Research Article

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Allergic Diseases and Risk of Hematopoietic Malignancies in a Cohort of Postmenopausal Women: A Report from the Iowa Women's Health Study

Amy M. Linabery[1,2], Anna E. Prizment[2,3], Kristin E. Anderson[2,3], James R. Cerhan[4], Jenny N. Poynter[1,2], and Julie A. Ross[1,2]

Abstract

Background: Allergic diseases signify immune dysregulation attributable to underlying genetics and environmental exposures. Associations between various allergies and hematopoietic cancers have been observed, albeit inconsistently; however, few prospective studies have examined the risk, and even fewer among older adults.

Methods: We examined risk of incident hematopoietic cancers in those reporting allergic diseases in a population-based cohort of 22,601 older women (Iowa Women's Health Study). Self-reported allergic status, including asthma, hay fever, eczema, and/or other allergies, was determined via questionnaire in 1997 (mean age, 72 years; range, 63–81 years). Incident cancers were ascertained by linkage with the Iowa Cancer Registry from 1997 to 2011. Cox proportional hazards regression was performed to estimate multivariate-adjusted HR and 95% confidence intervals (CI) for myeloid ($N = 177$) and lymphoid ($N = 437$) malignancies, respectively.

Results: Allergic diseases were not associated with risk of myeloid (HR, 1.00; 95% CI, 0.72–1.37) or lymphoid (HR, 0.99; 95% CI, 0.81–1.22) malignancies overall, or for most allergic and malignant subtypes examined. Self-reported asthma was positively associated with development of myelodysplastic syndrome (MDS; HR, 2.00; 95% CI, 0.93–4.32). In addition, there was a 30% to 40% decrease in risk of both lymphoid and myeloid cancers in those reporting rural residences but no association in those reporting urban residences; the interaction between residence and allergy was statistically significant for lymphoid malignancies ($P_{\text{interaction}} = 0.05$).

Conclusions and Impact: These results suggest that asthma may contribute to the pathogenesis of MDS, a finding consistent with the chronic antigen stimulation hypothesis. Susceptibility differences by location of residence are concordant with the hygiene hypothesis and merit additional exploration. *Cancer Epidemiol Biomarkers Prev; 23(9); 1903–12. ©2014 AACR.*

Introduction

An association between allergy and cancer was proposed in the medical literature as early as 1935 (1), has been formally examined since the 1950s (2, 3), and continues to be an active area of investigation today. Allergies result from an exaggerated response to environmental stimuli and signify immune dysregulation that has genetic underpinnings and that varies in symptoms and severity across individuals (4, 5). Both inverse and positive associations between allergic diseases and various cancers have been observed in children and adults, most notably inverse associations for gliomas, pancreatic cancer, and childhood acute lymphoblastic leukemia (ALL; ref. 6).

The study of allergic disease is of considerable interest in hematopoietic malignancies, given that the immune system itself is affected in both sets of conditions. Because of the relative rarity of these malignancies, association studies have been largely confined to case–control designs; notably, the few cohort studies on the topic have generally failed to replicate the associations observed in case–control studies. The most consistent finding in the literature to date suggests a personal history of allergies may be inversely associated with development of B lineage non-Hodgkin lymphoma (NHL). A metaanalysis of 13

[1]Division of Epidemiology and Clinical Research, Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota. [2]Masonic Cancer Center, University of Minnesota, Minneapolis, Minnesota. [3]Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota. [4]Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota.

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Corresponding Author: Amy M. Linabery, University of Minnesota, 420 Delaware Street SE, MMC 715, Minneapolis, MN 55455. Phone: 612-626-0278; Fax: 612-624-7147; E-mail: linabery@umn.edu

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case–control studies conducted by the InterLymph Consortium reported modest inverse associations between any specific allergy (OR, 0.84; 95% CI, 0.76–0.93) and hay fever (OR, 0.85; 95% CI, 0.77–0.95) and incident B-cell NHL, respectively (7). A small Swedish registry study likewise observed an inverse association between asthma and NHL mortality (8), whereas other cohort studies have reported null (9, 10) or positive associations for specific allergies and/or population subgroups and occurrence of NHL (11–15). Importantly, Melbye and colleagues (16) found an inverse association for serum levels of immunoglobulin E (IgE), a biomarker for allergy, only in blood samples collected <5 years before NHL diagnosis, but no association in samples collected ≥5 years before diagnosis, strongly suggesting that the inverse associations observed in other studies are attributable to reverse causality, where the developing lymphoma causes a suppression of allergic response.

