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Associations between Allergies and Risk of Hematologic Malignancies: Results from the VITamins and Lifestyle (VITAL) Cohort Study

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Abstract

Immune dysregulations associated with allergies may affect cancer cell biology but studies on the relationship between allergies and risk of hematologic malignancies (HM) yielded inconsistent results. Herein, we used the VITamins and Lifestyle (VITAL) cohort to examine this association. From 2000–2002, 66,212 participants, aged 50–76, completed a baseline questionnaire on cancer risk factors, medical conditions, allergies, and asthma. Through 2009, incident HMs (n=681) were identified via linkage to the Surveillance, Epidemiology and End Results cancer registry. After adjustment for factors possibly associated with HMs, a history of airborne allergy was associated with increased risk of HMs (hazard ratio [HR]=1.19 [95% confidence interval: 1.01–1.41], $P=0.039$) in Cox proportional hazards models. This association was limited to allergies to plants/grass/trees (HR=1.26 [1.05–1.50], $P=0.011$) and was strongest for some mature B-cell lymphomas (HR=1.50 [1.14–2.00], $P=0.005$). Gender-stratified analyses revealed that the associations between airborne allergies overall and those to plants, grass, and trees were only seen in women (HR=1.47 [1.14–1.91], $P=0.004$; and HR=1.73 [1.32–2.25], $P<0.001$) but not men (HR=1.03 [0.82–1.29], $P=0.782$; and HR=0.99 [0.77–1.27], $P=0.960$). Together, our study indicates a moderately increased risk of HMs in women but not men with a history of allergies to airborne allergens, especially to plant, grass or trees.

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Conflict of Interest

The authors declare no relevant financial interests.

Authorship

M.S., E.W., and R.B.W. designed and performed research, analyzed and interpreted data, and wrote the manuscript. A.J.D. interpreted data and wrote the manuscript.

Keywords

allergies; cancer risk; epidemiology; hematologic malignancies; prospective cohort study; VITamins And Lifestyle (VITAL) study

INTRODUCTION

The interplay between the immune system and cancer is an ongoing focus of scientific interest. Increasing evidence indicates that dysregulation of the immune system, as for example found in allergic and autoimmune disorders, can affect survival of cells in developing tumors [1]. This observation suggests that the cancer rates in individuals affected by such disorders might be different from those in individuals that do not suffer from allergies or autoimmune diseases. However, conceptually, general mechanisms could be proposed that might lead to either a decrease or increase in individual or overall risk of cancer. For example, immunologic surveillance and anti-neoplastic defense could decrease the risk of cancer by eliminating malignant cells at an early stage of a developing malignancy [2]; conversely, chronic immune stimulation could promote carcinogenesis [3].

A possible association between allergies and risk of hematologic malignancies has been examined in several epidemiologic studies but results have been inconsistent [4]. While case-control studies have generally shown an inverse relationship [5, 6], prospective cohort studies failed to confirm these findings and, rather, suggested an increased risk of hematologic malignancies [7, 8]. Given these discordant results, we herein examined the association between allergies and incidence of hematologic malignancies using data from the large prospective VITamins and Lifestyle (VITAL) cohort study [9].

METHODS

Study Cohort

Details of the VITAL study, which was approved by the institutional review board at the Fred Hutchinson Cancer Research Center, have previously been described [9]. Briefly, questionnaires were mailed to 364,418 men and women age 50 to 76 years who lived in the 13-county area in western Washington State covered by the Surveillance, Epidemiology and End Results (SEER) cancer registry. 79,300 questionnaires were returned between October 2000 and December 2002, and 77,719 were deemed eligible. We excluded 11,487 participants with either a prior history of malignancies other than non-melanoma skin cancers (n= 11,273) or missing information on baseline cancer history (n=214). Additionally, 14 participants with missing information on medical history and 6 with reported hematologic cancer on death certificate but missing diagnosis date were excluded. Thus, a total of 66,212 individuals were included in this analysis.

