhood passive smoking and head and neck cancer risk but a two-fold increase in the risk of oropharyngeal cancer (OR = 2.02, 95%CI = 1.02, 4.06) [4]. Finally, a case-control study of 238 female oral cavity cancer patients in China reported more than two-fold increases in risk due to passive smoking with dose-response relations for both frequency and duration of exposure [5]. On the other hand, several studies reported either null associations with involuntary smoking or positive associations with wide confidence intervals [6–10].

Since the previous studies have not been consistent in supporting associations between involuntary smoking and head and neck cancer, and few studies have been conducted in Asia, we investigated involuntary smoking as a risk factor for head and neck cancer, and for oral cavity cancer in a multicenter study in an East Asian population.

2. Methods

We conducted a multicenter case-control study in East Asia including eight centers (Beijing, Fujian, Henan, Jiangsu, Liaoning, Shanghai, Sichuan, and Taiwan). Between December 2010 to February 2015, 921 incident cases of HNC cases, including oral cavity, oropharynx, hypopharynx and larynx and 806 controls were recruited. The face-to-face interview of both cases and controls were structured to obtain information on current and previous alcohol consumption, dietary habits, tobacco consumption and other lifestyle factors. Written consent for participation were obtained from all study participants. Ethical approval for human subject research was obtained at the University of Utah, Fujian, Henan, Shanghai, Sichuan, Taiwan, and Beijing. The institutions, which recruited the study population, included National Office of Cancer Prevention & Control Cancer Institute & Hospital in Beijing, National Taiwan University Hospital in Taiwan, Sichuan University in Sichuan, Nanjing Medical University in Jiangsu, Fujian Medical University in Fujian, Fudan University Shanghai Cancer Center in Shanghai, China Medical University in Liaoning, and Henan Cancer Hospital in Henan.

The inclusion criteria for cases were 1) age 18–80 years old at diagnosis, 2) incident cases of HNC (tumors were assigned to one of the five categories as follows: (1) oral cavity (includes lip, tongue, gum, floor of mouth, and hard palate): codes C00.3 to C00.9, C02.0 to C02.3, C03.0, C03.1, C03.9, C04.0, C04.1, C04.8, C04.9, C05.0, C06.0 to C06.2, C06.8, and C06.9; (2) oropharynx (includes base of tongue, lingual tonsil, soft palate, uvula, tonsil, and oropharynx): codes C01.9, C02.4, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0, C10.2-C10.4, C10.8, and C10.9; (3) hypopharynx (includes pyriform sinus and hypopharynx):codes C12.9, C13.0 to C13.2, C13.8, and C13.9; (4) oral cavity, pharynx unspecified or overlapping: codes C02.8, C02.9, C05.8, C05.9, C14.0, C14.2, and C14.8; and (5) larynx (includes glottis, supraglottis, and subglottis): codes C10.1, C32.0 to C32.3 and C32.8 to C32.9), 3) final diagnosis based on histological or cytological confirmation, and 4) interviews conducted within six months of cancer diagnosis. Controls were frequency-matched by sex, 5-year age group, ethnicity, and residence area from hospitals at each of the centers. Controls were recruited from the outpatient clinics of each hospital. Approximately 99% of the interviews for cases were conducted within 6 months of diagnosis. Cases could be included even after treatment started. Controls were selected from a strictly defined list of diseases unrelated to alcohol, tobacco, or dietary practices and were required to be cancer-free. This list of diseases included: 1) benign disorders, 2) endocrine and metabolic, 3) skin, subcutaneous tissue, and musculoskeletal disorders, 4) trauma, 5) circulatory disorders, 6) ear, eye and mastoid disorders, 7) diseases of upper-respiratory tract, 8) diseases of the oral cavity, salivary gland and jaws, 9) gastro-intestinal, 10) nervous system, 11) other diseases, and 12) no diagnosis (healthy population at wellness checkup). The proportion of hospital controls within a particular diagnostic group did not exceed 33%. Hospital controls, if hospitalized, were required to have been in the hospital for less than one month when recruited. In the final dataset, there were 921 cases (424 oral cavity, 106 oropharynx, 81 hypopharynx, 85 larynx, and 225 unspecified or overlapping) and 806 controls. For this analysis, we identified 303 head and neck cancer cases and 459 controls who were never tobacco smokers. For the subgroup of individuals who had never used tobacco and had never drank alcohol, we identified 243 head and neck cancer cases and 403 controls.

