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Research Article

Cancer Epidemiology, Biomarkers & Prevention

Allergies and Asthma in Relation to Cancer Risk

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Abstract

Background: Allergies and asthma, conditions commonly characterized by immunoglobulin E–mediated atopic reactions, may decrease cancer risk via increases in immunosurveillance, but may increase risk due to persistent immune stimulation. Associations between allergies and asthma and cancer risk remain unclear, and it is unknown whether associations vary by race/ethnicity.

Methods: We evaluated these associations in the Southern Community Cohort Study. At baseline (2002–2009), 64,170 participants were queried on history of allergies and asthma; participants were followed through 2011, during which time 3,628 incident, invasive cancers were identified, including 667 lung cancers, 539 breast cancers, and 529 prostate cancers. Cox proportional hazards regression was used to estimate multivariable-adjusted HRs and 95% confidence intervals (CI).

Results: Neither allergies nor asthma was associated with risk of developing invasive cancer overall. Asthma was associated with increased lung cancer risk (HR, 1.25; 95% CI, 1.00–1.57), with no variation by race/ethnicity ($P_{\text{interaction}} = 0.84$). Conversely, history of allergies was associated with decreased lung cancer risk (HR, 0.80; 95% CI, 0.65–1.00), with an inverse association observed among non-Hispanic whites (HR, 0.65; 95% CI, 0.45–0.94) but not non-Hispanic blacks (HR, 0.95; 95% CI, 0.73–1.25; $P_{\text{interaction}} = 0.10$). No statistically significant associations were observed for risk of breast or prostate cancers, overall or by race/ethnicity.

Conclusions: No associations were observed for risk of overall cancer, breast cancer, or prostate cancer. While asthma was associated with increased lung cancer risk, history of allergies was associated with decreased risk, an association driven by an inverse association among non-Hispanic whites.

Impact: Associations pertaining to lung cancer merit follow up in a large, diverse study.

Introduction

Atopic disease is characterized by the presence of immunoglobulin E (IgE)-mediated immune reactions (1). These IgE-mediated immune reactions have been hypothesized to play a role in immunosurveillance against cancer (2, 3). It is therefore possible that persons with asthma or allergies, conditions commonly characterized by IgE-mediated atopic reactions, may develop an IgE-mediated response against neoplasms, and consequently experience decreased risk of cancer.

To this end, several epidemiologic studies have observed history of asthma and/or allergies or higher serum IgE levels to be inversely associated with risk of various cancers (3–21). However, results have been inconsistent, and in fact, some research suggests that atopic disease may be associated with increased risk of cancer, potentially due to persistent immune stimulation (12, 22, 23). Beyond individual cancer sites, the association between atopic disease and overall risk of developing any invasive cancer has also been evaluated (5, 13, 14, 24–28). Results from these analyses have also been inconsistent. It is possible that differences across studies, for overall cancer and individual cancer sites, may arise due to differences in exposure definition or covariate adjustment, small sample sizes, multiple testing, and/or heterogeneity in study populations. Prior studies of atopic disease and cancer have generally been based in predominantly white populations, and few have evaluated heterogeneity by race/ethnicity (29–31). However, one study suggested that the inverse association between atopic conditions and glioma was limited to white persons, with no association observed among black persons (29), whereas a study of colorectal cancer observed no difference in association between groups (30). Understanding whether the association between atopic disease and cancer risk varies by racial/ethnic subgroup may help us better understand observed inconsistencies across study populations and may shed light on involved mechanisms.

We therefore evaluated the association between allergies and asthma and cancer risk in the Southern Community Cohort Study (SCCS). We evaluated risk of overall cancer, as well as risk of the most commonly diagnosed cancers: lung cancer, breast cancer (among women), and prostate cancer (among men); we further assessed whether any associations were modified by race/ethnicity, given potential differences in disease burden and subsequent treatment differences across groups (32, 33).

Materials and Methods

Study population

Study participants were drawn from the SCCS, an ongoing prospective cohort study focused on cancer disparities (34, 35). SCCS participants include over 85,000 men and women, recruited from 2002 to 2009 in one of 12 Southeastern states. English speaking persons between ages of 40 and 79 years were eligible for

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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inclusion if they reported no history of cancer in the prior year, with the exception of nonmelanoma skin cancer. Approximately 85% of SCCS participants were recruited in-person from community health centers (CHC), which provide health care to low-income and under-insured individuals. The remaining participants were recruited from the general population by mail. Of the 78,223 with no history of cancer at baseline (except for nonmelanoma skin cancer), 77,761 had data available for allergies or asthma variables, of which 64,170 had complete data on core covariates, except family history (as the definition varied by specific analysis). Of the 64,170 persons included, 67% were non-Hispanic black (NHB, $n = 43{,}026$), 29% were non-Hispanic white (NHW, $n = 18{,}772$), and 4% reported another race/ethnicity ($n = 2{,}372$).