There is also some evidence to suggest that allergies may confer reduced risk for ALL (10, 17–19). Case–control studies of incident childhood ALL have largely observed inverse associations with any allergies, and with asthma, eczema, and hay fever examined separately (17, 18); however, records-based studies have found null or positive associations (20, 21). In case–control studies of adult ALL, an inverse association was reported for asthma that required hospitalization in a large records-based Swedish study (OR, 0.6; 95% CI, 0.3–1.0; ref. 19), whereas a second questionnaire-based study showed no associations for asthma, eczema, or hay fever but a positive association for penicillin allergy (OR, 2.2; 95% CI, 1.0–4.4; ref. 22). Associations for Hodgkin lymphoma (HL), multiple myeloma (MM), myeloid leukemias, and myelodysplastic syndrome (MDS) have not been consistently observed or replicated (6, 23–26). For a more complete discussion, please see the reviews by Turner and colleagues (6, 25) and Martinez-Maza and colleagues (26).

Although the precise role of allergies in the development of hematopoietic malignancies is unknown, at least two commonly cited hypotheses have been offered to account for the observed associations, both positive and inverse. The antigen stimulation theory proposes that the immune system of allergic individuals is perpetually stimulated by allergens, resulting in chronic inflammation, stimulation of cell proliferation, and ultimately, increased risk for malignancy (27). In contrast, the immune surveillance theory (also called the prophylaxis theory; ref. 27) suggests that the presence of allergic diseases increases the capacity of the immune system to recognize and eliminate pathogens and other foreign bodies, including transformed cells, resulting in reduced cancer risk (27).

Because few prior prospective studies have examined the risk among older adults (11–13), with none of them examining MDS explicitly, and because women tend to have higher rates of allergy throughout the lifecourse (28) and lower rates of hematopoietic cancers than men (29), here we examined the association between a self-reported personal history of allergic diseases and risk of hematopoietic cancers in a well-characterized cohort of postmenopausal women from Iowa. Importantly, a sizable proportion of Iowa residents live in rural areas (39% in 1990; ref. 30) or specifically on farms (9.2% vs. 1.6% nationally in 1990; ref. 31). Given the previously observed links between agricultural exposures and both allergies (32–37) and hematopoietic malignancies (38–40), respectively, we examined possible differences in susceptibility for those with rural versus urban residences.

Materials and Methods

The methods of participant recruitment and enrollment, data collection, and follow-up for the Iowa Women's Health Study (IWHS) have been well described (38, 41, 42). Briefly, 98,030 women ages 55 to 69 years randomly identified through the 1985 Iowa driver's license records were contacted via mail in 1986 and asked to participate in a study of women's health. The 41,836 women who responded to the baseline questionnaire (42.7%) constituted the cohort. Responders and nonresponders to the baseline questionnaire had similar demographic characteristics (42). The baseline questionnaire requested information about anthropometry, physical activity, smoking, diet, personal and family medical history, and demographics. Follow-up questionnaires were administered to the cohort in 1987 (91% response rate), 1989 (90%), 1992 (83%), 1997 (79%), and 2004 (70%).

Subjects' affirmative responses to a multipart question from the 1997 follow-up questionnaire were used to classify individuals as allergic in the current analysis. [Question: "Have you ever been told by a doctor that you have: (a) asthma, (b) hay fever, (c) eczema or allergy of the skin, (d) other allergic conditions?" Responses: "Yes," "No," "Not sure."] A dichotomous summary variable of "any allergies," as well as a variable summing the number of allergies, was created for individuals responding definitively to at least one part of the question; individuals that did not respond to the question were excluded from analysis. There were no questionnaire items about medication use for allergic conditions.

The outcomes of incident lymphoid and myeloid malignancies were identified via linkage to the State Health Registry of Iowa, an NCI-designated Surveillance, Epidemiology, and End Results (SEER) cancer registry. International Classification of Diseases for Oncology, 3rd Edition (ICDO-3; ref. 43) morphology codes were provided for all cancers diagnosed in subjects from 1997 through 2011. The ICDO-3 codes were classified by study investigators based on the HAEMACARE (44) and 2008 World Health Organization classification systems (45; myeloid malignancies) and the SEER-InterLymph classification system (46; lymphoid malignancies). These classifications include any myeloid neoplasm, including MDS and myeloproliferative neoplasms (MPN; including chronic myelogenous leukemia, CML), as well as any lymphoid neoplasm, including NHL (including chronic lymphocytic

leukemia, CLL) and MM (Supplementary Table S1). Individuals diagnosed with a cancer reported at baseline and those with a cancer before the 1997 follow-up questionnaire were excluded. There were too few acute myelogenous leukemia (AML, $N = 37$) and HL ($N = 10$) cases to examine these groups separately.

