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Allergies and risk of head and neck cancer

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Abstract

Background—Individuals with allergies have a heightened Th2 (T helper 2) immunity which may provide advantages in controlling tumor growth. Inverse associations have been reported among individuals with allergies and risk of brain and pancreatic cancers.

Methods—We examined the relationship between allergies and risk of head and neck squamous cell carcinoma (HNSCC) in a population-based case-control study with 1014 cases and 1193 frequency-matched controls. Logistic regression models were used to estimate odds ratio (OR) and 95% confidence intervals (95% CI) controlling for age, sex, race, smoking history, alcohol consumption, and education. In addition, in a subset of the population, models were adjusted for HPV16 status.

Results—Individuals with allergies had a 19% lower risk of HNSCC (OR = 0.81, 95% CI = 0.67-0.98). Associations with allergies were stronger for laryngeal (OR = 0.66, 95% CI = 0.45-0.97) and oropharyngeal (OR =0.73, 95% CI=0.57-0.92) cancers, while no association was observed for oral cavity cancers (OR = 0.98, 95% CI = 0.76-1.26). History of asthma was not associated with overall HNSCC, but the association was statistically significant for oropharyngeal cancer (OR = 0.67, 95% CI = 0.44-0.99). HPV16 status did not confound or modify the associations with allergies.

Conclusions—Elevated Th2 immunity in individuals with history of allergies and asthma may reduce the risk of HNSCC. Additional research into related mechanisms may provide new insights into how to treat HNSCC.

Impact—These findings may provide new insight into biological pathways that could lead to a better understanding of the etiology of this disease.

Keywords

allergies; atopy; head and neck cancer

Introduction

A growing number of epidemiological studies support the hypothesis that individuals with allergies have a lower risk of cancer. The most consistent inverse associations have been observed for brain tumors [1], pancreatic cancer [2], and childhood leukemia [3]; results for other cancer sites are less consistent or data are sparse [4, 5]. Two case-control studies observed greater than 50% reductions in cancer risk of the oral cavity and pharynx, and of the larynx, among individuals who reported a history of allergies [6], or among men who reported a history of hay fever or other allergies[7]. Furthermore, lower risk of cancer of the lip and pharynx [8], and of the larynx [9], were observed in cohorts of asthmatic patients compared with the national population.

Individuals with allergies may have an enhanced immune-surveillance through heightened Th2 immunity which may assist in tumor cell recognition and destruction through antibody-dependent cellular cytotoxicity [10]. The exact mechanisms, however, are not clear and the role of immunoglobulin E (IgE), as recently studied in relation to risk of glioma [11, 12], is complex.

The importance of human papillomavirus type 16 (HPV16) in head and neck cancer has been clarified in the past decade and highlights the critical role of the immune system in relation to risk. Over 52,000 individuals are diagnosed annually with head and neck cancer in the US [13]. While approximately 75% of these cancers could be prevented by eliminating exposure to smoking and alcohol, understanding other risk factors could provide new clues to mechanisms which may lead to improved treatment options.

Using self-reported history of allergy in a large US population-based case control study, we sought to further clarify the role of allergies in head and neck cancer. Unlike previous studies, we were able to adjust for HPV16 status and reported allergy prevalence similar to those observed in the general population. Additionally, we assessed whether the association is modified by HPV16 status, tumor site or smoking.

Materials and Methods

Study population

Incident cases of head and neck squamous cell carcinoma (HNSCC) were identified and recruited from head and neck clinics and departments of otolaryngology or radiation oncology at 9 medical facilities in the Greater Boston metropolitan area. Our method identified 99% of the cases in the catchment area (confirmed using state cancer registry). Patients with a confirmed incident diagnosis of HNSCC were included if they were residents in the study area and 18 years or older. Recurrent cases and incident cases diagnosed more than 6 months prior to contact were excluded. HNSCC cases consist of those with a diagnosis code of 141-146, 148, 149, or 161 based on the International Classification of Disease, Ninth Revision (ICD-9). Controls were randomly selected from the same population and frequency-matched to cases by sex, age (+/− 3 yrs), and town of residence using the Massachusetts town lists. The study population for this analysis includes data collected from two periods of recruitment from the same population; the first period was between December 1999 and December 2003 (Phase I) and the second was between October 2006 and June 2011 (Phase II). Participation rates for cases and controls were 78% and 47%, respectively. A total of 1056 cases and 1252 controls were available for this analysis after combining both phases of the study.

