

ALLERGY-RELATED DISEASES AND CANCER: AN INVERSE ASSOCIATION

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This paper presents the results of a retrospective study that examines the association of cancer with a history of asthma, hay fever, hives, and other allergy-related diseases. This study is based on interview data collected from 13,665 cancer cases and 4,079 nonneoplastic controls who were admitted to Roswell Park Memorial Institute from 1957 to 1965. Although there is a general tendency for the age- and cigarette smoking-adjusted odds ratios associated with a history of asthma and hay fever to be less than 1, for both males and females, there is stronger evidence for a decreased risk of cancer associated with a history of hives and other allergy-related diseases. Decreased risks associated with a history of hives and other allergies are seen in males for oral cancer, cancers of the lung, larynx, digestive system, urinary system, and cancers of all sites combined and in females for cancers of the digestive system, reproductive system, in particular, cancer of the cervix, and cancers of all sites combined. None of the few odds ratios over 1 associated with a history of any allergy-related condition are statistically significant ($\alpha = 0.05$). These findings suggest that individuals with allergy-related disorders may be at decreased risk of cancer, although reasons for cautious interpretation of the findings are emphasized. Prospective studies of carefully defined allergic disease cohorts are needed.

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Several studies suggest that allergy is negatively associated with cancer (1-11),

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others show no association (12-14), and even fewer report increased risk of cancer associated with allergy-related disorders (15, 16). The studies done to date have included descriptive (8, 11, 12), case-control (1-6, 10, 13, 14, 16), and cohort (7, 9, 15) study designs and are summarized in table 1.

The findings suggested the need for examination of the association between allergy-related disorders and cancer in a large population. This report presents the results of a retrospective study based on a series of 13,665 cancer cases and 4,079 controls in which the association between cancer and the report of previous diagnoses of asthma, hay fever, hives, and other allergy-related

disorders is examined in site- and sex-specific analyses. Briefly, our findings suggest an inverse association between these allergy-related diseases and cancer at several sites.

MATERIALS AND METHODS

This case-control study is based on detailed epidemiologic data gathered by interview and questionnaire on all patients admitted from 1957 to 1965 to Roswell Park Memorial Institute. During this time period, each patient completed a preadmission questionnaire concerning demographic and certain behavioral characteristics and was interviewed upon admission to obtain medical history, alcohol use, and cigarette consumption. Complete medical history and cigarette smoking data were obtained for 7,128 white female cancer cases and 6,537 white male cancer cases. Cases with unknown medical history or smoking data (681 males, 380 females) were not included in the study. Nonwhites were not included in this study because of their small number of admissions during the study period. Controls used in this study were all whites with nonneoplastic diseases, excluding those admitted for disorders of the skin (*International Classification of Diseases*, Seventh Revision (ICD 7) 014, 084, 085, 088, 280–282, and 690–716) and disorders of the respiratory system (ICD 7 001–008, 470–527, and 783) because of possible allergic etiologies, as well as those admitted for allergic disorders (ICD 7 240–245). Also, mental, psychoneurotic and personality disorders (ICD 7 300–326), and senility (ICD 7 794) were excluded because of possible unreliable recall. Controls with unknown medical history or smoking data (211 males, 105 females) were not included in the study. After exclusions, the control series consisted of 2,500 females and 1,579 males. The female control series included diseases of the genitourinary system (38 per cent), diseases of the digestive system (20 per cent), women with no pathology or in whom no diagnosis could be made (19 per cent),

endocrine, metabolic, and nutritional diseases (7 per cent), and diseases of the circulatory system (6 per cent). Each of the remaining individual diagnoses in the females comprised less than 3 per cent of the total. The male control series included diseases of the digestive system (40 per cent), diseases of the genitourinary system (15 per cent), men with no pathology or in whom no diagnosis could be made (24 per cent), diseases of the circulatory system (7 per cent), endocrine, metabolic, and nutritional diseases (4 per cent), and diseases of the musculoskeletal system (4 per cent). Each of the remaining individual diagnoses in the males comprised less than 3 per cent of the total.