Data Collection

Baseline data were collected using a 24-page self-administered, gender-specific questionnaire that focused on 3 major areas: health history and cancer risk factors, medication and supplement use, and diet. Participants provided information on age, race/

ethnicity, education, smoking, diet (fruit and vegetable intake), other lifestyle characteristics, self-rated health, medical history, and family history of leukemia or lymphoma. A history of allergies was ascertained by asking "Do you currently have allergies to any of the following?" with responses: "plants, grasses, or trees"; "mold or dust"; "cats, dogs or other animals"; "insect bites or stings"; "foods"; "medications"; or "other". Finally, asthma was assessed by asking "Has a doctor ever told you that you had Asthma?". The participants were not asked about the duration of reported allergies or any prior allergies that had resolved.

Identification of Incident Hematologic Malignancies

Incident hematologic malignancies (ICD-O-3 morphology codes 9590/3-9989/3) and other malignancies were identified by linking to the western Washington SEER cancer registry using matching algorithms [9]. The linkage was performed annually through December 2009. Hematologic malignancies were categorized using the 2008 WHO classification system [10].

Follow-Up

Patients were followed until the earliest date of: diagnosis of hematologic malignancy (1.03%), withdrawal from the study (0.03%), residential moves away from the SEER region (6.7%), cancer diagnosis other than hematologic malignancy or non-melanoma skin cancer (10.7%), death (3.6%), or last linkage to the SEER registry (December 31, 2009; 77.8%). We used the U.S. Post Office National change of address file, follow-up letters, and phone calls in order to assess moves from the SEER region. Deaths were ascertained via linkage to the Washington State death file.

Statistical Analyses

We used multivariable-adjusted Cox proportional hazards models with robust standard errors to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between allergies and risk of hematologic malignancies. Age was the time metric in regression models, with participants entering at the age of completing the baseline questionnaire and exiting at their age at end of follow-up. The models were controlled for the following variables that could potentially confound the association of interest: sex, race/ethnicity, education, history of smoking, consumption of vegetables and fruits, level of exercise, family history of leukemia/lymphoma and self-reported health status. In addition to hematologic malignancies overall, we also assessed the association between allergies and specific types of hematologic malignancies. In these cancer subtype analyses, cases of the other hematologic morphologies were censored at the time of cancer diagnosis. All reported *P*-values are two-sided, and were considered statistically significant if $P < 0.05$. The analyses were performed using STATA 11 (StataCorp, College Station, TX).

RESULTS

The 66,212 participants, aged 61.5 ± 7.4 (mean $\pm$ SD) years at baseline, were followed for a median of 7.9 ± 2.1 years. During this follow-up, 681 incident cases (1.03% of cohort) of hematologic malignancies were identified. Baseline characteristics of cases and non-cases

are presented in Table 1. As expected, participants who developed a hematologic malignancy were older than those who did not (65.2 ± 7.2 vs. 61.4 ± 7.3 years, $P < 0.001$). Cases were also more likely to: be male ($P < 0.001$), have 2 first-degree relatives with a family history of leukemia or lymphoma ($P = 0.002$), rate their health in the lower 3 of 5 categories (all $P < 0.03$), and be less physically active than non-cases. As expected, mature B-cell neoplasms, excluding chronic lymphocytic leukemia and small lymphocytic lymphoma (CLL/SLL) or plasma cell disorders were the most common cancers ($n = 262$ [0.4%]), followed by myeloid neoplasms ($n = 170$ [0.25%]), CLL/SLL ($n = 107$ [0.16%]), and plasma cell neoplasms ($n = 83$ [0.13%]; Table 2).

Overall, a history of allergies to airborne antigens was associated with higher incidence of hematologic malignancies both in the age/sex-adjusted Cox model (HR=1.27 [95% CI: 1.09–1.49], $P = 0.002$) and multivariate model (HR=1.19 [1.01–1.41], $P = 0.039$). However, this association did not appear uniform across different subtypes of airborne allergies. While, as shown in Table 3, a statistically significant association was seen in participants who reported a history of allergies to plants, grass, and trees (HR=1.26 [1.05–1.50], $P = 0.011$) in the multivariable model, the association with allergies to mold/dust or cats, dogs, or other animals did not reach statistical significance due to lack of power. Likewise, there was no significant association between development of hematologic malignancies and self-reported allergies to insect bites or stings, food, or medications; nor was there an association between physician-established diagnosis of asthma and risk of hematologic malignancy. There was a statistically non-significant association with “other” allergies in both the age/sex adjusted and fully-adjusted models.