All cases and controls enrolled in the study provided written informed consent as approved by the Institutional Review Boards of the participating institutions.

Exposure data

Cases and controls responded to a self-administered questionnaire to collect data on demographic characteristics, medical history, family history of cancer, detailed smoking and drinking habits, occupational history, and residential history. Frequency of alcoholic beverage consumption measured in drinks (where 1 drink = 5 oz wine, 12 oz beer, 1.5 oz liquor) was combined to provide a total alcohol variable. Questions on ever history of allergies and asthma were included in the medical history section. Subjects who responded ever having had allergies were asked to write-in what type of allergies they had (all but six subjects with allergies completed this section). Questionnaires were provided to cases during their initial clinic visit and were mailed to controls, and were returned and reviewed by study personnel during the second visit for cases and first in-person visit for controls. Visits were typically conducted at home or at the workplace (depending on their preference), and controls received $75 as compensation for their time.

Blood specimens were collected from 81% of cases and 80% of controls to measure human papillomavirus type 16 (HPV-16) seropositivity (data only available for Phase I; 414 cases and 529 controls with HPV and questionnaire data). Serum from venous blood was separated within 12-24 hr of blood drawing and stored at −80°C. To detect antibodies against HPV type 16 L1, E6 and E7 proteins, a glutathione S-transferase capture enzyme-linked immunosorbent assay was used in combination with fluorescent bead technology [14-18].

Statistical Analysis

After excluding 86 participants with missing data on allergies, a total of 1021 cases and 1201 controls were available for this analysis. An additional 15 participants were missing data on asthma and were removed for the analyses for asthma. Case and control differences across baseline characteristics were assessed using t-test for categorical variables and ANOVA for continuous variables. Odds ratios (OR) and 95% confidence intervals (CIs) were estimated for history of allergies or asthma compared to no history of these conditions using unconditional logistic regression and controlling for known risk factors, including age, sex, race (white or other), smoking (pack-years as a continuous variable), smoking status (ever/never), average alcohol drinks per week (continuous), education (less/high school graduate or more) and study phase (I/II). We applied multiple imputation methods using age and sex to assign values to missing values for alcohol (7 missing), race (5 missing) and education (56 missing); using multiple imputation results in less biased findings when dealing with missing covariate data [19]. Additional control for body mass index (BMI) or income (below/above $50K per year), or including an interaction term for alcohol and smoking, did not change the observed associations with allergies or asthma and were left out of the final model. We conducted analyses to examine potential confounding and effect modification by HPV16 status on Phase I participants (as HPV status not available for Phase II participants).

In addition, we examined the association between allergies and HNSCC risk by tumor site (oral cavity, oropharynx, larynx) assigned according to the American Joint Committee on Cancer (AJCC) classification guidelines [20]. Oral cavity tumors corresponded to ICD-9 codes 143, 144, 145, and, if located at the anterior of the tongue, 141; pharyngeal tumors corresponded to ICD-9 codes 146, 148, 149, and if at the base of the tongue, 141; and laryngeal tumors corresponded to ICD-9 code 161. Potential modification by sex, smoking, alcohol and education was examined in stratified analyses and tests for interaction were conducted using cross-product terms in the logistic regression models.

All analyses were conducted in R (Version 2.14) and all tests were two-sided. Multiple imputation was carried out using the R package mi [21].

Results

The distributions of known risk factors of HNSCC are shown in Table 1 by case-control status. As expected, smoking, alcohol consumption and HPV16 seropositivity were higher among cases than controls. Controls were more educated than cases. The mean age was 60 years, approximately two-thirds of subjects were males and most subjects were white.

The prevalence of self-reported history of allergy and asthma among controls was 40% (473/1193) and 10% (121/1193), respectively. We observed a statistically significant inverse association between allergies and risk of HNSCC in this study population (OR = 0.81, 95% CI = 0.67-0.98, p=0.02; Table 2). The association with history of asthma and risk of HNSCC was weaker and not statistically significant, but in the same direction (OR = 0.89, 95% CI = 0.66-1.22, p = 0.47; Table 2). In addition, we examined associations with different types of allergies, but observed no significant difference by type (e.g., compared to no allergies: OR for food allergies = 0.71, 95% CI = 0.48 - 1.04, and OR for non-food allergies = 0.84, 95% CI = 0.69 - 1.03).

