

Allergy symptoms, serum total immunoglobulin E, and risk of head and neck cancer

Hsiao-Chen Liao¹ · Shang-Yin Wu² · Chun-Yen Ou¹ · Jenn-Ren Hsiao¹ · Jehn-Shyun Huang³ · Sen-Tien Tsai¹ · Cheng-Chih Huang¹ · Tung-Yiu Wong³ · Wei-Ting Lee¹ · Ken-Chung Chen³ · Sheen-Yie Fang¹ · Jiunn-Liang Wu¹ · Tze-Ta Huang³ · Yuan-Hua Wu⁴ · Wei-Ting Hsueh⁴ · Chia-Jui Yen² · Ming-Wei Yang⁴ · Forn-Chia Lin⁴ · Yu-Hsuan Lai⁴ · Jang-Yang Chang² · Chen-Lin Lin⁵ · Yi-Hui Wang⁶ · Ya-Ling Weng⁶ · Han-Chien Yang⁶ · Yu-Shan Chen¹ · Jeffrey S. Chang⁶

Received: 18 February 2016 / Accepted: 14 July 2016
© Springer International Publishing Switzerland 2016

Abstract

Purpose Allergy symptoms have been associated with a reduced head and neck cancer (HNC) risk, while elevated blood immunoglobulin E (IgE) levels have been associated with an increased HNC risk. According to the “prophylaxis hypothesis,” allergic reaction is the body’s way of expelling carcinogens. IgE level may be increased by exposure to environmental carcinogens, including alcohol and cigarette smoke. We hypothesized that individuals with elevated serum IgE without allergy symptoms (i.e., asymptomatic atopic) would have the highest HNC risk.

Methods A case–control study of HNC (576 cases and 740 controls) was conducted to evaluate the association between allergy symptoms or serum total IgE and HNC

risk and the effect modification of allergy symptoms on the association between serum total IgE and HNC risk.

Results Elevated serum total IgE was associated with a significantly increased HNC risk [odds ratio (OR) 1.71, 95 % confidence interval (CI) 1.21–2.42]. Having allergy symptoms was associated with a significantly reduced HNC risk (OR 0.56, 95 % CI 0.43–0.73). Compared to subjects with normal serum total IgE and no allergy symptoms, asymptomatic atopic individuals had a significantly increased HNC risk (OR 2.12, 95 % CI 1.33–3.35). **Conclusions** Our results provided further evidence to support the “prophylaxis hypothesis.” Further investigations regarding the immune profiles of asymptomatic atopic individuals may provide additional clues for the biological mechanisms underlying the association between allergy symptoms, IgE, and HNC risk.

Hsiao-Chen Liao and Shang-Yin Wu have contributed equally to this work.

Electronic supplementary material The online version of this article (doi:10.1007/s10552-016-0788-4) contains supplementary material, which is available to authorized users.

✉ Jeffrey S. Chang
jeffreychang@nhri.org.tw

¹ Department of Otolaryngology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, 138 Sheng Li Road, Tainan 70456, Taiwan

² Division of Hematology/Oncology, Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, 138 Sheng Li Road, Tainan 70456, Taiwan

³ Department of Stomatology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, 138 Sheng Li Road, Tainan 70456, Taiwan

⁴ Department of Radiation Oncology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, 138 Sheng Li Road, Tainan 70456, Taiwan

⁵ Department of Nursing, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, 138 Sheng Li Road, Tainan 70456, Taiwan

⁶ National Institute of Cancer Research, National Health Research Institutes, 1F No. 367, Sheng-Li Road, Tainan 70456, Taiwan

Abbreviations

CI	Confidence interval
HNC	Head and neck cancer
HPV	Human papillomavirus
IgE	Immunoglobulin E
OR	Odds ratio

Introduction

Each year, approximately 600,000 people are diagnosed with head and neck cancer (HNC) (cancers of the oral cavity, oropharynx, hypopharynx, and larynx) worldwide, making it the fifth most common cancer in the world [1]. Alcohol drinking, cigarette smoking, and betel quid chewing are the well-established risk factors for HNC [2]. In addition, studies have shown that the incidence of human papillomavirus (HPV)-associated oropharyngeal cancer has been increasing [3]. Less is known about the factors associated with a reduced HNC risk, with the inverse association between higher consumption of fruits and vegetables and HNC risk being the most consistent finding [4].

Many studies have investigated the association between allergy and cancer. Allergy usually results from an overactive immune function of people with atopic tendency in response to substances in the environment. Individuals with atopic tendency have higher genetic predisposition to produce immunoglobulin E (IgE) against common allergens [5–7]. The binding of the allergens to the IgE molecules on the surface of mast cells and basophils results in the cross-linkage of IgE molecules to generate a cascade of events leading to the manifestation of various allergic diseases, including allergic rhinitis, asthma, eczema, drug allergy, and food allergy [6]. Although people with higher levels of serum IgE tend to develop more allergy symptoms, the correlation is not absolute. Some people with elevated serum IgE do not develop allergy symptoms, which is defined as “asymptomatic atopy” [8], while some people may have allergy symptoms without elevated levels of serum IgE, which is known as “non-atopic allergies” [9].

Among the studies of the association between allergy and cancer, an inverse association has been consistently observed between history of allergy and risk of pancreatic cancer or brain glioma, and less consistent findings have been found for other cancers, suggesting that the reduced risk of cancer associated with allergy may be tumor site-specific [10]. “Immunosurveillance hypothesis” and the “prophylaxis hypothesis” are the two hypotheses that have been proposed to explain the inverse association between allergy and cancer [11]. According to the “immunosurveillance hypothesis,” allergy is not directly involved in

preventing the development of cancer and is merely a side effect of an overactive immune function that surveys and eradicates cancer cells with high efficiency [11]. According to the “prophylaxis hypothesis,” allergic reaction is the body’s way of expelling carcinogens, and thus, allergy plays a direct role in reducing the risk of cancer [11, 12]. Sherman et al. [11] suggested that the “prophylaxis hypothesis” may be the more likely explanation for the inverse association between allergy and certain cancers. They reached this conclusion after observing that the reduced cancer risk associated with allergy symptoms was more commonly observed among tissues or organ systems that interface the external environment (i.e., glia, mouth and throat, colon and rectum, pancreas, skin, uterus and cervix, lung, bladder, and gastrointestinal tract) than among those that do not (i.e., ovaries, meninges, prostate, breast, and blood cells) [11].