Exposure

Primary analyses focused on history of allergies (irrespective of asthma) and any history of asthma (irrespective of allergies). In the baseline questionnaire, participants were asked if "a doctor ever told you that you have had, or have you ever been treated for hay fever, skin allergy, food allergy, or other allergy." Participants reporting "yes" were classified as having a history of allergies, while those who reported "no" were classified as having no history; those who refused to answer the question or reported "don't know" were classified as missing. Participants were also asked if "a doctor ever told you that you have had, or have you ever been treated for asthma." Participants who reported "yes" were classified as having a history of asthma, while those who reported "no" were classified as not having a history of asthma; those who refused or reported "don't know" were classified as missing.

In secondary analyses, a four-level variable was created to examine the joint association between allergies and asthma and risk of cancer, with the idea that a history of both allergies and asthma may reflect true atopic IgE-mediated immune responses (20). This variable was defined as follows: no history of allergies or asthma, asthma only, allergies only, or both allergies and asthma.

Outcome

Over an average of 6.3 years of follow-up, 3,628 incident, invasive cancers of any site were identified, exclusive of nonmelanoma skin cancers. All cases were diagnosed between study enrollment (2002–2009) and December 31, 2011. Cancers were primarily identified by linkage to state cancer registries in the states of SCCS enrollment, although for a small number of cases not reported by the registries, deaths due to cancer were also identified by linkage to the National Death Index.

We also examined associations for the most common cancer sites, for which statistical power was sufficient to conduct site-specific analyses, including lung cancer ($n = 667$), breast cancer ($n = 539$, women only), and prostate cancer ($n = 529$, men only). Given concern about indolent, low-grade prostate cancers, exploratory analyses were also conducted disaggregating high-grade prostate cancer from low-grade prostate cancer. Information on grade was available from state registries for 369 cases, 92 of which were high grade (Gleason pattern 4+3 or Gleason score 8–10) and 277 of which were low grade (Gleason score 2–6 or Gleason pattern 3+4).

Statistical analysis

Cox proportional hazards regression was used to estimate HRs and corresponding 95% confidence intervals (CI). Person-time at risk was accrued from date of baseline interview to date of the first cancer diagnosis, date of death, or December 31, 2011, whichever occurred earliest. For cases diagnosed only through the National Death Index, date of death was used as a surrogate for date of diagnosis. In analyses of site-specific cancers, each was analyzed using separate Cox regression models such that only cancer at a specific site was considered as an event and cancers at other sites were censored.

Minimally adjusted analyses were adjusted for age (time axis), sex (in analyses of overall cancer and lung cancer), race/ethnicity (NHB, NHW, and other), and enrollment source (CHC vs. general population). For analyses of overall cancer risk, multivariable-adjusted models for analyses of total cancer were further adjusted for the additional *a priori*-determined "core" covariates: household income (<15,000, 15,000–<25,000, 25,000–<50,000, or 50,000+), insurance status (uninsured vs. insured), time since last seen a doctor (<3 months, 3–<12 months, or 12 months+), body mass index (BMI; <25, 25–<30, 30–<35, or 35+ kg/m^2), history of smoking (never smoker, tertiles of pack-years smoked among former smokers, and tertiles of pack-years smoked among current smokers), alcohol intake (nondrinker and categories of g/day: 0.1–<5, 5–<15, 15–<30, 30–<45, or 45+), moderate/vigorous physical activity [sex-specific quartiles of metabolic equivalent of task (MET)-hours/week], postmenopausal hormone use (premenopausal, postmenopausal and never use, or postmenopausal and ever use), and family history of any cancer (none or any).

For analyses of site-specific cancers, some adaptations were made to the multivariable-adjusted models to ensure appropriate covariate adjustment. Specifically, instead of adjusting for family history of any cancer, we adjusted for family history of the specific cancer under study. Models of lung cancer were additionally adjusted for history of chronic obstructive pulmonary disease (COPD). It should also be noted that in analyses of lung cancer, sensitivity analyses were conducted further adjusting for quartiles of pack-years smoked among current and former smokers separately; because effect estimates did not materially change, the tertile categories were retained in final models. Analyses of breast cancer risk were further adjusted for history of mammogram (never, not recent: >2 years, or recent: $\leq$2 years ago), whereas analyses of prostate cancer risk were further adjusted for prostate-specific antigen screening (never, not recent: >2 years ago, or recent: $\leq$2 years ago), and history of digital rectal exam (never, not recent: >2 years ago, or recent: $\leq$2 years ago). Given differences in adjustment factors in analyses of site-specific cancers, coupled with the use of complete case analyses, the sample size for each outcome varied, such that the final sample size for analyses pertaining to each cancer was as follows: lung cancer ($n = 58{,}046$), breast cancer (women only, $n = 35{,}956$), and prostate cancer (men only, $n = 22{,}898$).

To test whether the exposure–outcome relationship differed by race/ethnicity, an interaction term was included in the multivariable-adjusted model and statistical significance of interaction was evaluated using the Likelihood Ratio test. Effect estimates specific to NHB persons and NHW persons were estimated from the interaction model. Finally, in sensitivity analyses of high-grade prostate cancer, low-grade prostate cancers were censored at

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date of diagnosis; conversely, in analyses of low-grade prostate cancer, high-grade cancers were censored at diagnosis.

All study participants provided written informed consent and the study was approved by the Institutional Review Boards of Vanderbilt University, Meharry Medical College (Nashville, TN), and the Harvard T.H. Chan School of Public Health (Boston, MA). All analyses were conducted in SAS version 9.4.