Inverse associations were observed for history of allergy and asthma with oropharyngeal and laryngeal cancers; no relations were apparent for oral cavity cancers (Table 2). Comparing a history of allergy and/or asthma with those who had neither, the association with cancer risk was similar (OR = 0.80, 95% CI = 0.67-0.96). When comparing history of asthma and allergy with no allergies, the association was slightly stronger, but not statistically significant (OR = 0.70, 95% CI = 0.47-1.02). The association between allergy and HNSCC was similar for males (OR = 0.82, 95% CI = 0.66-1.03) and females (OR = 0.76, 95% CI = 0.54-1.07), and by smoking status (never smokers: OR = 0.75, 95% CI = 0.54-1.04; former smokers: OR = 0.80, 95% CI = 0.62-1.02) or alcohol (less than 7 drinks per week: OR = 0.78, 95% CI = 0.60-1.01; greater than 25 drinks per week: OR = 0.59, 95% CI = 0.37-0.95). While the associations with allergy and asthma were slightly strong among individuals who had less education, there were fewer participants in those strata (127 cases, 84 controls) and tests for interaction were not statistically significant.

We examined whether HPV 16 serostatus was confounding or modifying the association with allergies using Phase I data (HPV 16 status was not available on Phase II data); results for allergies were similar by HPV serostatus (Table 3). Similarly, there were no interactions between HPV16 serostatus and allergies for oral or pharyngeal cancer.

Discussion

In this large US case-control study, we observed inverse associations for history of allergy and asthma and risk of head and neck cancers. Inverse associations were observed for history of allergy and asthma with oropharyngeal and laryngeal cancers, but not with oral cancer. The findings were consistent across sex, smoking status, and HPV16 serostatus, suggesting that allergies lower risk independently of the main causal factors.

In a large cohort study, individuals with self-reported history of both hay fever and asthma had a lower risk of overall cancer mortality compared with those who reported no history of hay fever or asthma (RR = 0.88, 95% CI = 0.83-0.93)[22]. For cancer specific mortality, pancreatic cancer mortality was significantly lower among those with a history of hay fever (RR = 0.85, 95% CI = 0.77-0.95) while colorectal cancer mortality was lower among those with a history of both hay fever and asthma (RR = 0.76, 95% CI = 0.64-0.91)[22]; the association between allergies and HNSCC mortality was not assessed. Few cohorts have

sufficient data to allow for prospective examination of the relation between allergies and head and neck cancers, although some studies have reported lower risk of head and neck cancers among asthmatic patients[8, 9].

Two previous case-control studies examined the relation between allergies and risk of head and neck cancers [6, 7]. As with our current study, results from the two previous studies were based on self-reported history of allergies. In contrast, both earlier studies were hospital-based case-control studies and neither included data on HPV serostatus. Inverse associations with allergies from the two prior studies on head and neck cancer were stronger than those observed in our study. However, prevalence rates for any allergies among controls were lower than expected (8.7% [7]; 17.5% in men and 26.5% in women [6]), which may have led to biased results.

Associations between allergies and risk of head and neck cancers did not to apply to oral cancers in this study population. This may be simply due to lower power in this subset, although cancers of the oral cavity comprise 60% of our total HNSCC cases. Alternatively, it is plausible that the response is different for these tumors. Given that a history of allergy is not ubiquitously related to all cancer sites, it may also apply to head and neck cancer subsites. Potential mechanisms for the apparent protective effect of allergies on the development of certain tumors are not well understood. Research is being conducted in this field with efforts to understand pathways to develop new treatments [10]. It has been proposed that immunoglobulin E (IgE), which is elevated in individuals with allergies, may have a natural surveillance function in certain malignancies. A high number of IgE-positive cells was found in tumor tissue compared to normal hypopharyngeal mucosa, but no significant differences were observed for IgG, IgA and IgM [23].

The strengths of this study include a large number of cases with head and neck cancer, and detailed data on potential confounders, including smoking, alcohol and HPV16 serostatus. Limitations include the retrospective study design and the low response rates among controls that could have introduced selection bias. However, selection bias is unlikely to explain our findings given that the prevalence of allergies among controls (40%) is similar to the reported prevalence in NHANES data (34% had diagnosed allergies overall age groups[24]; as the younger age groups have lower prevalence, the prevalence would be higher for the comparable age group from this study). Finally, history of allergies and asthma were self-reported by study participants and confirmation of these conditions was not possible.