When the associations between different types of allergies and the most common subtypes of hematologic malignancies were evaluated (Table 4), a history of allergies to “plant, grass, and trees” was found to be significantly associated with mature B-cell neoplasms other than CLL/SLL or plasma cell disorders (HR=1.50 [1.14–2.00], $P = 0.005$). In addition, there was an increased risk of plasma cell neoplasms for participants reporting a history of allergies to cats, dogs, or other animals (HR=1.92 [1.04–3.57], $P = 0.038$).

When we stratified the entire cohort by gender (Table 5), a history of allergy to airborne antigens was associated with increased incidence of hematologic malignancies in women (HR=1.47 [1.14–1.91], $P = 0.004$) but not in men (HR=1.03 [0.82–1.29], $P = 0.782$). Among women, there were also statistically significant associations between incident hematologic malignancies and a history of allergies to plants, grass, and trees (HR=1.73 [1.32–2.25], $P < 0.001$), to insect bites or stings (HR=1.48 [1.01–2.19], $P = 0.047$), and to “other allergies” (HR=1.68 [1.09–2.58], $P = 0.018$). No statistically significant associations were found between specific allergies and incident hematologic malignancies in men.

DISCUSSION

The results presented in this report from the VITAL study cohort support 2 major findings. First, we found that an allergy history to the airborne allergens and, specifically, allergies to plants, grass, and trees were associated with an increased risk of hematologic malignancies. However, this association was not uniform across all the subtypes of hematologic

malignancies we assessed, but, rather, was primarily found for some mature B-cell cells neoplasms. Second, gender-stratified analyses indicated that the association between certain allergies and incident hematologic malignancies we observed was limited to women.

Several previous studies have investigated the relationship between allergies and hematologic malignancies, with positive associations reported in some [2, 5, 6, 11]. Our findings are in line with results of some of the prospective cohort studies. For example, in a US veterans study, a history of “total allergic conditions” as documented in the hospital records was associated with a diagnosis of non-Hodgkin’s lymphoma (NHL) (risk ratio [RR]=1.4 [1.3–1.5]). Significant associations were also observed with the specific allergic conditions of alveolitis, dermatitis, and erythema, but not asthma [6]. Also, an analysis of the Multiethnic Cohort suggested an increased risk of NHL in participants with allergies and asthma that was restricted to Latinos [5]. In a Swedish cohort of more than 16,000 twins, the risk of leukemia was higher in patients with self-reported history of hives (RR=2.1 [1.0–4.5]) while no association was found between different subtypes of allergies and incidence of leukemia, CLL, NHL or myeloma [2]. Positive associations have also been reported in some case-control studies. For instance, in a population-based study from the Swedish cancer registries, an increased risk of lymphoplasmacytic lymphoma was reported in patients who had history of “any allergy or chronic inflammatory conditions” based on previous hospital discharge information (RR=1.2 [1.0–1.4]) [11]. The risk of childhood acute lymphoblastic leukemia (ALL) was also found to be higher in patients with a history of allergies based on a population-based study using the national health insurance research database of Taiwan [12]. In contrast, no associations or inverse associations were reported by other studies, mainly with a case-control design. While the investigations have been diverse both with regard to the definition and measurement of asthma or allergies and the subtypes of hematologic malignancies assessed, an inverse association with history of allergies has been reported for hematologic malignancies as a group [13], lymphoma overall [7, 14], Hodgkin’s lymphoma [14], NHL [8, 13–16], childhood ALL [17, 18], and multiple myeloma [14, 19]. Some of the discrepancy in results may be explained by common limitations of the various study designs, reverse causality, selection bias, and perhaps recall bias [15, 20] [4, 17].

To the best of our knowledge, ours is the first study to suggest important gender differences in the association between allergies and hematologic malignancies. Gender differences are reported in the association between history of allergies and head and neck cancers [21] and between allergen-specific IgE levels and glioblastoma [22]. However, given the differences in the direction of both main and the gender effects in those studies and also different environmental risk factors especially for head and neck cancers, a common explanation for the gender effect cannot be suggested. It is tempting to speculate that the additional effect of allergy may reach statistical significance in women because of their lower baseline risk for the development of hematologic malignancies compared to men. However, hormonal effects on the (dysregulated) immune system and interactions with carcinogenesis may offer an alternative biological explanation that will required further mechanistic studies, in particular if our findings are replicated in an independent study cohort.

