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Childhood Passive Smoke Exposure is Associated With Adult Head and Neck Cancer

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Abstract

Introduction—Passive smoke is carcinogenic but its association with head and neck squamous cell carcinoma (HNSCC) is uncertain.

Methods—We conducted a case-control study of childhood passive smoke exposure (CPSE) and HNSCC in 858 cases and 806 frequency-matched controls using an interviewer-administered questionnaire. Odds ratios (OR) and 95% confidence intervals (CI) were estimated with logistic regression controlling for adult smoking in the total study population, and in never-smokers only (184 cases and 415 controls). CPSE was also studied in oropharyngeal separately from other HNSCC using polytomous logistic regression.

Results—CPSE was associated with HNSCC (OR, 1.28; 95% CI, 1.01-1.63) after controlling for adult smoking and other factors. This association was similar in magnitude, although not statistically significant, among subjects who never smoked as adults (OR, 1.19, 95% CI, 0.80-1.76). CPSE was associated more strongly with oropharyngeal cancer (a HNSCC subtype commonly associated with human papillomavirus (HPV) infection) than with HNSCC at non-oropharyngeal sites (OR, 2.02; 95% CI, 1.01-4.06, N=52 cases vs. OR, 1.04; 95% CI, 0.68-1.60, N=132 cases; P-for-heterogeneity=0.08).

Conclusions—Data from this large US-based case control study suggest a role for CPSE in HNSCC etiology.

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Conflict of Interest Statement
None of the authors have any conflict of interest to declare.

Keywords

adolescent; child; head and neck neoplasms; infant; oropharyngeal neoplasms; tobacco smoke pollution

Introduction

Head and neck squamous cell carcinomas (HNSCC) occur in the oral cavity, pharynx, and larynx,[1] and contribute substantially to the worldwide burden of cancer.[2] The majority of HNSCC are associated with tobacco and alcohol use.[1] However, declining smoking rates have revealed a newly-emerged epidemic of oropharyngeal tumors caused by human papillomavirus (HPV).[3-7] HPV-associated tumors are typically diagnosed in patients with little or no smoking history. However, most current patients were born when smoking was common and may have experienced childhood passive smoke exposure (CPSE).[4, 5]

Passive smoke is a human carcinogen[8] and exposure during adulthood is associated with increased risk of lung cancer in never-smokers.[9] CPSE has been associated with increased risk of adult bladder[10] and pancreas[11] cancers in never-smokers. However, little is currently known about CPSE and risk of adult HNSCC. Ramroth, et al.[12] observed no significant association between CPSE and laryngeal cancer after adjustment for smoking. One other study reported on risk of upper aerodigestive tract cancers associated with CPSE in never-smokers, but did not report results separately for HNSCC.[11]

We used data from a large US-based case-control study of HNSCC enrolling 858 cases (184 never-smokers) and 806 controls (415 never-smokers) to investigate the association between CPSE and HNSCC. CPSE and other risk factors for HNSCC were collected using an interviewer-administered questionnaire. We evaluated the association between CPSE and HNSCC after controlling for smoking status, and investigated CPSE separately in oropharyngeal and other HNSCCs among never-smokers. To our knowledge, ours is the first report of CPSE and HNSCC in a US population.

Methods

Study Population

Between August 4, 2004 and December 31, 2010, 907 HNSCC cases and 807 cancer-free controls were recruited from the University of Pittsburgh Medical Center otolaryngology clinics for a case-control study on the etiology of HNSCC. Cases were age 18-79 at diagnosis with pathologically verified HNSCC within 1 year of enrollment (primary tumors [excluding *in situ* cancer] of the lip, oral cavity, pharynx [including base of tongue, soft palate, and uvula], larynx, nasal cavity, and paranasal sinuses). Controls were patients age 18-80 seeking treatment for non-malignant conditions of the head and neck, and who were free of HNSCC by clinical exam. Controls were frequency-matched to cases on age (5-year intervals), sex, race, and month of enrollment. Participants completed an interviewer-administered questionnaire, collecting demographic and risk factor data, including history of CPSE. Written informed consent was obtained from all participants prior to enrollment and the study was approved by the University of Pittsburgh Institutional Review Board.