Results

In this study of 64,170 persons, 15,758 (24.6%) reported allergies, and 9,416 (14.7%) reported asthma (Table 1). A higher percentage of NHW participants (31.7%) reported a history of allergies than NHB participants (20.9%; Supplementary Table S1); the difference between these two groups was less marked for a history of asthma (16.6% vs. 13.5%, respectively). The following characteristics were more common among persons reporting allergies than those without allergies (as shown in Table 1): being female, being NHW, reporting a recent visit to the doctor (i.e., within the last 3 months), being severely obese (BMI 35+ kg/m^2), being a never smoker, having a family history of cancer, and ever using postmenopausal hormones (women only). The following characteristics were more common among persons reporting asthma than those without: being female, having a low household income, reporting a more recent visit to the doctor (i.e., within the last 3 months), being severely obese (BMI 35+ kg/m^2), being a nondrinker, low physical activity, and having family history of cancer.

Overall cancer

In minimally adjusted and in multivariable-adjusted analyses of overall cancer risk, we observed no association between history of asthma and subsequent cancer risk (multivariable-adjusted HR, 1.02; 95% CI, 0.93–1.13; Table 2). No association was similarly observed for history of allergies (multivariable HR, 0.96; 95% CI, 0.88–1.04; Table 2). Results did not vary by race/ethnicity (Table 3).

Lung cancer

In multivariable-adjusted models, history of asthma was associated with 25% increased risk of lung cancer (HR, 1.25; 95% CI, 1.00–1.57), and the positive association between asthma and lung cancer was comparable across race/ethnicity ($P_{interaction}$ = 0.85), with an HR of 1.25 observed among NHB persons (95% CI, 0.94–1.66) and an HR of 1.20 (95% CI, 0.82–1.74) observed among NHW persons (Table 3). History of allergies was associated with 20% reduced risk (HR, 0.80; 95% CI, 0.65–1.00; Table 2); although this association did not significantly vary by race/ethnicity ($P_{interaction}$ = 0.10), the inverse association was only observed among NHW persons (HR, 0.65; 95% CI, 0.45–0.94; Table 3). Notably, sensitivity analyses revealed that the effect estimates for allergies and asthma did not markedly change when analyses pertaining to each condition (allergies and asthma) were mutually adjusted for one another. Sensitivity analyses examining associations by duration of asthma/allergy (as stratified at the median), revealed no marked difference in the asthma–lung cancer association by duration: those with asthma ≤22 years experienced a nonsignificant 31% increased risk of lung cancer (HR, 1.31; 95% CI, 0.97–1.76) and those with asthma >22 years experienced nonsignificant 21% increased risk (HR, 1.21; 95% CI, 0.89–1.65). For allergies, the association strengthened among those with longer duration exposure: for those with allergies ≤24 years, the effect estimate was 0.92 (95% CI, 0.70–1.21) and for those with allergies >24 years, the effect estimate was 0.70 (95% CI, 0.52–0.96).

Breast cancer

In multivariable-adjusted analyses, history of asthma was associated with a nonsignificant 18% reduced risk of breast cancer (HR, 0.82; 95% CI, 0.63–1.05), and history of allergies was not associated (HR, 1.01; 95% CI, 0.84–1.23). These estimates did not vary by race/ethnicity (Table 3).

Prostate cancer

Finally, no significant association was observed between asthma and risk of prostate cancer (HR, 1.07; 95% CI, 0.78–1.45), nor was a significant association observed between allergies and risk of prostate cancer (HR, 0.90; 95% CI, 0.69–1.17; Table 2). Neither of these associations varied by race/ethnicity (Table 3).

In exploratory analyses in which prostate cancers were disaggregated into high-grade and low-grade cancers, we observed a nonsignificant inverse association for both asthma (HR, 0.56; 95% CI, 0.20–1.55) and allergies (HR, 0.46; 95% CI, 0.20–1.07) in relation to high-grade cancer (text only). No association was observed for allergies nor asthma for low-grade cancers (HR, 1.01; 95% CI, 0.66–1.55 and HR, 1.15; 95% CI, 0.83–1.59, respectively). Grade-specific associations were not evaluated for heterogeneity by race/ethnicity, given limited power.

Exploratory analyses of combined allergies and asthma

No association was observed for both asthma and allergies as compared with neither condition in relation to risk of overall cancer (multivariable HR, 1.00; 95% CI, 0.87–1.15); similarly, no association was observed for either condition alone (Supplementary Table S2). While no association was observed for history of both conditions in relation to lung cancer risk (HR, 0.98; 95% CI, 0.68–1.40), a positive association was observed for asthma alone (HR, 1.31; 95% CI, 1.00–1.71), and a nonsignificant inverse association was observed for allergies alone (HR, 0.79; 95% CI, 0.62–1.02). No significant associations were observed for this four-level exposure in relation to breast or prostate cancer (Supplementary Table S2)

Discussion

In this study, no association was observed between history of allergy and/or asthma and risk of cancer overall. History of asthma was associated with increased risk of lung cancer, with comparable effect estimates observed among NHW and NHB persons. Conversely, history of allergies was associated with decreased risk of lung cancer; although this difference was not statistically significant, the association was mainly evident among NHW persons. No statistically significant associations were observed for either exposure with regard to risk of breast or prostate cancer.