We previously published a meta-analysis of 14 studies to show an inverse association between allergy symptoms and HNC risk [meta-odds ratio (OR) 0.76, 95 % confidence interval (CI) 0.63–0.91] [13], giving support to the “prophylaxis hypothesis.” In contrast, two prospective cohort studies showed that higher serum IgE levels were associated with an increased risk of HNC [14]. In a study with a cohort of 14,849 persons, Skaaby et al. [14] reported that individuals who tested positive for serum-specific IgE against inhalant allergens had a non-significantly increased risk of HNC (OR 1.74, 95 % CI 0.98–3.09). In a cohort of 37,747 individuals, Helby et al. [15] found that high levels of plasma total IgE was associated with an increased risk of oral and pharyngeal cancer (OR 1.38, 95 % CI 1.04–1.84), although statistical significance was not reached after correcting for multiple testing.

Given that the correlation between allergy symptoms and IgE in the blood is not absolute, the discrepant results for the association between allergy symptoms and HNC risk versus IgE in the blood and HNC risk may not be totally unexpected. Furthermore, if the “prophylaxis hypothesis” is true, we hypothesized that allergy symptoms rather than serum IgE are the key factors for the reduced HNC risk. Elevated levels of IgE in the blood may indicate exposure to environmental carcinogens. Both alcohol drinking and cigarette smoking have been associated with higher levels of serum total IgE [16–18]. Therefore, we hypothesized that higher levels of serum total IgE, which may indicate exposure to environmental carcinogens, would be associated with an increased HNC risk. We further hypothesized that the highest risk of HNC would be found in individuals with elevated serum IgE and no history of allergy symptoms (i.e., individuals with asymptomatic atopy), because these are individuals who are likely to have been exposed to carcinogens but have a

reduced ability to expel carcinogens out of the body. To test our hypotheses, we analyzed data from a case–control study of HNC to evaluate the association between allergy symptoms or serum total IgE and HNC risk and the effect modification of allergy symptoms on the association between serum total IgE and HNC risk.

Materials and methods

Ethics statement

This study was approved by the institutional review boards of the National Health Research Institutes and the National Cheng Kung University Hospital. All study subjects signed an informed consent.

Recruitment of study subjects

All subjects of the current study were recruited from the Department of Otolaryngology and the Department of Stomatology at the National Cheng Kung University Hospital from 1 September 2010 to 30 March 2015. The eligibility criteria for cases included: (1) diagnosis of squamous cell carcinoma of the head and neck, including oral cavity, oropharynx, hypopharynx, or larynx; (2) no previous diagnosis of other cancers; and (3) age between 20 and 80 years old. The diagnosis of HNC case was pathologically confirmed by the Department of Pathology at the National Cheng Kung University Hospital. For comparing the risk of HNC, sex- and age-matched (± 5 years) controls were recruited and their eligibility criteria were: (1) subjects who received surgery for non-cancerous conditions that are unrelated to alcohol drinking, betel quid chewing, and cigarette smoking; (2) no previous diagnosis of other cancers; and (3) age between 20 and 80 years old.

Data collection for allergy symptoms and lifestyle factors

In-person interview was conducted by a trained interviewer with each study participant to collect information on history of allergy symptoms, including allergic rhinitis, skin allergy, food allergy, drug allergy, and asthma. Those with a positive response were further asked about the age when allergy symptoms first occurred. Demographic variables, including sex, age, and educational level, and lifestyle factors, including alcohol drinking, cigarette smoking, and betel quid chewing, were collected to account for the potential confounding effect of these variables on the association between allergy symptoms or serum total IgE and HNC risk.

Collection and processing of blood sample

Blood sample was collected from each participant in a red-top Vacutainer blood collection tube, which was then centrifuged to separate out the serum. All of the blood samples were collected before treatment (surgery, radiation therapy, or chemotherapy) of the HNC patients or before the surgery of the controls, before the subjects received any medications or intravenous fluid. All serum samples were stored in Eppendorf tubes in the -80°C refrigerator until ready to use.

Measurement of serum total IgE

Serum total IgE was measured using Phadia ImmunoCAP assay (Thermo Fisher Scientific, Waltham, MA, USA). Total IgE was measured with antibodies against the heavy chains (constant regions) of IgE. First, 40 μL of serum sample was incubated with anti-IgE antibodies covalently bound to solid phase to capture the IgE in the serum sample of the patient. After washing, enzyme-labeled anti-IgE antibodies were then added to bind to the patient serum IgE solid phase anti-IgE complex. Unbound enzyme-labeled anti-IgE antibodies were then washed away. Developing agent was then added. After incubation, the developing reaction was stopped and the fluorescence, which is proportional to the concentration of total IgE in the patient's serum, was measured. The level of the serum total IgE was categorized by standard cut points: normal (<25 kU/L), borderline (25–100 kU/L), and elevated (>100 kU/L).

Statistical analysis

T tests (for continuous variables) and Chi-squared tests (for categorical variables) were performed to compare the distributions of demographic variables and lifestyle factors (alcohol drinking, betel quid chewing, and cigarette smoking) between cases and controls.

Unconditional logistic regression was performed to estimate the OR and 95 % CI for the association between allergy symptoms or serum total IgE and HNC risk overall or by each HNC site (oral cavity, oropharynx, hypopharynx, and larynx), adjusted for age, sex, education, cigarette smoking, betel quid chewing, and alcohol drinking. Although adjustment for age, sex, and education did not have much impact on the results (OR change $<10\%$), we decided to keep these covariates in the statistical models for completeness. Because serum total IgE is related to both allergy and environmental carcinogens, we also included allergy symptom as a covariate in the analysis on the association between serum total IgE and HNC risk in order to evaluate the effect of serum total IgE that is more attributed to exposure to environmental carcinogens. To

evaluate the potential reverse causality between allergy symptoms and HNC risk, sensitivity analysis was performed by censoring allergy symptoms at 5, 10, 15, 20 years before the reference date (date of HNC diagnosis for the cases and date of interview for the controls).

