Research Article

Cancer Epidemiology, Biomarkers & Prevention

Allergies and the Subsequent Risk of Cancer among Elderly Adults in the United States

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Abstract

Background: Allergic conditions may prevent some cancers by promoting immune surveillance. We examined associations of allergic rhinitis, asthma, and eczema with cancer risk among elderly Americans.

Methods: We used Surveillance Epidemiology and End Results (SEER)-Medicare linked data to perform a case–control study. Cases were individuals with first cancer diagnosed in SEER registries (1992–2013, ages 66–99; $N = 1{,}744{,}575$). Cancer-free controls ($N = 100{,}000$) were randomly selected from Medicare and matched on sex, age, and selection year. Allergic conditions were identified using Medicare claims, and logistic regression was used to estimate adjusted ORs (aOR) with significance gauged with a Bonferroni P cutoff ($P < 0.00034$).

Results: Allergic rhinitis, asthma, and eczema were present in 8.40%, 3.45%, and 0.78% of controls, respectively. For allergic rhinitis, strong inverse associations (aORs, 0.66–0.79) were observed for cancers of the hypopharynx, esophagus (squamous cell), cervix, tonsil/oropharynx, and vagina/vulva. More modest but significant inverse associations were noted for cancers of the esophagus (adenocarcinoma), stomach, colon, rectosigmoid/rectum, liver, gallbladder, lung, uterus, bladder, and miscellaneous sites. Associations were stronger in analyses requiring a dispensed medication to confirm the presence of allergic rhinitis. Asthma was associated with reduced risk of liver cancer [aOR 0.82; 95% confidence interval (CI), 0.75–0.91], whereas eczema was associated with elevated risk of T-cell lymphoma (aOR, 4.12; 95% CI, 3.43–4.95).

Conclusions: Inverse associations with allergic rhinitis are present for multiple cancers and require etiologic investigation.

Impact: Understanding of mechanisms by which allergic conditions reduce cancer risk may advance cancer prevention and treatment.

Introduction

Allergic rhinitis, asthma, and atopic dermatitis (eczema), often collectively referred to as allergic or atopic conditions, occur when an environmental substance (antigen) binds to immunoglobulin E (IgE) present on mast cells in mucosal tissue or the skin. Binding to IgE triggers mast cells to release mediators such as histamine, leukotrienes, and cytokines, causing a subsequent influx of inflammatory cells to the site of the allergic response (1). Furthermore, these local allergic reactions can have systemic effects associated with a cascade of inflammatory events at distant sites (2–4). Allergic rhinitis, asthma, and eczema are relatively common and treatable conditions in the U.S. adult population, with an estimated prevalence of 11%–33%, 8%, and 4%–10%, respectively (5–8). These conditions are associated with substantial morbidity (e.g., depression, lost sleep), lost productivity, and high medical costs (9–12).

There is emerging evidence that some allergic conditions may alter cancer risk, but the proposed mechanisms suggest opposing effects. It has been postulated that an allergic response may lead to heightened immunosurveillance, in which immune cells activated by the allergic response may direct the destruction of abnormal precancerous cells, thereby preventing the development of cancer (13). This hypothesis has inspired interdisciplinary research into the biological intersection of allergies and oncology (14). Alternatively, chronic inflammation associated with an allergic response may cause tissue damage, leading to an increased risk of cancer (15). Given the complex biological pathways and resultant effects of allergic conditions, both hypotheses may be correct in different contexts, with the role of allergies varying according to the allergic condition and cancer site.

Epidemiologic evidence documenting associations between allergic conditions and cancer has been mixed (16, 17). The most consistent and robust inverse associations have been reported between all three allergic conditions and risk of brain cancer, with relative risks varying between 0.3 and 0.8 (17–25). However, associations seem to vary according to the percentage of proxy respondents (with stronger protective associations reported in studies with a higher percentage of proxy respondents; ref. 26) and the type of brain cancer (stronger for glioma than meningioma; refs. 19, 25). Moreover, associations of serum IgE levels with brain cancer have been inconsistent (27–29). Moderate inverse associations have also been reported between allergic rhinitis and risk of pancreatic cancer (17, 30, 31) and colorectal cancer (32, 33). In contrast, several studies have described a positive association between eczema and risk of T-cell lymphoma (34, 35).

Previous studies generally identified the presence of allergic conditions using reports by participants or their proxies. However, allergic conditions can present with mild and nonspecific symptoms, and studies relying on self or proxy report may be susceptible to exposure misclassification if participants have trouble

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accurately reporting minimally symptomatic conditions. A few studies assessed circulating IgE levels, but this approach was the exception (27–29, 36–39). Although many studies focused on a specific cancer site, some studies have examined the association between allergic conditions and more than a single cancer site (38–48).

In this study, we utilized the Surveillance Epidemiology and End Results (SEER)-Medicare linked database to comprehensively assess associations between these three common allergic conditions and cancer risk among elderly US adults (49).

Material and Methods

We used the SEER-Medicare database to perform a case–control study of cancer (49). SEER-Medicare is a linkage between 18 SEER cancer registries and Medicare. SEER covers approximately 28% of the U.S. population, and Medicare is a federally funded program that provides hospital (part A) benefits to all Americans age 65 years or older. A majority of Medicare beneficiaries also enroll in part B, which covers physician visits (50). SEER-Medicare links 93% of cancer cases to their Medicare claims (50). The SEER-Medicare database also contains a 5% random sample of individuals living within SEER areas and their corresponding Medicare claims (49).

Medicare claims include diagnosis codes for medical conditions, including allergic conditions, for which hospitals or physicians request reimbursement. Since 2007, Medicare has provided outpatient pharmacy benefits (part D) in which beneficiaries can enroll. Part D claims can be used to identify individuals who received medications appropriate to treat allergic conditions.

We selected, as cases all individuals' ages 66–99 years with invasive first cancers recorded in SEER registries and diagnosed during 1992–2013. Availability of the SEER data allows evaluation of all cancer cases in the participating cancer registry areas. Cancers diagnosed only at autopsy or on death certificate were excluded. Controls ($N = 100{,}000$) were randomly selected from the 5% sample and were required to be alive and cancer free as of July 1 in the calendar year of selection. They could be selected more than once across calendar years and could also later become a case. Controls were frequency matched to cases overall in strata of sex, age category, and calendar year (see Table 1 note).