The analysis cohort included 22,601 women at risk after excluding nonrespondents to the 1997 follow-up questionnaire ($N = 12{,}606$), those with a cancer diagnosis other than nonmelanoma skin cancer at baseline ($N = 2{,}366$) or before the 1997 follow-up questionnaire ($N = 2{,}477$), and those with missing allergy status ($n = 1{,}786$; categories are not mutually exclusive). Follow-up time (in person-years) was calculated for each subject as the period between the date of the 1997 follow-up survey and the end of follow-up, defined as the date of the hematologic cancer diagnosis, date of death (if death occurred in Iowa), date of Iowa emigration (if known), midpoint of the interval between the last follow-up contact and December 31, 2011 (if date of emigration was unknown), the midpoint of the interval between the last contact and date of death (if death occurred outside of Iowa), or December 31, 2011, whichever came first. Because data on MDS were first collected by SEER in 2001, we restricted the follow-up period for the analysis of MDS to 2001 to 2011.

The IWHS protocol and materials were approved by the University of Minnesota Institutional Review Board. Subjects indicated their consent for participation by returning completed questionnaires.

Statistical analysis

We performed Cox proportional hazards regression to estimate the associations of allergic conditions with risk of hematologic malignancies, producing both age-adjusted and multivariate-adjusted HRs and 95% confidence intervals (CI). Analyses were carried out by hematopoietic lineage (myeloid and lymphoid) and for malignant subgroups with 50 or more cases (MDS, MPN, NHL, and MM) for allergy overall, and for the specific allergic conditions queried; individuals reporting no history of any of the allergic conditions were used as the referent group. We adjusted for age (continuous), education (less than high school, high school, more than high school), body mass index (BMI) in 1997 (<25, 25–29.9, $\geq$30 kg/m^2), cigarette smoking status in 1997 (yes or no), and location of residence (urban or rural) in multivariable models as these variables were associated with hematologic cancers or allergy in prior IWHS analyses; results from the two sets of models (i.e., age-adjusted and fully adjusted) are presented. Because the inclusion of hormone replacement therapy or multivitamin use did not materially change the regression estimates, these variables were not retained in the final multivariate models. There was no evidence of effect modification by age, BMI, education, or smoking status at baseline or in 1997 (all $P_{\text{interaction}} \geq 0.10$). We then performed a subgroup analysis wherein we censored individuals at the time of their first cancer diagnosis in the follow-up period (1997–2011); age- and multivariate-adjusted HRs were estimated for the associations between allergic conditions and first myeloid ($N = 162$) and lymphoid ($N = 417$) malignancies, respectively. The proportional hazards assumption was evaluated by including an interaction between the allergy exposure variable and follow-up time in the Cox models. Given that there was no evidence against the proportional hazards assumption, interaction terms were not retained.

We also calculated separate HRs for those reporting rural (farm, a rural area but not a farm) versus urban (town with $\leq$2,499 residents, city with 2,500–>10,000 residents) residence at baseline to examine possible effect modification due to agricultural exposures. Heterogeneity of the HRs was tested by including an interaction term in the multivariable models; Wald χ^2 test P values are provided below.

All analyses were performed using Statistical Analysis Software (version 9.3; SAS Institute Inc.).

Results

The 22,601 older women included in the current analysis were followed for a median of 14.8 years and contributed 264,184 person-years of follow-up. In total, 177 myeloid cancers were identified among the analytical cohort, including 59 MDS and 64 MPN (including CML), and 437 were diagnosed with lymphoid malignancies, including 327 NHL (including CLL) and 79 MM. Selected subject characteristics are displayed in Table 1 by allergy status. Individuals with allergies were somewhat more likely to report, on average, an educational attainment of a high school diploma or more, a higher BMI at follow-up, rural residence, prior use of hormone replacement therapy, and multivitamin consumption. A personal history of allergic disease was not associated with risk of myeloid cancers after multivariate adjustment (HR, 1.00; 95% CI, 0.72–1.37; Table 2), although an inverse association was suggested in those reporting two or more conditions (HR, 0.53; 95% CI, 0.26–1.08). In examining specific cancer classifications, a modest, nonsignificant association was observed for any allergy and MDS overall; however, a strong positive association was observed for asthma and MDS (HR, 2.00; 95% CI, 0.93–4.32). Notably, the asthma association persisted upon restriction to MDS as the first cancer (54 cases, HR, 2.15; 95% CI, 0.99–4.64; not shown in tables).