For overall cancer, no associations were observed for history of allergy, asthma, or the combination of the two. Overall cancer was of interest because one of the hypothesized mechanisms by which allergies and asthma are suspected to affect cancer risk was expected to apply regardless of site. Specifically, it is hypothesized that IgE-mediated allergic reactions may signify a state of heightened immunosurveillance, characterized by interleukins and eosinophils (36), resulting in reduced risk of cancer among those

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Table 1. Population characteristics, by history of allergies and asthma

		Allergies		Asthma	
	Total	**No**	**Yes**	**No**	**Yes**
	***N* = 64,170**	***n* = 48,388**	***n* = 15,758**	***n* = 54,719**	***n* = 9,416**
	***N* (%)**	**(75.4%)**	**(24.6%)**	**(85.3%)**	**(14.7%)**
Age (years)					
40–44	14,642 (23%)	11,420 (24%)	3,217 (20%)	12,446 (23%)	2,191 (23%)
45–49	15,056 (23%)	11,493 (24%)	3,560 (23%)	12,815 (23%)	2,233 (24%)
50–54	12,997 (20%)	9,642 (20%)	3,349 (21%)	11,000 (20%)	1,989 (21%)
55–59	9,233 (14%)	6,673 (14%)	2,557 (16%)	7,817 (14%)	1,411 (15%)
60–64	6,115 (10%)	4,462 (9%)	1,648 (10%)	5,249 (10%)	862 (9%)
65+	6,127 (10%)	4,698 (10%)	1,427 (9%)	5,392 (10%)	730 (8%)
Sex					
Male	26,286 (41%)	22,003 (45%)	4,274 (27%)	23,470 (43%)	2,808 (30%)
Female	37,884 (59%)	26,385 (55%)	11,484 (73%)	31,249 (57%)	6,608 (70%)
Race/ethnicity					
NHB	43,026 (67%)	34,025 (70%)	8,982 (57%)	37,193 (68%)	5,810 (62%)
NHW	18,772 (29%)	12,825 (27%)	5,942 (38%)	15,645 (29%)	3,117 (33%)
Other	2,372 (4%)	1,538 (3%)	834 (5%)	1,881 (3%)	489 (5%)
Enrollment source					
CHC	58,701 (91%)	44,595 (92%)	14,083 (89%)	49,828 (91%)	8,838 (94%)
General population	5,469 (9%)	3,793 (8%)	1,675 (11%)	4,891 (9%)	578 (6%)
Household income ($)					
<15,000	35,781 (56%)	27,706 (57%)	8,061 (51%)	29,922 (55%)	5,835 (62%)
15,000–<25,000	13,906 (22%)	10,586 (22%)	3,316 (21%)	11,988 (22%)	1,913 (20%)
25,000–<50,000	8,767 (14%)	6,294 (13%)	2,468 (16%)	7,687 (14%)	1,077 (11%)
50,000 +	5,716 (9%)	3,802 (8%)	1,913 (12%)	5,122 (9%)	591 (6%)
Insurance status					
Uninsured	26,306 (41%)	20,317 (42%)	5,980 (38%)	22,643 (41%)	3,651 (39%)
Insured	37,864 (59%)	28,071 (58%)	9,778 (62%)	32,076 (59%)	5,765 (61%)
Last doctor exam					
≤3 Months	45,234 (70%)	33,179 (69%)	12,036 (76%)	37,769 (69%)	7,436 (79%)
>3 Months–≤1 year	13,529 (21%)	10,628 (22%)	2,897 (18%)	12,015 (22%)	1,510 (16%)
>1 Year	5,407 (8%)	4,581 (9%)	825 (5%)	4,935 (9%)	470 (5%)
BMI (kg/m^2)					
<25	16,321 (25%)	12,948 (27%)	3,368 (21%)	14,448 (26%)	1,864 (20%)
25–<30	19,134 (30%)	14,773 (31%)	4,357 (28%)	16,788 (31%)	2,341 (25%)
30–<35	13,972 (22%)	10,280 (21%)	3,684 (23%)	11,846 (22%)	2,119 (23%)
35+	14,743 (23%)	10,387 (21%)	4,349 (28%)	11,637 (21%)	3,092 (33%)
Smoking status[a]					
Never smoker	23,392 (36%)	17,107 (35%)	6,277 (40%)	20,097 (37%)	3,283 (35%)
Former smoker: T1 pack-years	4,670 (7%)	3,298 (7%)	1,369 (9%)	4,010 (7%)	658 (7%)
Former smoker: T2 pack-years	4,582 (7%)	3,345 (7%)	1,237 (8%)	3,915 (7%)	666 (7%)
Former smoker: T3 pack-years	4,719 (7%)	3,408 (7%)	1,308 (8%)	3,812 (7%)	903 (10%)
Current smoker: T1 pack-years	8,873 (14%)	7,056 (15%)	1,813 (12%)	7,670 (14%)	1,196 (13%)
Current smoker: T2 pack-years	8,977 (14%)	7,125 (15%)	1,850 (12%)	7,687 (14%)	1,287 (14%)
Current smoker: T3 pack-years	8,957 (14%)	7,049 (15%)	1,904 (12%)	7,528 (14%)	1,423 (15%)
Alcohol intake (g/day)					
Nondrinker	27,266 (42%)	20,177 (42%)	7,080 (45%)	22,768 (42%)	4,481 (48%)
0.1–<5	17,917 (28%)	12,961 (27%)	4,948 (31%)	15,306 (28%)	2,603 (28%)
5–<15	6,176 (10%)	4,796 (10%)	1,377 (9%)	5,393 (10%)	779 (8%)
15–<30	4,092 (6%)	3,229 (7%)	863 (5%)	3,579 (7%)	510 (5%)
30–<45	2,244 (3%)	1,829 (4%)	414 (3%)	1,984 (4%)	259 (3%)
45+	6,475 (10%)	5,396 (11%)	1,076 (7%)	5,689 (10%)	784 (8%)
Moderate/vigorous physical activity (MET-hours/week)[b]					
Q1 (Sex specific)	16,020 (25%)	12,175 (25%)	3,837 (24%)	13,282 (24%)	2,723 (29%)
Q2	16,037 (25%)	11,993 (25%)	4,038 (26%)	13,672 (25%)	2,359 (25%)
Q3	16,068 (25%)	12,028 (25%)	4,034 (26%)	13,885 (25%)	2,179 (23%)
Q4	16,045 (25%)	12,192 (25%)	3,849 (24%)	13,880 (25%)	2,155 (23%)
Postmenopausal hormone use[c]					
Premenopausal	12,409 (33%)	9,074 (34%)	3,330 (29%)	10,397 (33%)	2,006 (30%)
Postmenopausal, never PMH use	15,487 (41%)	11,392 (43%)	4,089 (36%)	12,864 (41%)	2,612 (40%)
Postmenopausal, ever PMH use	9,988 (26%)	5,919 (22%)	4,065 (35%)	7,988 (26%)	1,990 (30%)
Family history of any cancer					
0 First degree relatives	32,330 (50%)	25,460 (53%)	6,857 (44%)	27986 (51%)	4,333 (46%)
1+ First degree relatives	31,840 (50%)	22,928 (47%)	8,901 (56%)	26733 (49%)	5,083 (54%)