Eligibility for the Present Analysis

We selected cases from the parent study who were diagnosed with squamous cell carcinoma (SCC) of the oral cavity, pharynx, or larynx representing, to the best of our knowledge, the patient's first-ever HNSCC (history of cancer at other sites was allowed) and who provided

data on CPSE. Beginning with the 907 cases in the parent study, we excluded 9 lip, 6 nasal cavity/middle ear, 8 sinus tumors, 11 tumors with ill-defined/overlapping sites, 6 unknown primaries, and 2 cases of *in situ* disease. We also excluded 3 cases with missing CPSE data and 4 cases missing data on confounding factors included in our final logistic regression models. Therefore, we included 858 cases in our current analysis. We excluded only 1 control due to missing CPSE data, leaving 806 controls for analysis. Excluded cases did not differ from included cases with respect to age, sex, race, smoking, drinking, body mass index (BMI) one year before diagnosis, or CPSE ($P > 0.20$ for all).

Exposure Variables

Data on CPSE were obtained by asking participants Up until the age of 18 did your father, mother, or anyone else in your household smoke cigarettes? If the participant answered *Yes* then they were asked to indicate each household member who smoked (mother, father, sibling, or other), the number of years each household member smoked while the participant lived in the home, and how many cigarettes/day, on average, each household member smoked during the time the participant lived in the home. Using the participants' responses, we defined several variables measuring CPSE. First, we defined a dichotomous variable indicating ever-exposure to CPSE (yes/no). Next, we defined the following for exposed persons: father smoked, mother smoked, sibling(s) smoked, and other person(s) in the household smoked (yes/no for each), number of household smokers (continuous), years of CPSE (maximum duration of smoking among all household smokers, up to 18 years), number of cigarettes/day smoked by household members (sum of cigarettes/day for each household smoker), and pack-years of CPSE (product of cigarettes/day smoked in household [divided by 20] and years of CPSE). We also defined other variables to explore confounding and interaction using participants' responses to other questions: ever smoked (yes/no, where ever-smoking was defined as smoking at least one cigarette/day for six months or longer), ever drank alcohol (yes/no, where ever-drinking was defined as drinking at least one drink/month for one year or longer), BMI at reference (one year prior to diagnosis [for cases] or ascertainment [for controls]) (using World Health Organization (WHO) categories [kg/m^2]: underweight [<18.5], normal [18.5-24.9], overweight [25.0-29.9], and obese [>=30]), level of education (grade school, high school, vocational, or college), ever smoked cigars (yes/no, defined as smoking at least one cigar per week for six months or longer), ever smoked a pipe (yes/no, defined as smoking at least one pipe per day for six months or longer), ever used smokeless tobacco (yes/no, defined as using tobacco/chew/snuff at least once a day for three months or longer), personal history of any cancer (yes/no), and history of cancer in a first-degree relative (natural parents, brothers, sisters, or children) (yes/no). For smokers, we defined: maximum number of cigarettes smoked/day (continuous), duration of smoking (continuous), pack-years (continuous; product of maximum number of cigarettes/day and duration), and years since quitting (continuous). For drinkers, we defined: usual number of drinks/day (continuous). Variables representing the frequency-matched factors were defined as: age (continuous), sex (male, female), race (White, non-White/unknown), and recruitment period (early [2004,2005], middle [2006-2008], and late [2009,2010]). The use of these definitions produced similar results compared with using the 5-year age categories and month of enrollment used to match controls to cases during the recruitment process (data not shown). The frequency match yielded a difference in frequency of ~10% or less comparing cases and controls on all levels of each categorical matched factor.

Statistical Analysis

We began by identifying demographic and lifestyle factors associated with HNSCC by comparing cases and controls using logistic regression adjusted for the frequency-matched factors only. We also used univariable logistic regression to identify factors associated with CPSE in the control group (Supplementary Table 1). Factors associated (alpha=0.10) with

both HNSCC and CPSE in the controls were entered simultaneously into a base model that included the frequency matched factors, smoking status, drinking status, and CPSE. Next, we identified other important main effects by testing factors (one-at-a-time) known to be associated with HNSCC, or that might be associated with cancer risk in general. All significant (alpha=0.10) factors were entered into the model simultaneously. We then removed factors with the highest p-value (one at a time) until all remaining factors were part of our base model or were significant at alpha=0.05. No first-order interactions were observed between any of the remaining factors. The final model included the frequency matched factors, smoking status, drinking status, personal history of cancer, education, and CPSE (see above for variable definitions). The same covariates were used in polytomous logistic regression (generalized logit) models with a 3-level nominal response (oropharyngeal cancer, other HNSCC [oral cavity, other pharynx, or larynx], and controls). All models were run in the entire study population and in never-smokers only. We also estimated the association between CPSE and HNSCC in participants who reported both never-smoking and never-drinking. Adjustment for patterns of adult smoking (cigarettes/day, years smoked, and pack-years) and alcohol consumption (drinks/day) did not result in appreciable changes in the OR estimate for CPSE and were not included in our final model (data not shown).