The medical portion of the interview obtained the history of a series of diseases and conditions, including any lifetime history of asthma, hay fever, hives, and eczema. More generally, participants were also queried about ever having had “an allergy.” Any positive response was followed by other questions about whether the diagnosis was made by a physician, the age at onset, and duration of the condition. A history of asthma, hay fever, hives, eczema, and an allergy was taken as positive only when the patient reported that the condition was first diagnosed by a physician at least five years prior to admission to Roswell Park Memorial Institute. Conditions diagnosed within five years of admission were excluded because of the possibility that cancer cases might have confused allergy-type symptoms with those related to early clinical manifestation of the cancer. In addition, when an individual reported both an allergy and one or more of the other specific allergy-related conditions, a report of an allergy was counted as a positive response only if the age of onset was different from any of the other reported conditions. This allowed an allergy to be considered an independent response, separate from the other allergy-related disorders. Those responses comprise the other allergies category. The exact nature of the

TABLE 1

Epidemiology studies that have assessed the relationship between allergy and cancer

Principal investigator and year of study (reference no.)	Study design	Cancer sites (no. of cases)	Independent variables	Risk (increases (+), no effect (0), decreases (-))	Limitations
Fisherman, 1960 (1)	Case-control, clinic	All sites combined (1,185), 8 other groupings	Asthma, hay fever, or eczema	(-)	No age adjustment, no sex-specific analysis
Johnson, 1966 (2)	Case-control, clinic	All sites combined (1,000), 5 other groupings	Any of 28 distinct allergic diagnoses	(-)	No age adjustment, included allergic episodes after diagnosis of cancer, no sex-specific analysis
Mackay, 1966 (3)	Case-control, hospital ward	All sites combined (150)	Asthma, hay fever, nettle rash, or eczema	(-)	Sample size
Ure, 1969 (4)	Cross-sectional, gynecology	Gynecologic cancers (40)	Common allergies	(-)	No age adjustment
Gabriel, 1972 (5)	Case-control, hospitals	Lung cancer (150)	Childhood asthma, hay fever, eczema, hives, or food reaction	(-)	Small sample, no smoking adjustment
Meers, 1973 (6)	Case-control	All sites combined (546)	Asthma or hay fever	(-)	No sex-specific analysis
Alderson, 1974 (7)	Prospective, mortality	All sites (63), lung (16), Hodgkin's (2), leukemia (2)	Asthma only	(-)	Smoking not adjusted, mortality study
Ford, 1978 (8)	Descriptive	Lung cancer (2)	Asthma only	(-)	No control or standard, methods of follow-up not stated
Hughes, 1979 (9)	Prospective, clinic	All sites (26)	Asthma or rhinitis and positive skin tests	(-)	Followed only 141 patients over age 50 years
Cockcroft, 1979 (10)	Case-control, hospital	Grouped by embryonic germ cell layer of origin (392)	Childhood asthma or hay fever	(-)	No sex-specific analysis
Rozencwaig, 1982 (11)	Descriptive	All sites combined (47)	Positive allergy test	(-)	Sample size
Dworin, 1955 (12)	Descriptive	Hodgkin's (200)	Hay fever, asthma, hives, eczema, or angioneurotic edema	(0)	No controls
McKee, 1967 (13)	Case-control, surgical	All sites combined (104)	Asthma or seasonal rhinitis, possible allergy	(0)	No age adjustment, no sex-specific analysis
Shapiro, 1971 (14)	Case-control, hospitals	All sites combined (605), lung (184), breast (136)	Hay fever, skin manifestation, serum reaction	(0)	Wide confidence limits in risks
Robinette, 1978 (15)	Prospective, mortality	All sites combined (328), lung (156), pancreas (17)	Asthma only	(+)	Selective study population, nasopharyngitis controls, smoking not adjusted, mortality study
Logan, 1953 (16)	Case-control	All sites combined (195), mostly cervix (113)	Hay fever, asthma, or eczema	(+)	No age or sex adjustment, data collection methods differed among cases, cases selected differently from controls

allergy-related conditions included in the other allergy category is unknown.