Abbreviations: BMI (body mass index); CHC (community health center); MET (metabolic equivalent of task); NHB (non-Hispanic black); NHW (non-Hispanic white); PMH (post-menopausal hormone); T1 (tertile 1); T2 (tertile 2); T3 (tertile 3); Q1 (quartile 1); Q2 (quartile 2); Q3 (quartile 3); Q4 (quartile 4).

[a]Former smoker (T1: <6.8; T2: 6.8-<24; T3: ≥24); Current smoker (T1: <12.5; T2: 12.5-<27; T3: ≥27).

[b]Women (Q1: ≤9.85, Q2: 9.86–17.24, Q3: 17.25–28.04, and Q4: ≥28.05); men (Q1 : ≤7.99, Q2: 8.00–18.39, Q3: 18.40–36.89, and Q4: ≥ 36.90).

[c]Restricted to women.

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Table 2. Association between allergies, asthma, and atopic disease and overall and site-specific cancer risk

	Cohort *N* (%)	Case *N* (%)	Minimally adjusted[a] HR (95% CI)	Multivariable adjusted[b] HR (95% CI)
Overall cancer[c]				
Asthma				
No	54,685 (85%)	3,092 (86%)	1.00	1.00
Yes	9,411 (15%)	509 (14%)	1.07 (0.97–1.17)	1.02 (0.93–1.13)
Allergies				
No	48,358 (75%)	2,797 (78%)	1.00	1.00
Yes	15,749 (25%)	803 (22%)	0.93 (0.86–1.01)	0.96 (0.88–1.04)
Lung cancer[d]				
Asthma				
No	49,558 (85%)	479 (82%)	1.00	1.00
Yes	8,442 (15%)	102 (18%)	1.38 (1.11–1.72)	1.25 (1.00–1.57)
Allergies				
No	43,688 (75%)	471 (81%)	1.00	1.00
Yes	14,316 (25%)	109 (19%)	0.75 (0.60–0.92)	0.80 (0.65–1.00)
Breast cancer[e,f]				
Asthma				
No	29,700 (83%)	431 (86%)	1.00	1.00
Yes	6,220 (17%)	70 (14%)	0.84 (0.65–1.08)	0.82 (0.63–1.05)
Allergies				
No	24,995 (70%)	345 (69%)	1.00	1.00
Yes	10,937 (30%)	156 (31%)	1.05 (0.86–1.27)	1.01 (0.84–1.23)
Prostate cancer[g,h]				
Asthma				
No	20,517 (90%)	417 (90%)	1.00	1.00
Yes	2,369 (10%)	45 (10%)	1.07 (0.79–1.46)	1.07 (0.78–1.45)
Allergies				
No	19,213 (84%)	393 (85%)	1.00	1.00
Yes	3,672 (16%)	69 (15%)	0.95 (0.74–1.23)	0.90 (0.69–1.17)

Abbreviations: HR (hazard ratio); 95% CI (95% confidence interval).