There was little evidence of an association between allergies and lymphoid malignancies overall, either when examining allergies as a dichotomous variable (HR, 0.99; 95% CI, 0.81–1.22; Table 2) or in examining the risk associated with 2 or more concurrent allergies (HR, 0.99; 95% CI, 0.62–1.29). Similarly, there were no associations with the individual allergies queried or with the cancer subtypes examined.

Importantly, nearly identical results were observed upon excluding the first 3 years of follow-up for both myeloid and lymphoid malignancies (not shown).

Table 1. Selected characteristics [mean (SD) or percentage] of IWHS subjects ($N = 22{,}601$) by self-reported allergic status at the fourth follow-up questionnaire in 1997

	Allergy		
Characteristic	**No ($N = 15{,}449$)**	**Yes ($N = 7{,}152$)**	***P* value[a]**
Mean age at 1997 follow-up (SD; years)	72.23 (4.14)	72.08 (4.16)	0.01
Mean age at myeloid cancer diagnosis (SD; years)	79.99 (4.88)	80.42 (4.29)	0.58
Mean age at lymphoid cancer diagnosis (SD; years)	79.32 (5.17)	78.76 (5.35)	0.30
Education (>high school)[b]	40.19	45.50	<0.0001
BMI $\geq$30 kg/m^2[c]	22.71	26.69	<0.0001
Cigarette smoking status (yes)[c]	6.01	5.97	0.90
Rural residence[b,d]	29.75	24.57	<0.0001
Hormone replacement therapy use (yes)[c]	20.68	26.75	<0.0001
Multivitamin use (yes)[b]	31.76	37.16	<0.0001

[a]*P* values from general linear model or χ^2 test for continuous and categorical variables, respectively.
[b]Measured in 1986 baseline questionnaire.
[c]Measured in 1997 follow-up questionnaire, when allergic conditions were first queried. Notably, results were nearly identical upon adjustment for BMI, and smoking status and duration at baseline.
[d]Where rural was defined as living on a farm and a rural area but not a farm, and urban was defined as any town or city.

Upon stratification by location of residence, inverse associations between self-reported allergies and myeloid and lymphoid cancers, respectively, were observed for individuals reporting a rural residence, whereas modest positive associations were observed for those reporting urban residences (myeloid, $P_{\text{interaction}} = 0.14$; lymphoid, $P_{\text{interaction}} = 0.05$; Table 3). The interaction was also observed in examining only the first lymphoid cancers (417 cases, HR_{rural}, 0.68; 95% CI, 0.44–1.03; HR_{urban}, 1.17; 95% CI, 0.90–1.50; $P_{\text{interaction}} = 0.03$; not shown).

Discussion

We examined incident hematopoietic malignancies in a cohort of Caucasian women from Iowa ages $\geq$63 years in relation to their self-reported allergic status over a median follow-up time of 14.8 years. Overall, there was little evidence to support an association between allergic conditions and risk of lymphoid or myeloid malignancies, except for a 2-fold higher risk of MDS in those with self-reported asthma compared with those with no known allergy. In addition, a pattern based on location of residence was observed, where inverse allergy–cancer associations were suggested for those living in rural areas.

Allergies are often thought of as a childhood affliction; however, they commonly persist into adulthood and may manifest for the first time in older adults (47, 48). In general, the process of aging induces immunosenescence, with a variety of manifestations: decreased function, and in some cases lower numbers, of innate immune cells; reductions in circulating naïve T cells and B cell precursors (but increases in memory T cells); reduced diversity of T-cell receptor and antibody repertoires with diminished antibody affinity for antigens; chronic systemic inflammation; increases in circulating autoantibodies; and declines in serum IgE and decreased sensitization to allergens (47, 48). These patterns may be altered in the presence of individual allergic conditions: individuals with eczema, but not asthma or hay fever, maintain elevated IgE levels into late adulthood (49). Despite the effects of immunosenescence, allergies are regularly observed among Caucasian women >65 years, with lifetime prevalence estimated at 8.4% for asthma and 7.9% for hay fever in the United States in 2000 (28). Notably, these percentages are similar to those observed in the IWHS cohort (10.0% and 10.8%, respectively).