Data from the control subjects were used to evaluate the association between consumption of alcohol, betel quid, or cigarette and the risk of having elevated serum total IgE, using unconditional logistic regression, adjusted for age, sex, and education. Adjustment was also made for allergy symptom to focus on the level of serum total IgE that is more due to alcohol drinking, betel quid chewing, or cigarette smoking. Alcohol, betel quid, and cigarette were first evaluated separately for their association with elevated serum total IgE and then jointly for their combined effect on the level of serum total IgE.

Two methods were used to evaluate the effect modification of allergy symptoms on the association between serum total IgE and HNC risk. In the first method, study subjects were divided into six groups according to the combination of serum total IgE level and allergy symptom (yes/no). Association between these six groups and the HNC risk was performed using unconditional logistic regression, adjusted for age, sex, education, cigarette smoking, betel quid chewing, and alcohol drinking. In the second method, the association between serum total IgE levels and HNC risk was evaluated stratified by allergy symptom (yes/no).

Results

From 1 September 2010 to 30 March 2015, 609 HNC cases and 745 controls agreed to join the study. The participation rate was 77 and 86 % for the cases and controls, respectively. Serum samples were unavailable for 33 cases and 5 controls, and thus, the final sample for this analysis included 576 HNC cases (375 oral cancers, 69 oropharyngeal cancers, 69 hypopharyngeal cancers, and 63 laryngeal cancers) and 740 controls. The distribution of the clinical diagnoses among controls is shown in Supplementary Table 1. No significant difference in mean age was observed between cases and controls ($p = 0.20$) (Table 1). Controls had more years of education than cases, with 29 % of controls versus 10 % of cases having education beyond high school ($p < 0.0001$). Compared to controls, cases consumed more alcohol, betel quid, and cigarette ($p < 0.0001$).

Higher levels of serum total IgE were associated with having allergy symptoms (Supplementary Table 2). Sixty-five percent of control subjects with elevated serum total IgE reported ever having allergy symptoms compared to 59 % of control subjects with borderline elevated serum

Table 1 Demographic and lifestyle characteristics of the head and neck cancer patients and control subjects

Characteristics	Case <i>N</i> = 576 <i>n</i> (%)	Control <i>N</i> = 740 <i>n</i> (%)	<i>p</i>
Age (years)			
Mean (SE)	55.0 (0.4)	54.2 (0.4)	0.20
Sex			
Men	542 (94.1)	718 (97.0)	0.01
Women	34 (5.9)	22 (3.0)	
Education			
≤ Elementary school	169 (29.3)	124 (16.8)	<0.0001
Junior high	171 (29.7)	138 (18.6)	
High school/technical school	179 (31.1)	263 (35.5)	
Some college or more	57 (9.9)	215 (29.1)	
Alcohol drinking			
Never + occasional	185 (32.1)	395 (53.4)	<0.0001
Former regular	80 (13.9)	92 (12.4)	
Current regular	311 (54.0)	253 (34.2)	<0.0001
Never	165 (28.7)	342 (46.2)	
1 drink or less per month	20 (3.5)	53 (7.2)	
1–2 drinks per week	22 (3.8)	50 (6.8)	
3–5 drinks per week	40 (6.9)	57 (7.7)	
Daily drinkers	315 (54.7)	232 (31.3)	
Unknown	14 (2.4)	6 (0.8)	
Betel quid chewing			
Never	175 (30.4)	532 (71.9)	<0.0001
Former	217 (37.7)	132 (17.8)	
Current	184 (31.9)	76 (10.3)	<0.0001
Never	175 (30.4)	532 (71.9)	
0.1–9.9 pack-years	80 (13.9)	70 (9.5)	
10.0–19.9 pack-years	70 (12.2)	39 (5.3)	
20.0–29.9 pack-years	56 (9.7)	30 (4.0)	
30.0 or more pack-years	177 (30.7)	67 (9.0)	
Unknown	18 (3.1)	2 (0.3)	
Pack-years (SE)	25.9 (1.6)	8.0 (0.8)	
Cigarette smoking			
Never	77 (13.4)	231 (31.2)	<0.0001
Former	109 (18.9)	150 (20.3)	
Current	389 (67.5)	358 (48.4)	<0.0001
Unknown	1 (0.2)	1 (0.1)	
Never	77 (13.4)	231 (31.2)	
0.1–9.9 pack-years	27 (4.7)	60 (8.1)	
10.0–19.9 pack-years	58 (10.0)	95 (12.8)	
20.0–29.9 pack-years	99 (17.2)	99 (13.4)	
30.0 or more pack-years	307 (53.3)	250 (33.8)	
Unknown	8 (1.4)	5 (0.7)	
Pack-years (SE)	35.7 (1.2)	23.6 (1.0)	

N number, *SE* standard error

total IgE and 43 % of control subjects with normal serum total IgE. However, the correlation between the level of serum total IgE and allergy symptoms was not absolute. Thirty-five percent of the control subjects with elevated serum total IgE had never experienced any allergy symptoms while 43 % of the control subjects with normal serum total IgE reported having allergy symptoms.

Elevated serum total IgE was associated with a significantly increased risk of HNC (OR 1.71, 95 % CI 1.21–2.42) (Table 2). Elevated serum total IgE was also associated with an increased risk of the different sites of HNC but only oral cancer reached statistical significance and oropharyngeal cancer had the weakest positive association.