[a]Adjusted for age (time axis of analysis), sex, race/ethnicity (NHB, NHW, and other), and enrollment source (CHC vs. general population).

[b]Adjustment variables depend on the outcome of interest.

[c]Analyses of overall cancer adjusted for factors listed in footnote "a" above, as well as household income (<15,000, 15,000–<25,000, 25,000–<50,000, or 50,000+), insurance status (uninsured vs. insured), time since last seen a doctor (<3 months, 3–<12 months, or 12 months+), BMI (<25, 25–<30, 30–<35, or 35+), history of smoking (never smoker, tertiles of pack-years smoked among former smokers, and tertiles of pack-years smoked among current smokers), alcohol intake (nondrinker, and categories of g/day: 0.1–<5, 5–<15, 15–<30, 30–<45, or 45+); moderate/vigorous physical activity (sex-specific quartiles of MET-hours/week); postmenopausal hormone use (premenopausal; postmenopausal and never use; or postmenopausal and ever use); family history of any cancer (none or any).

[d]Analyses of lung cancer adjusted for factors listed in footnote "c" above, except for family history of any cancer. Instead, we adjusted for family history of lung cancer (none or any), as well as history of COPD.

[e]Analyses of breast cancer limited to women.

[f]Analyses of breast cancer adjusted for factors listed in footnote "c" above, except for sex and family history of any cancer. Instead, we adjusted for family history of breast cancer (none or any), as well as history of mammogram (never, not recent: >2 years, or recent: ≤2 years ago).

[g]Analyses of prostate cancer limited to men.

[h]Analyses of prostate cancer adjusted for factors listed in footnote "c" above, except for sex and family history of any cancer. Instead, we adjusted for family history of prostate cancer (none or any), as well as prostate-specific antigen screening (never, not recent: >2 years ago, or recent: ≤2 years ago), and history of digital rectal exam (never, not recent: >2 years ago, or recent: ≤2 years ago).

with these conditions. Our findings did not indicate overall cancer protection afforded by these conditions, and prior analyses of risk of overall cancer have been inconsistent (5, 7, 13, 14, 24–28), potentially reflecting differences in exposure definition, small sample sizes, multiple testing generating spurious findings, or differential composition of cancers, by site (5, 7, 13, 14, 24–28). This is relevant, as another purported mechanism by which atopic disease may affect cancer risk is that these conditions lead to an inflammatory state—the impact of which would likely vary by site, given that (i) we would expect more profound inflammation along the passageways by which allergens enter the body (e.g., through the respiratory system and digestive tract) and (ii) the role of inflammation in the etiology of cancer varies by site, with some sites strongly linked to an inflammatory etiology and others less so (37). We therefore also sought to examine associations by cancer site, where power permitted.

For lung cancer, we observed asthma to be associated with a statistically significant 25% increased risk of lung cancer, with the association comparable among NHB persons and NHW persons. These results are generally consistent with the literature, which largely suggests a positive association between asthma and lung cancer risk (7, 16, 24, 26, 31, 38–40). However, one meta-analysis found that association appeared to be driven by cases diagnosed within 2 years of asthma diagnosis and given that the association among never smokers was weak, authors noted that the association was unlikely causal (41). Here, we observe an association even among those diagnosed >22 years ago, suggesting that this association is not merely the result of reverse causation. Although we did carefully adjust for smoking, residual confounding is possible. Although prior work has reported that the association appears comparable among Asians and Caucasians (31), our study is the first to evaluate whether this association is comparable across other racial/ethnic groups (NHW and NHB). It is speculated that asthma is associated with increased risk of lung cancer due to localization of inflammation in the lung that occurs with asthma, given that the lung is a site for which inflammation is

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Table 3. Results, stratified by race/ethnicity[a]

	NHB			NHW			
	Cohort *n* (%)	Case *n* (%)	Multivariable adjusted[b] HR (95% CI)	Cohort *n* (%)	Case *n* (%)	Multivariable adjusted[b] HR (95% CI)	$P_{interaction}$
Overall cancer[c]							
Asthma							0.74
No	37,172 (86%)	2,170 (87%)	1.00	15,632 (83%)	841 (85%)	1.00	
Yes	5,809 (14%)	335 (13%)	1.03 (0.92–1.16)	3,113 (17%)	152 (15%)	1.00 (0.84–1.19)	
Allergies							0.77
No	34,007 (79%)	2,012 (80%)	1.00	12,813 (68%)	712 (72%)	1.00	
Yes	8,978 (21%)	492 (20%)	0.97 (0.88–1.08)	5,937 (32%)	281 (28%)	0.95 (0.83–1.09)	
Lung cancer[d]							
Asthma							0.85
No	33,548 (87%)	318 (85%)	1.00	14,290 (83%)	146 (80%)	1.00	
Yes	5,180 (13%)	58 (15%)	1.25 (0.94–1.66)	2,825 (17%)	36 (20%)	1.20 (0.82–1.74)	
Allergies							0.10
No	30,636 (79%)	309 (82%)	1.00	11,653 (68%)	145 (80%)	1.00	
Yes	8,094 (21%)	66 (18%)	0.95 (0.73–1.25)	5,462 (32%)	37 (20%)	0.65 (0.45–0.94)	
Breast cancer[e,f]							
Asthma							0.56
No	19,931 (84%)	303 (86%)	1.00	8,739 (81%)	123 (86%)	1.00	
Yes	3,793 (16%)	48 (14%)	0.85 (0.63–1.16)	2,084 (19%)	20 (14%)	0.72 (0.45–1.16)	
Allergies							0.19
No	17,453 (74%)	260 (74%)	1.00	6,759 (62%)	81 (57%)	1.00	
Yes	6,275 (26%)	91 (26%)	0.93 (0.73–1.18)	4,070 (38%)	62 (43%)	1.22 (0.88–1.71)	
Prostate cancer[g,h]							
Asthma							0.99
No	14,173 (90%)	329 (90%)	1.00	5,655 (88%)	78 (90%)	1.00	
Yes	1,499 (10%)	36 (10%)	1.10 (0.78–1.55)	765 (12%)	9 (10%)	1.10 (0.55–2.19)	
Allergies							0.51
No	13,633 (87%)	318 (87%)	1.00	4,963 (77%)	66 (76%)	1.00	
Yes	2,039 (13%)	47 (13%)	0.87 (0.64–1.18)	1,456 (23%)	21 (24%)	1.05 (0.64–1.72)	

