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Original Contribution

Active and Passive Smoking and Risk of Nasopharyngeal Carcinoma: A Population-Based Case-Control Study in Southern China

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The magnitude and patterns of associations between smoking and risk of nasopharyngeal carcinoma (NPC) in high-incidence regions remain uncertain. Associations with active and passive tobacco smoking were estimated using multivariate logistic regression in a population-based case-control study of 2,530 NPC cases and 2,595 controls in Guangdong and Guangxi, southern China, in 2010–2014. Among men, risk of NPC was significantly higher in current smokers compared with never smokers (odds ratio (OR) = 1.32, 95% confidence interval (CI): 1.14, 1.53) but not in former smokers (OR = 0.92, 95% CI: 0.73, 1.17). Risk increased with smoking intensity (per 10 cigarettes/day, OR = 1.09, 95% CI: 1.03, 1.16), smoking duration (per 10 years, OR = 1.11, 95% CI: 1.06, 1.16), and cumulative smoking (per 10 pack-years, OR = 1.08, 95% CI: 1.04, 1.12). Risk decreased with later age at smoking initiation (per year, OR = 0.97, 95% CI: 0.96, 0.98) but not greater time since smoking cessation. Exposures to passive smoking during childhood (OR = 1.24, 95% CI: 1.03, 1.48) and from a spouse during adulthood (OR = 1.30, 95% CI: 1.03, 1.63) were independently associated with increased NPC risk in never-smoking men and women, but exposure-response trends were not observed. In conclusion, active and passive tobacco smoking are associated with modestly increased risk of NPC in southern China; risk is highest among long-term smokers.

case-control studies; China; nasopharyngeal carcinoma; passive smoking; smoking; tobacco smoking

Abbreviations: CI, confidence interval; NPC, nasopharyngeal carcinoma; OR, odds ratio.

On the basis of 19 case-control studies and 2 cohort studies of tobacco smoking and risk of nasopharyngeal carcinoma (NPC), the International Agency for Research on Cancer concluded in 2004 that there was "sufficient evidence in humans that tobacco smoking causes cancer of the [nasopharynx]" (1, p. 1187). This conclusion was confirmed in 2012 based on additional studies (2). In a meta-analysis of 28 case-control studies and 4 prospective cohort studies published between 1979 and 2011, Xue et al. (3) found a significant excess of NPC among ever smokers compared with never smokers (odds ratio (OR) = 1.60, 95% confidence interval (CI): 1.38, 1.87), based on a total of 10,274 NPC cases and 415,266 comparison subjects. Significant heterogeneity was observed across studies, with stronger odds ratios for case-control studies than for cohort studies, regions with low NPC incidence than high-incidence regions, squamous cell carcinoma than undifferentiated NPC, and lower-quality studies than higher-quality studies (3). In particular, the odds ratio for ever smoking was approximately 1.3 in high-risk Chinese populations and for undifferentiated NPC, which comprises the vast majority of NPC in high-incidence regions (4).

The etiology of squamous cell NPC, which represents a substantial proportion of NPC in low-risk regions and is more strongly associated with tobacco smoking, appears to be distinct from that of undifferentiated NPC (5). Thus, the relationship between tobacco smoking and risk of undifferentiated NPC in high-risk regions such as Asia, where over 80% of the world's NPC cases and deaths occur (6), remains

somewhat unclear. Whether duration of smoking, timing of smoking initiation, or intensity of smoking is most important in mediating the association also is uncertain. Additionally, given the relatively modest magnitude of the excess risk of NPC due to active smoking and the lack of a significant association with passive smoking in the meta-analysis (OR = 1.29, 95% CI: 0.80, 2.09; based on 5 case-control studies) (3), questions persist about whether passive smoking exposure increases NPC risk.

The high prevalence of tobacco smoking and the heavy burden of NPC in southern China make it an important public health priority to understand the impact of active and passive smoking on NPC development. Therefore, we undertook an analysis of smoking and NPC risk in a large, population-based, rigorously designed case-control study in southern China, where NPC incidence rates are among the highest in the world (7, 8).

