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Allergy and Cancer: Organ Site-Specific Results from the Adventist Health Study

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The relation between allergy and risk of cancer was evaluated in a cohort study of 34,198 Seventh-day Adventists in California. Information on prevalence of asthma, hay fever, and reactions to chemicals, medications, bee stings, and poison oak (or ivy) was obtained by questionnaire in 1976. The reported allergies must have been serious enough to require treatment by a physician. The cohort was then followed for 6 years (1977–1982). Both stratified analysis and Cox proportional hazards regression analyses were utilized to evaluate the relation of allergy to cancer after taking into account several potentially confounding variables. For all cancer sites combined in males, there was a 33% increased risk associated with reaction to medications. In contrast, among females, reaction to medications was associated with a 21% decrease in risk. Both results were statistically significant. Prostate and breast cancer risk were elevated in persons who reported any type of allergic history, as was risk of lymphatic or hematopoietic cancers and sarcoma. For each of these types of cancer, risk increased with increasing numbers of allergies. However, ovarian cancer risk was decreased in persons with any allergic history and increasing numbers of allergies was associated with decreasing risk of this form of cancer. These results suggest that the association between allergy and cancer is complex and depends on the specific allergy and the specific organ site under consideration. *Am J Epidemiol* 1992;136:287–95.

allergens; allergy; neoplasms; risk

In 1985, the epidemiologic evidence relating allergic history to cancer risk was summarized by Vena et al. (1), who came to the general conclusion that the association is inverse in nature (1). Their conclusion was based on 11 studies in which there appeared to be an inverse association, three studies in which no association was observed, and two studies in which positive results were reported. Since that time, we have identified an additional five studies in the literature, two of which support an inverse association (1, 2), one that supports no association (3), and two that support a positive association (4, 5).

The reasons for the discrepancy in results are manyfold, and they include differences in study design, differences in the definition of "allergy" and/or "cancer," as well as the usual problems in recall, selection, and attrition bias, small numbers, and lack of appropriate control groups. Despite the inconsistency of results observed to date, the "hyperimmune" theory of allergic response seems to be plausible and currently enjoys a certain amount of acceptance (e.g., ref. 2). The theory postulates that individuals with highly competent immune response are able to detect and destroy incipient malignant lesions, whereas those individuals with nor-

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Abbreviations: CI, confidence interval; RR, relative risk.

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mal or compromised immune systems are less able to do so and are at relatively increased risk of cancer. This theory is also supported by studies which suggest immuno-compromised animals are at increased cancer risk in laboratory studies (6, 7). Human patients who are immunosuppressed for medical reasons experience elevated risk of lymphoma and some, but not great, increased cancer risk for other cancer sites (8). However, to date, there have been few prospective studies of this putative association and none which have controlled for several potentially confounding variables.

In 1976, approximately 34,000 Seventh-day Adventists in California were enrolled in a prospective study of cancer. By church proscription, Adventists avoid tobacco and alcohol and many adhere to a vegetarian life-style. These life-style characteristics make this population a low risk group for cancer development (9). On enrollment in the study, participants provided a detailed medical history including information on allergic history. The cohort was then followed for 6 years, and all newly diagnosed cancers were ascertained. In this report, the relation between self-reported allergic history in 1976 and risk of cancer during 1977–1982 is described.

MATERIALS AND METHODS

Population, exposure, and outcome information

In 1976, 34,198 white, non-Hispanic members of the Seventh-day Adventist church in California completed a detailed life-style questionnaire which elicited information on medical history, menstrual and reproductive history among females, smoking history, a brief occupational history, and dietary habits. In the medical history section of the questionnaire (which was on the first page of the questionnaire), participants were asked, "Have you ever been bothered enough by any of these allergic disorders to require you to seek treatment from a physician?" The question was followed by entries for the following allergies: asthma, hay fever, and reactions to medications, chemicals, bee sting, and poison oak (or ivy) or other plants. At the bottom of the list was an entry for "none of these" with the accompanying instruction, "If none of these apply, *be sure* to mark none."