Abbreviations: HR (hazard ratio); NHB (non-Hispanic black); NHW (non-Hispanic white); 95% CI (95% confidence interval).

[a]Adjusted for age (time axis of analysis), sex, and race/ethnicity (NHB, NHW, and other).

[b]Adjustment variables depend on the outcome of interest.

[c]Analyses of overall cancer adjusted for factors listed in footnote "a" above, as well as family income (<15,000, 15,000- <25,000, 25,000–<50,000, or 50,000+), insurance status (uninsured vs. insured), time since last seen a doctor (<3 months, 3–<12 months, or 12 months+), BMI (<25, 25–<27.5, 27.5–<30, or 30+), history of smoking (never smoker, tertiles of pack-years smoked among former smokers, and tertiles of pack-years smoked among current smokers), and family history of any cancer (none or any).

[d]Analyses of lung cancer adjusted for factors listed in footnote "c" above, except for family history of any cancer. Instead, we adjusted for family history of lung cancer (none or any), as well as history of COPD.

[e]Analyses of breast cancer limited to women.

[f]Analyses of breast cancer adjusted for factors listed in footnote "c" above, except for sex and family history of any cancer. Instead, we adjusted for family history of breast cancer (none or any), as well as history of mammogram (never, not recent: >2 years, or recent: ≤2 years ago).

[g]Analyses of prostate cancer limited to men.

[h]Analyses of prostate cancer adjusted for factors listed in footnote "c" above, except for sex and family history of any cancer. Instead, we adjusted for family history of prostate cancer (none or any), as well as prostate-specific antigen screening (never, not recent: >2 years ago, or recent: ≤2 years ago), and history of digital rectal exam (never, not recent: >2 years ago, or recent: ≤2 years ago).

speculated to play a role in cancer etiology (42–44). It should be noted that corticosteroids, which decrease inflammation, have been associated with decreased lung cancer risk (45–49); therefore, the use of these medications is unlikely to explain the observed positive association.

The only association consistent with our hypothesis that atopic conditions may decrease the risk of cancer was that observed for allergies and lung cancer risk; this finding is consistent with the, albeit limited, literature, which generally suggests an inverse association (38, 50, 51). It is possible that immunosurveillance associated with allergies may explain this result; although it is unclear why this mechanism would impact the lung specifically, this observed pattern is consistent with an observation in the literature that the association between allergies and cancer risk is more apparent for organs that interact with the environment (22). Given that we do not have data on specific types of allergies, it remains unclear whether this association may vary by allergy type (38). Sensitivity analyses disaggregating exposure by duration further reveal that the association between allergies and lung cancer appears stronger among those with longer standing allergies; whereas it is possible that this pattern reflects chance, it may also reflect the underlying biologic mechanism. If disease duration and severity are associated, this difference in association may reflect differences in disease severity and/or subsequent treatment. In investigating potential racial differences in the association between allergies and lung cancer risk, we found suggestive evidence of differential associations, with the inverse association seemingly limited to NHW persons. Allergies were more common among NHW persons in this study, and we might speculate that the difference in association by race/ethnicity may be driven by differences in the duration, severity, type of allergy, or bias in report. While we do not have information on severity or type of allergy, we do have information on the age at first diagnosis; our data indicate that there are not large differences in age at diagnosis

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(29% of NHB persons were diagnosed in childhood, compared with 35% of NHW persons), and thus this is unlikely to explain any difference by racial/ethnic groups. It is also possible that NHB participants were less likely to have the allergic condition diagnosed, resulting in more measurement error and attenuation in this group. Furthermore, due to higher income and access to care, NHW persons may be more likely to treat allergies, and it may be that subsequent treatment, and not the underlying condition itself, is driving the observed associations, as supported by a prior study indicating a potentially stronger association between treated versus untreated eczema (the most common type of which is the atopic condition, atopic dermatitis) and risk of lung cancer (38). However, we hope that some of the racial/ethnic socioeconomic differences with regard to access to care have been mitigated, given that the SCCS is predominantly a low-income cohort, recruited mostly within CHCs, and we adjusted for household income, insurance coverage, and time since last doctor visit. Finally, it is possible that these differences are the result of chance, and should note that $P_{interaction}$ was not statistically significant. Further study will be needed to confirm any racial differences in this association, as well as to pinpoint how particular types of allergies, severity, and/or subsequent treatment may affect lung cancer risk.

