

Association between Common Allergic Symptoms and Cancer in the NHANES III Female Cohort

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Abstract

Background: Previous epidemiological studies have investigated the association between allergic symptoms and cancer occurrence. However, the role of allergy in cancer has been elusive, especially for the female population.

Methods: We examined the relationship between cancer prevalence and common allergic symptoms of rhinoconjunctivitis (RC) and wheezing (WZ) among NHANES III female participants.

Results: Among 4600 people, 36.3% (n = 1669) did not have any allergic symptoms (NO), while 47.6% (n = 2188) reported RC, and 16.2% (n = 743), WZ. The proportion of cancer among NO groups was 5.43% (91/1669), among RC group, 7.63% (167/2188), and among WZ group, 11.23% (83/743) (RC group- OR 1.44 with 95% CI 1.00–2.08; p = 0.05 while for WZ group- OR 2.20 with 95%CI 1.27–3.80; p = 0.01). After adjusting for all the possible confounding variables including age, smoking, or COPD, having symptoms of RC (AOR 1.49 with 95%CI 1.12–2.36; p = 0.01) or WC (AOR 2.08 with 95%CI 1.11–3.89; p = 0.02) demonstrated consistent strong association with cancer. Among nonsmokers (n = 2505, 54.5%) only symptoms of RC showed association with cancer (AOR 1.51 with 95%CI 1.00–2.28; p = 0.05). Among former or current smokers (n = 2094, 45.5%), only symptoms of WZ demonstrated association with cancer (AOR 2.38 with 95%CI 1.16–4.87; p = 0.02). Among different types of cancers, odds of having breast cancer among participants with symptoms of RC or WZ were approximately twice the odds of having breast cancer among participants without any of these symptoms. AOR for RC group was 1.89 with 95%CI 1.04–3.42 and p = 0.04 while AOR for WC group was 2.08 with 95%CI 0.90–4.78 and p = 0.08.

Conclusions: In summary, we found associations between common allergic symptoms like rhinitis/conjunctivitis and wheezing and prevalence of cancer, specifically between rhinitis/conjunctivitis and breast cancer that were not found in previous studies. Larger prospective studies are required to validate our findings.

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Introduction

Numerous epidemiological studies have investigated the association between allergic symptoms and cancer occurrence. There are two plausible theories that explain the relationship between allergy and cancer [1,2]. One regards allergy as hyperstimulation of immune response to our body. Thus, allergy has potential to confer protective effect to cancer development with improved cancer cell immune surveillance. The suggested protective role of atopic allergy for lung and brain tumors supports this idea [3–5]. The other deems allergy as a constant state of inflammation in our body. Therefore, allergy may play a role in carcinogenesis via various inflammation pathway mediators. The fact that asthma has long been reported to be associated with increased lung cancer risk corroborates this notion [6]. Whether allergy actually moderates risk of cancer is still an area of controversy. Some epidemiologic studies have found positive association between

allergy and cancer [6–12], while other studies have reported inverse association [3–5,12–37]. Some studies showed no correlation between the two [1,12,38–45].

Many previous epidemiologic studies harbor limitations such as usage of different definition of allergy, small sample size of study population, and lack of control of possible confounders. Noticeably, most of previous reports have focused on symptoms of urticaria, bee sting allergy, hay fever, asthma, or atopic dermatitis/eczema. Few studies have examined the effect of common allergic symptoms such as conjunctivitis and rhinitis on cancer. In this study, we were able to obtain information on the symptoms of rhinitis and conjunctivitis as well as wheezing. In addition, we were able to control for various validated confounders such as smoking, asthma and chronic obstructive pulmonary disease (COPD) to better assess the effect of those symptoms on cancer in a NHANES III study participants, a reasonably large size cohort. We confined our analyses to female participants, first to

better assess the effect of common allergic symptoms in a nonsmoker predominant female population, and, second to better evaluate the association between allergy and female hormone related tumors such as breast and uterine cancer that has previously been reported to be inconsistent and equivocal [12,34,45,46].