In this large population-based case-control study, we observed an inverse association between allergies and risk of HNSCC, as previously reported in two case-control studies. The association was not confounded or modified by HPV16 serostatus or smoking and appeared to be strongest among oropharyngeal and laryngeal cancers. These findings are consistent with inverse associations which have been reported for other types of cancers, and suggest that the Th2 immune function may play a key role in carcinogenesis in HNSCC.

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Table 1

Selected descriptive statistics for case subjects with head and neck squamous cell carcinoma and control subjects*

Characteristic	Case subjects (n = 1056)	Control subjects (n = 1252)	p-value§
Age (years)			
Mean (SD)	59.7 (11.4)	60.8 (11.2)	
Sex			
Male	765 (72.4%)	913 (72.9%)	
Female	291 (28.6%)	339 (27.1%)	
Race			
White	948 (90.0%)	1119 (89.6%)	0.09
Other	106 (10.0%)	130 (10.4%)	
Education			
High school diploma or Higher	900 (87.1%)	1134 (93.0%)	0.002
Did not finish high school	133 (12.9%)	85 (7.0%)	
Smoking, pack-years			
None	253 (24.0%)	502 (40.1%)	<0.001
>0 to <20	246 (23.3%)	304 (24.3%)	
20 to 45	272 (25.8%)	264 (21.1%)	
≥ 45	285 (27.0%)	182 (14.5%)	
Alcohol consumption, average drinks per week			
<3	223 (21.2%)	377 (30.2%)	0.05
3 to <8	234 (22.2%)	399 (31.9%)	
8 to <25	276 (26.2%)	315 (25.2%)	
≥ 25	319 (30.3%)	158 (12.7%)	
HPV 16 serology#			
Negative	318 (74.6%)	517 (95.0%)	<0.001
Positive	108 (25.4%)	27 (5.0%)	

*SD = standard deviation, HPV16 = human papilloma virus type 16.

§*P*-values using t-tests for categorical variables and ANOVA for continuous variables.

#HPV serology only available for phase I subjects, E6 or E7 positive.

Table 2

Odds ratios (OR) and 95% confidence intervals (95% CI) for history of allergy and risk of head and neck cancer, overall, by tumor site and smoking status.

	Cases/Controls	OR (95% CI)	p-value
History of Allergy *			
Overall			
No allergy	687/720	1.0 (referent)	
Allergy	327/473	0.81 (0.67-0.98)	0.03
By tumor site			
Oral cavity			
No allergy	240/727	1.0 (referent)	
Allergy	141/474	0.98 (0.76-1.26)	0.86
Oropharyngeal			
No allergy	324/727	1.0 (referent)	
Allergy	138/474	0.73 (0.57-0.92)	0.01
Laryngeal			
No allergy	119/727	1.0 (referent)	
Allergy	46/474	0.66 (0.45-0.97)	0.03
History of Asthma **			
Overall			
No asthma	927/1072	1.0 (referent)	
Asthma	87/121	0.89 (0.66-1.22)	0.47
By tumor site			
Oral cavity			
No asthma	349/1110	1.0 (referent)	
Asthma	40/132	0.90 (0.61-1.33)	0.58
Oropharyngeal			
No asthma	438/1110	1.0 (referent)	
Asthma	34/132	0.67 (0.44-0.997)	0.05
Laryngeal			
No asthma	152/1110	1.0 (referent)	
Asthma	14/132	0.72 (0.39-1.33)	0.29

* Multivariate models include age, sex, race, education, alcohol (drinks per week), and smoking (pack-years), and smoking status (ever/never), and history of asthma.

** Multivariate models include age, sex, race, education, alcohol (drinks per week), and smoking (pack-years), and smoking status (ever/never), and history of asthma.

Table 3

Association between allergies and HNSCC by HPV16 status in the Phase I data

	Cases/Controls	OR (95% CI)	p-value
All Phase I*			
No allergy	300/328	1.0 (reference)	
Allergy	114/201	0.65 (0.47, 0.90)	0.008
By HPV 16 Serostatus**			
HPV16 negative			
No allergy	229/313	1.0 (reference)	
Allergy	80/189	0.65 (0.46, 0.92)	0.02
HPV16 positive			
No allergy	71/15	1.0 (reference)	
Allergy	34/12	0.63 (0.25, 1.55)	0.31

*Multivariate models include HPV16 status in addition to age, sex, race, education, alcohol (drinks per week), and smoking (pack-years) and smoking status (ever/never).

**Multivariate models are adjusted for age, sex, race, education, alcohol (drinks per week), smoking (pack-years), and smoking status (ever/never).