The lack of an allergy–hematopoietic cancer association in the current study is in general agreement with results from other prospective cohort studies of older adults, although different specific allergy–cancer associations were observed in each (11–13). The VITAL study, a cohort of adults in Washington State with a mean age of 62 years at baseline and followed for 8 years, also failed to observe an association except for a positive association between airborne allergies and development of mature B-cell lymphomas (HR, 1.50; 95% CI, 1.14–2.00). Upon stratification by sex, associations were observed between airborne allergens and hematologic malignancies in women (HR, 1.47; 95% CI, 1.14–1.91), but not in men (13). Likewise, no association was observed between a history of any allergic condition and incidence of hematologic malignancies in a cohort of Swedish twins (median age, 56 years; median follow-up, ~25 years; ref. 11). The Swedish study did find 3.6-fold increased leukemia risk in those with a personal history of hives and 2.3-fold increased NHL risk in those reporting childhood eczema (11). The multiethnic cohort, a study of U.S. adults in 5 ethnic groups ages 45 to 75 years followed for 10 years, reported no association for NHL risk with allergies

Table 2. Association between allergic diseases and hematologic malignancies in IWHS subjects (1997–2011)

			Age-adjusted	Multivariable-adjusted
	N	Person-years	HR[a] (95% CI)	HR[b] (95% CI)
Myeloid neoplasms				
No allergy[c]	122	183,223	Ref.	Ref.
Allergy[d]	55	80,961	1.03 (0.75–1.42)	1.00 (0.72–1.37)
No allergy[c]	122	183,223	Ref.	Ref.
1 allergy[d]	33	44,152	1.13 (0.77–1.66)	1.08 (0.73–1.60)
2+ allergies[d]	8	22,220	0.55 (0.27–1.12)	0.53 (0.26–1.08)
No allergy[c]	122	183,223	Ref.	Ref.
Asthma[e]	18	18,497	1.49 (0.91–2.45)	1.36 (0.82–2.27)
Hay fever[e]	14	21,056	1.00 (0.58–1.75)	1.00 (0.58–1.75)
Skin allergy[e]	14	31,892	0.66 (0.38–1.15)	0.65 (0.38–1.14)
Other allergy[e]	29	45,284	0.97 (0.65–1.45)	0.95 (0.63–1.42)
MDS[f]				
No allergy[c]	38	122,441	Ref.	Ref.
Allergy[d]	21	53,059	1.27 (0.75–2.17)	1.20 (0.70–2.03)
No allergy[c]	38	122,441	Ref.	Ref.
Asthma[e]	8	11,874	2.17 (1.01–4.64)	2.00 (0.93–4.32)
Hay fever[e]	5	13,858	1.15 (0.45–2.91)	1.06 (0.42–2.70)
Skin allergy[e]	5	20,931	0.77 (0.30–1.95)	0.73 (0.29–1.85)
Other allergy[e]	13	29,716	1.30 (0.68–2.48)	1.22 (0.64–2.34)
MPN (includes CML)				
No allergy[c]	46	183,373	Ref.	Ref.
Allergy[d]	18	81,034	0.90 (0.52–1.56)	0.84 (0.48–1.46)
No allergy[c]	46	183,373	Ref.	Ref.
Asthma[e]	4	18,519	0.90 (0.32–2.50)	0.67 (0.21–2.15)
Hay fever[e]	5	21,077	0.97 (0.39–2.44)	0.99 (0.39–2.50)
Skin allergy[e]	3	31,911	0.38 (0.12–1.22)	0.38 (0.12–1.22)
Other allergy[e]	11	45,327	1.08 (0.57–2.04)	1.05 (0.56–1.00)
Lymphoid neoplasms				
No allergy[c]	306	182,300	Ref.	Ref.
Allergy[d]	131	80,469	0.99 (0.81–1.21)	0.99 (0.81–1.22)
No allergy[c]	306	182,300	Ref.	Ref.
1 allergy[d]	77	43,835	1.05 (0.82–1.35)	1.07 (0.83–1.38)
2+ allergies[d]	33	22,071	0.99 (0.63–1.29)	0.99 (0.62–1.29)
No allergy[c]	306	182,300	Ref.	Ref.
Asthma[e]	35	18,329	1.14 (0.80–1.62)	1.10 (0.77–1.63)
Hay fever[e]	26	20,950	0.75 (0.50–1.12)	0.77 (0.51–1.16)
Skin allergy[e]	50	31,719	0.98 (0.73–1.32)	1.03 (0.76–1.38)
Other allergy[e]	68	45,053	0.91 (0.70–1.18)	0.93 (0.72–1.33)
NHL (includes CLL)				
No allergy[c]	232	182,504	Ref.	Ref.
Allergy[d]	95	80,558	0.93 (0.73–1.18)	0.95 (0.75–1.22)