Model fit was evaluated using the Hosmer-Lemeshow test. Delta-deviance plots and sensitivity analyses were used to verify there were no influential covariate patterns. Statistical significance was evaluated using the likelihood ratio chi-square test. Categorical variables were treated as indicators. Continuous variables were separated into quartiles or tertiles according to their distribution in the control group. Tests for trend in log-odds of HNSCC (interpreted as a trend in risk) were performed among participants with the factor of interest by entering a continuous variable into the model, or by treating ordinal variables as continuous. Formal tests of heterogeneity of odds ratios (ORs) in polytomous models were done using the Wald test. ORs from logistic regression models were interpreted as estimates of relative risk. Finally, comparison of risk factors by tumor site within the case series (oropharyngeal vs. other sites) was performed using Fisher's exact test.

Analyses were performed using SAS 9.2 (SAS Institute, Cary, NC).

Results

A total of 858 cases and 806 controls were included in this analysis. Table 1 shows comparisons between cases and controls, adjusted for the frequency-matched factors only. A total of 64% of controls had CPSE in our study. This is consistent with ever-smoking rates among US adults when considering the likely birth cohorts of our study participant's parents, and the time period when our study participants were exposed.[13] The frequency of CSPE in our case series was 73.8%. After control for frequency-matched factors, this translated to an estimated 60% increased risk of HNSCC associated with CPSE (OR, 1.60; 95% CI, 1.29-1.98). Ever-smoking, ever-drinking, use of smokeless tobacco, and personal history of cancer were also significantly associated with increased risk of HNSCC ($P < 0.05$ for all). Higher education and BMI were associated with reduced risk of HNSCC (P-trend < 0.0001 for both). No significant association was observed for ever use of pipes or cigars, and cancer in first-degree relatives ($P > 0.05$ for all). Differences between oropharyngeal and other cases were consistent with prior reports[7] (Supplementary Table 2).

Childhood passive smoke exposure and head and neck cancer after adjustment for smoking

CPSE was associated with a 28% increased risk of HNSCC after adjustment for adult smoking and other factors (OR, 1.28; 95% CI, 1.01-1.63) (Table 2). We did not observe any

trends in HNSCC risk with respect to years of CPSE, cigarettes/day smoked by household members, pack-years of CPSE, number of household smokers, or the presence of maternal, paternal, sibling, or other household smokers (P > 0.05 for all).

Childhood Passive Smoke Exposure in Never-smokers and Risk of Head and Neck Cancer

As shown in Table 3, CPSE was unrelated to HNSCC in never-smokers after multiple adjustment (OR, 1.19; 95% CI, 0.80-1.76). However, among exposed persons, having siblings who smoked was associated with increased risk of HNSCC (P=0.01), and risk of HNSCC increased with each additional household smoker (P=0.04). Years of CPSE, cigarettes/day smoked by household members, pack-years of CPSE, or smoking by the mother, father, or other household members were unrelated to HNSCC (P > 0.05 for all).

The association between CPSE and HNSCC was similar in male and female never-smokers, and we did not observe any difference in risk among never-smokers across age categories (data not shown). When restricting our analysis to participants who were both never-smokers and never-drinkers, the association between CPSE and HNSCC was elevated, although still non-significant (OR, 1.32; 95% CI, 0.71-2.43; N=75 cases, and N=157 controls; data not shown).