Various explanations have been proposed to account for the observed increased incidence of hematologic malignancies in patients with immune dysregulation, including shared genetic and environmental risk factors, chronic activation and replication of lymphocytes and the subsequent increased chance of mutations and finally epigenetic changes, e.g. via effects on antigen recognition by T cells [1, 23]. However, additional biological studies will be required to understand the mechanisms underlying this association. Effects of the treatments used by patients with allergies on the cancer risk do not seem to explain the association, as to our knowledge, associations between use of antihistamines, leukotriene agonists or other common therapeutic agents for allergies with hematologic malignancies have not been reported. Furthermore, these medications are very commonly used by patients with history of allergies, making the distinction between the disease and its treatment in an observational study extremely difficult.

Our study has several strengths, including the large number of participants with comprehensive baseline information on cancer risk factors and medical conditions, its prospective design, and case ascertainment through the SEER registry with disease classification based on current WHO criteria. On the other hand, some limitations of our analyses need to be acknowledged. Most importantly, given the limited number of cases within each subtype of hematologic cancer subset, the risk estimates need to be interpreted with caution in our subtype analyses, and the possibility of chance finding due to multiple testing should be recognized. Furthermore, allergies were self-reported and, therefore, subject to measurement error; however, such an error, which would be non-differential in a prospective study, would likely lead to attenuation of associations. And finally, we only asked about the “current” allergies whereas information on the duration of reported allergies or past allergies was not collected. Participants with past allergies that were inactive at the time of completion of the baseline questionnaires might have responded “No” to the allergy question; such participants could lead to attenuation of associations. However, since allergies are often lifelong conditions, this possibility is unlikely to impact our analyses significantly.

In conclusion, our study suggests an increased risk of hematologic malignancies in women but not men with self-reported history of airborne allergies, in particular to plants, grass, and trees. Further epidemiologic studies that include the disease biomarkers (plasma proteins, genetic polymorphism, etc.) will be needed for independent confirmation of this gender-specific association. While no causality can be inferred, these results suggest a possible gender-specific role of chronic stimulation of the immune system for the development of hematologic cancers.

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TABLE 1

Baseline Characteristics of Study Cohort

Characteristics	Cases (N=681)	Non-cases (N=65,531)	Age- and sex-adjusted HR (95% CI)
Age, N (%)			N/A
50 to <55 years	64 (9.4)	16,441 (25.1)	
55 to <60 years	128 (18.8)	15,511 (23.7)	
60 to <65 years	116 (17.0)	11,925 (18.2)	
65 to <70 years	144 (21.2)	10,314 (15.7)	
70	229 (33.6)	11,340 (17.3)	
Gender, N (%)			
Female	272 (40.0)	33,361 (50.9)	1.00 (Reference)
Male	409 (60.0)	32,170 (49.1)	1.65 (1.41–1.92), <i>P</i> <0.001
Race/Ethnicity, N (%)			
White	631 (92.7)	59,948 (91.5)	1.00 (Reference)
Hispanic	9 (1.3)	576 (0.9)	1.73 (0.89–3.35), <i>P</i> =0.103
Other	32 (4.7)	3,910 (6.0)	0.81 (0.57–1.16), <i>P</i> =0.249
Missing Information	9 (1.3)	1,097 (1.7)	
Education, N (%)			
High school graduate or less	150 (22.0)	12,504 (19.1)	1.00 (Reference)
Some college	233 (34.2)	24,674 (37.7)	0.93 (0.76–1.14), <i>P</i> =0.495
College or advanced degree	289 (42.4)	27,276 (41.6)	1.02 (0.84–1.25), <i>P</i> =0.813
Missing Information	9 (1.3)	1,077 (1.6)	
Smoking Status (Cigarettes)			
No, N (%)	307 (45.1)	31,329 (47.8)	1.00 (Reference)
Yes, N (%)	367 (53.9)	33,775 (51.5)	
Pack-years, mean (SD)*	27.5 (23.6)	25.7 (23.2)	1.00 (1.00–1.00), <i>P</i> =0.917
Missing Information, N (%)	7 (1.0)	427 (0.7)	
Family History of Leukemia/Lymphoma, N (%)			
None	615 (90.3)	61,239 (93.5)	1.00 (Reference)
1 first degree relative	42 (6.2)	3,338 (5.1)	1.23 (0.90–1.68), <i>P</i> =0.188
2 first degree relatives	6 (0.9)	147 (0.2)	3.65 (1.63–8.20), <i>P</i> =0.002
Missing Information	18 (2.6)	807 (1.2)	
Vegetable Intake (servings/day), N (%)			
1 st tertile (<1.25)	213 (31.2)	19,874 (30.3)	1.00 (Reference)
2 nd tertile (1.25–2.16)	219 (32.1)	19,867 (30.3)	1.02 (0.84–1.23), <i>P</i> =0.875
3 rd tertile (>2.16)	194 (28.5)	19,954 (30.5)	0.96 (0.79–1.17), <i>P</i> =0.683
Missing Information	55 (8.1)	5,836 (8.9)	
Fruit Intake (servings/day), N (%)			
1 st tertile (<0.93)	218 (32.0)	19,868 (30.3)	1.00 (Reference)