METHODS

Study population

The NPC Genes, Environment, and Epstein-Barr Virus Study is a population-based case-control study conducted in the Zhaoqing area of Guangdong Province and the Wuzhou and Guiping/Pingnan areas of Guangxi Autonomous Region in southern China. A combined total of approximately 8 million people reside in the study area. Eligible subjects were persons aged 20–74 years who were officially residing in the study area at diagnosis, with no history of malignant disease or congenital or acquired immunodeficiency.

Cases were patients with histologically confirmed first incident NPC. Prompt and thorough case identification was accomplished by creating a rapid case ascertainment system including 10 hospitals and 2 cancer research institutions that directly notified study investigators of newly diagnosed NPC cases. In the Zhaoqing area, eligible cases were diagnosed between March 2010 and August 2013. Cases in the Wuzhou area were diagnosed between April 2010 and September 2013, and those in the Guiping/Pingnan area were diagnosed between July 2010 and December 2013. A total of 3,027 incident NPC cases were identified, closely matching the estimated total number of incident NPC cases (approximately 850 per year) based on historical incidence rates in the region. Of the eligible case-patients, 2,554 (84%) consented to participate. Information on NPC histopathological subtype was not available from all cases at the time of this analysis.

Controls were randomly selected every 6–12 months from computerized, continuously updated total population registries covering the Zhaoqing, Wuzhou, and Guiping/Pingnan populations. The 5-year age and sex distribution was frequency matched to that among the NPC cases by geographic region. Potential controls with outdated contact information or a history of working outside of the study area for more than 10 years, according to the local government in each town or community, were replaced. Between November 2010 and July 2014 in the Zhaoqing area, between September 2011 and November 2014 in the Wuzhou area, and between October 2011 and October 2014 in the Guiping/Pingnan area, a total of 3,202 controls were selected; of these persons, 2,648 (83%) consented to participate.

Data were misplaced for 1 case and 17 controls, and 6 controls were excluded because they were outside of the eligible age range when interviewed. After additional exclusion of 15 cases and 25 controls deemed by interviewers to have provided unreliable questionnaire data, 6 cases and 5 controls with missing data for active smoking, and 2 cases with missing data for passive smoking, we included 2,530 cases and 2,595 controls in the analysis.

This study was approved by institutional/ethics review boards at all participating research centers. All subjects granted written or oral informed consent to participate.

Data collection and classification

Information on known and potential risk factors for NPC was collected by trained interviewers who administered an electronic structured questionnaire. Although blinding to case-control status was not feasible, interviewers were trained to interact in the same manner with cases and controls. Each interviewer was assigned to approximately equal numbers of cases and controls. Questionnaire data were automatically flagged for logic errors and missing values; these were corrected by making comparisons against audio recordings or by recontacting participants.

Ever smoking tobacco was defined as ever having smoked the equivalent of at least 1 cigarette every 1–3 days for at least 6 months. To avoid reverse causation among cases, current smokers were defined as those who had smoked within the last 3 years, and former smokers were those who had quit at least 4 years before diagnosis. Among controls, reverse causation was not a concern; however, to allow for a lag period after cessation, we defined current smokers as those who had smoked within the last year before interview. Use of other cutoffs for current smoking versus former smoking among cases (e.g., 1 year or 5 years) did not appreciably change results. Cigarette equivalents were one-quarter of a cigar or 1 g of tobacco in a hand-rolled cigarette, water pipe, dry pipe, or other form of smoking tobacco. Because of the low frequency of smoking tobacco in forms other than cigarettes (among male controls, 1,218 (64%) had smoked cigarettes, 404 (21%) had smoked hand-rolled cigarettes, 9 (0.5%) had smoked water pipes, 3 (0.2%) had smoked dry pipes, none had smoked cigars, and 1 (0.05%) had smoked another form of tobacco), we combined all forms of tobacco for analysis. Smoking assessment is described in detail in the Web Appendix (available at http://aje.oxfordjournals.org/).