Ascertainment of allergic conditions for each study participant began at the latest of age 65 or initial year of availability of Medicare claims data in SEER-Medicare (which varied by selection year) and ended 1 year prior to cancer diagnosis or study selection (49). All study participants were enrolled in Medicare parts A and B, and not enrolled in a health organization (HMO), for at least 1 month after study entry and excluding the year prior to case diagnosis/control selection, and all participants had $\geq$1 claim during this period. We required enrollment outside an HMO because Medicare does not receive claims for specific services from HMOs.

Study participants were classified as having an allergic condition (allergic rhinitis, asthma, and eczema) if there was $\geq$1 inpatient claim or $\geq$2 physician or outpatient claims at least 30 days apart specifying that condition, with the claims occurring between study entry and 1 year prior to case diagnosis/control selection (claims within the year prior to diagnosis/selection were not assessed to prevent bias due to reverse causation or differential work-up of cases and controls; ref. 49). International Classification of Diseases version 9 (ICD-9) codes for these conditions are in the notes below Tables 2–4.

We used a modified version of the SEER site-recode variable, based on ICD-03 site and histology coding, to classify 53 cancer sites. For each allergic condition, we examined associations with cancer sites for which at least 10 affected cases were expected under the null hypothesis of no association with that condition, based on the frequency of the condition among the controls. This rule was applied separately for each allergic condition, so the assessed cancer sites varied across allergic conditions. We combined a few cancer sites that were similar but for which there were otherwise too few cases to evaluate, and we used histology codes to further classify selected cancer sites (Supplementary Table S1).

We used logistic regression with robust standard errors (SE) to estimate odds ratios (OR) and 95% confidence intervals (CI) for associations between cancers and allergic conditions. ORs were adjusted (aOR) for sex, age, race, calendar year of selection, and measures of socioeconomic status and healthcare utilization (see Tables 2–4 notes for details). Chronic obstructive pulmonary disease (COPD) is largely caused by smoking, and there is substantial overlap in symptoms for asthma and COPD (51). We classified participants as having COPD if they had at least 1 inpatient, physician, or outpatient claim with a COPD diagnosis code (ICD-9 496) at any point after study entry. To control for smoking, we adjusted logistic regression models for COPD status (allergic rhinitis and eczema analyses) or excluded individuals with COPD (asthma analysis). We present 95% CIs but focus on associations that met a Bonferroni level of significance ($P = 0.05/149$ combinations of allergic conditions and cancer sites $= 0.00034$).

In sensitivity analyses, we used Medicare Part D claims to increase the specificity of our assessment of allergic conditions. Approximately 60% of Part A/Part B beneficiaries elect Part D benefits. In the sensitivity analyses, we restricted to participants selected in 2008 or later, who had Part D coverage at case diagnosis/control selection and who had at least one Part D claim before 1 year prior to that date. We then categorized participants as affected by an allergic condition if they had both an ICD-9 diagnosis code for the allergic condition (as described above) and a part D claim between study entry and 1 year prior to cancer diagnosis/control selection for a medication commonly used to treat that condition: oral antihistamines and intranasal corticosteroids for allergic rhinitis; bronchodilators, inhaled corticosteroids, and leukotriene modifiers for asthma; and topical corticosteroids for eczema (see Supplementary Materials and Methods).

We hypothesized that some cases of these cancers may present with vague and nonspecific symptoms more than 1 year prior to diagnosis, leading to differential misclassification of the exposure status of cases. Therefore, in final sensitivity analyses we examined the associations in a subset of cancers with selected characteristics (e.g., population-based screening is recommended, or typically diagnosed at late stage), in which we excluded the 2 or 3 years immediately prior to cancer diagnosis/control selection.

Results

Our study included 1,744,575 cancer cases and 100,000 matched cancer-free controls (Table 1). By design, cases and controls were perfectly matched according to sex, age category, and calendar year of selection. Prior to selection, cases and controls had similar duration of Medicare part A, part B, and non-HMO coverage (median 52 months), and both groups had on average approximately five physician office visits per year. Cases

Table 1. Characteristics of cancer cases and controls

Characteristic	Number of subjects (%) or median (IQR)			
	Cases (n = 1,744,575)		Controls (n = 100,000)	
Age at diagnosis/selection (years)				
66–69	306,001	17.5	17,541	17.5
70–74	462,536	26.5	26,512	26.5
75–79	414,100	23.7	23,735	23.7
80–84	307,545	17.6	17,629	17.6
85–99	254,393	14.6	14,583	14.6
Sex				
Male	919,112	52.7	52,683	52.7
Female	825,463	47.3	47,317	47.3
Race				
White	1,470,432	84.3	82,658	82.7
Black	147,835	8.5	7,375	7.4
Other	126,308	7.2	9,967	10.0
Year of diagnosis/selection				
1992–1996	234,125	13.4	13,421	13.4
1997–2001	289,514	16.6	16,596	16.6
2002–2007	606,081	34.7	34,740	34.7
2008–2013	614,855	35.2	35,243	35.2
Total months part A, part B, non-HMO coverage[a]	52	(25–70)	52	(23–66)
Number of physician claims per year[a]	5.1	(2.1–9.6)	5.1	(2.0–9.7)
Percentage of residents in zip code living below poverty	11.6	(6.9–18.3)	11.6	(7.0–18.4)
COPD diagnosis[b]	410,288	23.5	18,766	18.8
Individuals in sensitivity analyses[c]	323,118	18.5	17,880	17.8

Abbreviation: IQR, interquartile range.
[a]The variable is evaluated between study entry and 1 year prior to selection or diagnosis.
[b]A person is classified as having a COPD claim if there is a claim for COPD at any point after study entry. COPD is a proxy for current or past heavy smoking status.
[c]These analyses are restricted to individuals selected in 2008 or later, who were enrolled in part D at selection and who had at least one part D claim between study entry and 1 year prior to selection.

and controls were nearly identical with respect to the percentage of people in their zip code living below poverty (11.6%). Compared with controls, a higher percentage of cancer cases had a COPD diagnosis (23.5% vs. 18.8%). For the sensitivity analyses, 323,118 cases and 17,880 controls were available (i.e., selected in 2008–2013 with part D coverage and at least one part D claim).