After return of the questionnaire, members of the cohort were followed for 6 years. Follow-up was completed by annual contact with each member of the study population via mailed questionnaires. Each annual questionnaire elicited information on any hospitalization which occurred in the previous 12 months. If a hospitalization occurred, permission to review the medical record was requested. A second method of case ascertainment involved a computerized record linkage with the two population-based tumor registries operational in California during the period of follow-up (the Cancer Surveillance Program in Los Angeles County and the Resources for Cancer Epidemiology in the San Francisco Bay Area) (10). This was done in order to economize on the cost of gathering medical records. Follow-up of the population by these two mechanisms resulted in greater than 97 percent follow-up of the cohort during the 6-year period of study. These procedures have been described in detail (11).

The cancer outcomes examined in this analysis included cancer of the breast, colon, rectum, prostate, bladder, stomach, kidney, lung, uterine cervix, endometrium, ovary, and malignant melanoma, lymphoma, leukemia, multiple myeloma, and sarcoma. Non-melanoma skin cancers were not ascertained during the follow-up period. Since female members of the cohort were at risk of developing reproductive organ cancers only if they had intact reproductive organs, analyses of these sites were restricted to those women who reported on the 1976 questionnaire that they had never had a hysterectomy. A subsequent follow-up study has revealed that hysterectomy rates during the period of follow-up were minimal (<2 percent of the female members of the cohort had a hysterectomy between 1976 and 1982).

Statistical analysis

Person-years at risk were calculated for each member of the cohort beginning at the date that the life-style questionnaire was returned and ending with the earliest of the following: date of cancer diagnosis, date of death, date of loss to follow-up, or December 31, 1982. For each allergy and each cancer site examined, age-, sex-, and smoking-stratified incidence rate ratios (relative risks) were calculated and 95 percent confidence intervals were constructed. These relative risks were calculated using a Mantel-Haenszel procedure that has been modified for person time data (12). The Mantel-Haenszel analyses were performed for each allergy and each organ site-specific outcome before more sophisticated analyses with proportional hazards regression models were completed. The results of the Mantel-Haenszel analyses were used as a check on the multivariate models. In order to take into account additional potentially confounding variables, relative hazards were calculated using Cox proportional hazards regression analysis (13). Cox proportional hazards regression models are the model of choice for the cancer incidence outcomes where time to event in the cohort study is the variable of primary interest. These models control for several covariates (depending on the organ site-specific cancer) and were fitted by the BMDP2L procedure (14). The proportionality assumption was checked by visual inspection of the log-log plots.

RESULTS

The sex-specific prevalence of six different types of allergies and any type of allergy are presented in table 1. Female members of the cohort uniformly reported higher prevalence of allergic disorders than their male counterparts. For any type of allergic history, the prevalence in the females was 50.6 percent; among males, the corresponding figure was 43.0 percent.

In table 2, the adjusted relative risks for all cancer sites combined as associated with the various allergies are presented separately for each sex. Among males, reaction to medications is associated with a statistically significant 33 percent increased risk of all cancer sites combined. In contrast, the females experienced a 21 percent decreased risk associated with reaction to medications which is also statistically significant. There are no other allergic disorders associated with altered risk for all cancer sites combined after adjusting for age, smoking history, and time since last physician contact.

The relative risks associating the six types of allergies with eight solid tumors are presented in table 3. The relative risks are derived from Cox proportional hazards regression analyses and are adjusted for several potentially confounding variables depending on the individual type of tumor. These covariates are identified in the footnote to the table. Overall, there is no departure from the null hypothesis of no association between the various allergies and the various tumors, although for prostate cancer in men

TABLE 1. Sex-specific prevalence (in percent) of self-reported allergies in the Adventist Health Study incidence population, California, 1976

Allergy*	Females	Males	Total
Asthma	6.5	6.1	6.4
Hay fever	18.6	15.6	17.4
Reaction to medication	20.7	11.6	17.0
Reaction to chemicals	4.7	2.6	3.8
Reaction to bee sting	5.6	4.9	5.3
Reaction to poison oak (ivy) or other plants	20.2	17.1	18.9
History of any allergy	50.6	43.0	47.5

* Refers to allergic disorders sufficiently serious to require treatment from a physician.