Characteristics	Cases (N=681)	Non-cases (N=65,531)	Age- and sex-adjusted HR (95% CI)
2 nd tertile (0.93–1.94)	190 (27.9)	19,969 (30.4)	0.84 (0.69–1.01), <i>P</i> =0.070
3 rd tertile (>1.94)	218 (32.0)	19,931 (30.4)	1.01 (0.83–1.22), <i>P</i> =0.957
Missing Information	55 (8.1)	5,836 (8.9)	
Self-Reported Health, <i>N</i> (%)			
Excellent	78 (11.5)	10,220 (15.6)	1.00 (Reference)
Very Good	255 (37.4)	25,467 (38.9)	1.24 (0.96–1.59), <i>P</i> =0.100
Good	241 (35.4)	21,571 (32.9)	1.34 (1.03–1.72), <i>P</i> =0.026
Fair	78 (11.5)	6,242 (9.5)	1.52 (1.11–2.08), <i>P</i> =0.009
Poor	15 (2.2)	1,028 (1.6)	2.09 (1.21–3.63), <i>P</i> =0.009
Missing Information	14 (2.1)	1,003 (1.5)	
Physical Activity average in 10 years (MET hours/week), <i>N</i> (%)			
None	123 (18.1)	9,550 (14.6)	1.00 (Reference)
1 st quartile (3.0)	124 (18.2)	13,629(20.8)	0.74 (0.58–0.95), <i>P</i> =0.018
2 nd quartile (>3.0–8.1)	138 (20.3)	13,805 (21.1)	0.77 (0.60–0.98), <i>P</i> =0.032
3 rd quartile (>8.1–17.8)	137 (20.1)	13,744 (21.0)	0.73 (0.57–0.93), <i>P</i> =0.012
4 th quartile (>17.8)	144 (21.2)	13,916 (21.2)	0.72 (0.56–0.91), <i>P</i> =0.007
Missing Information	15 (2.2)	887 (1.4)	

* Among smokers and former smokers.

Abbreviations: CI, confidence interval; HR, hazard ratio; N/A, not applicable; SD standard deviation

TABLE 2

Incident Hematologic Malignancies by Subtype

Disease	Cases N (%)	Incidence in the cohort (%)
Myeloid neoplasms	170 (24.9)	0.25
Myelodysplastic syndrome (MDS)	69 (10.1)	0.10
Acute myeloid leukemia (AML)	41 (6.0)	0.06
Myeloproliferative neoplasms	60 (8.8)	0.09
Mature B-cell neoplasms	452 (66.4)	0.69
CLL/SLL	107 (15.7)	0.16
Plasma cell disorders	83 (12.2)	0.13
Other Mature B-cell neoplasms (excluding CLL/SLL and plasma cell disorders)	262 (38.5)	0.40
Hodgkin lymphoma	23 (3.4)	0.03
Mature T-cell and natural killer cell neoplasms	22 (3.2)	0.03
Other [*]	14 (2.1)	0.02
Total	681 (100)	1.03

* Includes cases of malignant lymphoma, not otherwise specified [NOS]; leukemia, NOS; acute biphenotypic leukemia; and precursor B-cell lymphoblastic leukemia.