Polytomous logistic regression in never-smokers (Table 4) showed CPSE was associated with oropharynx (OR, 2.02; 95% CI, 1.01-4.06) but not other HNSCCs (OR, 1.04; 95% CI, 0.68-1.60), although this difference was not significant (P-for-heterogeneity=0.08). However, we noted increasing risk of oropharynx cancer with an increasing number of cigarettes/day smoked by household members (P=0.01), with >20 cigarettes/day associated with substantially higher risk than <= 20 cigarettes/day (OR, 3.78; 95% CI, 1.40-10.22). We noted a similar result for pack-years of CPSE. Risk of oropharynx cancer also increased with the number of household smokers (P=0.01). The presence of two or more smokers was associated with twice the risk of oropharynx cancer vs. one household smoker (OR, 2.15; 95% CI, 1.03-4.46). Duration of CPSE, and having a mother, father, sibling, or other household members who smoked were unrelated to oropharynx cancer (P > 0.05 for all). With the exception of having siblings who smoked (OR, 3.99; 95% CI, 1.42-11.22), risk of HNSCC risks at sites other than the oropharynx was independent of CPSE.

Discussion

In this large, single-institution case-control study, CPSE was associated with increased risk of adult HNSCC after adjustment for multiple factors, including adult smoking. In addition, our data are suggestive of an association between CPSE and oropharynx cancer in never-smokers.

We identified only two prior studies of CPSE and HNSCC. The first was a case-control study showing no association between CPSE and larynx cancer after adjustment for smoking.[12] This result is consistent with our observation that CPSE is not a strong risk factor for non-oropharyngeal HNSCC. The second study was a prospective cohort study of upper aerodigestive tract (UADT) cancers (tumors at several sites, including HNSCC) in never-smokers.[11] Although no association was reported between CPSE and UADT cancers, it is difficult to interpret these results for HNSCC alone.[11] Evidence for carcinogenicity of CPSE at other anatomical sites in adulthood is mixed. CPSE does not appear to be a strong risk factor for adult lung cancer[9] and reports of CPSE and breast cancer are inconsistent.[14] However, CPSE has been associated with increased risk of adult bladder[10] and pancreas cancer,[11] and nasopharyngeal carcinoma.[15, 16]

Our results for CPSE and HNSCC are bolstered by certain strengths. We noted a strong and statistically significant association for cancer at a specific anatomical site (the oropharynx) in never-smokers. In addition, we noted trends in risk wherein various patterns of CPSE were associated with oropharynx cancer but not other HNSCCs in never-smokers. Using our interviewer-administered questionnaire, we were able to explore confounding and interaction with a variety of other lifestyle factors related to HNSCC or cancer in general.

Passive smoke consists of sidestream smoke (emitted from the cigarette) and mainstream smoke (exhaled by the smoker) and contains at least fifty carcinogens, including polycyclic aromatic hydrocarbons (PAH) and N-nitrosamines, which are found in the bloodstream of non-smokers exposed to passive smoke.[9] The US Surgeon General has concluded there is a causal relationship between passive smoke exposure during adulthood and lung cancer in never-smokers.[9] Cigarette smoking causes cancer through a variety of mechanisms, including formation of DNA adducts, disruption of DNA repair and cell cycle control, and activation of cytoplasmic signaling networks relevant to cell growth and proliferation.[17] The carcinogenic mechanisms of passive smoke exposure are likely similar.[9] However, our observation of increased risk of oropharyngeal cancer in never-smokers is interesting given the high frequency of HPV detection in these tumors.[7] While oral[18-21] and oropharyngeal[20, 22] HPV infection is detectable in children, these infections are transient[23] and unrelated to parental smoking.[18, 19] Therefore, it seems unlikely that childhood HPV infection and interaction with CPSE promote adult HNSCC. However, it is possible that long-term effects of CPSE on the immune system may increase susceptibility to, or facilitate persistence of, HPV later in life. Indeed, at least one lasting immunological consequence of CPSE is known: asthma.[24] Another possible explanation is that CPSE may promote HNSCC through induction of genetic changes in oropharyngeal epithelium during childhood, and this may be unrelated to HPV.[25]

Our study has several limitations. First, we were unable to obtain an adequate sample of tumors to study the association between HPV and CPSE in oropharyngeal cases due to the time period during which our cases were diagnosed, which pre-dates the routine practice of HPV testing and reflects a paucity of archival tissue (data not shown). Nonetheless, we view our results as informative for public health prevention and future study of disease mechanisms. We also asked participants to recall exposures that happened several decades in the past. Therefore, it is possible that recall was different in cases and controls, particularly in never-smokers who might place blame on others for their diagnosis with a typically smoking-related illness. However, the specificity of our findings within the never-smoking subgroup, i.e., increased risk of oropharynx cancer and not other HNSCCs, argues against the presence of recall bias. If such bias were present, we might expect it to affect our risk estimates for HNSCC at all anatomic sites.