Study participants were asked about involuntary smoking exposures as a child (before age 18) and as an adult. They were asked about average hours/day of exposure and total years of exposure as an adult (at age 18 and older) and as a child (before age 18). Ever involuntary smoking took into account involuntary exposure as a child or adult. The frequency of exposure (hours per day) were weighted by the years of exposure to that frequency and divided by the total years of involuntary smoking exposure. Years of involuntary exposure as a child (before age 18) and as an adult (at age 18 and older) were summed for total years of involuntary smoking exposure.

For this study, we restricted the cases and control to never tobacco smokers, and further to never tobacco smokers/alcohol drinkers. Never tobacco smokers were defined as individuals who had not used cigarettes and pipes during their lifetimes. Cigar and chewing tobacco were not considered in this study since none of the cases or controls reported these habits in this study population.

2.1. Statistical methods

We used chi-square tests to assess differences in the distribution of demographics between cases and controls. The odds ratios (OR) and 95% confidence intervals (CI) were estimated using unconditional logistic regression. The adjustment variables included age (categories as shown in Table 1), sex, education (categories as shown in Table 1), center, ethnicity (categories as shown in Table 1), and alcohol drinking frequency (never drinker, < 2 drinks/day, and > = 2 drinks/day) in the analysis of never tobacco smokers.

3. Results

As shown in Table 1, the cases were older, with a higher proportion of women, with more education than the control group. The predominant cancer subsite was oral cavity cancer.

Among never tobacco smokers, involuntary smoking was associated with a 1.47-fold increase in risk of head and neck cancer (Table 2). The point estimate was higher for adulthood exposure (OR = 1.40, 95% CI 0.97, 2.01) than childhood exposure (OR = 1.20, 95% CI 0.94, 2.52) though the 95% CI overlapped. Involuntary smoking exposure for more than 3 h per day was associated with a 1.84-fold increase in head and neck cancer risk, with a dose-response trend (p for trend = 0.025). We did not observe clear dose-response trends for years of involuntary smoking and the risk of head and neck cancer among never smokers.

Table 1
Characteristics of head and neck cancer cases and controls.

	Never tobacco smokers				Never tobacco/alcohol users			
	Cases (n = 303)		Controls (n = 459)		Cases (n = 243)		Controls (n = 403)	
	n	%	n	%	n	%	n	%
Center								
Beijing	12	4.0	31	6.8	7	2.9	20	5.0
Jiangsu	41	13.5	56	12.2	38	15.6	56	13.9
Shanghai	9	3.0	23	5.0	7	2.9	17	4.2
Henan	12	4.0	35	7.6	10	4.1	34	8.4
Fujian	35	11.6	33	7.2	32	13.2	27	6.7
Liaoning	25	8.3	42	9.2	18	7.4	32	7.9
Sichuan	61	20.1	32	7.0	50	20.6	30	8.4
Taiwan	109	35.6	207	45.1	81	33.3	187	46.4
P for χ^2 test				< 0.0001				< 0.0001
Age (year)								
< 45 years old	55	18.2	162	35.3	49	20.2	140	34.7
45- < 55 years old	61	20.1	117	25.5	45	18.5	102	25.3
55- < 65 years old	99	32.7	110	24.0	80	32.9	94	23.3
65+ years old	88	29.0	70	15.3	69	28.4	67	16.6
P for χ^2 test				< 0.0001				< 0.0001
Sex								
Male	126	41.6	224	48.8	72	29.6	178	44.2
Female	177	58.4	235	51.2	171	70.4	225	55.8
P for χ^2 test				0.050				< 0.0001
Education								
Illiterate	36	11.9	17	3.7	32	13.2	17	4,2
Primary school	67	22.1	72	15.7	58	23.9	61	15.1
Junior/middle school	72	23.8	77	16.8	53	21.8	71	17.6
Senior/high school	70	23.1	85	18.5	51	21.0	76	18.9
College/university and above	58	19.1	208	45.3	49	20.2	178	44.2
P for χ^2 test				< 0.0001				< 0.0001
Ethnicity								
Han	213	70.3	252	54.9	180	74.1	218	54.1
Others	90	29.7	207	45.0	63	25.9	185	45.9
P for χ^2 test				< 0.0001				< 0.0001
Subsite								
Oral cavity	168	55.5			133	54.7		
Oropharynx	23	7.6			20	8.2		
Hypopharynx	5	1.7			2	0.8		
Larynx	12	4.0			8	3.3		
Unspecified or overlapping	95	31.4			80	32.9		