Having any allergy symptoms was associated with a significantly reduced risk of HNC (OR 0.56, 95 % CI 0.43–0.73) (Table 3). This reduction in risk was seen across all sites of HNC, although statistical significance was reached for oral cancer (OR 0.51, 95 % CI 0.38–0.69) and oropharyngeal cancer (OR 0.56, 95 % CI 0.33–0.97), but not for hypopharyngeal cancer (OR 0.56, 95 % CI 0.31–1.02) and laryngeal cancer (OR 0.76, 95 % CI 0.43–1.33). Specific allergy symptoms associated with a significantly reduced risk of HNC included nasal allergy (OR 0.43, 95 % CI 0.32–0.58), skin allergy (OR 0.60, 95 % CI 0.42–0.87), and asthma (OR 0.38, 95 % CI 0.21–0.70). Drug allergy was associated with a non-significantly reduced risk of HNC (OR 0.72, 95 % CI 0.46–1.14), while food allergy was not associated with HNC risk (OR 0.95, 95 % CI 0.60–1.50). The results of the sensitivity analysis showed that censoring allergy symptoms at 5, 10, 15, and 20 years before the reference date did not affect the inverse association between allergy symptoms and HNC risk (Supplementary Table 3).

Cigarette smoking was associated with elevated serum total IgE levels, particularly for current smokers (elevated vs. normal serum total IgE: OR 1.92, 95 % CI 1.19–3.10) and those who had smoked 20 pack-years or more (elevated vs. normal serum total IgE: OR 1.82, 95 % CI 1.12–2.96). Betel quid chewing was also associated with elevated serum total IgE levels, although not statistically significant. Current alcohol drinking was associated with significantly elevated serum total IgE levels (elevated vs. normal serum total IgE: OR 1.62, 95 % CI 1.04–2.53). When we combined alcohol, betel quid, and cigarette, we found that those who used all three showed the strongest association with elevated serum total IgE levels (elevated vs. normal serum total IgE: OR 2.65, 95 % CI 1.38–5.07; elevated vs. borderline serum total IgE: OR 2.18, 95 % CI 1.25–3.80) (Table 4).

Compared to subjects with normal serum total IgE and no allergy symptoms, those with elevated serum total IgE and no allergy symptoms had a significantly increased

Table 2 Association between serum total IgE and risk of head and neck cancer overall and by sites

Serum IgE	Controls N = 740 n (%)	All head and neck cancer N = 576 n (%)	OR (95 % CI) ^a	Oral cavity N = 375 n (%)	OR (95 % CI) ^a	Oropharynx N = 69 n (%)	OR (95 % CI) ^a	Hypopharynx N = 69 n (%)	OR (95 % CI) ^a	Larynx N = 63 n (%)	OR (95 % CI) ^a
Total IgE status											
Normal	193 (26.1)	114 (19.8)	Referent	71 (18.9)	Referent	21 (30.4)	Referent	13 (18.8)	Referent	9 (14.3)	Referent
Borderline	300 (40.5)	212 (36.8)	1.25 (0.89–1.75)	145 (38.7)	1.43 (0.96–2.13)	21 (30.4)	0.76 (0.38–1.53)	22 (31.9)	1.10 (0.48–2.54)	24 (38.1)	1.65 (0.71–3.85)
Elevated	247 (33.4)	250 (43.4)	1.71 (1.21–2.42)	159 (42.4)	1.75 (1.16–2.62)	27 (39.2)	1.38 (0.68–2.80)	34 (49.3)	1.97 (0.87–4.49)	30 (47.6)	1.95 (0.84–4.52)

N number; CI confidence interval, OR odds ratio

^a OR and 95 % CI were calculated using unconditional logistic regression, adjusted for, age, sex, education, cigarette smoking (pack-year categories), betel quid chewing (pack-year categories), alcohol drinking (frequency), and allergy symptom

Table 3 Association between allergy symptom and risk of head and neck cancer overall and by sites