Allergic rhinitis

A total of 138,405 cases and 8,399 controls had a diagnosis of allergic rhinitis (7.93% vs. 8.40%, Table 2). A total of 51 cancer sites were assessed individually, and the proportion of cases with allergic rhinitis varied considerably by cancer site, from 5.33% among tonsil/oropharynx cancer cases to 11.27% among thyroid cancer cases.

Allergic rhinitis was significantly associated with reduced risk for 16 cancers (Table 2). The strongest inverse associations were with cancers of the hypopharynx (aOR 0.68; 95% CI, 0.56–0.83), esophagus (squamous cell; aOR, 0.66; 95% CI, 0.58–0.74), cervix (aOR, 0.74; 95% CI, 0.66–0.83), tonsil/oropharynx (aOR, 0.77; 95% CI, 0.70–0.85), and vagina/vulva (aOR, 0.79; 95% CI, 0.71–0.87). There were more modest inverse associations (aOR, 0.80–0.95) between allergic rhinitis and cancers of the esophagus (adenocarcinoma), stomach, colon, rectosigmoid/rectum, liver, gallbladder, lung, uterus, bladder, and miscellaneous sites. Allergic rhinitis was associated with increased risk of follicular non-Hodgkin lymphoma (NHL; aOR, 1.14; 95% CI, 1.07–1.22) and cancers of the prostate (aOR, 1.10; 95% CI, 1.06–1.14) and thyroid (aOR, 1.16; 95% CI, 1.09–1.23). Allergic rhinitis was not significantly associated with risk of brain cancer overall (aOR, 1.02; 95%CI, 0.95–1.08) or specifically glioma (aOR, 1.05; 95% CI, 0.98–1.13).

In our sensitivity analysis that incorporated use of medications in a stricter definition of allergic rhinitis, results were generally similar (Table 2). Notably, however, most inverse associations became stronger, including for cancers of the esophagus (squamous cell; aOR, 0.55; 95% CI, 0.42–0.72), esophagus (adenocarcinoma; aOR, 0.68; 95% CI, 0.55–0.85), stomach (aOR, 0.76; 95% CI, 0.68–0.85), colon (aOR, 0.79; 95% CI, 0.70–0.83), rectosigmoid/rectum (aOR, 0.78; 95% CI, 0.70–0.87), liver (aOR, 0.76; 95% CI, 0.68–0.86), lung (aOR, 0.79; 95% CI, 0.74–0.85), cervix (aOR, 0.60; 95% CI, 0.47–0.78), uterus (aOR, 0.74; 95% CI, 0.66–0.83), bladder (aOR, 0.83; 95% CI, 0.76–90), and miscellaneous sites (aOR, 0.77; 95% CI, 0.71–0.83). Allergic rhinitis was inversely associated with pancreatic cancer in the sensitivity analysis (aOR, 0.78; 95% CI, 0.71–0.85) but not the primary analysis. After Bonferroni correction, allergic rhinitis was not significantly associated with follicular NHL or cancers of the prostate or thyroid in the sensitivity analyses, although the aORs were similar to the main analysis (Table 2). The association between allergic rhinitis and brain cancer moved below the null in this analysis but was not significant (aOR, 0.87; 95% CI, 0.75–1.01). Compared with the primary analysis, sensitivity analyses in which we excluded 2 or 3 years of exposure classification prior to cancer diagnosis or control selection (Supplementary Tables S1 and S2) resulted in several associations moving further below the null (e.g., for cancers of the esophagus, colon, rectum, lung and kidney, and T-cell lymphoma), and the association with pancreatic cancer became statistically significant at $P < 0.00034$.

Asthma

Our analysis of asthma excluded individuals with a COPD diagnosis, leaving 1,334,287 cases and 81,234 controls. Among remaining subjects, 44,254 cases and 2,804 controls had a diagnosis of asthma (3.31% vs. 3.45%; Table 3). For 51 individually