TABLE 2. Mantel-Haenszel adjusted* relative risks (RR) and 95 percent confidence intervals (CI) for all cancer sites combined associated with several allergies in males and females in the Adventist Health Study, California, 1977–1982

Allergy	Males†		Females‡	
	RR	95% CI	RR	95% CI
Asthma	0.78	0.48–1.27	0.96	0.69–1.34
Hay fever	1.06	0.79–1.41	1.15	0.94–1.41
Reaction to medications	1.33	1.02–1.74	0.79	0.65–0.98
Reaction to chemicals	0.67	0.32–1.41	0.80	0.53–1.21
Reaction to bee sting	0.67	0.40–1.11	1.06	0.77–1.47
Reaction to poisonous plants	1.13	0.87–1.45	0.98	0.81–1.20
History of any allergy				
No§	1.00		1.00	
Yes	1.13	0.92–1.39	1.00	0.85–1.17
No. of allergies				
0§	1.00		1.00	
1	1.13	0.90–1.43	1.01	0.83–1.22
2	1.30	0.95–1.78	1.01	0.79–1.30
3+	0.68	0.37–1.25	0.92	0.67–1.26
Trend *p*	0.58		0.76	

* Adjusted for age, smoking history, and time since last physician visit.
† Cancer sites among males include: colon, rectum, prostate, lung, bladder, melanoma, stomach, kidney, lymphoma, leukemia, multiple myeloma, and sarcoma.
‡ Cancer sites among females include: colon, rectum, breast, endometrium, cervix, ovary, lung, bladder, melanoma, stomach, kidney, lymphoma, leukemia, multiple myeloma, and sarcoma.
§ Reference category.

there is a suggestive though nonsignificant elevation in risk associated with any type of allergy.

The relation between four female cancers and the six allergies are presented in table 4. For breast cancer, there is a suggestive increased risk associated with a history of hay fever which is of borderline statistical significance. This is also true for endometrial cancer where there is also an increased risk estimate associated with reactions to bee stings. Again, this is of borderline statistical significance. Asthma is associated with an elevated risk estimate for cervical cancer. Reactions to poisonous plants are associated with a statistically significant 87 percent decreased risk of ovarian cancer.

The relative risks for the lymphatic and hematopoietic cancers and sarcomas are presented in table 5. For each of these types of cancers, the relative risk associated with a history of any type of allergy is elevated, although none attain statistical significance. For sarcomas, there is a 6.5-fold elevation in the risk estimate associated with reaction to medication, which is statistically significant. Indeed, for sarcomas, the risk estimates are elevated for all types of allergy which were evaluated.

For those cancer sites where there was some suggestion of altered risk associated with any allergy, an index of number of allergies was constructed. The results are presented in table 6. For ovarian cancer, there was a statistically significant decrease in risk associated with increasing numbers of allergies. In contrast, for sarcoma, there was a trend of increasing risk associated with increased numbers of allergic disorders. This trend is of borderline statistical significance. For the other cancer sites, no significant trends were observed.

DISCUSSION

The results indicate that those individuals who reported a history of physician-treated allergy in 1976 were at somewhat increased risk of breast and prostate cancer during the follow-up period. The risk estimates were also elevated for lymphatic and hematopoietic cancers and sarcomas. No clear as-

TABLE 3. Incidence rate ratios (relative risks (RR)) (and 95 percent confidence intervals (CI)) derived from Cox proportional hazards regression analysis of allergies associated with various cancer sites in the Adventist Health Study, California, 1976–1982

Allergy	Cancer site															
	Colon* (*n* = 138)		Rectum* (*n* = 58)		Prostate† (*n* = 180)		Lung* (*n* = 62)		Bladder* (*n* = 54)		Malignant melanoma (*n* = 45)		Stomach* (*n* = 18)		Kidney§ (*n* = 14)	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Asthma	0.99	0.48–2.02	0.56	0.14–2.32	0.99	0 51–1.93	1.18	0.43–3.27	0.38	0 05–2.78		‡		‡		‡
Hay fever	1.08	0.68–1.72	0.76	0.34–1.67	1.20	0 77–1.85	1.23	0.60–2.52	1 26	0.56–2.83	0.70	0.30–1.67	1.07	0.24–4.71		‡
Reaction to medications	0.72	0.44–1.17	1.29	0.69–2.42	1.34	0.89–2 03	0.59	0.25–1.37	0.68	0.27–1.72	0.89	0.39–2.00	1.37	0.39–4.79	0.88	0.19–4.01
Reaction to chemicals	0.40	0.10–1 62	1.43	0.44–4.58	0.47	0.12–1.88		‡	0.70	0.10–5.10	0.58	0.08–4.24	2.04	0.27–15.35		‡
Reaction to bee sting	0.70	0 31–1.58	0.29	0.04–2.07	0.64	0.30–1.37	0.90	0.28–2.89	0.35	0.05–2.52	1.23	0.38–3.96		‡	1.28	0.17–9.82
Reaction to poisonous plants	0.75	0.47–1.19	0.67	0.32–1.42	1.28	0.88–1.85	0.91	0 44–1.85	0.85	0.38–1.90	0.77	0.34–1.72	0 32	0.04–2.42	0.82	0.18–3.68
History of any allergy																
No¶	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Yes	0.96	0.69–1.33	0.86	0.51–1.44	1.25	0.93–1.69	1.02	0.60–1.72	0 87	0.49–1.56	0.67	0.36–1.22	0.68	0.25–1.82	0.50	0.15–1.59