(Continued on the following page)

Table 2. Association between allergic diseases and hematologic malignancies in IWHS subjects (1997–2011) (Cont'd)

			Age-adjusted	Multivariable-adjusted
	N	Person-years	HR[a] (95% CI)	HR[b] (95% CI)
No allergy[c]	232	182,504	Ref.	Ref.
Asthma[e]	25	18,365	1.07 (0.71–1.62)	1.03 (0.65–1.63)
Hay fever[e]	21	20,963	0.78 (0.51–1.25)	0.83 (0.52–1.31)
Skin allergy[e]	40	31,732	1.00 (0.71–1.39)	1.05 (0.75–1.47)
Other allergy[e]	48	45,105	0.85 (0.62–1.15)	0.88 (0.64–1.20)
MM				
No allergy[c]	53	183,443	Ref.	Ref.
Allergy[d]	26	81,029	1.17 (0.70–1.79)	1.15 (0.72–1.85)
No allergy[c]	53	183,443	Ref.	Ref.
Asthma[e]	5	18,518	0.95 (0.38–2.37)	0.94 (0.38–2.36)
Hay fever[e]	3	21,086	0.50 (0.16–1.60)	0.51 (0.16–1.62)
Skin allergy[e]	10	31,905	1.09 (0.56–2.15)	1.13 (0.57–2.23)
Other allergy[e]	14	45,334	1.08 (0.60–1.95)	1.11 (0.61–2.01)

[a]Adjusted for age (years, continuous).

[b]Adjusted for age (years, continuous), education (less than high school, high school, more than high school), BMI (kg/m^2, categorical; <25, 25–29.9, ≥30 per 1997 follow-up questionnaire), smoking status (yes, no), and residence (rural, urban).

[c]No allergy reference group includes only individuals indicating no asthma, hay fever, skin allergies, or other allergies.

[d]The number of cases reporting any allergy is higher than for the sum of those reporting 1 or >2 allergies because individuals with missing responses for specific allergies were excluded from the latter analysis.

[e]Column may total more than the number of affected cases because some individuals reported more than one allergic condition.

[f]Follow-up time for MDS analysis calculated for the period of 2001 to 2011 because data on MDS were first collected by SEER in 2001. The analysis cohort for MDS ($N = 21,293$) is smaller than the overall analysis cohort because all cancer cases diagnosed before 2001 were excluded ($N = 1,308$).

overall, but found a modest positive association (HR, 1.46) among the Latino subset (12). It is noteworthy that only positive, and not inverse, associations were observed for specific allergy–hematopoietic cancer pairings in these studies.

To our knowledge, this is the first prospective epidemiologic study to examine and report a positive association between asthma and MDS, although cooccurrence of asthma and MDS has been documented (50–52) and a range of other pulmonary complications have been linked

Table 3. Association between allergic diseases and hematologic malignancies in IWHS subjects by location of residence[a,b] (1997–2011)

	Rural[b]			Urban[b]			
	N	Person-years	HR[c] (95% CI)	*N*	Person-years	HR[c] (95% CI)	$P_{interaction}$[d]
Myeloid neoplasms							
No allergy[e]	37	56,483	Ref.	85	125,835	Ref.	
Allergy	8	20,840	0.60 (0.28–1.30)	47	59,730	1.14 (0.79–1.63)	0.14
Lymphoid neoplasms							
No allergy[e]	115	56,130	Ref.	190	125,275	Ref.	
Allergy	30	20,718	0.69 (0.46–1.04)	101	59,360	1.14 (0.89–1.46)	0.05

[a]One subject (without allergy) did not report her residence.