Allergy symptom	Controls N = 740 n (%)	All head and neck cancer N = 576 n (%)	OR (95 % CI) ^a	OR (95 % CI) ^a	Oropharynx N = 69 n (%)	OR (95 % CI) ^a	Hypopharynx N = 69 n (%)	OR (95 % CI) ^a	Larynx N = 63 n (%)	OR (95 % CI) ^a
Any allergy symptom										
No	314 (42.4)	341 (59.2)	Referent	Referent	40 (58.0)	Referent	43 (62.3)	Referent	34 (54.0)	Referent
Yes	415 (56.1)	232 (40.3)	0.56 (0.43–0.73)	0.51 (0.38–0.69)	28 (40.6)	0.56 (0.33–0.97)	26 (37.7)	0.56 (0.31–1.02)	29 (46.0)	0.76 (0.43–1.33)
Unknown	11 (1.5)	3 (0.5)	–	–	1 (1.4)	–	0 (0.0)	–	0 (0.0)	–
Nasal allergy										
No allergy	314 (42.4)	341 (59.2)	Referent	Referent	40 (58.0)	Referent	43 (62.3)	Referent	34 (54.0)	Referent
Yes	301 (40.7)	126 (21.9)	0.43 (0.32–0.58)	0.40 (0.28–0.57)	20 (29.0)	0.57 (0.31–1.05)	13 (18.8)	0.42 (0.20–0.86)	11 (17.4)	0.40 (0.19–0.85)
Other allergies	111 (15.0)	103 (17.9)	0.90 (0.63–1.28)	0.80 (0.53–1.20)	8 (11.6)	0.54 (0.23–1.29)	13 (18.8)	0.91 (0.41–2.02)	17 (27.0)	1.49 (0.75–2.99)
Unknown	14 (1.9)	6 (1.0)	–	–	1 (1.4)	–	0 (0.0)	–	1 (1.6)	–
Skin allergy										
No allergy	314 (42.4)	341 (59.2)	Referent	Referent	40 (58.0)	Referent	43 (62.3)	Referent	34 (54.0)	Referent
Yes	129 (17.4)	75 (13.0)	0.60 (0.42–0.87)	0.56 (0.37–0.86)	6 (8.7)	0.39 (0.15–0.97)	9 (13.0)	0.59 (0.24–1.44)	9 (14.3)	0.82 (0.36–1.88)
Other allergies	283 (38.3)	157 (27.3)	0.56 (0.42–0.75)	0.50 (0.36–0.70)	22 (31.9)	0.63 (0.37–1.22)	17 (24.6)	0.59 (0.30–1.15)	20 (31.7)	0.73 (0.39–1.39)
Unknown	14 (1.9)	3 (0.5)	–	–	1 (1.4)	–	0 (0.0)	–	0 (0.0)	–
Food allergy										
No allergy	314 (42.4)	341 (59.2)	Referent	Referent	40 (58.0)	Referent	43 (62.3)	Referent	34 (54.0)	Referent
Yes	64 (8.6)	57 (9.9)	0.95 (0.60–1.50)	0.97 (0.58–1.62)	4 (5.8)	0.46 (0.14–1.55)	5 (7.3)	0.79 (0.26–2.44)	6 (9.5)	1.14 (0.40–3.23)
Other allergies	350 (47.3)	175 (30.4)	0.51 (0.38–0.66)	0.43 (0.31–0.60)	24 (34.8)	0.58 (0.33–1.02)	21 (30.4)	0.52 (0.28–0.99)	23 (36.5)	0.70 (0.38–1.28)
Unknown	12 (1.6)	3 (0.5)	–	–	1 (1.4)	–	0 (0.0)	–	0 (0.0)	–
Drug allergy										
No allergy	314 (42.4)	341 (59.2)	Referent	Referent	40 (58.0)	Referent	43 (62.3)	Referent	34 (54.0)	Referent
Yes	76 (10.3)	49 (8.5)	0.72 (0.46–1.14)	0.72 (0.43–1.22)	4 (5.8)	0.60 (0.20–1.85)	5 (7.3)	0.79 (0.26–2.39)	7 (11.1)	1.01 (0.40–2.59)
Other allergies	338 (45.7)	183 (31.8)	0.53 (0.41–0.70)	0.47 (0.34–0.65)	24 (34.8)	0.56 (0.31–0.99)	21 (30.4)	0.52 (0.28–0.99)	22 (34.9)	0.70 (0.38–1.30)
Unknown	12 (1.6)	3 (0.5)	–	–	1 (1.4)	–	0 (0.0)	–	0 (0.0)	–
Asthma										
No allergy	314 (42.4)	341 (59.2)	Referent	Referent	40 (58.0)	Referent	43 (62.3)	Referent	34 (54.0)	Referent
Yes	50 (6.8)	23 (4.0)	0.38 (0.21–0.70)	0.30 (0.14–0.64)	3 (4.4)	0.41 (0.10–1.67)	3 (4.4)	0.37 (0.08–1.66)	5 (7.9)	0.78 (0.25–2.40)
Other allergies	365 (49.3)	209 (36.3)	0.59 (0.45–0.77)	0.54 (0.41–0.74)	25 (36.2)	0.58 (0.33–1.02)	23 (33.3)	0.59 (0.32–1.09)	24 (38.1)	0.75 (0.42–1.36)
Unknown	11 (1.5)	3 (0.5)	–	–	1 (1.4)	–	0 (0.0)	–	0 (0.0)	–

N number, CI confidence interval, OR odds ratio

^a OR and 95 % CI were calculated using unconditional logistic regression, adjusted for, age, sex, education, cigarette smoking (pack-year categories), betel quid chewing (pack-year categories), and alcohol drinking (frequency)

Table 4 Association between serum total IgE and consumption of cigarette, betel quid, and alcohol among controls

	Normal serum total IgE <i>N</i> = 193	Borderline serum total IgE <i>N</i> = 300	Elevated serum total IgE <i>N</i> = 247	OR (95 % CI) ^a elevated versus normal serum total IgE	OR (95 % CI) ^a elevated versus borderline serum total IgE
Cigarette smoking					
Never	78 (40.6)	93 (31.0)	60 (24.3)	Referent	Referent
Former	33 (17.2)	68 (22.7)	49 (19.8)	1.46 (0.81–2.64)	1.08 (0.66–1.79)
Current	81 (42.2)	139 (46.3)	138 (55.9)	1.92 (1.19–3.10)	1.50 (0.99–2.30)
Never	78 (40.4)	93 (31.0)	60 (24.3)	Referent	Referent
0.1–19.9 pack-years	37 (19.2)	64 (21.3)	54 (21.9)	1.65 (0.92–2.96)	1.32 (0.80–2.19)
20.0 or more pack-years	76 (39.4)	143 (47.7)	130 (52.6)	1.82 (1.12–2.96)	1.34 (0.88–2.05)
Unknown	2 (1.0)	0 (0.0)	3 (1.2)	–	–
Test for trend				0.02	0.19
Betel quid chewing					
Never	148 (76.7)	223 (74.3)	161 (65.2)	Referent	Referent
Former	29 (15.0)	50 (16.7)	53 (21.4)	1.42 (0.83–2.43)	1.49 (0.94–2.35)
Current	16 (8.3)	27 (9.0)	33 (13.4)	1.69 (0.84–3.39)	1.65 (0.93–2.93)
Never	148 (76.7)	223 (74.3)	161 (65.2)	Referent	Referent
0.1–19.9 pack-years	27 (14.0)	39 (13.3)	43 (17.4)	1.34 (0.76–2.37)	1.53 (0.94–2.51)
20.0 or more pack-years	18 (9.3)	38 (12.7)	41 (16.6)	1.66 (0.88–3.16)	1.48 (0.88–2.47)
Unknown	0 (0.0)	0 (0.0)	2 (0.8)	–	–
Test for trend				0.09	0.07
Alcohol drinking					
Never + occasional	114 (59.1)	163 (54.3)	118 (47.8)	Referent	Referent
Former	20 (10.3)	38 (12.7)	34 (13.8)	1.70 (0.89–3.25)	1.12 (0.66–1.91)
Current	59 (30.6)	99 (33.0)	95 (38.4)	1.62 (1.04–2.53)	1.30 (0.89–1.89)
Never	95 (49.2)	145 (48.3)	102 (41.3)	Referent	Referent
2 drinks or less per week	28 (14.5)	35 (11.7)	40 (16.2)	1.74 (0.94–3.21)	1.63 (0.96–2.76)
3 drinks or more per week	70 (36.3)	118 (39.3)	101 (40.9)	1.49 (0.96–2.33)	1.16 (0.80–1.69)
Unknown	0 (0.0)	2 (0.7)	4 (1.6)	–	–
Test for trend				0.08	0.41
Combinations of smoking, betel quid and cigarette					
No use	60 (31.2)	74 (24.7)	46 (18.6)	Referent	Referent
Smoking only	36 (18.7)	62 (20.7)	49 (19.8)	1.46 (0.79–2.71)	1.30 (0.76–2.23)
Smoking + betel quid or smoking + alcohol	51 (26.6)	98 (32.7)	75 (30.4)	1.62 (0.91–2.87)	1.13 (0.69–1.84)
Smoking + alcohol + cigarette	27 (14.1)	47 (15.7)	63 (25.5)	2.65 (1.38–5.07)	2.18 (1.25–3.80)
Other combinations	18 (9.4)	19 (6.2)	14 (5.7)	1.03 (0.44–2.43)	1.11 (0.50–2.44)