Our study used clinic controls. If the controls' disease were associated with CPSE, this could also bias our results.[26] However, our controls had a variety of non-malignant conditions of the head and neck not known to be related to CPSE (data not shown). In addition, the higher frequency of college education among controls compared with cases in our study is noteworthy as adult smoking is inversely associated with education.[27] Therefore, one might suspect a systematically lower probability of CPSE in the control group if controls were also more likely to have spent their childhood in homes with college-educated adults. However, we expect this is unlikely because adult smoking rates were more similar across strata of education during the time when our study participants had CPSE as compared to contemporary society.[13]

Because of practical considerations, our risk factor questionnaire could include only a limited number of items about historical passive smoke exposures. Therefore, we were not

able to explore all potentially interesting aspects of CPSE. For example, our observation that sibling smoking was associated with increased risk of HNSCC in never-smokers was based on a small number of cases, and we were unable to investigate effects of birth order. However, we did observe an increasing risk of HNSCC in never-smokers associated with an increasing number of household smokers. This suggests that cumulative exposure, regardless of the source, may influence HNSCC risk. Finally, while the reliability and validity of self-reported CPSE has been demonstrated using standardized questionnaires, self-reported details of the extent of exposure may be less reliable.[28] Therefore, caution is warranted in interpretation of our results regarding patterns of exposure among the exposed.

Residual confounding is also possible. In particular, we did not have data on adult passive smoke exposure (APSE), although evidence linking APSE and HNSCC is mixed. A US case-control study of never-smokers observed an association between APSE in the home and the workplace and cancer of the oral cavity, pharynx, larynx, and sinus.[29] However, APSE was not related to cancer of the oral cavity, pharynx, larynx, sinus, lip, salivary glands, and esophagus among never-smokers in another US study.[30] Furthermore, there was no association between lifetime passive smoke exposure and larynx cancer in German never-smokers.[12] However, a pooled analysis of case-control studies showed increased risk of laryngeal and pharyngeal cancer associated with more than fifteen years of APSE in the home, and that laryngeal cancer was associated with the same duration of workplace APSE, among never-smokers.[31] In contrast, more than fifteen years of APSE—whether at work or at home--was not associated with laryngeal and hypopharyngeal cancer (combined) in a multicenter case-control study, but more than fifteen years of workplace APSE was associated with oral and oropharyngeal cancer (combined).[32] Finally, a prospective study observed no association between APSE at home or in the workplace and respiratory disease (including pharyngeal, laryngeal, and lung cancers, and chronic obstructive pulmonary disease) among never smokers.[33]

In summary, our results support an etiologic role for CPSE in HNSCC. In particular, CPSE may be associated with oropharynx cancer in never-smokers. The biological mechanism through which this occurs is uncertain and may involve direct effects of carcinogens in passive smoke, or possibly disruptions in immunological development effecting response to HPV infection later in life. Studies of CPSE and tumor HPV status in never-smoking oropharyngeal cases may improve understanding of this mechanism, although pooled studies may be required to achieve adequate sample size. Finally, despite declining smoking rates, [4] children in the US continue to suffer ill effects of passive smoke exposure.[34] Our data suggest that these effects include an increased risk of adult HNSCC, thus adding further support for public policy restricting the opportunity for CPSE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Analysis of Factors Associated With Head and Neck Cancer, Adjusted for Frequency Matched Factors Only