[b]Where rural was defined as living on a farm or a rural area but not a farm, and urban was defined as any town or city.

[c]Adjusted for age (years, continuous), education (less than high school, high school, more than high school), BMI (kg/m^2, categorical; <25, 25–29.9, ≥30 per 1997 follow-up questionnaire), smoking status (yes, no), and residence (rural, urban).

[d]*P* value for heterogeneity of the HRs obtained by inclusion of interaction term in the multivariable model.

[e]No allergy reference group includes only individuals indicating no asthma, hay fever, skin allergies, or other allergies.

to MDS, including infections, tumors, pleural effusion, various pneumonias, pulmonary fibrosis, autoimmune vasculitis, Sweet syndrome, and pulmonary arterial hypertension (53). Two prior hospital-based case–control studies failed to detect an association between self-reported allergies and MDS; however, neither of them examined asthma history and MDS explicitly (23, 24); indeed, one study did not incorporate asthma in its summary definition of allergies (24).

The immunologic state preceding MDS is not well characterized; however, dysregulation in the form of autoimmunity is frequently observed (54). The elevated HR for MDS in those with asthma observed herein may be attributable to overlapping genetic susceptibility. For example, different variants in *GATA2*, a gene encoding a transcription factor that regulates gene expression in hematopoietic progenitor cells, have been associated with elevated eosinophil counts (55), as well as sporadic and familial MDS (56, 57). Or, the association may result from chronic antigenic stimulation, where inflammatory cells release cytokines, chemokines, growth factors, and eicosanoids in response to environmental triggers (reviewed in ref. 58), thereby creating an environment conducive to MDS development.

Importantly, diagnosing asthma in older adults is not as straightforward as it is in younger people due to a number of factors, including patients' failure to acknowledge the severity or significance of symptoms, the fact that wheeze and dyspnea are symptoms of multiple, sometimes coexisting, conditions, and the underutilization of objective measures like spirometry in obtaining a differential diagnosis (59). The net result is that asthma remains undiagnosed in approximately half of older adults with the disease (60), and has likely been underascertained in the IWHS. Conversely, study subjects may have misattributed other pulmonary conditions as asthma. Validation studies in younger subjects have shown that questionnaire-based assessment of physician-diagnosed asthma has high specificity, although modest sensitivity (61), meaning that although some exposed individuals may not be identified, those that self-identify as having allergies or asthma are likely truly affected. A related issue is that asthma can be caused by hypersensitivity reactions, often originating in childhood, or may be a nonallergic, adult-onset form due to obesity, occupational exposures, or other causes (62). We were unable to differentiate between allergic and nonallergic asthma; however, based on estimates from NHANES III, where 75.3% of subjects with asthma ages 40 to 59 years were considered atopic by skin prick testing (63), we assume a majority of asthmatics are similarly atopic. Further, it is not clear that this distinction is important, because elevated levels of immune mediators IgE, IL3, IL4, IL5, IL13, and GM-CSF have been demonstrated in both groups (64). We conclude that the asthma–MDS observation has generated a new hypothesis worthy of future investigation.

This is also the first study we are aware of to report that allergies are inversely associated with hematologic cancers in a rural setting, but positively associated in more urban environments. Importantly, women residing on farms or in rural areas may have had contact with a variety of agriculture-specific exposures, such as raw milk (33), pesticides, and the dust, pathogens (including endotoxin), molds, and ammonia associated with livestock and their care (65). The observation of lower risk in rural residents is consistent with the hygiene hypothesis (66, 67): increased microbial challenges or other immune-modulating exposures in rural settings may facilitate the development of a more robust immune system that elicits an appropriately regulated response to environmental allergens and that may have enhanced capacity for tumor immunosurveillance. With regard to potential anticarcinogenic mechanisms, exposure to pathogens may serve as an adjuvant to enhance the immune response, may activate antitumor effector cells due to cross-reactivity of antigens from infectious organisms and neoplastic cells, or may help to establish normal regulation of immune responses, including suppression of Th2 responses and inappropriate chronic inflammation by Tregs that allows for Th1 antitumor responses (67).