Statistical analysis

We used multivariate unconditional logistic regression models to estimate odds ratios and 95% confidence intervals for associations between active or passive smoking and risk of incident NPC. All multivariate models included the frequency-matching variables, age and residential area. Analyses of active smoking were stratified by sex due to the low prevalence of ever smoking among women, which permitted analyses only of ever smoking versus never smoking. Both sexes were included in the analysis of passive smoking because exposure

frequencies were more comparable between men and women. Analyses of passive smoking were restricted to never smokers to exclude residual confounding by active smoking, and results were additionally adjusted for sex.

Identification of potential confounders was based on prior knowledge or 10% changes in odds ratio estimates. Covariates included in additionally adjusted multivariate models were educational attainment, current housing type, current occupation, first-degree family history of NPC, current tea drinking, and consumption of salt-preserved fish in 2000–2002. Some analyses were additionally adjusted for history of chronic rhinitis, chronic pharyngitis, chronic otitis, nasal polyps, or septal abnormalities.

Tests for linear trend were conducted using continuous variables for active smoking (to facilitate quantitative interpretation across studies) and using the median within each categorical variable for passive smoking. Additional tests for trend were performed with log-transformed active smoking variables. We tested for modification of active smoking associations among male ever smokers by self-reported use of unfiltered cigarettes and deep inhalation (both of which have been shown to confer higher risk of smoking-associated cancers (1)) and for modification of passive smoking associations among never smokers by sex, using likelihood ratio tests for nested models with and without interaction terms.

Population attributable risks (i.e., the proportion of cases that would be prevented in the population if a cause were eliminated) adjusted for age and residential area (and sex, in the case of passive smoking) were calculated using the "AF" package in R (R Foundation for Statistical Computing, Vienna, Austria) (9). All other analyses were performed with SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina). All statistical tests were 2-sided, and a *P* value less than 0.05 was considered statistically significant.

RESULTS

Active smoking

Characteristics of the 2,530 cases with NPC and the 2,595 population-based controls, stratified by sex, are shown in Table 1. Only 13 female cases (1.9%) and 19 female controls (2.8%) reported ever having smoked at least 1 cigarette every 1–3 days for at least 6 months. After adjustment for age and geographic area, ever smoking was not significantly associated with NPC risk among women (OR = 0.77, 95% CI: 0.37, 1.58).

By contrast, among men, 75.1% of cases and 71.5% of controls were ever smokers (OR = 1.25, 95% CI: 1.08, 1.45). The risk of NPC was higher among current smokers compared with never smokers (OR = 1.32, 95% CI: 1.14, 1.53) but not among former smokers (OR = 0.92, 95% CI: 0.73, 1.17), adjusting for age and geographic area (Table 2). Additional adjustment for level of education, housing type, occupation, family history of NPC, tea drinking, and past consumption of salt-preserved fish did not substantially alter these or other associations with smoking (Table 2), nor did further adjustment for chronic ear, nose, and throat conditions (data not shown).

Earlier age at smoking initiation, greater daily smoking intensity, longer duration of smoking, and more cumulative pack-years of smoking were all significantly associated with increased NPC risk among men (Table 2). Significant exposure-response trends were detected between each of these measures of smoking exposure, whether classified as categorical or continuous variables, and risk of NPC. Results were similar after exclusion of former smokers (data not shown). NPC risk did not decline with greater time since smoking cessation.

Associations with current smoking, earlier initiation, and longer duration were stronger among persons who smoked only unfiltered cigarettes (mostly hand-rolled cigarettes) or both filtered and unfiltered cigarettes than among those who smoked only filtered cigarettes (Web Table 1). Stronger associations among persons who smoked both types of cigarettes, as well as the lack of an association in the highest category of cumulative pack-years among those who smoked only unfiltered cigarettes, may be explained by the lower number of cigarettes smoked daily by smokers of unfiltered cigarettes. Associations with active smoking also were generally stronger among persons who had ever engaged in deep inhalation than in those who had not, although differences were not statistically significant (Web Table 2).