We abide by the broad definition of allergy to mean the development of altered physiology in an organ system as a result of an immunologic reaction or process. The disease states identified retrospectively in this study and taken to represent "allergy" may or may not be accompanied by altered humoral or cellular immunity. Thus, asthma and rhinitis may be nonallergic in a number of patients; likewise, urticaria and eczema frequently do not have detectable immunologic precipitants. The clinical presentation of these diseases is similar whether or not an immunologic basis can be ascertained. Although the present retrospective analysis utilizes only those responses indicated as being diagnosed by a physician, we cannot be certain about the presence or absence of immunologic abnormalities in the participants because they were not routinely determined upon admission to Roswell Park Memorial Institute as part of this study. Therefore, we have elected to use the term "allergy-related disease," recognizing that allergy proper is a sufficient but not exclusive cause of the syndromes recognized clinically as asthma, rhinitis, urticaria, and eczema.

Malignancies were grouped by specific sites whenever sample size was greater than 60 and by system for comparison to the common set of controls with regard to reported history of each allergy-related condition. Eczema was not studied separately because of a low lifetime prevalence (below 3 per cent), but was included whenever combinations of allergy-related problems were studied.

Cases and controls whose specific allergy-related condition was first diagnosed within five years of admission to Roswell Park Memorial Institute or had an unknown history for a specific condition were omitted from the risk analyses for that specific allergy-related condition. Odds ratios were calculated as measures of association between cancer and each allergy-re-

lated condition as well as combinations of conditions. Summary odds ratio estimates adjusting for both age and cigarette smoking were calculated and tested for statistical significance by the Mantel-Haenszel method (17). An adjustment was made for prior lifetime cigarette smoking because tobacco is a known risk factor for many cancers. Also, although tobacco smoke allergy is unproven in humans, exposure to tobacco and tobacco products, including smoke, has been associated with the development or aggravation of allergic or allergic-like symptoms (18). Lifetime cigarette use was measured by pack-years which was computed for each individual by multiplying the number of years the individual smoked by the average number of packs smoked per day.

RESULTS

The sample size of the control group, cancer site categories, and the proportion of study participants reporting each specific allergy-related condition are presented in table 2 for females and males.

Estimates of site- and sex-specific relative risk of cancer with a history of asthma, hay fever, hives, and other allergies are presented in table 3 as age- and smoking-adjusted odds ratios. Most of the risk estimates for males and females are close to unity, with the majority being less than one across each cancer site category and across all four types of allergy-related conditions. The exceptions are cancer of the corpus uteri and cancer of the testis where the majority of the risks are greater than one. None of the risks associated with a history of asthma in males and females are statistically significant, although nine of the 15 risks in males and 10 of the 16 risks in females are less than one. A similar pattern of risk associated with a history of hay fever is seen. Although there is a general tendency for risks to be less than one, the only statistically significant finding is a decreased risk for oral cancer in males. None of the risks greater than one are statisti-

TABLE 2

The number of controls and cancer cases by site and the per cent† reporting asthma, hay fever, hives, and other allergies, by sex, Roswell Park Memorial Institute, 1957-1965*

	Males (no.)	Females (no.)	Per cent with asthma		Per cent with hay fever		Per cent with hives		Per cent with other allergies	
			Males	Females	Males	Females	Males	Females	Males	Females
Controls	1,562	2,477	3.8	3.2	2.6	3.3	3.8	6.4	4.2	8.3
Cancer site										
Oral	727	223	3.0	5.9	1.2	4.9	2.4	5.4	2.4	6.8
Pharynx	262	63	2.7	4.8	0.8	0.0	2.3	7.9	2.3	8.1
Digestive system‡	964	733	3.4	2.1	3.0	2.6	2.2	4.1	2.4	4.8
Stomach	210	101	3.9	0.0	1.4	4.0	2.4	2.0	1.9	4.1
Colon	265	314	5.0	1.9	3.8	2.9	3.0	3.9	2.3	5.8
Rectum	366	286	2.0	2.8	3.3	1.8	2.0	4.6	2.2	4.6
Larynx	368		5.8		1.6		3.8		2.2	
Bronchus, lung, tra- chea	1,053	133	5.9	3.0	2.3	2.3	2.0	7.6	2.7	4.7
Reproductive system§	402	4,224	2.5	3.1	3.2	2.9	5.3	4.8	3.8	6.2
Prostate	263		1.5		2.7		4.6		3.5	
Testis	77		5.3		5.2		6.5		2.6	
Breast		1,835		3.4		3.1		4.6		6.5
Cervix		1,430		2.1		2.9		4.2		5.1
Corpus uteri		471		4.3		3.4		6.5		7.7
Ovary		317		3.5		2.5		5.7		6.4
Urinary system	488	191	4.6	1.1	3.9	1.1	2.3	4.8	2.3	6.3
Malignant melanoma	111	106	1.8	3.9	4.5	3.8	2.7	5.8	2.7	5.8
Other skin	960	562	2.9	2.9	3.0	3.6	3.7	4.7	2.7	6.3
All cancer sites	6,494	7,077	3.8	3.0	2.7	3.0	3.1	4.8	2.9	6.0