N number, *CI* confidence interval, *OR* odds ratio

^a OR and 95 % CI were calculated using unconditional logistic regression, adjusted for age, sex, education, and allergy symptom

HNC risk (OR 2.12, 95 % CI 1.33–3.35) and this increased risk was seen in all sites of HNC, except for oropharyngeal cancer (OR 1.13, 95 % CI 0.44–2.91) (Table 5). In contrast, those with elevated serum total IgE and allergy symptoms showed no statistically significant difference in the risk of HNC compared to subjects with normal serum total IgE and no allergy symptoms (OR 1.01, 95 % CI

0.64–1.57). This indicates that allergy symptoms may mitigate the increased HNC risk associated with elevated serum total IgE. Another way to support this statement is to examine the association between serum total IgE and HNC risk stratified by allergy symptom (Table 6). Compared to normal serum total IgE, elevated total serum IgE was associated with an increased HNC risk among individuals

Serum total IgE	Allergy symptom	Control <i>n</i> (%)	All head and neck cancer <i>n</i> (%)	OR (95 % CI) ^a	Oral cavity <i>n</i> (%)	OR (95 % CI) ^a	Oropharynx <i>n</i> (%)	OR (95 % CI) ^a	Hypopharynx <i>n</i> (%)	OR (95 % CI) ^a	Larynx <i>n</i> (%)	OR (95 % CI) ^a
Normal	No	107 (14.7)	73 (12.7)	Referent	48 (12.9)	Referent	13 (19.1)	Referent	7 (10.1)	Referent	5 (7.9)	Referent
Borderline	No	121 (16.6)	130 (22.7)	1.57 (1.01–2.46)	91 (24.4)	1.65 (0.99–2.76)	16 (23.5)	1.17 (0.50–2.73)	12 (17.4)	1.84 (0.60–5.63)	11 (17.5)	1.87 (0.58–5.99)
Elevated	No	86 (11.8)	138 (24.1)	2.12 (1.33–3.35)	85 (22.8)	1.91 (1.12–3.26)	11 (16.2)	1.13 (0.44–2.91)	24 (34.8)	3.82 (1.32–11.04)	18 (28.6)	2.89 (0.95–8.78)
Normal	Yes	80 (11.0)	41 (7.2)	0.86 (0.50–1.50)	23 (6.2)	0.65 (0.33–1.26)	8 (11.8)	0.80 (0.28–2.31)	6 (8.7)	2.03 (0.55–7.54)	4 (6.3)	1.26 (0.31–5.22)
Borderline	Yes	174 (23.8)	81 (14.1)	0.74 (0.47–1.16)	53 (14.2)	0.71 (0.42–1.22)	5 (7.3)	0.27 (0.09–0.80)	10 (14.5)	0.92 (0.30–2.85)	13 (20.6)	1.61 (0.53–4.98)
Elevated	Yes	161 (22.1)	110 (19.2)	1.01 (0.64–1.57)	73 (19.5)	0.90 (0.54–1.52)	15 (22.1)	0.96 (0.40–2.26)	10 (14.5)	1.31 (0.41–4.17)	12 (19.1)	1.43 (0.45–4.57)

^a OR and 95 % CI were calculated using unconditional logistic regression, adjusted for, age, sex, education, cigarette smoking (pack-year categories), betel quid chewing (pack-year categories), and alcohol drinking (frequency)

Our analysis showed a positive association between elevated levels of serum total IgE and HNC risk. Since the levels of IgE were measured at the time of diagnosis in our study, the result could have been affected by reverse causality; however, results from two cohort studies also reported an increased HNC risk associated with higher blood IgE levels [14]. Using data from a cohort of 14,849 persons, Skaaby et al. [14] showed that individuals who tested positive for serum-specific IgE against inhalant allergens had a non-significantly increased risk of HNC (OR 1.74, 95 % CI 0.98–3.09). Helby et al. [15] found that high levels of plasma total IgE were associated an increased risk of oral and pharyngeal cancer (OR 1.38,

95 % CI 1.04–1.84) among a cohort of 37,747 individuals, although after correcting for multiple testing the result was no longer statistically significant. Because only three studies to date have examined the association between blood IgE and HNC risk, more investigations are needed to confirm the positive association between blood IgE and HNC.

An elevated serum total IgE level may indicate exposure to environmental carcinogens. In the current study, cigarette smoking was associated with elevated levels of serum total IgE. In addition, the highest prevalence of elevated serum total IgE was found among individuals who consumed cigarette, alcohol, and betel quid. Previous studies also supported a positive association between elevated levels of serum IgE and cigarette smoking or alcohol drinking. In a longitudinal study of about 3,000 subjects and a follow-up time up to 20 years, Sherrill et al. [18] reported that cigarette smoking was associated with elevated serum total IgE levels. A review by Gonzalez-Quintela et al. [16] stated that the positive association between alcohol and elevated levels of serum total IgE is supported by: (1) the strength of the association; (2) consistent results from studies with different populations under different settings; (3) the presence of dose–response; and (4) the decrease in IgE levels after alcohol abstinence. Besides cigarette smoking and alcohol drinking, other environmental carcinogens may also raise the level of serum IgE. Emara et al. [20] reported that compared to healthy controls, dry cleaners exposed to tetrachloroethylene [classified by the International Agency for Research on Cancer as a group 2A agents (probably carcinogenic to humans)] had higher levels of serum IgE.