Among never tobacco smokers who were also never alcohol drinkers, increased risks were detected for more than 3 h per day of involuntary smoking exposure and for 15 or more years of exposure. Dose-response trends were supported for the years of involuntary smoking and the risk of head and neck cancer among never tobacco smokers and never alcohol drinkers (p for trend = 0.027).

For oral cavity cancer risk, we observed a 1.8-fold increase in risk for ever involuntary smoking among never tobacco smokers (Table 3). A dose-response relation was suggested for frequency of exposure (p for trend = 0.014) and for years of exposure (p for trend = 0.010). The associations were also observed among individuals who did not smoke and did not drink alcohol, with dose response trends with both frequency (p for trend = 0.051) and duration (p for trend = 0.014).

We did not report the association for the other head and neck cancer subsites individually due to limited sample sizes. Thus, we also estimated the risk of other head and neck cancer subsites combined (oropharynx, hypopharynx, larynx, unspecified; data not shown) but did not detect clear increased risks due to involuntary smoking. The risk for ever involuntary smoking was 1.25 (95%CI = 0.78, 2.00). Dose-response relations were not observed for the hours/day of involuntary smoking (p = 0.183) nor for years of involuntary smoking (p = 0.262). No heterogeneity in the associations were detected by sex (data not shown).

4. Discussion

Our study supports the association between involuntary smoking and the risk of oral cavity cancer as well as head and neck cancer. The associations were observed among never tobacco smokers as well as in a stricter group of individuals who did not smoke tobacco nor drink alcohol. Dose-response relationships for frequency of exposure in hours per day and for duration of involuntary smoking exposure and the risk of oral cavity cancer were observed. Our results suggest that involuntary smoking is a stronger risk factor for oral cavity cancer than for the other head and neck cancer subsites.

Our study is consistent with the INHANCE consortium study results [2], with risk detected for head and neck cancer overall among individuals exposed to ≥15 years of involuntary smoke. In contrast to the INHANCE consortium study which did not detect any increased risks for more hours per day of involuntary smoking, we detected increased risks of 1.84-fold for more than 3 h of exposure per day. Pharyngeal and laryngeal cancers were more strongly associated in the INHANCE pooled analysis, while our study suggested that involuntary smoking was more strongly associated with oral cavity cancer. Similar to our study, the Western Europe multicenter study also provided more support for oral cavity and oropharyngeal cancer being more strongly associated with involuntary smoking rather than with hypopharyngeal/laryngeal cancers or with esophageal cancer [3].

Table 2
Involuntary smoking exposure and the risk of head and neck cancer.

	Never tobacco smokers		Never tobacco/alcohol users	
	Cases/ controls	OR* (95% CI)	Cases/ controls	OR* (95% CI)
Involuntary smoking				
Never	175/305	1.00	149/277	1.00
Yes	123/153	**1.47 (1.02, 2.13)**	92/125	1.45 (0.98, 2.16)
Childhood exposure	54/89	1.20 (0.94, 1.52)	40/74	1.16 (0.90, 1.48)
Exposure as an adult	103/119	1.40 (0.97, 2.01)	74/95	1.40 (0.93, 2.11)
Frequency of exposure (hour/day)				
1 - 3	57/90	1.15 (0.73, 1.79)	44/75	1.12 (0.70, 1.82)
> 3	59/60	**1.84 (1.11, 3.06)**	40/48	**1.75 (1.00, 3.07)**
P_{trend}		**0.025**		0.063
Years exposed				
< 15	25/47	1.24 (0.67, 2.26)	14/36	0.98 (0.46, 2.08)
> = 15	93/106	1.44 (0.95, 2.17)	80/90	**1.62 (1.06, 2.45)**
P_{trend}		0.595		**0.027**

* Adjusted for center, age, sex, race/ethnicity, education, and alcohol drinking frequency (for never tobacco smokers only).