When smoking intensity and duration were cross-classified, the highest risk of NPC was observed among men with the highest intensity (≥30 cigarettes/day) and the longest duration (≥30 years) of smoking (OR = 1.90, 95% CI: 1.30, 2.78), adjusting for age, geographic area, and time since smoking cessation (Table 3). NPC risk was not significantly increased among men who smoked for less than 20 years, regardless of smoking intensity. When age at smoking initiation and smoking duration were cross-classified, the highest risk of NPC was observed among men with the earliest age at initiation (<20 years) and the longest duration (≥30 years) of smoking (OR = 1.66, 95% CI: 1.34, 2.05) (Web Table 3). Neither characteristic appeared to be a stronger determinant of NPC risk than the other, but numbers were limited.

The stronger association of smoking duration than of intensity with NPC risk was confirmed in models that mutually adjusted for smoking characteristics classified as continuous variables, as well as age and geographic area (Web Table 4). In these models, smoking duration was significantly associated with NPC risk, as was time since smoking cessation, whereas smoking intensity was not. Likewise, age at initiation was significantly inversely associated with NPC risk, whereas smoking intensity was not after mutual adjustment. In a model including smoking duration, pack-years, and time since cessation, all 3 factors were significantly associated with NPC risk. After log-transformation of data on smoking intensity, pack-years, and time since cessation (but not duration, which was approximately normally distributed), none of the factors were significantly associated with NPC risk in models that mutually adjusted results for either duration or age at initiation, log-pack years or log-intensity, and log time since cessation (data not shown).

Based on the odds ratio for ever smoking and the prevalence of smoking among male controls, it appeared that eliminating smoking would prevent up to 16% (95% CI: 6, 26) of all male NPC cases in the study region.

Table 1. Characteristics of Nasopharyngeal Carcinoma Cases and Population-Based Controls, by Sex, Guangdong Province and Guangxi Autonomous Region, China, 2010–2014

Characteristic and Category	Cases ($n = 673$ Women, $n = 1,857$ Men)				Controls ($n = 688$ Women, $n = 1,907$ Men)				χ^2 *P* Value[a]	
	Women		Men		Women		Men			
	No.	%[b]	No.	%	No.	%	No.	%	Women	Men
Age group, years									0.36	0.03
20–29	34	5	52	3	33	5	48	3		
30–39	116	17	307	17	106	15	266	14		
40–49	259	38	650	35	254	37	634	33		
50–59	163	24	522	28	164	24	565	30		
60–74	101	15	326	18	131	19	394	21		
Geographic area of residence									0.86	0.29
Zhaoqing	345	51	938	51	360	52	960	50		
Wuzhou	184	27	504	27	179	26	485	25		
Guiping/Pingnan	144	21	415	22	149	22	462	24		
Educational level, years									0.14	0.03
≤6	406	60	599	32	380	55	551	29		
7–9	191	28	821	44	204	30	836	44		
10–12	53	8	353	19	72	10	411	22		
≥13	23	3	84	5	32	5	109	6		
Current housing type									<0.001	<0.001
Building (concrete structure)	473	70	1,347	73	571	83	1,447	76		
Cottage (clay brick structure)	199	30	501	27	117	17	457	24		
Boat	1	0.1	9	0.5	0	0	2	0.1		
Missing	0	0.0	0	0	0	0	1	0.1		
Current occupation									0.07	<0.001
Unemployed	52	8	26	1	67	10	29	2		
Farmer	316	47	537	29	332	48	651	34		
Blue-collar	178	26	844	45	142	21	758	40		
White-collar	72	11	278	15	92	13	324	17		
Other, unknown, or missing	55	8	172	9	55	8	145	8		
First-degree family history of nasopharyngeal carcinoma									<0.001	<0.001
No	587	87	1,619	87	654	95	1,827	96		
Yes	72	11	200	11	19	3	51	3		
Unknown	12	2	35	2	15	2	28	1		
Missing	2	0.3	3	0.2	0	0	1	0.1		
Current tea drinking									0.04	<0.001
Less than daily	575	85	1,041	56	560	81	953	50		
Daily	96	14	814	44	127	18	954	50		
Missing	2	0.3	2	0.1	1	0.1	0	0		
Salt-preserved fish consumption in 2000–2002									0.02	0.29
Yearly or less	506	75	1,351	73	520	76	1,382	72		
Monthly	118	18	365	20	141	20	401	21		
Weekly or more	49	7	139	7	27	4	122	6		
Missing	0	0	2	0.1	0	0	2	0.1		

[a] Missing values were excluded from χ^2 tests. Fisher's exact χ^2 test was used for current housing type.
[b] Some percentages may not sum to 100% because of rounding.