Table 2. Associations between allergic rhinitis and cancer risk

Cancer site	Total	Allergic rhinitis[a] *N* (%)	Primary analysis[b] aOR (95% CI)	Sensitivity analysis[b] aOR (95% CI)
Controls	100,000	8,399 (8.40)	—	—
Cancer overall	1,744,575	138,405 (7.93)		
Lip	3,102	196 (6.32)	0.89 (0.76–1.03)	0.80 (0.56–1.15)
Tongue/mouth/gums	10,354	844 (8.15)	0.93 (0.86–1.00)	0.82 (0.69–0.98)
Salivary gland	4,040	321 (7.95)	0.92 (0.81–1.03)	1.00 (0.78–1.29)
Nasopharynx	1,142	115 (10.07)	1.18 (0.97–1.45)	1.56 (1.06–2.30)
Tonsil/oropharynx	7,954	502 (6.31)	**0.77 (0.70–0.85)**	0.79 (0.65–0.97)
Hypopharynx	2,083	111 (5.33)	**0.68 (0.56–0.83)**	0.80 (0.52–1.22)
Esophagus[c]	17,204	1,091 (6.34)	**0.77 (0.72–0.82)**	**0.62 (0.52–0.73)**
Adenocarcinoma	9,318	670 (7.19)	**0.87 (0.80–0.94)**	**0.68 (0.55–0.85)**
Squamous cell	6,221	335 (5.38)	**0.66 (0.58–0.74)**	**0.55 (0.42–0.72)**
Stomach	33,084	2,644 (7.99)	**0.90 (0.86–0.95)**	**0.76 (0.68–0.85)**
Small intestine	6,529	581 (8.90)	0.94 (0.86–1.03)	0.86 (0.71–1.05)
Colon	154,846	11,066 (7.15)	**0.87 (0.84–0.90)**	**0.79 (0.73–0.84)**
Rectosigmoid/rectum	47,731	2,950 (6.18)	**0.85 (0.81–0.89)**	**0.78 (0.70–0.87)**
Anus	4,146	363 (8.76)	0.95 (0.85–1.07)	0.81 (0.63–1.04)
Liver	19,263	1,747 (9.07)	**0.83 (0.78–0.88)**	**0.76 (0.68–0.86)**
Intrahepatic bile duct	3,250	297 (9.14)	1.00 (0.88–1.13)	0.87 (0.67–1.13)
Gallbladder	5,924	459 (7.75)	**0.82 (0.74–0.91)**	0.84 (0.68–1.04)
Pancreas	55,415	4,862 (8.77)	0.94 (0.90–0.98)	**0.78 (0.71–0.85)**
Nose/nasal cavity/middle ear	2,218	191 (8.61)	1.01 (0.86–1.17)	1.16 (0.85–1.59)
Larynx	11,714	791 (6.75)	0.90 (0.83–0.97)	0.89 (0.74–1.07)
Lung	274,214	22,027 (8.03)	**0.85 (0.83–0.88)**	**0.79 (0.74–0.85)**
Bone and joints	1,165	94 (8.07)	0.91 (0.73–1.13)	0.86 (0.53–1.39)
Soft tissue	7,567	631 (8.34)	0.95 (0.87–1.03)	0.86 (0.53–1.39)
Melanoma of skin	48,113	4,038 (8.39)	0.99 (0.95–1.04)	0.93 (0.85–1.03)
Nonepithelial skin cancer	6,964	622 (8.93)	0.94 (0.86–1.02)	0.79 (0.64–0.98)
Breast	203,086	19,078 (9.39)	0.98 (0.94–1.01)	0.96 (0.89–1.04)
Cervix	5,574	375 (6.73)	**0.74 (0.66–0.83)**	**0.60 (0.47–0.78)**
Uterus	42,113	3,107 (7.38)	**0.84 (0.80–0.88)**	**0.74 (0.66–0.83)**
Ovary	24,471	2,221 (9.08)	1.00 (0.95–1.06)	0.82 (0.72–0.93)
Vagina/vulva	6,120	490 (8.01)	**0.79 (0.71–0.87)**	0.73 (0.58–0.91)
Prostate	318,238	20,855 (6.55)	**1.10 (1.06–1.14)**	1.06 (0.96–1.16)
Urinary bladder	94,996	7,203 (7.58)	**0.92 (0.88–0.95)**	**0.83 (0.76–0.90)**
Renal pelvis/ureter	7,372	689 (9.35)	1.02 (0.94–1.11)	1.00 (0.83–1.20)
Kidney	39,258	3,340 (8.51)	0.96 (0.92–1.00)	0.86 (0.78–0.95)
Eye and orbit	2,319	199 (8.58)	1.05 (0.90–1.22)	1.00 (0.71–1.41)
Brain[c]	15,205	1,261 (8.29)	1.02 (0.95–1.08)	0.87 (0.75–1.01)
Glioma	12,901	1,076 (8.34)	1.05 (0.98–1.13)	0.92 (0.78–1.08)
Thyroid	12,556	1,415 (11.27)	**1.16 (1.09–1.23)**	1.17 (1.03–1.32)
Hodgkin lymphoma	3,054	309 (10.12)	1.17 (1.03–1.32)	1.25 (0.97–1.62)
NHL/CLL[c]	91,381	8,308 (9.09)	1.03 (1.00–1.07)	1.00 (0.93–1.08)
DLBCL	26,387	2,366 (8.97)	1.00 (0.95–1.05)	0.92 (0.83–1.03)
T cell	4,387	408 (9.30)	1.03 (0.92–1.14)	0.89 (0.69–1.14)
Marginal zone	6,307	658 (10.43)	1.05 (0.96–1.14)	0.99 (0.82–1.19)
Follicular	11,865	1,142 (9.62)	1.14 (1.07–1.22)	1.21 (1.04–1.41)
CLL/SLL	25,107	2,177 (8.67)	1.03 (0.98–1.09)	1.08 (0.97–1.22)
Lymphoplasmacytic	1,164	110 (9.45)	1.02 (0.83–1.25)	1.16 (0.76–1.78)
Mantle cell	2,825	260 (9.20)	1.07 (0.94–1.23)	0.88 (0.65–1.20)
Myeloma	26,107	2,313 (8.86)	1.02 (0.97–1.08)	0.97 (0.87–1.08)
AML	13,031	1,182 (9.07)	0.97 (0.91–1.04)	0.78 (0.66–0.91)
CML	5,795	504 (8.70)	0.95 (0.86–1.04)	1.01 (0.83–1.24)
Mesothelioma	5,008	398 (7.95)	1.05 (0.94–1.17)	0.89 (0.67–1.17)
Kaposi sarcoma	896	76 (8.48)	1.00 (0.78–1.27)	0.96 (0.58–1.61)
Miscellaneous	99,523	8,495 (8.54)	**0.85 (0.82–0.88)**	**0.77 (0.71–0.83)**

NOTE: Bold values are significant at $P < 0.00034$.

Abbreviations: AML, acute myeloid leukemia; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic leukemia; CML chronic myeloid leukemia; DLBCL, diffuse large B-cell lymphoma.

[a]ICD-9 codes used to classify allergic rhinitis are: 477, 477.0, 477.2, 477.8, and 477.9.

[b]Logistic regression models were adjusted for sex (excluding sex-specific cancers, for which we restricted to the appropriate sex), age (66–69, 70–74, 75–79, 80–84, and 85–99 years), race (white, black, and other), quantiles of the percentage of individuals living in poverty in zip code, number of physician visits per year excluding the year prior to selection or diagnosis, and diagnosis of COPD (a proxy for heavy smoking status).

[c]Subtype histology codes are listed in Supplementary Table S3.

evaluated cancer sites, the proportion of cases with asthma varied from 2.01% among hypopharynx cancer cases to 5.13% among thyroid cancer cases.