Methods

We did not obtain ethics approval for our study. Ethics approval was not necessary for this retrospective analysis of data available in literature in the already published NHANES III study, with anonymous subjects. For the same reason informed consent from participants involved in study could not be obtained and was not necessary being provided at the initial NHANES study.

Study population

The Third National Health and Nutrition Examination Survey (NHANES III) is a stratified probability sample of the U.S. noninstitutionalized civilian population, conducted by the National Center for Health Statistics from 1988 through 1994. 4600 adults who were not pregnant and without any missing variables were selected out of 5,076 female adults aged ≥ 40 years who participated in both interview and physical examination in the NHANES III study. The prevalence of cancer excluding skin cancer was obtained by personal medical interview. Self-reported allergic symptoms were categorized into three categories: no symptoms (NO), rhinoconjunctivitis without wheezing (RC), and wheezing (WZ). First, the RC group was defined by those that answered “yes” to “During the past 12 months, have you had any episodes of stuffy, itchy or runny nose, or watery or itchy eyes?” questionnaire excluding those who had wheezing. Since allergic rhinoconjunctivitis can coexist with asthma or any nonspecific bronchial hyperreactivity, this question was designed to examine the effect of allergic rhinoconjunctivitis without bronchial over-reactivity [40,47]. Second, the WZ group was defined by those that answered yes to “Have you had any wheezing or whistling in your chest at any time in the past 12 months?” questionnaire to see the effect of nonspecific bronchial hypersensitivity irrespective of asthma. Asthma and COPD were controlled for in our multivariate analyses because these symptoms can be manifestations of such underlying disease. Other risk factors such as obesity, physical inactivity, and C-reactive protein level were defined by NHANES III questionnaire, results of physical examination and blood test.

Cancer was defined by self-reported physician diagnosed cancer as well as a cancer diagnosis listed on the records of hospital or nursing home, or on death certificate if hospital record of cancer was not available. Nonmelanoma skin cancers and diagnosis listed as questionable were excluded as cancer diagnosis.

Statistical Analyses

All analysis was done with consideration of sampling methods and weights using STATA version 10 (College Station, TX). Pearson chi-square was used for categorical variables. Linear regression with Wald test was performed for continuous variables. Univariate and multivariate logistic regression was used to obtain odds ratios of cancer according to the existence of allergic symptoms. Stratified analyses were performed among smokers and nonsmokers. Interaction analyses were performed using Wald test. For multivariate analyses, adjustments were made for other possible confounding variables such as age, race, education, income, asthma, COPD, C-reactive protein, obesity, smoking, alcohol drinking, physical inactivity, and menopausal status. P

value of 0.05 was used to determine statistical significance. Data used in the analyses are derived from the population estimates.

Results

Among 4600 study participants, cancer was present in 7.41% ($n = 341$). The most common cancer was breast cancer (2.80%, $n = 129$), followed by uterine cancer (0.91%, $n = 42$), cervix cancer (0.89%, $n = 41$), and colon cancer (0.81%, $n = 37$). Interestingly, more than half of participants reported having common allergic symptoms including allergic rhinitis and conjunctivitis. Of the study group, 36.3% ($n = 1669$) did not have any allergic symptoms (NO), while 47.6% ($n = 2188$) reported RC, and 16.2% ($n = 743$), WZ. Demographic and clinical variables have been compared among people with the mentioned three different symptom categories (Table 1). Both RC and WZ groups were associated with having cancer and WZ group seemed to have stronger association with cancer than RC group (Table 2). The proportion of cancer among NO groups was 5.43% (91/1669), among RC group, 7.63% (167/2188), and among WZ group, 11.23% (83/743). Compared to the NO group, the odds ratio of cancer in the RC group was OR = 1.44 with 95% CI 1.00–2.08 and $p = 0.05$. For WZ group OR was 2.20 with 95% CI 1.27–3.80 and $p = 0.01$.