* Adjusted for age, sex, smoking history, and time since last physician contact.
† Adjusted for age, smoking history, and time since last physician contact.
‡ *No cases exposed.*
§ Adjusted for age, sex, smoking, aspirin use, and time since last physician contact.
¶ Reference category.

TABLE 4. Incidence rate ratios (relative risks (RR)) (and 95 percent confidence intervals (CI)) derived from Cox proportional hazards regression analysis of allergies associated with various cancer sites among females in the Adventist Health Study, California, 1976–1982

Allergy	Cancer site							
	Breast* (*n* = 215)		Endometrium† (*n* = 122)		Cervix‡ (*n* = 28)		Ovary§ (*n* = 38)	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Asthma	1.19	0.72–1.99	0.68	0.25–1.85	2.61	0.89–7.67	1.00	0.24–4.22
Hay fever	1.34	0.97–1.86	1.53	0.94–2.49	0.52	0.15–1.74	0.92	0.35–2.42
Reaction to medications	0.95	0.68–1.33	0.99	0.59–1.65	0.77	0.26–2.27	0.70	0.27–1.84
Reaction to chemicals	1.18	0.64–2.17		¶		¶		¶
Reaction to bee sting	1.23	0.71–2.11	1.96	0.94–4.06	0.74	0.10–5.45	1.76	0.53–5.82
Reaction to poisonous plants	1.24	0.91–1.70	0.81	0.47–1.39	1.07	0.40–2.87	0.13	0.02–0.95
History of any allergy								
No‖	1.00		1.00		1.00		1.00	
Yes	1.23	0.94–1.63	1.04	0.68–1.59	0.82	0.54–2.75	0.75	0.36–1.54

* Adjusted for age, age at menarche, first pregnancy, menopause, education, maternal history of breast cancer, smoking, and time since last physician contact.
† Adjusted for age, education, smoking, Quetelet index, age at menopause, parity, use of hormone replacement therapy, and time since last physician contact.
‡ Adjusted for age, smoking, age at first marriage, parity, and time since last physician contact.
§ Adjusted for age, smoking, parity, and time since last physician contact.
¶ No cases exposed.
‖ Reference category.

TABLE 5. Incidence rate ratios (relative risks (RR)) and 95 percent confidence intervals (CI) derived from Cox proportional hazards regression analysis of several allergies as associated with lymphatic/hematopoietic tumors and sarcomas in the Adventist Health Study, California, 1976–1982

Allergy	Cancer site							
	Lymphoma* (*n* = 46)		Leukemia* (*n* = 46)		Myeloma* (*n* = 23)		Sarcoma* (*n* = 15)	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Asthma	0.35	0.05–2.54	1.61	0.58–4.52	0.81	0.11–6.05	2.66	0.59–11.93
Hay fever	1.00	0.45–2.27	0.78	0.31–1.99	1.54	0.51–4.64	1.57	0.43–5.73
Reaction to medications	1.58	0.80–3.14	1.33	0.63–2.79	1.20	0.39–3.62	6.53	2.21–19.29
Reaction to chemicals	1.30	0.31–5.39	0.65	0.09–4.77	1.34	0.18–10.05	2.08	0.27–16.05
Reaction to bee sting	1.14	0.35–3.68	0.80	0.19–3.32	1.80	0.42–7.73	1.26	0.16–9.62
Reaction to poisonous plants	1.54	0.80–2.99	1.19	0.57–2.48	1.12	0.38–3.35	1.73	0.54–5.54
History of any allergy								
No†	1.00		1.00		1.00		1.00	
Yes	1.71	0.95–3.09	1.35	0.75–2.46	1.67	0.70–4.00	2.78	0.86–8.91

* Adjusted for age, sex, smoking history, and time since last physician contact.
† Reference category.

sociation emerged between allergies and cancer of the colon, rectum, bladder, lung, stomach, or kidney, or malignant melanoma. This lack of any clear association with allergic history was also observed in the analysis of pancreas cancer in this cohort (15). However, for ovarian cancer, allergic history appeared to be associated with somewhat decreased risk.