Most associations between asthma and specific cancer sites were null (Table 3). Only liver cancer was significantly associated with asthma after the Bonferroni correction (aOR, 0.82; 95% CI,

Table 3. Associations between asthma and cancer risk

Cancer site	Total	Asthma[a] *N* (%)	Primary analysis[b] aOR (95% CI)	Sensitivity analysis[b] aOR (95% CI)
Controls	81,234	2,804 (3.45)	—	—
Cancer overall	1,334,287	44,254 (3.31)		
Lip	2,383	69 (2.90)	1.08 (0.84–1.38)	0.88 (0.48–1.63)
Tongue/mouth/gums	7,663	228 (2.98)	0.85 (0.74–0.97)	0.82 (0.61–1.10)
Salivary gland	3,197	100 (3.13)	0.94 (0.76–1.15)	0.68 (0.41–1.14)
Nasopharynx	866	29 (3.35)	0.94 (0.65–1.37)	0.76 (0.31–1.87)
Tonsil/oropharynx	5,686	153 (2.69)	1.01 (0.91–1.11)	0.95 (0.68–1.34)
Hypopharynx	1,343	27 (2.01)	0.72 (0.49–1.06)	0.78 (0.32–1.92)
Esophagus[c]	12,248	308 (2.51)	0.84 (0.75–0.95)	0.71 (0.53–0.95)
Adenocarcinoma	6,759	172 (2.54)	0.88 (0.75–1.03)	0.73 (0.49–1.07)
Squamous cell	4,302	108 (2.51)	0.80 (0.66–0.98)	0.81 (0.52–1.26)
Stomach	25,416	878 (3.45)	1.01 (0.93–1.09)	0.91 (0.76–1.09)
Small intestine	5,187	215 (4.14)	1.11 (0.98–1.26)	1.03 (0.77–1.38)
Colon	122,479	3,772 (3.08)	0.94 (0.89–0.99)	0.93 (0.83–1.05)
Rectosigmoid/rectum	38,539	1,038 (2.69)	0.92 (0.85–0.99)	0.90 (0.76–1.07)
Anus	3,200	134 (4.19)	1.12 (0.94–1.34)	0.99 (0.68–1.43)
Liver	14,491	494 (3.41)	**0.82 (0.75–0.91)**	0.85 (0.70–1.04)
Intrahepatic bile duct	2,594	112 (4.32)	1.18 (0.97–1.43)	1.17 (0.79–1.74)
Gallbladder	4,787	170 (3.55)	0.92 (0.79–1.08)	0.76 (0.53–1.09)
Pancreas	43,232	1,540 (3.56)	0.94 (0.88–1.01)	0.80 (0.69–0.92)
Nose/nasal cavity/middle ear	1,666	58 (3.48)	1.04 (0.79–1.35)	0.70 (0.36–1.36)
Larynx	7,443	177 (2.38)	0.90 (0.77–1.06)	0.76 (0.51–1.13)
Lung	154,890	4,988 (3.22)	0.99 (0.95–1.04)	1.02 (0.91–1.13)
Bone and joints	940	26 (2.77)	0.77 (0.52–1.14)	0.44 (0.14–1.36)
Soft tissue	6,111	221 (3.62)	1.03 (0.89–1.18)	0.81 (0.58–1.14)
Melanoma of skin	40,167	1,341 (3.34)	0.98 (0.91–1.05)	0.86 (0.73–1.01)
Nonepithelial skin cancer	5,518	205 (3.72)	1.02 (0.88–1.19)	1.10 (0.81–1.50)
Breast	170,441	7,506 (4.40)	1.04 (0.98–1.10)	1.01 (0.90–1.14)
Cervix	4,552	158 (3.47)	0.88 (0.74–1.04)	1.01 (0.72–1.42)
Uterus	37,058	1,466 (3.96)	0.96 (0.90–1.04)	0.96 (0.82–1.13)
Ovary	20,502	837 (4.08)	1.00 (0.92–1.09)	0.82 (0.67–1.00)
Vagina/vulva	4,827	208 (4.31)	1.07 (0.92–1.24)	0.94 (0.67–1.32)
Prostate	265,042	6,591 (2.49)	1.04 (0.97–1.12)	0.98 (0.84–1.16)
Urinary bladder	69,346	1,928 (2.78)	0.92 (0.87–0.98)	0.85 (0.73–0.98)
Renal pelvis/ureter	5,507	198 (3.60)	1.01 (0.87–1.17)	0.79 (0.55–1.13)
Kidney	31,366	1,176 (3.75)	1.04 (0.97–1.11)	0.91 (0.78–1.07)
Eye and orbit	1,866	62 (3.32)	0.98 (0.75–1.27)	1.04 (0.60–1.81)
Brain[c]	12,630	458 (3.63)	1.06 (0.96–1.18)	0.92 (0.72–1.16)
Glioma	10,841	394 (3.63)	1.08 (0.97–1.20)	0.91 (0.71–1.18)
Thyroid	10,632	545 (5.13)	1.15 (1.04–1.26)	1.08 (0.89–1.31)
Hodgkin lymphoma	2,433	96 (3.95)	1.08 (0.87–1.33)	0.96 (0.60–1.54)
NHL/CLL[c]	73,802	2,690 (3.64)	1.01 (0.95–1.07)	0.97 (0.86–1.10)
DLBCL	21,395	763 (3.57)	0.98 (0.90–1.06)	0.95 (0.79–1.14)
T cell	3,556	146 (4.11)	1.08 (0.91–1.28)	0.99 (0.68–1.44)
Marginal zone	5,057	239 (4.73)	1.14 (0.99–1.31)	1.16 (0.88–1.54)
Follicular	9,772	363 (3.71)	1.02 (0.91–1.14)	0.86 (0.66–1.12)
CLL/SLL	20,283	698 (3.44)	1.01 (0.92–1.10)	0.99 (0.81–1.20)
Lymphoplasmacytic	947	47 (4.96)	1.36 (1.01–1.83)	1.05 (0.51–2.19)
Mantle cell	2,247	77 (3.43)	1.02 (0.81–1.29)	1.04 (0.65–1.66)
Myeloma	21,101	789 (3.74)	1.03 (0.95–1.12)	0.96 (0.80–1.15)
AML	10,068	361 (3.59)	0.97 (0.87–1.09)	0.74 (0.56–0.97)
CML	4,360	180 (4.13)	1.18 (1.01–1.37)	1.10 (0.77–1.57)
Mesothelioma	3,895	95 (2.44)	0.84 (0.68–1.04)	1.33 (0.88–2.00)
Kaposi sarcoma	688	28 (4.07)	1.26 (0.86–1.84)	1.67 (0.82–3.42)
Miscellaneous	73,773	2,582 (3.50)	0.92 (0.87–0.97)	0.88 (0.78–1.00)

NOTE: Bold values are significant at $P < 0.00034$.