Our analysis showed that the highest HNC risk occurred among asymptomatic atopic individuals, which were those with an elevated level of serum total IgE but no history of allergy symptoms. This result is consistent with the “prophylaxis hypothesis” which hypothesized that allergic reaction is the body’s way of expelling carcinogens to reduce the risk of cancer, particularly for cancers occurring in body sites that interface the outside environment, such as HNC [11, 12]. As previously stated, elevated IgE levels may be a marker for exposure to environmental carcinogens. The incapability of asymptomatic atopic individuals to expel carcinogens through allergic reaction may increase the risk of HNC. Our results further supported the “prophylaxis hypothesis” by showing that elevated serum total IgE levels were not associated with an increased HNC risk in the presence of allergy symptoms, suggesting that allergic reaction is able to ameliorate the increased HNC risk associated with higher serum total IgE levels (a proxy for possible exposure to environmental carcinogens).

The biological mechanisms to explain the higher HNC risk among asymptomatic atopic individuals are unclear,

but it is possible that the immune activities of asymptomatic atopic individuals may differ from symptomatic atopic or non-atopic individuals. A study by von Bubnoff et al. [21] showed that asymptomatic atopic individuals had higher indoleamine 2,3-dioxygenase (IDO) activity and increased IL-10 levels during seasonal allergen exposure compared to symptomatic atopic individuals with allergic rhinitis and non-atopic individuals. Both IDO and IL-10 have been shown to down-regulate immune function. IDO catabolizes tryptophan resulting in the inhibition of T cells [22]. IL-10 is an immunosuppressive cytokine produced by regulatory T cells and is involved in immune tolerance to allergens [23]. The down-regulated immune function in asymptomatic atopic individuals may contribute to their increased HNC risk; however, this needs to be confirmed by further investigations.

When we examined the association between HNC risk and serum total IgE or the combination of serum total IgE and allergy symptoms by HNC sites, we found similar results for all sites except for oropharyngeal cancer, which showed a non-significantly weak positive association with elevated serum total IgE. In addition, the risk of oropharyngeal cancer was not elevated among those with elevated serum total IgE and no allergy symptoms (asymptomatic atopic individuals). Among all the HNCs, oropharyngeal cancer has the strongest association with HPV and HPV-positive HNCs are molecularly and clinically different from HPV-negative HNCs [24]. This may explain partly why the results of oropharyngeal cancer were different from those of other HNC sites. Unfortunately, due to the unavailability of the tissue samples, we could not evaluate the status of HPV infection for the HNC cases. More investigations with direct testing of HPV status would be needed to confirm our observation.

Table 6 Association between serum total IgE level and risk of head and neck cancer by allergy symptom

Serum total IgE	Case <i>n</i> (%)	Control <i>n</i> (%)	OR (95 % CI) ^a
Allergy symptom, no			
Normal	73 (21.4)	107 (34.1)	Referent
Borderline	130 (38.1)	121 (38.5)	1.58 (1.01–2.48)
Elevated	138 (40.5)	86 (27.4)	2.12 (1.33–3.39)
Allergy symptom, yes			
Normal	41 (17.7)	80 (19.3)	Referent
Borderline	81 (34.9)	174 (41.9)	0.90 (0.52–1.55)
Elevated	110 (47.4)	161 (38.8)	1.23 (0.72–2.11)

N number, *CI* confidence interval, *OR* odds ratio

^a OR and 95 % CI were calculated using unconditional logistic regression, adjusted for, age, sex, education, cigarette smoking (pack-year categories), betel quid chewing (pack-year categories), and alcohol drinking (frequency)

This study has several limitations. Because data on allergy symptoms were collected retrospectively, recall bias and error could have affected the results of the study. Often, in a case-control study, case subjects may be more likely to ruminate about the possible factors for their development of cancer than control subjects, resulting in an overestimated positive association between the exposure of interest and disease; however, this is not the situation in our study because allergy symptoms were inversely associated with HNC risk. In addition, the general public is mostly unaware of the inverse association between allergy and cancer, making recall bias of allergy history less likely. Recall error could be an issue. It is possible that the study participants could have mistaken non-allergic symptoms for allergy symptoms and over-reported the allergy symptoms. Among our controls, nasal allergy (also known as allergic rhinitis) was the most frequently reported allergy symptom at 41 %. Using data from 2000 to 2007 recorded by the National Health Insurance Research Database of Taiwan, Hwang et al. [25] reported that the 8-year prevalence of allergic rhinitis in Taiwan was 26.3 % overall and 37.8 % for those younger than 20 years old. This study reported the 8-year prevalence, whereas our study asked the study participants about the lifetime history of allergy symptoms. In addition, Hwang et al. only reported allergies recorded by hospital visits and might not have captured those who did not visit doctors due to minor symptoms. All together, we feel that the allergy symptoms were unlikely to be over-reported by our study participants. In addition, any over- or under-reporting of allergy symptom was more likely to be non-differential, biasing the association toward the null and underestimating the inverse association between allergy symptoms and HNC risk. Furthermore, we performed sensitivity analysis assigning those with ≥ 2 allergy symptoms as having allergy to reduce misclassification, and the results were similar (Supplementary Tables 4 and 5). Another limitation is that association between allergy symptoms and cancer appears to be site-specific [10]; therefore, the results of the current study may not be generalizable to cancers occurring in other body sites.