TABLE 3

Association between Allergies and Asthma and Hematologic Malignancies.

	Cases (681) N (%)	Non-cases (65,531) N (%)	Age and sex-adjusted HR (95% CI)	Multivariable[*]-adjusted HR (95% CI)
Airborne Allergens	251 (36.9%)	22,188 (33.9%)	1.27 (1.09–1.49), <i>P</i> =0.002	1.19 (1.01–1.41), <i>P</i> = 0.039
Plants, Grass, Trees	199 (29.2%)	16,666 (25.4%)	1.34 (1.13–1.58), <i>P</i> =0.001	1.26 (1.05–1.50), <i>P</i> =0.011
Mold, Dust	138 (20.3%)	13,393 (20.4%)	1.11 (0.92–1.34), <i>P</i> =0.274	1.06 (0.87–1.30), <i>P</i> =0.551
Cats, Dogs, other Animals	72 (10.6%)	6,697 (10.6%)	1.19 (0.93–1.51), <i>P</i> =0.169	1.13 (0.87–1.46), <i>P</i> =0.371
Insect Bites or Stings	49 (7.2%)	4,390 (6.7%)	1.19 (0.89–1.59), <i>P</i> =0.241	1.25 (0.93–1.69), <i>P</i> =0.131
Food	49 (7.2%)	5,161 (7.9%)	1.02 (0.76–1.36), <i>P</i> =0.913	1.02 (0.76–1.39), <i>P</i> =0.895
Medications	148 (21.7%)	13,456 (20.5%)	1.20 (0.99–1.44), <i>P</i> =0.057	1.16 (0.96–1.42), <i>P</i> = 0.119
Other	35 (5.1%)	2,989 (4.6%)	1.25 (0.89–1.76), <i>P</i> =0.202	1.36 (0.97–1.93), <i>P</i> =0.079
Asthma	64 (9.4%)	6,354 (9.7%)	1.05 (0.82–1.37), <i>P</i> =0.685	0.91 (0.69–1.22), <i>P</i> =0.534

* All models adjusted for age, sex, race/ethnicity, education, smoking, family history of leukemia/lymphoma, self-reported health, consumption of vegetables and fruits and exercise.

Abbreviations: CI, confidence interval; HR, hazard ratio.

TABLE 4

Association between Allergies/Asthma and Subtypes of Hematologic Malignancies.