Table 2. Exposure Frequencies and Odds Ratios for Associations Between Active Smoking and Risk of Nasopharyngeal Carcinoma Among Men, Guangdong Province and Guangxi Autonomous Region, China, 2010–2014

Exposure and Category	No. of Cases	No. of Controls	Age- and Area-Adjusted[a]		Multivariate-Adjusted[b]	
			OR	95% CI	OR	95% CI
Smoking status						
Never smoker[c]	462	544	1.00	Referent	1.00	Referent
Former smoker	179	242	0.92	0.73, 1.17	0.92	0.72, 1.18
Current smoker	1,216	1,121	1.32	1.14, 1.53	1.34	1.15, 1.57
Age at smoking initiation, years						
<20	671	544	1.49	1.26, 1.77	1.49	1.25, 1.78
20–29	591	633	1.14	0.96, 1.35	1.17	0.98, 1.39
≥30	121	181	0.85	0.65, 1.11	0.90	0.68, 1.18
Per year (ever smokers)			0.97	0.96, 0.98	0.97	0.96, 0.98
No. of cigarettes smoked per day						
<10	345	357	1.24	1.01, 1.51	1.23	1.00, 1.52
10–19	372	392	1.15	0.95, 1.39	1.17	0.96, 1.42
20–29	507	479	1.27	1.07, 1.52	1.31	1.08, 1.57
≥30	158	130	1.49	1.15, 1.95	1.52	1.15, 2.01
Per 10 cigarettes (ever smokers)			1.09	1.03, 1.16	1.10	1.04, 1.17
Duration of smoking, years						
<10	100	99	1.05	0.77, 1.44	1.08	0.78, 1.49
10–19	227	257	0.95	0.76, 1.18	0.96	0.77, 1.21
20–29	434	393	1.31	1.09, 1.57	1.34	1.10, 1.63
≥30	622	609	1.47	1.22, 1.77	1.47	1.21, 1.79
Per 10 years (ever smokers)			1.11	1.06, 1.16	1.11	1.05, 1.16
Time since smoking cessation, years[d]						
4–9 (cases) or 2–9 (controls)	69	150	0.57	0.41, 0.77	0.54	0.39, 0.75
≥10	100	92	1.40	1.02, 1.92	1.44	1.04, 2.00
Pack-years of smoking						
<10	369	384	1.18	0.97, 1.42	1.18	0.97, 1.43
10–19	270	285	1.11	0.90, 1.36	1.13	0.91, 1.41
20–29	293	293	1.20	0.98, 1.47	1.23	0.99, 1.52
≥30	450	392	1.53	1.26, 1.85	1.55	1.27, 1.91
Per 10 pack-years (ever smokers)			1.08	1.04, 1.12	1.09	1.15, 1.13

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

[a] Adjusted for age and geographic area.

[b] Adjusted for age, geographic area, educational level, current housing type, current occupation, first-degree family history of nasopharyngeal carcinoma, tea drinking, and consumption of salt-preserved fish in 2000–2002.

[c] Never smokers were the reference group for all comparisons.

[d] Current smokers were included in the analysis as a separate category but are not shown here.

Passive smoking

Among controls who had never smoked, 58% of females and 54% of males were exposed to passive smoking at their residence during childhood, and 66% and 36%, respectively, were exposed during adulthood. Childhood residential passive smoking and adulthood passive smoking specifically from one's spouse were both significantly associated with increased NPC risk (Table 4). However, having a greater number of relatives who smoked in one's childhood or adulthood was not associated with progressively higher NPC risk, nor were significant associations detected with estimates of combined passive smoking intensity, longest duration, or cumulative exposure during childhood or adulthood, or with daily or total duration of passive smoking exposure at one's workplace (some data not shown).