The major strength of the current study is that it is the first to evaluate the association between the combinations of allergy symptoms and serum IgE and HNC risk. By combining allergy symptoms and serum IgE, we were able to generate additional evidence to support the “prophylaxis hypothesis” to explain the inverse association between allergy and HNC cancer. Because our study is the only one to date to combine allergy symptoms and serum IgE to assess HNC risk, more studies are needed to confirm our results.

In summary, our study showed that elevated serum total IgE levels were associated with an increased HNC risk

while a reduced HNC risk was observed among individuals with allergy symptoms. The highest HNC risk was observed among individuals with an elevated level of serum total IgE without allergy symptoms. Further investigations regarding the immune profiles of asymptomatic atopic individuals may provide additional clues for the biological mechanisms underlying the association between allergy symptoms, IgE, and HNC risk.

Acknowledgments This work was supported by the Establishment of Cancer Research System Excellence Program funded by the Ministry of Health and Welfare, Taiwan (MOHW105-TDU-B-211-134-004, MOHW105-TDU-B-212-134-013) and by the National Health Research Institutes (CA-105-SP-01).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al (2013) GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. International Agency for Research on Cancer, Lyon, France. <http://globocan.iarc.fr>. Accessed on 15 Oct 2015
2. Boyle P, Levin B (2008) World cancer report. International Agency for Research on Cancer, Lyon
3. Young D, Xiao CC, Murphy B, Moore M, Fakhry C, Day TA (2015) Increase in head and neck cancer in younger patients due to human papillomavirus (HPV). *Oral Oncol* 51:727–730
4. Bravi F, Edefonti V, Randi G, Ferraroni M, La Vecchia C, Decarli A (2012) Dietary patterns and upper aerodigestive tract cancers: an overview and review. *Ann Oncol* 23:3024–3039
5. Kay AB (2000) Overview of ‘allergy and allergic diseases: with a view to the future’. *Br Med Bull* 56:843–864
6. Durham SR, Smurthwaite L, Gould HJ (2000) Local IgE production. *Am J Rhinol* 14:305–307
7. Hoddeson EK, Pratt E, Harvey RJ, Wise SK (2010) Local and systemic IgE in the evaluation and treatment of allergy. *Otolaryngol Clin North Am* 43:503–520
8. von Bubnoff D, Scheler M, Hinz T, Matz H, Koch S, Bieber T (2004) Comparative immunophenotyping of monocytes from symptomatic and asymptomatic atopic individuals. *Allergy* 59:933–939
9. Groot Kormelink T, Thio M, Blokhuis BR, Nijkamp FP, Redegeld FA (2009) Atopic and non-atopic allergic disorders: current insights into the possible involvement of free immunoglobulin light chains. *Clin Exp Allergy* 39:33–42
10. Josephs DH, Spicer JF, Corrigan CJ, Gould HJ, Karagiannis SN (2013) Epidemiological associations of allergy, IgE and cancer. *Clin Exp Allergy* 43:1110–1123
11. Sherman PW, Holland E, Sherman JS (2008) Allergies: their role in cancer prevention. *Q Rev Biol* 83:339–362
12. Profet M (1991) The function of allergy: immunological defense against toxins. *Q Rev Biol* 66:23–62
13. Hsiao JR, Ou CY, Lo HI, Huang CC, Lee WT, Huang JS et al (2013) Allergies and risk of head and neck cancer: an original study plus meta-analysis. *PLoS ONE* 8:e55138
14. Skaaby T, Nystrup Husemoen LL, Roswall N, Thuesen BH, Linneberg A (2014) Atopy and development of cancer: a

- population-based prospective study. *J Allergy Clin Immunol Pract* 2:779–785
15. Helby J, Bojesen SE, Nielsen SF, Nordestgaard BG (2015) IgE and risk of cancer in 37,747 individuals from the general population. *Ann Oncol* 26:1784–1790
 16. Gonzalez-Quintela A, Vidal C, Gude F (2004) Alcohol, IgE and allergy. *Addict Biol* 9:195–204
 17. Friedrich N, Husemoen LL, Petersmann A, Nauck M, Volzke H, Linneberg A (2008) The association between alcohol consumption and biomarkers of alcohol exposure with total serum immunoglobulin E levels. *Alcohol Clin Exp Res* 32:983–990
 18. Sherrill DL, Halonen M, Burrows B (1994) Relationships between total serum IgE, atopy, and smoking: a twenty-year follow-up analysis. *J Allergy Clin Immunol* 94:954–962
 19. Grimes DA, Schulz KF (2002) Cohort studies: marching towards outcomes. *Lancet* 359:341–345
 20. Emara AM, Abo El-Noor MM, Hassan NA, Wagih AA (2010) Immunotoxicity and hematotoxicity induced by tetrachloroethylene in egyptian dry cleaning workers. *Inhal Toxicol* 22:117–124
 21. von Bubnoff D, Fimmers R, Bogdanow M, Matz H, Koch S, Bieber T (2004) Asymptomatic atopy is associated with increased indoleamine 2,3-dioxygenase activity and interleukin-10 production during seasonal allergen exposure. *Clin Exp Allergy* 34:1056–1063
 22. Mellor AL, Munn D, Chandler P, Keskin D, Johnson T, Marshall B et al (2003) Tryptophan catabolism and T cell responses. *Adv Exp Med Biol* 527:27–35
 23. Palomares O, Martin-Fontecha M, Lauener R, Traidl-Hoffmann C, Cavkaytar O, Akdis M et al (2014) Regulatory T cells and immune regulation of allergic diseases: roles of IL-10 and TGF-beta. *Genes Immun* 15:511–520
 24. Mehanna H, Beech T, Nicholson T, El-Hariry I, McConkey C, Paleri V et al (2013) Prevalence of human papillomavirus in oropharyngeal and nonoropharyngeal head and neck cancer—systematic review and meta-analysis of trends by time and region. *Head Neck* 35:747–755
 25. Hwang CY, Chen YJ, Lin MW, Chen TJ, Chu SY, Chen CC et al (2010) Prevalence of atopic dermatitis, allergic rhinitis and asthma in Taiwan: a national study 2000 to 2007. *Acta Derm Venereol* 90:589–594