Abbreviations: AML, acute myeloid leukemia; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic leukemia; CML chronic myeloid leukemia; DLBCL, diffuse large B-cell lymphoma.

[a]ICD-9 codes used to classify asthma are: 493, 493.0, 493.00, 493.01, 493.02, 492.1, 493.10, 493.11, 493.12, 493.2, 493.20, 493.21, 493.22, 493.8, 493.81, 493.82, 493.9, 492.90, and 493.91. Individuals with a COPD (a proxy for heavy smoking status) diagnosis code appearing at any point after study entry were excluded.

[b]Logistic regression models were adjusted for sex (excluding sex-specific cancers, for which we restricted to the appropriate sex), age (66–69, 70–74, 75–79, 80–84, and 85–99 years), race (white, black, and other), quantiles of the percentage of individuals living in poverty in zip code, number of physician visits per year excluding the year prior to selection or diagnosis.

[c]Subtype histology codes are listed in Supplementary Table S3.

Table 4. Associations between eczema and cancer risk

Cancer site	Total	Eczema[a] *N* (%)	Primary analysis[b] aOR (95% CI)	Sensitivity analysis[b] aOR (95% CI)
Controls	100,000	779 (0.78)	—	—
Cancer overall	1,744,575	14,197 (0.81)		
Lip	3,102	21 (0.68)	1.03 (0.66–1.60)	0.42 (0.10–1.76)
Tongue/mouth/gums	10,354	88 (0.85)	1.11 (0.88–1.39)	1.04 (0.65–1.66)
Salivary gland	4,040	32 (0.79)	0.98 (0.68–1.39)	0.60 (0.24–1.47)
Nasopharynx	1,142	NA	NA	NA
Tonsil/oropharynx	7,954	63 (0.79)	1.25 (0.96–1.62)	0.74 (0.37–1.45)
Hypopharynx	2,083	21 (1.01)	1.56 (1.00–2.42)	2.05 (0.88–4.78)
Esophagus[c]	17,204	157 (0.91)	1.29 (1.08–1.54)	1.18 (0.79–1.75)
Adenocarcinoma	9,318	81 (0.87)	1.24 (0.97–1.58)	1.12 (0.67–1.87)
Squamous cell	6,221	62 (1.00)	1.38 (1.06–1.80)	1.36 (0.76–2.42)
Stomach	33,084	355 (1.07)	1.16 (1.01–1.32)	1.13 (0.87–1.47)
Small intestine	6,529	53 (0.81)	1.01 (0.76–1.34)	0.84 (0.46–1.51)
Colon	154,846	1,188 (0.77)	1.03 (0.93–1.13)	0.91 (0.74–1.12)
Rectosigmoid/rectum	47,731	315 (0.66)	1.02 (0.89–1.17)	1.00 (0.75–1.35)
Anus	4,146	48 (1.16)	1.55 (1.15–2.10)	1.49 (0.82–2.73)
Liver	19,263	216 (1.12)	1.03 (0.88–1.21)	1.01 (0.75–1.37)
Intrahepatic bile duct	3,250	38 (1.17)	1.28 (0.92–1.78)	0.91 (0.43–1.97)
Gallbladder	5,924	45 (0.76)	0.86 (0.63–1.17)	0.64 (0.31–1.31)
Pancreas	55,415	473 (0.85)	1.00 (0.89–1.13)	0.84 (0.65–1.08)
Nose/nasal cavity/middle ear	2,218	18 (0.81)	1.06 (0.66–1.69)	0.22 (0.03–1.59)
Larynx	11,714	89 (0.76)	1.24 (0.98–1.57)	0.87 (0.50–1.53)
Lung	274,214	2,219 (0.81)	1.11 (1.01–1.21)	1.03 (0.85–1.24)
Bone and joints	1,165	NA	NA	NA
Soft tissue	7,567	54 (0.71)	0.87 (0.66–1.15)	0.88 (0.50–1.55)
Melanoma of skin	48,113	382 (0.79)	1.07 (0.94–1.22)	0.99 (0.75–1.31)
Nonepithelial skin cancer	6,964	81 (1.16)	1.26 (0.99–1.59)	1.25 (0.78–2.02)
Breast	203,086	1,562 (0.77)	0.98 (0.87–1.09)	0.99 (0.78–1.25)
Cervix	5,574	33 (0.59)	0.77 (0.53–1.11)	0.94 (0.46–1.89)
Uterus	42,113	269 (0.64)	0.93 (0.79–1.09)	0.84 (0.58–1.22)
Ovary	24,471	189 (0.77)	1.02 (0.86–1.22)	0.83 (0.55–1.26)
Vagina/vulva	6,120	60 (0.98)	1.15 (0.88–1.52)	1.71 (1.03–2.84)
Prostate	318,238	2,149 (0.68)	1.20 (1.07–1.35)	0.93 (0.73–1.19)
Urinary bladder	94,996	835 (0.88)	1.15 (1.04–1.28)	0.97 (0.77–1.22)
Renal pelvis/ureter	7,372	67 (0.91)	1.06 (0.82–1.36)	0.83 (0.47–1.46)
Kidney	39,258	283 (0.72)	0.94 (0.82–1.08)	0.75 (0.56–1.02)
Eye and orbit	2,319	26 (1.12)	1.60 (1.08–2.38)	1.03 (0.38–2.81)
Brain[c]	15,205	130 (0.85)	1.22 (1.01–1.47)	1.10 (0.73–1.65)
Glioma	12,901	112 (0.87)	1.30 (1.06–1.59)	1.21 (0.78–1.87)
Thyroid	12,556	112 (0.89)	1.11 (0.90–1.36)	0.87 (0.55–1.38)
Hodgkin lymphoma	3,054	49 (1.60)	**2.09 (1.56–2.81)**	1.79 (0.94–3.42)
NHL/CLL[c]	91,381	974 (1.07)	**1.33 (1.21–1.47)**	1.23 (1.00–1.51)
DLBCL	26,387	265 (1.00)	1.20 (1.04–1.39)	0.94 (0.69–1.28)
T cell	4,387	147 (3.35)	**4.12 (3.43–4.95)**	**3.22 (2.14–4.84)**
Marginal zone	6,307	82 (1.30)	**1.47 (1.17–1.85)**	**1.88 (1.24–2.83)**
Follicular	11,865	101 (0.85)	1.18 (0.95–1.45)	1.18 (0.76–1.83)
CLL/SLL	25,107	200 (0.80)	1.06 (0.90–1.25)	1.10 (0.79–1.54)
Lymphoplasmacytic	1,164	NA	NA	NA
Mantle cell	2,825	30 (1.06)	1.41 (0.97–2.05)	1.29 (0.62–2.68)
Myeloma	26,107	253 (0.97)	1.21 (1.04–1.40)	1.25 (0.94–1.67)
AML	13,031	132 (1.01)	1.11 (0.92–1.35)	0.93 (0.61–1.41)
CML	5,795	54 (0.93)	1.06 (0.80–1.41)	1.34 (0.79–2.28)
Mesothelioma	5,008	42 (0.84)	1.16 (0.85–1.60)	1.04 (0.51–2.14)
Kaposi sarcoma	896	NA	NA	NA
Miscellaneous	99,523	985 (0.99)	1.09 (0.99–1.20)	0.90 (0.73–1.12)