	Cases (N=858)	Controls (N=806)		
	n(%)[1]	n(%)[1]	OR[2]	CI[2]
Age				
<50	153 (17.8)	169 (21.0)		
50-59	276 (32.2)	285 (35.4)		
60-69	277 (32.3)	228 (28.3)		
>=70	152 (17.7)	124 (15.4)		
Sex				
Male	628 (73.2)	503 (62.4)		
Female	230 (26.8)	303 (37.6)		
Race				
White	817 (95.2)	768 (95.3)		
Non-White/Unknown[3]	41 (4.8)	38 (4.7)		
Recruitment Period				
Early (2004-2005)	137 (16.0)	143 (17.7)		
Middle (2006-2008)	419 (48.8)	466 (57.8)		
Late (2009-2010)	302 (35.2)	197 (24.4)		
Childhood Passive Smoke				
No	225 (26.2)	290 (36.0)	1.00	Referent
Yes	633 (73.8)	516 (64.0)	1.60	1.29, 1.98
Ever Smoked				
No	184 (21.4)	415 (51.5)	1.00	Referent
Yes	674 (78.6)	391 (48.5)	3.63	2.92, 4.52
Ever Drank Alcohol				
No	158 (18.4)	238 (29.5)	1.00	Referent
Yes	700 (81.6)	568 (70.5)	1.70	1.33, 2.18
BMI 1 year pre-diagnosis				
<18.5	20 (2.3)	5 (0.6)	3.78	1.37, 10.41
18.5-24.9	268 (31.4)	210 (26.1)	1.00	Referent
25.0-29.9	291 (34.1)	314 (39.0)	0.64	0.50, 0.82
>=30	275 (32.2)	277 (34.4)	0.72	0.56, 0.92
Highest Level of Education				
Grade school	39 (4.5)	3 (0.4)	5.63	1.71, 18.49
High school	531 (61.9)	245 (30.4)	1.00	Referent
Vocational	48 (5.6)	52 (6.5)	0.48	0.31, 0.73
College	240 (28.0)	506 (62.8)	0.22	0.17, 0.27
Ever Smoked Cigars				
No	771 (89.9)	752 (93.3)	1.00	Referent

	Cases (N=858)	Controls (N=806)		
	n(%)[1]	n(%)[1]	OR[2]	CI[2]
Yes	87 (10.1)	54 (6.7)	1.30	0.90, 1.88
Ever Used Smokeless Tobacco				
No	739 (86.1)	737 (91.4)	1.00	Referent
Yes	119 (13.9)	69 (8.6)	1.52	1.10, 2.11
Ever Smoked Pipe				
No	801 (93.4)	758 (94.0)	1.00	Referent
Yes	57 (6.6)	48 (6.0)	0.82	0.54, 1.24
Personal History of Cancer				
No	703 (81.9)	726 (90.1)	1.00	Referent
Yes	155 (18.1)	80 (9.9)	1.90	1.41, 2.57
First-Degree Relative Had Cancer				
No	320 (37.6)	320 (40.1)	1.00	Referent
Yes	532 (62.4)	478 (59.9)	1.05	0.86, 1.29

OR=odds ratio; CI=confidence interval.

[1] Number may not sum to total due to missing values for some variables.

[2] Odds ratios and 95% confidence intervals were calculated using logistic regression models adjusted for the frequency matched factors (age, sex, race, and recruitment period). Estimates are not shown for the frequency matched factors.

[3] Non-White participants included 69 African Americans (36 cases, 33 controls), 6 Asians (3 cases, 3 controls), 1 American Indian/Eskimo control, 2 Other races (1 case, 1 control), and 1 case who did not report a race.

Table 2

Results of Logistic Regression: Childhood Passive Smoke Exposure as a Risk Factor for Head and Neck Cancer Among All Subjects, Adjusted for Smoking

	Cases (N=858)[1]	Controls (N=806)			
	n (%)[2]	n (%)[2]	OR[3]	95% CI[3]	P-Value[4]
Childhood Passive Smoke					0.04
No	225 (26.2)	290 (36.0)	1.00	Referent	
Yes	633 (73.8)	516 (64.0)	1.28	1.01, 1.63	
Years Exposed					0.38
<18	110 (17.5)	126 (24.6)	1.00	Referent	
18	519 (82.5)	386 (75.4)	1.17	0.84, 1.62	
Cigarettes/Day					0.80
<=10	72 (13.1)	69 (14.9)	1.00	Referent	
11-20	147 (26.8)	135 (29.2)	0.86	0.54, 1.38	
21-40	187 (34.1)	148 (32.0)	0.97	0.61, 1.52	
>40	142 (25.9)	110 (23.8)	0.96	0.60, 1.55	
Pack-Years					0.82
<=15	109 (20.0)	113 (24.6)	1.00	Referent	
>15-25	132 (24.2)	107 (23.3)	0.96	0.63, 1.47	
>25-40	169 (31.0)	137 (29.8)	0.99	0.66, 1.47	
>40	136 (24.9)	103 (22.4)	1.02	0.67, 1.56	
Number of Household Smokers					0.84
1	356 (56.3)	307 (59.5)	1.00	Referent	
2	235 (37.2)	188 (36.4)	0.97	0.73, 1.28	
>=3	41 (6.5)	21 (4.1)	1.13	0.61, 2.09	
Mother Smoked					0.47
No	314 (49.7)	249 (48.3)	1.00	Referent	
Yes	318 (50.3)	267 (51.7)	0.90	0.69, 1.19	
Father Smoked					0.53
No	103 (16.3)	103 (20.0)	1.00	Referent	