A history of asthma was associated with a nonsignificant 18% reduced risk of breast cancer, and allergies were not associated with risk. While most of the literature indicates no association (5, 7, 16, 19, 23, 24, 26), our results run contrary to another study that observed a history of allergies (but not asthma) to be modestly associated with reduced risk of breast cancer overall (19). No association was observed for allergies or asthma in relation to overall prostate cancer risk, although there was some indication of a nonsignificant inverse association among men with both allergies and asthma as compared with neither. The existing literature for the association between atopic disease and prostate cancer risk has been unclear (5, 7, 23, 24, 26, 52–55). For example, a meta-analysis found no association between asthma, hay fever, or any allergy and risk of prostate cancer, although did find an evidence of a slight positive association between IgE levels and risk of prostate cancer (23). Here, we found no evidence of heterogeneity by race/ethnicity with regard to overall prostate cancer risk. Our exploratory analyses revealed a nonsignificant inverse association for the clinically relevant high-grade cancers, with no association observed for low-grade cancers, corroborating a recently published study, comprised largely of white men that found asthma to be associated with decreased risk of lethal prostate cancer (53). However, in that same study, history of hay fever was not significantly associated with risk of lethal prostate cancer. In our study, power was very limited for these exploratory grade-specific analyses, and should be interpreted with caution. Given limited power, we were also unable to examine grade-specific associations by race/ethnicity; this represents an important point of follow-up in future studies, particularly given marked racial/ethnic disparities in risk of lethal prostate cancer.

This study has several important strengths. First, we examined results by race/ethnicity, which is important, given that most prior studies have been conducted in largely white populations. This is an ideal population in which to address racial/ethnic heterogeneity, given the large number of NHB participants, as well as the fact that this is largely a low-income cohort, reducing concern about residual confounding by socioeconomic differences and access to care across racial/ethnic groups. Furthermore, we examined both allergies and asthma separately, which is important, given that we and others, observed heterogeneity in association across conditions. Finally, as data were drawn from a cohort specifically designed to examine cancer risk factors, we were able to carefully adjust for known confounders for each cancer studied.

Even so, there are several limitations to consider. Although we were able to separate allergy from asthma, we were unable to distinguish the type of allergy (e.g., hay fever vs. skin allergy, food allergy, or other allergy), nor do we have information on eczema. Furthermore, participant report of allergy is subject to more error than a direct measure, particularly with regard to report of food/medication allergies (56–59). Granted, in this study, our exposure is determined by whether the participant has been diagnosed with or treated for the condition, and thus we would expect less measurement error than expected in a study in which exposure does not require doctor diagnosis or treatment. Any such measurement error would be expected to attenuate results toward the null, and it is possible that error varies by race/ethnicity. We did not have information on family history of allergy or asthma, nor do we have information on severity of symptoms, and it may be that there is a threshold effect that is not captured in this study. Along these lines, we also did not have information on treatment for these conditions, and it is possible that our inability to account for treatment may obscure results, particularly among those with more severe disease. For lung cancer–specific analyses, although we carefully adjusted for smoking, it would be ideal to conduct sensitivity analyses restricted to nonsmokers to reduce concern about residual confounding by smoking; however, a small number of nonsmokers precludes this analysis. While we were able to explore associations separately for high-grade and low-grade prostate cancers, we were not able to examine results specifically for lethal cancers, nor were we able to examine race-stratified results by prostate cancer grade, because of limited power. It would be interesting in future studies to see whether the association observed for high-grade cancer can be replicated and whether it varies by race/ethnicity, particularly given the disparities observed for this disease. While we conducted a number of statistical tests, these were chosen *a priori* based on biological plausibility; even so, it is possible that any observed significant results could be due to chance. Finally, despite the fact that the evaluation of this question in a low-income cohort may reduce residual confounding by SES and differences in access to care by race/ethnicity, it is possible that there are differences in access to care and subsequent misclassification of history of allergies/asthma as well as differences in medication use that might have differentially affected results by race/ethnicity.

In summary, allergies and asthma were not observed to be associated with overall risk of cancer, nor did we observe statistically significant associations for risk of breast cancer or prostate cancer. We observed asthma to be positively associated with increased risk of lung cancer, with no heterogeneity by race/ethnicity, and observed allergies to be associated with decreased risk of lung cancer. Results pertaining to lung cancer risk merit follow-up in a large, diverse, prospective study. Understanding these associations could provide additional insight into underlying etiology and biology of cancer, and help us understand observed differences across racial/ethnic groups.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): L.B. Signorello
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): E.D. Kantor, M. Hsu, L.B. Signorello
Writing, review, and/or revision of the manuscript: E.D. Kantor, M. Hsu, M. Du, L.B. Signorello

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Allergies and Asthma in Relation to Cancer Risk

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