NOTE: Bolded values are significant at $P < 0.00034$.

Abbreviations: AML, acute myeloid leukemia; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic leukemia; CML, chronic myeloid leukemia; DLBCL, diffuse large B-cell lymphoma; NA, not calculated because expected number of cases <10.

[a]We used the ICD-9 code 691.8 to classify individuals as having eczema.

[b]Logistic regression models were adjusted for sex (excluding sex-specific cancers, for which we restricted to the appropriate sex), age (66–69, 70–74, 75–79, 80–84, and 85–99 years), race (white, black, and other), quantiles of the percentage of individuals living in poverty in zip code, number of physician visits per year excluding the year prior to selection or diagnosis, and diagnosis of COPD (a proxy for heavy smoking status).

[c]Subtype histology codes are listed in Supplementary Table S3.

0.75–0.91). Asthma was not significantly associated with risk of brain cancer overall (aOR, 1.06; 95% CI, 0.96–1.18) or specifically glioma (aOR, 1.08; 95% CI, 0.96–1.18). Results of the sensitivity analysis requiring the presence of a medication claim to document the presence of asthma were largely similar to those in the primary analysis, and no association met the cutoff for

statistical significance. Several associations moved away from the null in sensitivity analyses in which we excluded 2 or 3 years of exposure classification prior to diagnosis or selection (Supplementary Tables S1 and S2) and some almost met the Bonferroni correction cutoff (e.g., esophageal and pancreatic cancers).

Eczema

A total of 14,197 cases and 779 controls had a diagnosis of eczema (0.81% vs. 0.78%; Table 4). The proportion of cases with eczema varied considerably across the 47 evaluated cancer sites, from 0.59% among cervical cancer cases to 3.35% among T-cell lymphoma cases.

Most associations between eczema and specific cancer sites were not significant (Table 4). Cancers significantly associated with eczema included Hodgkin lymphoma (aOR, 2.09; 95% CI, 1.56–2.81) and NHL; aOR, 1.33; 95% CI, 1.21–1.47), with the T-cell lymphoma subtype appearing to drive the global NHL association (aOR, 4.12; 95% CI, 3.43–4.95). Eczema was not significantly associated with risk of brain cancer after Bonferroni correction, either overall (aOR, 1.22; 95% CI, 1.01–1.47) or specifically glioma (aOR, 1.30; 95% CI, 1.06–1.59). In our sensitivity analysis requiring medication use to define the presence of eczema, many null or suggestively positive associations became qualitatively more inverse, but most remained nonsignificant. In the sensitivity analysis, eczema was only significantly associated with risk of T-cell lymphoma (aOR, 3.22; 95% CI, 2.14–4.84). Eczema remained positively associated with T-cell lymphoma after excluding 2 or 3 years of exposure classification time prior to diagnosis or selection, but the association was attenuated (aOR, 3.79 and 3.34, respectively).

Discussion

In this large population-based study, we examined the association between three common allergic conditions (allergic rhinitis, asthma, and eczema) and 51 specific cancers or cancer subtypes in older Americans using the SEER-Medicare linked database. We identified a diverse group of 19 cancers that were significantly associated with allergic rhinitis, mostly in a protective direction. In contrast, asthma was inversely associated only with liver cancer, and eczema was positively associated with three cancer sites.

We replicated some of the previously described inverse associations between allergic rhinitis and cancers of the colon, rectum, liver, esophagus, and lung (32, 33, 48, 52). In addition, we replicated the association with pancreatic cancer when we required a claim for allergic rhinitis medication as part of the exposure classification (30, 31). We also obtained similar estimates to a Nordic study that examined the association between allergic rhinitis and cancer using administrative data, including inverse associations with liver and esophageal cancers (48). Our observed association with cervical cancer is similar to that from a study that assessed gynecologic cancers combined (ovarian, cervical, and uterine cancers; ref. 39). It is notable that our strongest inverse associations were for cancers caused by with human papillomavirus (HPV) including cervical, tonsil/oropharynx, and vagina/vulva cancers. These findings are particularly intriguing because of the established association between immunosuppression and virus-related cancers (53–56). The association was also particularly strong for squamous cell carcinoma of the esophagus, a cancer for which data regarding involvement of HPV has been disputed (57–59). Interestingly, the same common genetic polymorphisms may predispose to both allergies and cervical cancer, and a reduced incidence of cervical cancer has been reported in women whose sons have allergic conditions (60, 61). These reports suggest a genetic component common to allergies and cervical cancer.

Most associations strengthened when our definition of allergic rhinitis required a claim for a medication used to treat allergic rhinitis. It is possible that, by requiring a dispensed medication claim, we detected only more severe allergic conditions, and that greater severity is associated with more of a reduced risk. For example, both pancreatic and brain cancers may cause vague symptoms prior to diagnosis. This scenario could mask an inverse association, because individuals with incipient cancer may have sought more medical care and had greater opportunity to be diagnosed with mild allergic rhinitis. To the extent that our sensitivity analysis using medication information identified only individuals with more severe allergic rhinitis, we speculate that both cases and controls would have had equivalent opportunities for diagnosis of their allergic rhinitis, thus unmasking the inverse associations. We also tested this hypothesis by increasing the amount of time between assessment of allergic conditions and cancer diagnosis/control selection (Supplementary Tables S1 and S2). Several associations moved away from the null, including the association with pancreatic cancer.