After mutual adjustment, as well as adjustment for age, sex, and geographic area, residing with a smoker during childhood

Table 3. Odds Ratios[a] for Associations Between Cross-Classified Smoking Duration and Smoking Intensity and Risk of Nasopharyngeal Carcinoma Among Ever Smoking Men (With Never Smokers as the Referent), Guangdong Province and Guangxi Autonomous Region, China, 2010–2014

Duration of Smoking, years	No. of Cigarettes Smoked per Day									
	0[b]		<10		10–19		20–29		≥30	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
0[b]	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
<10			0.70	0.41, 1.19	0.83	0.49, 1.42	1.26	0.73, 2.17	0.73	0.19, 2.82
10–19			0.74	0.47, 1.16	0.72	0.51, 1.02	1.02	0.75, 1.40	1.19	0.63, 2.24
20–29			1.71	1.20, 2.44	1.27	0.95, 1.72	1.12	0.88, 1.43	1.24	0.83, 1.85
≥30			1.39	1.08, 1.79	1.39	1.06, 1.81	1.58	1.22, 2.04	1.90	1.30, 2.78

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Adjusted for age, geographic area, and time since smoking cessation.
[b] Never smokers were the reference group for all comparisons.

and residing with a smoking spouse during adulthood were both significantly associated with increased NPC risk among never smokers (Table 4). The odds ratio for residential passive smoking exposure during childhood did not differ statistically between women (OR = 1.14, 95% CI: 0.90, 1.45) and men (OR = 1.44, 95% CI: 1.08, 1.93; $P_{\text{homogeneity}} = 0.43$), although it was stronger for men. The odds ratio for having a spouse who smoked was significantly stronger for men (OR = 4.33, 95% CI: 1.18, 15.85) than for women (OR = 1.32, 95% CI: 1.03, 1.71; $P_{\text{homogeneity}} = 0.04$). Nevertheless, associations with passive smoking among women were similar to those observed among men and women combined (Web Table 5).

Based on the mutually adjusted odds ratios and the prevalence of passive smoking exposure among never-smoking controls, it appeared that eliminating passive smoking among children would prevent up to 12% (95% CI: 2, 22) of NPC cases and that eliminating passive smoking among adult spouses would prevent up to 8% (95% CI: 4, 15) of cases among never smokers in the study region.

DISCUSSION

Consistently with most prior studies, we detected a significant excess of NPC associated with active tobacco smoking. This association was limited to men, but the prevalence of ever smoking among women was so low that analyses in this group were not informative. The odds ratio of 1.25 for ever smoking versus never smoking among men in our study is consistent with the corresponding meta-odds ratios for high-prevalence regions (OR = 1.29), undifferentiated NPC (OR = 1.27), and high-quality studies (OR = 1.29) calculated by Xue et al. (3). The higher risk of NPC with current smoking than with former smoking in our study is also consistent with the findings of Xue et al., who found a slightly, albeit nonsignificantly, greater risk of NPC for current smoking (OR = 1.47, 95% CI: 1.22, 1.77) than for former smoking (OR = 1.27, 95% CI: 1.01, 1.60) (3). Our findings of positive exposure-response trends with increasing intensity, duration, and pack-years of smoking also are consistent with previous results, although the trend with increasing time since cessation is not.

The stronger associations with duration of smoking than with intensity or other aspects of smoking history accord with the epidemiologic evidence for lung cancer, for which risk is related to the square of intensity but the fourth or fifth power of duration (10). The stronger influence of duration also is coherent with biological principles, in that many constituents of tobacco smoke act as tumor promoters, for which greater risk is expected to accrue as a function of duration of exposure than of intensity of exposure (11). Independent associations with age at smoking initiation and duration of smoking were difficult to distinguish due to correlation; larger studies are needed to address this issue.