To our knowledge, only a few studies have been conducted on involuntary smoking and head and neck cancer risk in the East Asian population [5–7]. In contrast to the study by Troy et al. which detected increased risks of oropharyngeal cancer for childhood exposure to involuntary smoke, we did not detect increased risks for childhood exposure alone [4]. We could not restrict our analysis to oropharyngeal cancer since our sample size was small for this subsite. In addition, in contrast to the study by He et al., we did not detect increased risks specifically for women [5]. Again our sample size for subgroup analysis was restricted.

Strengths of our study include focusing on never tobacco smokers and never alcohol drinkers with the largest number of cases in this region. Restricting to these subgroups allows us to minimize residual confounding since tobacco and alcohol are strong risk factors for head and neck cancer. We were also able to investigate dose-response relations since we collected information on the frequency and duration of involuntary smoking exposure. This is also one of the few studies focusing on an East Asian population to investigate involuntary smoking and the risk of head and neck cancer.

Some limitations of our study include the small sample size by head and neck cancer subsite. Although we had a sufficient sample size to investigate oral cavity cancer risk, we did not have enough cases to estimate risks for oropharyngeal cancer patients, or for other head and neck cancer subsites separately. Most of the cases in the other categories are undefined; therefore, it is likely to contain oral cavity cancers. Another potential limitation is recall bias since this was a case-control study and the patients knew of their cancer diagnosis or diagnosis of other diseases when they were being interviewed. It would be of interest to investigate these potential associations in a cohort study in an East Asian population where the study subjects reports involuntary smoking exposure before cancer diagnoses.

5. Conclusion

In conclusion, our study supports the hypothesis of an association between involuntary smoking and the risk of head and neck cancer overall and oral cavity cancer. The strength of the association with involuntary smoking with different head and neck cancer subsite varied across studies. However, involuntary smoking may be a risk factor for head and neck cancer in the East Asian population.

Conflict of interest

None declared by any of the authors.

Financial disclosures

None of the authors have any financial disclosures to make regarding the eventual acceptance and publication of this study.

Author statement

All authors contributed to carrying out the study, reviewing the manuscript and approving the final version of the manuscript. Mia Hashibe, Zuo-feng Zhang, Paolo Boffetta, Yuan-Chin Amy Lee and Min Dai designed the study and directed its implementation. Qian Li, Chien-Jen Chen, Wan-Lun Hsu, Pen-Jen Lou, Cairong Zhu, Jian Pan, Hongbing Shen, Hongxia Ma, Baochang He, Yu Wang, Xiaoyan Zhou, Qinghai Ji, Baosen Zhou, Wei Wu, and Jie Ma supervised the field activities and collected the data. Qian Li and Mia Hashibe analyzed the data and wrote the manuscript.

Table 3
Involuntary smoking exposure and the risk of oral cavity cancer.

	Never tobacco smokers		Never tobacco/alcohol users	
	Cases/ controls	OR* (95% CI)	Cases/ controls	OR* (95% CI)
Involuntary smoking				
Never	94/305	1.00	79/277	1.00
Yes	73/153	**1.83 (1.14, 2.92)**	53/125	**1.68 (1.01, 2.82)**
Childhood exposure	33/89	1.36 (0.97, 1.90)	22/74	1.26 (0.89, 1.78)
Exposure as an adult	61/119	1.59 (0.99, 2.56)	44/95	1.55 (0.92, 2.61)
Frequency of exposure (hour/day)				
1 - 3	36/90	1.36 (0.78, 2.38)	28/75	1.25 (0.67, 2.30)
> 3	32/60	**2.34 (1.19, 4.58)**	20/48	**2.20 (1.02, 4.73)**
P_{trend}		**0.014**		**0.051**
Years exposed				
< 15	12/41	1.44 (0.61, 3.41)	6/36	0.81 (0.28, 2.35)
> = 15	62/113	**1.90 (1.16, 3.12)**	48/90	**1.99 (1.16, 3.40)**
P_{trend}		**0.010**		**0.014**

* Adjusted for center, age, sex, race/ethnicity, education, and alcohol drinking frequency (for never tobacco smokers only).

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