* The maximum number used in an allergy-specific analysis; the total numbers differed slightly in each allergy category because of missing data and omission of conditions first diagnosed within five years of admission.

† Per cent that ever had the condition diagnosed by a physician more than five years prior to admission.

‡ Esophagus, stomach, colon, and rectum.

§ Male, prostate, testis, and other male genitalia; female, cervix, uterus, ovary, other female genitalia, and breast.

|| Kidney and bladder.

cally significant. Stronger evidence for a lower risk is seen with a history of hives and other allergies in both males and females. The most consistent findings in both males and females are a decreased relative risk associated with a history of hives and other allergies for cancer at all sites combined. Other notable associations seen with a history of hives and other allergies are a decreased risk for oral cancer, cancers of the lung and larynx, and cancer of the urinary system in males, and in females, for cancer of the reproductive system, particularly cancer of the cervix. None of the few relative risks over one associated with a history of hives or a history of other allergies were statistically significant.

In summary, there are some consistent statistically significant inverse associations, many inverse associations that are not statistically significant, and no statistically significant positive relationships ($\alpha = 0.05$).

Other findings

The risks of cancer at all sites combined and selected other sites were analyzed for each allergy-related condition at different ages of onset of the condition for males and females, whenever numbers allowed. Although it appears that associations with the least relative risks were seen when the onset of the allergy-related condition was

TABLE 3

Age- and smoking-adjusted odds ratios† of specific sites for asthma, hay fever, hives, and other allergies, males and females, Roswell Park Memorial Institute, 1957-1965

Cancer site	Type of allergy-related condition							
	Asthma		Hay fever		Hives		Other allergies	
	Males	Females	Males	Females	Males	Females	Males	Females
Oral	0.82	1.75	0.49**	1.72	0.60	0.90	0.53**	0.85
Pharynx	0.67	1.39	0.22*	0.00	0.60	1.32	0.50	0.96
Digestive system‡	0.90	0.64	1.01	0.88	0.64*	0.70*	0.58**	0.67**
Stomach	1.00	0.00	0.44	1.66	0.66	0.33	0.44	0.61
Colon	1.33	0.61	1.27	1.00	0.80	0.64	0.48	0.77
Rectum	0.60	0.82	1.22	0.61	0.54	0.80	0.50*	0.60
Larynx	1.49		0.50		0.88		0.48*	
Bronchus, lung, trachea	1.51*	0.79	0.85	0.73	0.52**	1.23	0.53**	0.55
Female reproductive system§		0.95		0.89		0.75**		0.74**
Breast		1.03		0.92		0.73**		0.80*
Cervix		0.65*		0.87		0.63**		0.57**
Corpus uteri		1.25		1.30		1.15		1.11
Ovary		1.14		0.72		0.88		0.76
Male reproductive system	0.65		0.98		1.55		0.90	
Prostate	0.36		0.91		1.44		0.82	
Testis	1.56		1.61		1.72		0.68	
Urinary system¶	1.13	0.33	1.33	0.39	0.58	0.81	0.48**	0.86
Malignant melanoma	0.45	1.16	1.20	1.13	0.70	0.88	0.68	0.66
Other skin	0.79	0.84	1.00	1.37	1.02	0.82	0.66*	0.87
All cancer sites	0.96	0.92	0.98	0.93	0.82	0.76**	0.71**	0.74**

* Significant at the 0.10 α level.

** Significant at the 0.05 α level.

† The odds that a case ever had the condition diagnosed by a physician more than five years prior to admission relative to the same odds for a control, adjusted over three age categories and three smoking levels by the Mantel-Haenszel method (17).

‡ Esophagus, stomach, colon, and rectum.

§ Cervix, corpus uteri, ovary, other female genitalia, and breast.

|| Prostate, testis, and other male genitalia.