Several studies have confirmed that childhood exposure to farming, particularly traditional dairy farming (32, 33, 35), confers protection from allergic conditions not only in childhood (32–34), but that the protection is extended into early (35–37) and later adulthood (37). There is also some epidemiologic research to suggest that the immune system, although largely developed by 5 years of age (68), is dynamic, such that exposures during adulthood continue to affect allergic sensitization (36, 37). A notable exception to the "farm effect" is the positive associations observed between exposure to swine and/or antibiotics added to swine feed, respectively, and asthma or asthma-like syndrome in studies of exposed children, farmers, and veterinarians (34, 69, 70). This observation is of particular relevance because Iowa leads the nation in hog production (71). Information about age at onset and severity of allergic disease, as well as lifetime residential or farming history, was not collected in the current study to permit examination of the etiologically relevant time periods or specific exposures.

Contact with agricultural pesticides is another potential concern (72, 73); however, pesticide exposure is unlikely to account for the inverse association between allergies and hematopoietic cancers among women living in rural areas in the current analysis (38).

This study is among the few to examine the allergy-hematologic cancer association prospectively among older women using a well-characterized, stable cohort. Strengths include the documented low annual emigration rate out of Iowa (<1%; ref. 42) and the linkage to the Iowa SEER Cancer Registry, which facilitated nearly complete detection of incident hematologic malignancies. In following these women for nearly 15 years, 177 myeloid and 437 lymphoid malignancies were ascertained, allowing for detection of relative risks on the order of 1.5 and 1.3,

respectively, with 80% power (two-sided α). Among subgroups, there was 80% power to detect RRs of 1.8 for MDS and MPN, 1.3 for NHL, and 1.7 for MM. By asking subjects about physician-diagnosed allergies over the course of the lifespan, we detected conditions that would not have been identified through other study designs that are largely limited to later adulthood, such as linkage to Medicare claims data.

There are also limitations. As discussed above, there is inherent misclassification in the self-report of allergic diseases (25, 61), as well as concerns about reverse causality (16). The "other allergy" category may be an especially heterogeneous grouping, encompassing both intolerance and true immune-mediated allergies to foods and medications (74–76). The association between allergies and cancer was not a primary aim of the IWHS and as such, limited exposure information was collected. Moreover, allergic conditions were first queried in the fourth follow-up questionnaire. A comparison of baseline characteristics for responders and nonresponders to the 1997 questionnaire showed they were very similar on some important demographic characteristics (e.g., age, BMI, multivitamin use), and somewhat less similar on others (e.g., educational attainment, smoking status, hormone replacement therapy use). Respondents to the 1997 follow-up questionnaire were also more likely to report "excellent" or "very good" general health at baseline compared with nonresponders (89.9% vs. 78.5%) and less likely to report one or more comorbidities (47.2% vs. 55.8%), suggesting some self-selection for continued participation by healthy (living) individuals. Further, although we recognize that each of the malignancies examined herein can be further divided into histologic and molecular subgroups with potentially unique etiologies, small sample sizes and lack of detailed clinical information precluded further stratification. This is particularly relevant for NHL, given that others have shown inverse associations with allergies and hay fever for B lineage NHLs (diffuse large B-cell and follicular NHL) and positive associations between eczema and T lineage NHL (7). Notably, although it did not achieve statistical significance, the HR describing the association between hay fever and NHL (HR = 0.77) is similar in magnitude to the OR reported by the aforementioned metaanalysis by the InterLymph Consortium (OR = 0.85; ref. 7). Finally, we did not adjust for multiple comparisons, and we acknowledge that HRs with P values near the 0.05 significance level, including those for the asthma–MDS association and the residence–allergies–lymphoid cancers interaction, may be spurious.

Conclusions

Self-reported asthma was positively associated with MDS in this cohort of older women; however, it is not clear from these data that allergic asthma, and not a different pulmonary complication, is the culprit. We have also reported possible differences in associations between allergic history and hematopoietic cancer development by location of residence, suggesting environmental exposures related to agriculture or city dwelling modulate the association. Clinical, molecular epidemiology, and mechanistic studies will be required to further our understanding of these observations.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

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Authors' Contributions

Conception and design: A.M. Linabery, J.R. Cerhan, J.N. Poynter
Development of methodology: A.E. Prizment
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.R. Cerhan
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.M. Linabery, A.E. Prizment, J.R. Cerhan, J.A. Ross
Writing, review, and/or revision of the manuscript: A.M. Linabery, A.E. Prizment, K.E. Anderson, J.R. Cerhan, J.N. Poynter, J.A. Ross
Study supervision: K.E. Anderson

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