	Cases (N=858)[1]	Controls (N=806)			
	n (%)[2]	n (%)[2]	OR[3]	95% CI[3]	P-Value[4]
Yes	529 (83.7)	413 (80.0)	1.12	0.79, 1.59	
Sibling(s) Smoked					0.55
No	579 (91.6)	487 (94.4)	1.00	Referent	
Yes	53 (8.4)	29 (5.6)	1.18	0.69, 2.01	
Other Household Members Smoked					0.70
No	610 (96.5)	493 (95.5)	1.00	Referent	
Yes	22 (3.5)	23 (4.5)	0.88	0.44, 1.73	

[1] 4 cases (2 oropharynx, 1 oral cavity, and 1 larynx) were dropped from this analysis due to missing data on drinking status or education.

[2] Numbers may not sum to total due to missing values for some variables.

[3] Odds ratios and 95% confidence intervals are adjusted for age, sex, race, recruitment period, drinking status, smoking status, personal history of cancer, and education. No statistically significant interactions were observed between any of these factors and therefore the final models included main effects only.

[4] P-values represent likelihood ratio Chi-square tests of variables representing a 1-unit change in the factor of interest (for continuous data), indicator variables (for 2-level nominal data), and ordinal categories (for multi-level ordered categories).

Table 3

Results of Logistic Regression: Childhood Passive Smoke Exposure as a Risk Factor for Head and Neck Cancer in Never-Smokers

	Cases (N=184)	Controls (N=415)			
	n (%)[1]	n (%)[1]	OR[2]	95% CI[2]	P-Value[3]
Childhood Passive Smoke					0.38
No	64 (34.8)	165 (39.8)	1.00	Referent	
Yes	120 (65.2)	250 (60.2)	1.19	0.80, 1.76	
Years Exposed					0.74
<18	30 (25.4)	74 (30.0)	1.00	Referent	
18	88 (74.6)	173 (70.0)	1.21	0.69, 2.11	
Cigarettes/Day					0.25
<=10	18 (18.2)	41 (18.6)	1.00	Referent	
11-20	20 (20.2)	65 (29.4)	0.62	0.28, 1.41	
21-40	37 (37.4)	63 (28.5)	1.29	0.60, 2.75	
>40	24 (24.2)	52 (23.5)	1.07	0.48, 2.40	
Pack-Years					0.24
<=15	26 (26.5)	65 (29.5)	1.00	Referent	
>15-25	16 (16.3)	47 (21.4)	0.65	0.29, 1.45	
>25-40	33 (33.7)	59 (26.8)	1.26	0.63, 2.51	
>40	23 (23.5)	49 (22.3)	1.14	0.55, 2.39	
Number of Household Smokers					0.04
1	70 (58.8)	163 (65.2)	1.00	Referent	
2	40 (33.6)	83 (33.2)	1.06	0.63, 1.78	
>=3	9 (7.6)	4 (1.6)	6.76	1.82, 25.06	
Mother Smoked					0.54
No	57 (47.9)	129 (51.6)	1.00	Referent	
Yes	62 (52.1)	121 (48.4)	1.17	0.72, 1.90	
Father Smoked					0.84
No	24 (20.2)	56 (22.4)	1.00	Referent	
Yes	95 (79.8)	194 (77.6)	1.06	0.58, 1.96	

	Cases (N=184)	Controls (N=415)			
	n (%)[1]	n (%)[1]	OR[2]	95% CI[2]	P-Value[3]
Sibling(s) Smoked					0.01
No	108 (90.8)	241 (96.4)	1.00	Referent	
Yes	11 (9.2)	9 (3.6)	3.46	1.28, 9.39	
Other Household Members Smoked					0.66
No	114 (95.8)	237 (94.8)	1.00	Referent	
Yes	5 (4.2)	13 (5.2)	0.77	0.24, 2.50	

[1] Numbers may not sum to total due to missing values for some variables.