¶ Kidney and bladder.

11-20 years prior to admission to Roswell Park Memorial Institute, inverse associations were suggested at all ages of onset. The risk associated with a history of asthma, hay fever, and/or eczema also was calculated to examine whether ever having had any one of the more classic allergy-related conditions was associated with a reduced risk. Only the age- and smoking-adjusted relative risks (RR) for cervical cancer (RR = 0.76, $p < 0.05$) and oral cancer in males (RR = 0.63, $p < 0.05$) were statistically significant. No statistically significant high risks were observed ($\alpha = 0.05$).

DISCUSSION

The evidence that allergy or allergy-related conditions is associated with an altered risk of cancer has been conflicting. Evaluation of the cause-effect relationship between allergy and cancer on the basis of prior studies is difficult because of differences in operational definitions of allergy, specific types of malignant neoplasms studied, and methodological limitations. For example, in the retrospective studies conducted to date, two studies did not use controls (8, 12), many of the studies did not adjust for age (1, 2, 4, 12, 16), and many

did not conduct sex-specific analyses (1, 2, 6, 10, 13, 16). All the retrospective studies are limited in statistical power and ability to study individual cancer sites because of limited sample sizes. Because of the small sample sizes, risk analyses have not generally been conducted for individual allergic or allergy-related disorders. The prospective studies also have limitations. Two followed asthma patients only (7, 15), and the third study followed only 141 allergic patients over the age of 50 years (9). Table 1 summarizes the previous epidemiologic research of allergy-related disorders as related to cancer risk.

Our findings are difficult to compare with previous research because previous retrospective studies were not able to examine separately risks associated with individual allergy-related conditions. Most studies operationally defined an atopic patient as reporting one or more of several diseases including asthma, hay fever, eczema, hives, or other miscellaneous conditions as illustrated in table 1. Our findings of a decreased risk associated with a history of hives and/or other allergies cannot, therefore, be compared with those from prior research. Our data suggesting that the negative association between allergy-related disorders and cancer risk is stronger in females than in males are similar to the findings of Mackay (3), Ure (4), and Shapiro et al. (14). Most notable in our study is the decreased risk for cancer of the cervix associated with a history of asthma, hives, and other allergies. These odds ratios were age- and smoking-adjusted. The decreased risks were consistent across all three interval levels of cigarette use (nonsmokers, one to 19 pack-years, and 20+ pack-years), suggesting no cigarette smoking effect modification. Although the relationship between allergy-related disease and cancer of the cervix has not been reported before, Ure (4) surveyed 140 gynecology patients for a history of common allergies and did not note any allergies among 40 patients with cancer compared with 28 instances of al-

lergy among 110 control subjects. Unfortunately, age was not controlled and the types of neoplasms were not specified. Shapiro et al. (14) reported a history of allergy in 7 per cent of patients with gynecologic cancer as compared with 10 per cent in the female controls.

While the present study offers evidence of an inverse association between allergy-related disease and cancer, cautious interpretation of the findings is warranted. This investigation utilized questionnaire and interview data collected on patients admitted to one large cancer hospital and therefore may be susceptible to selection bias. Comparisons of patients admitted to Roswell Park Memorial Institute who were residents of the Buffalo metropolitan area with a random sample of residents of the same area, however, have been reported (19, 20). No differences were shown for social class, smoking status, education, ethnic background, religion, nativity (19), and parity (20). Moreover, the controls used in this study appeared to be representative of the general population with regard to the lifetime prevalence of the allergy-related conditions that were studied (1, 3, 4, 6, 13, 14). The female controls were more atopic than the males, with 26.5 per cent ever reporting a diagnosis by a physician of either asthma, hay fever, hives, or eczema versus 17.5 per cent for the male controls. The male and female controls reported similar lifetime prevalence of asthma (3 per cent) and hay fever (3 per cent). The females, however, reported a higher prevalence of hives (6 per cent vs. 4 per cent) and other allergy-related disorders (8 per cent vs. 4 per cent). These figures are consistent with those reported by other investigators (1, 3, 4, 6, 13, 14) and the figures reported for general populations (21).