Amongst clinicopathological variables examined, race, alcohol, smoking, COPD, postmenopausal status, and WZ displayed statistically significant association with cancer (Table 2). Education, income, asthma, C-reactive protein level, obesity and physical inactivity were not found to be statistically significantly associated with cancer. RC exhibited borderline statistical significance in its association with cancer ($p = 0.05$). After adjusting for possible confounding variables such as race, alcohol, postmenopausal status, symptoms of rhinitis/conjunctivitis without wheezing and symptoms of wheezing remained statistically significant in their association with cancer (Table 2). Noticeably, besides postmenopausal status (AOR 7.42 with 95% CI 2.96–18.61; $p < 0.01$), having symptoms of RC (AOR 1.49 with 95% CI 1.12–2.36; $p = 0.01$) or WC (AOR 2.08 with 95% CI 1.11–3.89; $p = 0.02$) demonstrated consistent strong association with cancer.

Interestingly, among nonsmokers ($n = 2505$, 54.5%), only symptoms of RC showed association with cancer (AOR 1.51 with 95% CI 1.00–2.28; $p = 0.05$), while, among former or current smokers ($n = 2094$, 45.5%), only symptoms of WZ demonstrated association with cancer (AOR 2.38 with 95% CI 1.16–4.87, $p = 0.02$) (Table 3). With subgroup analyses among different types of cancer, the association with symptoms of RC remained statistically significant with breast cancer which was also the most common cancer (Table 4). Odds of having breast cancer among participants with symptoms of RC or WZ were approximately twice the odds of having cancer without any symptoms (RC group- AOR 1.89 with 95% CI 1.04–3.42; $p = 0.04$ and WC group- AOR 2.08 with 95% CI 0.90–4.78; $p = 0.08$).

Discussion

We have found that common allergic symptoms of rhinoconjunctivitis and wheezing were associated with cancer. Our NHANES III study results are consistent with previous studies that insinuated allergy as a risk factor for cancer [6–12]. Among them is a NHANES I follow up study from 1988, the first prospective study that controlled for the confounding factors such as age, gender, race, and smoking. It also illustrated a positive association between allergic symptoms and cancer (OR 1.40 with 95% CI 1.10–1.77). Interestingly, the association was stronger between hives and lymphatic-hematopoietic malignancies (OR 7.89 with 95% CI 3.13–19.89) [9]. While our study focused on

Table 1. Characteristics of study participants by allergic symptoms.

Characteristics	NO (n = 1669)	RC (n = 2188)	WZ (n = 743)	p value
% of the population	36.3	47.6	16.2	
Age (mean±SE, yrs)	59.5±0.69	57.6±0.55	57.4±0.74	0.02
Race				<0.01
White (%)	75.9	84.8	81.6	
African American (%)	11.5	7.9	9.0	
Hispanic (%)	4.3	2.3	3.4	
Etc. (%)	8.3	5.0	6.0	
Education				<0.01
≥12 years (%)	69.3	74.8	66.3	
9–11 years (%)	13.7	12.7	17.0	
<9 years (%)	17.2	12.5	16.7	
Income				0.01
>\$ 25000 (%)	47.7	52.4	44.1	
\$15000~25000 (%)	19.3	19.9	18.9	
<\$15000 (%)	24.5	19.6	30.0	
unknown (%)	8.5	8.1	7.0	
BMI (kg/m ²)				<0.01
<18.5 (%)	3.0	2.5	2.1	
>= 18.5 & <25 (%)	38.2	42.5	27.9	
>= 25 & <30 (%)	30.6	30.8	31.1	
>= 30 (%)	28.2	24.2	38.9	
Alcohol (drinks)				0.13
never (%)	23.8	23.4	18.6	
mild (not current or ≤10/mo., %)	61.4	60.0	67.1	
heavy (>10/mo., %)	14.8	16.6	14.3	
Smoking				<0.01
never (%)	56.6	58.1	39.0	
former (%)	25.6	26.8	26.0	
active (%)	17.8	15.1	35.0	
Physical activity				<0.01
active (%)	76.6	82.3	70.2	
inactive (%)	23.4	17.7	29.8	
Postmenopause (%)	72.7	67.4	74.9	0.01
CRP (mean±SE, mg/dl)	0.47±0.02	0.48±0.02	0.67±0.04	0.01
Asthma (%)	3.4	5.4	29.0	<0.01
COPD (%)	4.3	8.3	33.7	<0.01
Cancer (%)	5.4	7.6	11.2	0.01