[2] Odds ratios and 95% confidence intervals are adjusted for age, sex, race, recruitment period, drinking status, personal history of cancer, and education. No statistically significant interactions were observed between any of these factors and therefore the final models included main effects only.

[3] P-values represent likelihood ratio Chi-square tests of variables representing a 1-unit change in the factor of interest (for continuous data), indicator variables (for 2-level nominal data), and ordinal categories (for multi-level ordered categories).

Table 4

Results of Polytomous Logistic Regression: Childhood Passive Smoke Exposure as a Risk Factor for Oropharyngeal and Other Head and Neck Cancers in Never-Smokers

	Controls N=(415)	Oropharyngeal Case (N=52)				Other Case (N=132)[1]			
	n (%)	n (%)	OR[2]	95% CI[2]	P-Value[3]	n (%)	OR[2]	95% CI[2]	P-Value[3]
Childhood Passive Smoke					0.05				0.84
No	165 (39.8)	13 (25.0)	1.00	Referent		51 (38.6)	1.00	Referent	
Yes	250 (60.2)	39 (75.0)	2.024	1.01, 4.06		81 (61.4)	1.044	0.68, 1.60	
Years Exposed					0.99				0.72
<18	74 (30.0)	10 (25.6)	1.00	Referent		20 (25.3)	1.00	Referent	
18	173 (70.0)	29 (74.4)	1.39	0.60, 3.24		59 (74.7)	1.16	0.62, 2.16	
Cigarettes/Day					0.01				0.78
<=20	106 (48.0)	6 (20.0)	1.00	Referent		32 (46.4)	1.00	Referent	
>20	115 (52.0)	24 (80.0)	3.78	1.40, 10.22		37 (53.6)	1.15	0.64, 2.08	
Pack Years					0.01				0.79
<=20	111 (50.5)	7 (23.3)	1.00	Referent		31 (45.6)	1.00	Referent	
>20	109 (49.5)	23 (76.7)	3.62	1.40, 9.36		37 (54.4)	1.33	0.74, 2.41	
Number of Household Smokers					0.01				0.28
1	163 (65.2)	18 (46.2)	1.00	Referent		52 (65.0)	1.00	Referent	
>=2	87 (34.8)	21 (53.8)	2.15	1.03, 4.46		28 (35.0)	1.03	0.59, 1.80	
Mother Smoked					0.12				0.76
No	129 (51.6)	13 (33.3)	1.00	Referent		44 (55.0)	1.00	Referent	
Yes	121 (48.4)	26 (66.7)	1.86	0.86, 4.03		36 (45.0)	0.92	0.53, 1.58	
Father Smoked					0.32				0.86
No	56 (22.4)	7 (17.9)	1.00	Referent		17 (21.3)	1.00	Referent	
Yes	194 (77.6)	32 (82.1)	1.64	0.62, 4.34		63 (78.8)	0.94	0.48, 1.85	
Sibling Smoked					0.53				0.01
No	241 (96.4)	37 (94.9)	1.00	Referent		71 (88.8)	1.00	Referent	
Yes	9 (3.6)	2 (5.1)	1.71	0.32, 9.12		9 (11.3)	3.99	1.42, 11.22	
Other Smoked					0.50				0.99

	Controls N=(415)	Oropharyngeal Case (N=52)				Other Case (N=132)[1]			
	n (%)	n (%)	OR[2]	95% CI[2]	P-Value[3]	n (%)	OR[2]	95% CI[2]	P-Value[3]
No	237 (94.8)	38 (97.4)	1.00	Referent		76 (95.0)	1.00	Referent	
Yes	13 (5.2)	1 (2.6)	0.47	0.05, 4.22		4 (5.0)	1.01	0.29, 3.46	

OR=odds ratio; CI=confidence interval

[1]Other Cases include squamous cell cancers of the oral cavity, hypopharynx, nasopharynx, and larynx.

[2]Odds ratios and 95% confidence intervals are adjusted for age, sex, race, recruitment period, drinking status, personal history of cancer, and education (high school or less vs beyond high school). No statistically significant interactions were observed between any of these factors and therefore the final models included main effects only.

[3]Wald P-value for the model parameter predicting the log-odds of oropharynx (or other HNSCC) obtained by entering a continuous variable, representing a 1-unit change, into the polytomous model.

[4]P-for-heterogeneity=0.08 comparing odds ratios for oropharyngeal and other cases.