The indices of allergy-related disorders used in this study were obtained by a medical history that was dependent upon patient recall. For a number of reasons, we suspect that this has not introduced bias. First, although concerns might be well-

founded were subjects only to respond to simple questions regarding experiencing allergy, our questions were designed to be more definitive. Following the queries regarding allergies, we asked whether a physician diagnosed the allergy and the date of diagnosis. Rubin et al. (22) have shown that under similar circumstances (given the sample sizes and probabilities of allergy diagnosis in cases and controls) associations can be detected by the use of interviewers with equal to or better precision than that attained by clinical examinations. Unlike the present study, some of the previous studies had clinical measures of allergy but only on small numbers of patients.

Second, to minimize the effect of possible cause-effect transposition on the part of the cases, cases and controls with allergy-related diseases reported to be first diagnosed within five years of admission to Roswell Park Memorial Institute were omitted from particular analyses. To assess the magnitude of any differential response, the numbers omitted from individual analyses were tabulated. The controls, in fact, reported more allergy-related diseases first diagnosed within five years of admission than did the cases. Therefore, most of the associations reported in this study would be strengthened if those cases and controls were included in the analyses. Odds ratios were recalculated, including those cases and controls with allergy-related diseases first diagnosed within five years of admission. In most instances, the point estimate of odds ratios was lowered slightly and statistical significance increased. For example, in females, the odds ratio for digestive cancer associated with a history of hives was lowered from 0.70 to 0.65, and the *p* value became 0.05. In males, the same odds ratio was lowered from 0.64 to 0.60. The odds ratios for cancer of the female reproductive system associated with a history of hives and other allergies changed from 0.75 to 0.73 and 0.74 to 0.73, respectively. In each instance, the *p* value became smaller.

Third, although one could argue that cases would underreport, we think the allergy-related diseases studied are not trivial ailments that would be poorly recalled or differentially underreported by cases. Fourth, the reporting of allergy-related diseases among the cases and controls did not differ by socioeconomic status as measured by either education or occupation. Hence, even though many of the cancers involved are related to low socioeconomic status, it is not a confounding factor for the association between reported allergy and cancer.

Nevertheless, the self-reporting nature of the medical history necessitates caution in the interpretation of the findings. Even though only those conditions reported to be diagnosed by a physician were included in the analyses, those diagnoses could not be confirmed, asthma could not be delineated into intrinsic or extrinsic types, and individual perceptions of what defines "an allergy" might vary considerably. Finally, no good measure of the degree of atopy in individual patients could be constructed from the retrospective medical history data. The obvious advantage of the present study, however, was that history of physician-diagnosed allergy-related diseases was available on a very large number of cases and controls. Many statistical tests were conducted, and some of the findings are likely due to chance. No significantly high risks were observed, however ($\alpha = 0.05$), and most of the significantly low risks cannot be attributed to chance.

A review of the epidemiologic evidence concerning immunologic factors in the behavior of cancer (23) and the findings of this study suggest that immunologic factors could be important in the development of certain tumors but are not major factors in the etiology of most or all cancers. Perhaps some tumors, such as tumors of viral origin, are under more immunologic control than others, a view supported by animal studies (23, 24). Indeed, one of the strongest and most consistent inverse associations in our study was observed between several allergy-

related conditions and cancer of the cervix. Cervical cancer has been shown to be related to the number of sexual partners and having antibodies to herpes simplex virus type 2 (25).

Investigators have postulated specific immunologic mechanisms that could be important in the suppression of malignancy (5, 6, 13, 23), and more recently, much work has been done in the area of tumor immunology (24, 26-29). Although there is considerable functional overlap between cell-mediated immunity and the development of certain types of humoral (antibody-mediated) immunity, it has been postulated both that tumor-specific immunoglobulin E could be produced to the antigens of malignant cells and that the cell-mediated immune response is the first line of defense against newly transformed host tumor cells (26-29). Although a stronger inverse association was shown in the present study for hives and other allergies, the general nature of the diagnoses and the lack of any specific biologic markers of the degree of atopy in these patients (such as serum immunoglobulin E concentrations or the presence of immediate type skin test reactions to common allergens) preclude any definitive statements that can be made regarding the operation of an underlying immunologic/protective mechanism.

We hope that the nature and strength of the associations reported here will stimulate more interest in the relationship between allergy, allergy-related disorders, and cancer. More studies are needed, particularly prospective studies of carefully defined allergic disease cohorts.

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