NO: no allergic symptoms; RC: symptoms of allergic rhinitis or conjunctivitis without wheezing; WZ: wheezing, SE: standard error.; BMI: body mass index; CRP: C reactive protein.

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self-reported symptoms of common allergic symptoms other than skin manifestations of allergy, it used prior physician made diagnosis of asthma, hay fever, drug allergy, and hives.

Interestingly, self-reported symptoms of rhinitis and conjunctivitis in the recent 12 months remained strongly associated with cancer even after adjusting for smoking and previous diagnosis of asthma or COPD, while neither asthma nor COPD showed any statistically significant association with cancer in a multivariate model. In addition, symptoms of wheezing illustrated stronger association with cancer than symptoms of rhinoconjunctivitis without wheezing, irrespective of smoking, asthma, and COPD.

This finding may indicate that current or recent common symptoms of allergy may portray a stronger association with cancer than any past history of asthma, or COPD.

The strength of our study is the representative nature of our population based study cohort, which is derived from a national probability sample. This may have reduced probable selection bias. We also were able to control for possible confounders. Low socioeconomic status has been positively associated with both cancer [48] and allergy [49,50]. People with higher education or higher income may engage in healthier lifestyle that protects themselves from possible occupational or environmental hazards

Table 2. Univariate and multivariate analyses of cancer risk factors among female study participants.

Clinical variables	univariate model			multivariate model		
	OR	95% CI	p value	AOR	95% CI	p value
Age (yrs)	1.02	1.01–1.04	<0.01	1.01	0.98–1.02	0.68
Race						
White	1			1		
African American	0.55	0.39–0.78	<0.01	0.65	0.44–0.98	0.04
Hispanic	0.44	0.25–0.75	<0.01	0.58	0.30–1.10	0.09
Education						
≥12 years	1			1		
9–11 years	1.15	0.73–1.82	0.54	1.02	0.62–1.70	0.93
<9 years	1.15	0.79–1.67	0.46	1.09	0.71–1.67	0.69
Income						
>\$ 25000	1			1		
\$15000~25000	0.93	0.56–1.54	0.77	0.72	0.43–1.20	0.20
<\$15000	1.19	0.85–1.68	0.30	0.85	0.58–1.24	0.38
BMI (kg/m²)						
BMI<18.5	1.79	0.66–86	0.25	1.16	0.56–4.61	0.37
BMI>= 18.5 & <25	1			1		
BMI>= 25 & <30	0.84	0.57–1.22	0.35	0.73	0.51–1.05	0.09
BMI>= 30	0.82	0.51–1.32	0.41	0.74	0.45–1.21	0.23
Alcohol						
never	1			1		
mild (not current, or ≤ 10/mo.)	1.56	1.09–2.21	0.02	1.53	1.06–2.23	0.03
heavy (>10/mo.)	1.12	0.68–1.83	0.64	1.03	0.60–1.78	0.91
Smoking						
never	1			1		
former	1.62	1.11–2.36	0.01	1.37	0.94–2.00	0.10
active	1.24	0.79–1.96	0.34	0.95	0.56–1.60	0.85
Physical inactivity						
inactive	1.29	0.90–1.86	0.16	1.21	0.79–1.85	0.37
Postmenopause	7.52	3.20–17.67	<0.01	7.42	2.96–18.61	<0.01
CRP (mg/dl)	0.97	0.78–20	0.78	0.87	0.68–1.10	0.23
Asthma	1.20	0.77–1.86	0.41	0.91	0.52–1.58	0.73
COPD	1.87	1.29–2.76	<0.01	1.24	0.78–1.96	0.36
NO	1			1		
RC	1.44	1.00–2.08	0.05	1.49	1.12–2.36	0.01
WZ	2.20	1.27–3.80	0.01	2.08	1.11–3.89	0.02