Compared with lung cancer, however, the relative risk of NPC associated with smoking is at least an order of magnitude weaker (1). The relatively modest magnitude of the association between smoking—even heavy, long-term smoking—and NPC risk suggests that the exposure of the nasopharynx (which is located behind the nose at the upper part of the throat) to tobacco smoke is less than that of the lower respiratory tract, or perhaps that the nasopharyngeal epithelium is less susceptible to the carcinogenic effects of tobacco smoke. Carcinogenic *N*-nitroso compounds, which are constituents of tobacco smoke, induce nasal cavity tumors in rodents (12) and are suspected of mediating the carcinogenic effect of Chinese-style salt-preserved fish on NPC (13). These observations suggest that the nasopharyngeal epithelium may not be less sensitive than other respiratory tract epithelial cells to tobacco carcinogens, and that the weaker association with tobacco smoking is probably instead due to reduced exposure.

In 6 previous case-control studies of childhood passive smoking and NPC risk, significant positive associations were detected in 4 studies (14–17) but not in 2 others (18, 19). Although we did not observe significant associations with childhood or adulthood passive smoking overall among never smokers, childhood residential passive smoking and adulthood passive smoking from a spouse were both significantly associated with NPC risk after mutual adjustment.

Table 4. Exposure Frequencies and Odds Ratios for Associations Between Passive Smoking and Risk of Nasopharyngeal Carcinoma Among Never Smoking Women and Men, Guangdong Province and Guangxi Autonomous Region, China, 2010–2014

Exposure and Category	No. of Cases	No. of Controls	Age, Sex, and Area-Adjusted[a]			Multivariate-Adjusted[b]			Passive Smoking-Adjusted[c]	
			OR	95% CI	P_{trend}	OR	95% CI	P_{trend}	OR	95% CI
Passive smoking at residence in childhood										
No[d]	432	526	1.00	Referent		1.00	Referent		1.00	Referent
Yes	690	687	1.18	1.00, 1.40		1.17	0.99, 1.40		1.24	1.03, 1.48
No. of relatives who smoked in childhood										
1	611	605	1.19	1.01, 1.42		1.19	1.00, 1.42			
≥2	79	82	1.10	0.79, 1.54	0.11	1.04	0.73, 1.48	0.18		
Relationship of smoking relative(s) in childhood to case										
Parent	641	636	1.19	1.00, 1.41		1.18	0.99, 1.41			
Sibling	73	77	1.14	0.81, 1.62		1.07	0.75, 1.54			
Other	28	27	1.19	0.69, 2.07		1.05	0.59, 1.88			
Total intensity of passive smoking in childhood, cigarettes/day										
<10	120	111	1.26	0.94, 1.68		1.28	0.95, 1.72			
10–19	198	218	1.08	0.86, 1.36		1.08	0.85, 1.37			
≥20	326	349	1.10	0.90, 1.35	0.42	1.08	0.87, 1.32	0.60		
Longest duration of passive smoking in childhood, years										
<10	30	27	1.31	0.77, 2.24		1.32	0.76, 2.28			
≥10	660	660	1.18	1.00, 1.40	0.07	1.17	0.98, 1.39	0.09		
Cumulative passive smoking in childhood, pack-years										
<10	278	291	1.12	0.91, 1.38		1.13	0.91, 1.40			
10–19	289	317	1.08	0.88, 1.33		1.08	0.87, 1.33			
≥20	77	70	1.30	0.91, 1.84	0.19	1.20	0.83, 1.72	0.34		
Passive smoking at residence in adulthood										
No[e]	505	578	1.00	Referent		1.00	Referent			
Yes	617	635	1.07	0.90, 1.28		1.06	0.88, 1.27			
No. of relatives who smoked in adulthood										
1	496	519	1.06	0.88, 1.27		1.04	0.87, 1.26			
≥2	121	116	1.15	0.86, 1.53	0.34	1.12	0.83, 1.51	0.46		
Relationship of smoking relative(s) in adulthood to case										
Spouse	376	323	1.45	1.14, 1.84		1.42	1.11, 1.82		1.30	1.03, 1.63
Parent	227	264	0.96	0.77, 1.19		0.96	0.77, 1.20			
Sibling	63	74	0.95	0.66, 1.36		0.99	0.68, 1.44			
Child	36	47	1.02	0.63, 1.64		1.00	0.61, 1.62			
Other	35	34	1.13	0.68, 1.88		1.02	0.60, 1.75		0.80	0.64, 1.00
Passive smoking in the workplace										
No	615	646	1.00	Referent		1.00	Referent			
Yes	507	567	0.96	0.81, 1.14		0.94	0.79, 1.12			

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

[a] Adjusted for sex, age, and geographic area.