The inverse associations between allergic rhinitis and cancer that we report are compatible with the cancer immunosurveillance hypothesis (13). When the allergic reaction occurs, mast cells release mediators, such as cytokines, that may promote an immune response that eliminates or contains precancerous cells. Alternatively, it is possible that the observed associations partly reflect chemopreventive properties from the medications used to treat allergic rhinitis.

Although we found a large number of inverse associations, some of which were linked to a virus (HPV), it is unclear why inverse associations were present for certain virus-unrelated cancer sites but not others. Notably, some of the cancers for which the associations were strongest, including the HPV-related cancers, are associated with low socioeconomic status. Although we adjusted for socioeconomic status, these associations may be partially attributable to residual confounding. If, for example, individuals with lower socioeconomic status had less access to medical care then they would be less likely to receive an allergic rhinitis diagnosis and a cancer diagnosis.

Despite a large body of evidence describing reduced cancer risk associated with asthma, our findings for asthma were largely null, and when we required a more specific definition, the initial inverse association with liver cancer also became null. One possibility is that we missed some inverse associations due to confounding by smoking, which would have biased our ORs upwards. We used a claims-based diagnosis of COPD to identify and exclude smokers, but COPD diagnosis is only a proxy for long-term and heavy smokers. We therefore have likely included some light and moderate smokers. Nonetheless, we were encouraged to observe that the association between asthma and lung cancer was null, mirroring results from a previous study of nonsmokers and suggesting that any residual confounding was small (62).

Although numerous studies have reported inverse associations between eczema and several cancer sites (18, 23, 31, 33), we found largely null associations. One potential reason may be a lack of

power to identify moderate associations, because eczema, as defined in our population, was uncommon. The prevalence of eczema in our population was substantially lower than population prevalence estimates (e.g., 4%–10%; refs. 5, 7). Furthermore, eczema varies substantially in its severity, and our use of Medicare claims may have identified only the most severe cases. Over-the-counter treatment for eczema is common and patients receiving prescription treatment would likely have had more severe disease. We reproduced previous strong positive associations between eczema and T-cell NHL (34, 35). This association, however, may result from diagnostic confusion, because T-cell NHL can present in an indolent manner and be misdiagnosed as a non-neoplastic skin condition (63, 64). This hypothesis has some support given the association was slightly attenuated as we increased the amount of time between exposure assessment and diagnosis or selection, but the persistence of an association even over more than a 3-year interval indicates that it could partly reflect an etiologic relationship.

Surprisingly, we found no association between any of the three atopic conditions and brain cancer, specifically with glioma. With the exception of a few studies (48, 65), most have consistently shown inverse associations with glioma (18–20, 22–26, 37), although associations with meningioma have been more mixed (19, 25, 37). However, across these studies there were marked differences in the assessment of atopy (e.g., definition of allergy, circulating IgE levels). Furthermore, most studies that focused on atopy and brain cancer performed multiple analyses and only highlighted those results that were significant. There are no obvious significant associations that are common to all studies.

Our study varied considerably from most previous studies with respect to two key factors. First, our study used medical administrative claims to identify allergic conditions, whereas most previous studies generally used self or proxy report, with some studies relying on a fairly high percentage of proxy report due to the high lethality of brain cancer. Second, our study population was substantially older than previous study populations. The median age of our population was older than 70, whereas other populations were generally a 1–2 decades younger on average.

To the best of our knowledge, only one other study has used administrative data to examine the association between allergies and cancer, but this study was performed in a Swedish population, only examined the association with allergic rhinitis, and calculated standardized incidence ratios (48). Notably we observed similar associations for several of the cancer sites examined, including a null association for glioma, despite the Swedish study population being at least 1 decade younger than our Medicare sample. This provides some evidence that our null association with brain cancer may not solely be explained by the older age of our population.

Strengths of our study include its large size, population-based sampling, and the evaluation of all cancer cases in the participating cancer registry areas. We systematically classified individuals in our study as affected by allergic conditions using Medicare claims, and thus our study was not dependent on self-report or proxy recall. Because of our large sample size, we were able to assess previously unexamined associations for uncommon cancers. Although we examined many associations, we were conservative in our conclusions and used a Bonferroni correction to account for multiple testing. By incorporating claims for medications into our assessment, we were able to more accurately identify allergic conditions in a sensitivity analysis. Interestingly, most associations for allergic rhinitis strengthened when we classified a person as exposed using claims for the medications of interest.

The primary limitation of our study is that it was limited to Medicare beneficiaries older than age 65, and we lacked information from participants' medical history, specifically allergies, prior to Medicare enrollment. Although there is a diagnostic code (V15.09) for "history of allergies", the code is not specific, systematically used, or validated for the history of allergies. Codes are generally only used when there is financial reimbursement for the management of a medical condition. In particular, eczema is most common in young children, frequently resolving or reducing in severity with age (66). Because of the nature of claims data, we could not capture resolved conditions or especially mild conditions that did not prompt care by a physician. For less severe allergic rhinitis and eczema, patients can treat themselves with over-the-counter medications, which we could not capture. Unlike more traditional epidemiologic studies, we also lacked information on lifestyle factors such as diet and physical exercise, which might have modestly confounded our associations. Because we were particularly concerned about confounding by smoking status, we used COPD status to crudely address smoking status, but we note that residual confounding by light and moderate smoking may still exist. A final limitation is that we did not have access to laboratory data and were unable to assess biological markers of an allergic immune response or the impact of treatment on this response.

In conclusion, we found inverse associations between allergic rhinitis and risk of developing a number of cancers. Our findings support possible immune surveillance mechanisms. These results warrant further mechanistic studies to uncover the underlying mechanisms, and epidemiologic studies to examine whether allergic rhinitis confers a survival advantage for patients with cancer (67). A better understanding of the relationship of atopy and cancer may have implications for prevention and treatment of cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The interpretation and reporting of these data are the sole responsibility of the authors.

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