NO: no allergic symptoms; RC: symptoms of allergic rhinitis or conjunctivitis without wheezing; WZ: wheezing, SE: standard error; BMI: body mass index; CRP: C reactive protein, OR: odds ratio; CI: confidence interval; AOR: adjusted odds ratio.
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linked to both allergy and cancer. Also, people with symptoms of allergy may be exhibiting different lifestyle patterns compared with people with no symptoms. Thus, smoking status, physical inactivity, alcohol consumption as well as obesity were controlled for.

Symptoms of wheezing may result not only from allergy but from other causes including COPD, postnasal drip syndrome, pneumonia, vocal cord dysfunction, congestive heart failure, and exposure to irritants. Although asthma is one of the most common causes for wheezing, a finding of wheezing is neither sensitive nor specific for asthma [51]. In that regards, symptoms of RC may be a better index for allergy than WZ. In addition, people with very

mild or well controlled asthma may not have experienced any symptoms of WZ in the past 12 months. Also, postnasal drip syndrome from allergic rhinitis may cause WZ. Thus, in our study, we focused more on the symptom of WZ, rather than prior diagnosis of asthma. Therefore, it is interesting to note that symptoms of RC, not WZ, are linked with cancer among nonsmokers. Accordingly, in our multivariate model, we controlled for asthma and COPD when assessing the association between WZ and cancer.

Smoking is an important factor to take into consideration in assessing allergic symptoms. In people with smoking history, greater misclassification of asthma may occur. Possibly, people

Table 3. Association between allergic symptoms and cancer among smokers and nonsmokers.

Smoking status	Allergic symptoms	Univariate model			Multivariate model		
		OR	95% CI	p value	AOR	95% CI	p value
Never (n = 2505)	NO	1			1		
	RC	1.33	0.90–2.00	0.15	1.51	1.00–2.28	0.05
	WZ	1.65	0.80–3.42	0.17	1.45	0.54–3.92	0.45
Former or Active (n = 2094)	NO	1			1		
	RC	1.57	0.88–2.79	0.12	1.49	0.82–2.68	0.18
	WZ	2.43	1.24–4.75	0.01	2.38	1.16–4.87	0.02

NO: no allergic symptoms; RC: symptoms of allergic rhinitis or conjunctivitis without wheezing; WZ: wheezing, OR: odds ratio; CI: confidence interval; AOR: adjusted odds ratio.

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with allergic symptoms may opt not to smoke, or may quit smoking more frequently than people with no such symptoms [52]. Therefore, we did stratified analyses according to smoking status. Since we focused on female participants only, there were more never smokers (54.5%) than former or current smokers (45.5%) (Table 4). Intriguingly, among nonsmokers, the association between symptoms of RC and cancer remained statistically significant when controlled for possible confounders, indicating that mild common allergic symptoms may be linked with cancer more so in nonsmokers. To the contrary, among smokers, only symptoms of WZ were associated with cancer while symptoms of RC were not. This may mean that smoking may have affected the risk for developing symptoms of WZ or cancer in a differential fashion. However, there was no significant interaction of smoking on the association between allergy and cancer (Wald test $p = 0.78$).

Noticeably, breast cancer seems to be associated with symptoms of RC, rather than WZ. Consistent with our study, two prospective cohort studies including NHANES I follow up study found the same positive association between allergy and breast cancer [9,46]. Breast cancer has been initially suggested to have inverse association with asthma, but most recent studies have reported no significant association [12,34,45,46] with common allergic symptoms. While allergy was linked with reduced breast cancer risk for people diagnosed with breast cancer between age of 35 and 45 [21], average age for our study participants was close to 60 (Table 1).