	Multivariable* -adjusted HR (95% CI)			
	Myeloid Malignancies (N=170)	CLL/SLL (N=107)	Plasma Cell Disorders (N=83)	Other Mature B-cell neoplasms (excluding CLL/SLL and plasma cell disorders) (N=262)
Airborne Allergies (N=22,439)	1.13 (0.80–1.60), <i>P</i> =0.481 (n=56)	1.30 (0.87–1.96), <i>P</i> =0.203 (n=40)	1.50 (0.95–2.35), <i>P</i> =0.080 (n=39)	1.20 (0.91–1.59), <i>P</i> =0.189 (n=98)
Plants, Grass, Trees (N=16,865)	1.01 (0.69–1.48), <i>P</i> =0.938 (n=39)	1.23 (0.79–1.91), <i>P</i> =0.360 (n=29)	1.48 (0.91–2.40), <i>P</i> =0.114 (n=32)	1.50 (1.14–2.00), <i>P</i> =0.005 (n=86)
Mold, Dust (N=13,531)	1.07 (0.71–1.61), <i>P</i> =0.759 (n=32)	1.13 (0.69–1.84), <i>P</i> =0.625 (n=22)	1.22 (0.73–2.05), <i>P</i> =0.453 (n=19)	1.03 (0.74–1.44), <i>P</i> =0.860 (n=53)
Cats, Dogs, other Animals (N=7,039)	1.25 (0.75–2.09), <i>P</i> = 0.392 (n=18)	1.04 (0.55–1.99), <i>P</i> =0.898 (n=11)	1.92 (1.04–3.57), <i>P</i> =0.038 (n=14)	0.80 (0.49–1.30), <i>P</i> =0.376 (n=21)
Insect Bites or Stings (N=4,439)	1.33 (0.74–2.42), <i>P</i> =0.339 (n=12)	0.97 (0.42–2.25), <i>P</i> =0.944 (n=6)	1.26 (0.55–2.88), <i>P</i> =0.576 (n=6)	1.52 (0.97–2.39), <i>P</i> =0.066 (n=22)
Food (N=5,210)	1.15 (0.63–2.11), <i>P</i> =0.641 (n=13)	0.80 (0.34–1.86), <i>P</i> =0.603 (n=6)	1.02 (0.44–2.35), <i>P</i> =0.958 (n=7)	1.07 (0.66–1.74), <i>P</i> =0.784 (n=18)
Medications (N=13,604)	1.34 (0.92–1.96), <i>P</i> =0.124 (n=39)	1.30 (0.81–2.08), <i>P</i> =0.275 (n=24)	0.51 (0.26–1.03), <i>P</i> =0.064 (n=11)	1.19 (0.87–1.65), <i>P</i> =0.279 (n=58)
Other (N=3,024)	1.33 (0.66–2.70), <i>P</i> =0.427 (n=9)	1.74 (0.80–3.78), <i>P</i> =0.161 (n=7)	1.94 (0.84–4.44), <i>P</i> =0.116 (n=6)	1.16 (0.63–2.15), <i>P</i> =0.623 (n=11)
Asthma (N=6,418)	0.53 (0.26–1.08), <i>P</i> =0.08 (n=10)	1.23 (0.66–2.29), <i>P</i> =0.517 (n=11)	1.67 (0.85–3.29), <i>P</i> =0.136 (n=13)	0.82 (0.51–1.34), <i>P</i> =0.438 (n=24)

* All models adjusted for age, sex, race/ethnicity, education, smoking, family history of leukemia/lymphoma, self-reported health, consumption of vegetables and fruits and exercise. Abbreviations: CI, confidence interval; HR, hazard ratio.

TABLE 5

Association between Allergies/Asthma and Hematologic Malignancies stratified by Sex.

	Men (N=32,579)		Women (N=33,633)		P for interaction
	N**	Multivariable* -adjusted HR (95% CI)	N**	Multivariable* -adjusted HR (95% CI)	
Airborne Allergens (overall)	9,840	1.03 (0.82–1.29), P=0.782; (n=128)	12,599	1.47 (1.14–1.91), P=0.004; (n=123)	0.054
Plants, Grass, Trees	7,573	0.99 (0.77–1.27), P=0.960; (n=97)	9,292	1.73 (1.32–2.25), P<0.001; (n=102)	0.004
Mold, Dust	5,420	1.02 (0.77–1.34), P=0.900; (n=70)	8,111	1.13 (0.84–1.52), P=0.410; (n=68)	0.692
Cats, Dogs, other Animals	2,915	0.96 (0.66–1.41), P=0.856; (n=33)	4,124	1.34 (0.93–1.93), P=0.112; (n=39)	0.253
Insect Bites or Stings	1,463	1.01 (0.62–1.65), P=0.959; (n=17)	2,976	1.48 (1.01–2.19), P=0.047; (n=32)	0.240
Food Allergies	1,716	1.09 (0.70–1.69), P=0.701; (n=23)	3,494	0.97 (0.63–1.49), P=0.888; (n=26)	0.642
Medications Allergies	4,023	1.15 (0.87–1.53), P=0.331; (n=62)	9,581	1.18 (0.90–1.56), P=0.236; (n=86)	0.967
Other Allergies	943	0.98 (0.54–1.80), P=0.955; (n=12)	2,081	1.68 (1.09–2.58), P=0.018; (n=23)	0.171
History of Asthma	2641	0.86 (0.58–1.29), P=0.470; (n=34)	3,777	0.98 (0.65–1.49), P=0.942; (n=30)	0.764

* All models adjusted for age, race/ethnicity, education, smoking, family history of leukemia/lymphoma, self-reported health, consumption of vegetables and fruits and exercise.

** Number of male or female participants with history of specific allergy. Abbreviations: CI, confidence interval; HR, hazard ratio.