[b] Adjusted for sex, age, geographic area, educational level, current housing type, current occupation, first-degree family history of nasopharyngeal carcinoma, tea drinking, and consumption of salt-preserved fish in 2000–2002.

[c] Adjusted for sex, age, geographic area, residential passive smoking during childhood, and residential passive smoking from a spouse during adulthood.

[d] Persons who had never been exposed to residential passive smoking in childhood were the reference group for all comparisons with childhood residential passive smoking exposure.

[e] Persons who had never been exposed to residential passive smoking in adulthood were the reference group for all comparisons with adulthood residential passive smoking exposure.

These results might suggest a stronger association with exposure to passive smoking from relatives with whom one spends more time, on average. However, we found no exposure-response trends with increasing number of smoking relatives or increasing intensity, duration, or cumulative amount of passive smoking. Among prior studies that examined passive smoking with respect to NPC risk, 1 found evidence of positive exposure-response trends (15), but 2 did not (17, 19).

The lack of a positive exposure-response trend with passive smoking could be interpreted as evidence against a causal effect. Alternatively, it could be explained by exposure misclassification based on inaccurate self-reported information. Exposure misclassification also may explain the unexpectedly lower risk of NPC among recent quitters. Alternatively, these findings may be due to chance. Although it is possible that some cases may have quit smoking due to prediagnosis symptoms, reverse causation is unlikely to fully explain our results, because we classified cases who had quit smoking within the past 3 years as current smokers. Uncontrolled confounding also probably does not explain the results, given the lack of evidence of strong confounding of associations with smoking, including by past otolaryngological conditions.

In general, the self-reported nature of the smoking information, combined with the retrospective study design, was the main limitation of this study. Other studies have shown that self-reported smoking status tends to underestimate smoking prevalence as ascertained on the basis of cotinine measurement (20), including among patients with head and neck cancers (21). In retrospective case-control studies, disease status can influence recollection and reporting of smoking history, as well as smoking behavior. Thus, the degree and even the direction of misclassification may have differed between cases and controls, leading to either overestimated or underestimated associations.

Another limitation is that at the time of this analysis, we lacked tumor tissue from a sufficient number of cases to stratify results by NPC histopathological subtype. Therefore, we could not examine whether associations with smoking differed between undifferentiated NPC and squamous cell NPC. However, the proportion of squamous cell NPC cases in southern China is generally only about 1% (4), and this would be expected to have little influence on the overall results.

The limitations of our study are counterbalanced by its noteworthy strengths, which include its large size, enrollment of histopathologically confirmed incident NPC cases, high participation rates, and population-based design. These features enabled statistically robust analyses of detailed exposures, minimal outcome misclassification, low potential for selection bias, and broad generalizability. The largest previous population-based case-control study of smoking and NPC (15) included about one-third as many cases ($n = 935$) and was based in an intermediate-risk region.

In conclusion, we found significant positive associations of active tobacco smoking (among men) and passive smoking (among men and women) with risk of NPC, with greater excess risk in concert with longer smoking duration and exposure to passive smoking in childhood or from a spouse. In recent years, declines in NPC incidence and/or mortality trends have been documented in Guangzhou (22) but not in other areas of southern China (23, 24). Small decrements in the prevalence of tobacco smoking (25) have probably played a minor role, if any, in these trends. Among the many public health and socioeconomic benefits that would accrue from reducing smoking in China, diminishing the burden of NPC, the signature "Canton tumor," would be another important advance.

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