The role of allergy in carcinogenesis is still unclear. There are, however, multiple plausible mechanisms to explain our findings. First, contribution of chronic inflammation to carcinogenesis and

tumor progression has been well established [53]. Allergy is a chronic condition that involves release of pro-inflammatory cytokines and presence of asthma has been related to the risk of developing lung cancer [6]. Interestingly, CRP, a known marker for inflammation, was not found to be associated with cancer in our study (Table 2). However, the role of immune response from allergy may be more complex depending on what type of immune cells are primarily involved in the reaction and where the carcinogenesis occurs [1,2]. Second, rhinitis or asthma may cause reduced clearance of carcinogens that are found in the airway. Mucociliary dysfunction has been described in asthmatics [54]. Third, estrogen may play a role. Allergy after puberty is more common and more severe among females and estrogen is known to augment humoral immune reaction and activate mast cells [55,56]. It is noteworthy that breast cancer was associated with having common symptoms of allergy and that no significant association between allergy and cancer could be found among NHANES III male participants (data not shown).

We identified the following limitations in our study. First, our study is a cross sectional study enabling a spurious positive association to result if undiagnosed cancer was causing any symptoms of RC or WZ. Although undiagnosed lung tumor may cause wheezing, the chance of having undiagnosed cancer in the lung causing wheezing is deemed low. In addition, symptoms of RC are not typical symptoms of undiagnosed cancer. Second, ascertainment bias may be present since data are built mostly from answers from questionnaires, or self-reported symptoms. Presence of allergy, asthma or COPD are self reported by the participants and the diagnosis or severity of the symptoms have not been

Table 4. Association between cancer subtypes and allergic symptoms among female study participants.

Cancer types	numbers	proportion (%)	Allergic Symptoms					
			RC			WZ		
			AOR	95% CI	p value	AOR	95% CI	p value
All	341	6.55	1.49	1.12–2.36	0.01	2.08	1.11–3.89	0.02
Breast	129	2.8	1.89	1.04–3.42	0.04	2.08	0.90–4.48	0.08
Uterine	42	0.91	1.01	0.43–2.40	0.97	1.94	0.44–8.57	0.37
Cervix	41	0.89	0.69	0.27–1.77	0.43	0.52	0.11–2.37	0.39
Colorectal	37	0.81	1.24	0.49–3.15	0.65	1.92	0.50–7.42	0.34

NO: no allergic symptoms; RC: symptoms of allergic rhinitis or conjunctivitis without wheezing; WZ: wheezing, OR: odds ratio; CI: confidence interval; AOR: adjusted odds ratio.

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confirmed by any objective measures such as serum IgE levels or pulmonary function test. Although having symptoms of RC or WZ in the last 12 months may not necessarily mean that allergy is present, validity of self-reported allergic symptoms has been reported previously [57]. Third, differential recall bias may be present in assessing allergic symptoms between patients with cancer and without cancer. Fourth, there could be other missed confounders that can skew our results. For instance, antihistamines used in allergy have been suggested to be linked with cancer [58], although inconclusive [59]. Also use of inhaled corticosteroid has been associated with reduction of lung cancer risk in COPD patients [60].

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In summary, we found statistically significant associations between common allergic symptoms like rhinitis/conjunctivitis and wheezing and all cancers, specifically between rhinitis/conjunctivitis and breast cancer not found in previous studies. Larger prospective studies are required to validate our findings.

Author Contributions

Conceived and designed the experiments: YKC SN JK AS MG WT. Performed the experiments: YKC SN JK AS MG WT. Analyzed the data: YKC SN JK. Wrote the paper: YKC SN. Data collection: YKC SN JK AS MG WT. Coordinated the project: WT.

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