This prospective cohort study involving

TABLE 6. Mantel-Haenszel adjusted relative risks (RR) and 95 percent confidence intervals (CI) for selected cancer sites associated with numbers of allergies in the Adventist Health Study, California, 1976–1982

Cancer site	No. of allergies							Trend *p*
	0*	1		2		3+		
		RR	95% CI	RR	95% CI	RR	95% CI	
Breast†	1.00	1.11	0.79–1.56	1.21	0.79–1.84	1.25	0.76–2.07	0.23
Ovary†	1.00	0.68	0.32–1.47	0.16	0.02–1.21	0.26	0.03–1.99	0.02
Prostate†	1.00	1.40	0.98–2.00	1.65	1.03–2.64	0.66	0.24–1.79	0.20
Lymphoma‡	1.00	2.21	1.19–4.09	1.28	0.48–3.43	1.75	0.60–5.16	0.21
Sarcoma‡	1.00	4.41	1.10–17.77	3.33	0.52–21.43	5.06	0.81–31.78	0.06

* Reference category.
† Adjusted for age, smoking history, and time since last physician visit.
‡ Adjusted for age, sex, smoking history, and time since last physician visit.

approximately 200,000 person-years of observation during the follow-up period of 6 years does not agree with results from most prior epidemiologic investigations of allergic history and cancers. The great majority of these earlier studies utilized the case-control design (16–21) and provide evidence for an inverse association between allergic history and risk of cancer. The present report suggests that the relation depends on which allergies are examined and which organ site-specific cancer outcomes are evaluated. In these data, a positive relation exists between several allergies and two major hormone-dependent cancers (i.e., prostate and breast cancer), while a suggestive inverse relation exists between several allergies and a third hormone-dependent cancer (i.e., ovarian cancer). The findings presented herein, however, are generally consistent with the results from two earlier prospective studies which observed enhanced cancer risk associated with allergic history (5, 22). One of these earlier prospective studies (5) utilized a random sample of the total US population and found risk of breast and prostate cancer increased in those with any type of allergic history, results which are consistent with those of the present study. Moreover, risk of lymphoma, leukemia, and myeloma were also elevated fourfold in persons with an allergic history, results that are similar to those observed in the population that we studied.

Because persons with allergic disorders are more likely to have greater contact with physicians than persons without such disorders and because this greater frequency of clinical contact may result in greater detection of many forms of cancer (i.e., screening bias or surveillance bias), the prevalences of the allergies in this population have been cross-tabulated with time since last contact with a physician. Indeed, in every case, those persons with reported allergic disorders had visited a physician more recently than those without allergies (table 7). For persons who reported any type of allergic disorder, 74.8 percent had visited a physician within the last year; for those who reported no allergic disorders, only 65.0 percent had visited a physician within the last year. This evidence of greater clinical contact among those with allergies prompted the inclusion of a variable reflecting frequency of clinical contact as an adjustment variable in all allergy-cancer associations reported. Indeed, many observations initially made in the age-, sex-, and smoking-stratified analysis were substantially diminished when adjustment was also made for the time interval since last physician visit. For example, the age- and smoking-adjusted relative risk associating prostate cancer with any type of allergic history was 1.41, a statistically significant value. After incorporating a variable reflecting time since last physician contact, the relative risk was 1.25, a nonsignificant result. Similar results were obtained in the analysis of breast and ovarian cancer (i.e., the physician visit-adjusted results were closer to the null value than the nonadjusted results). This indicates

TABLE 7. Prevalence (in percent) of several reported allergies, cross-tabulated by time since last contact with a physician, in the Adventist Health Study population data, California, 1976

Allergy	Time (years) since last physician contact				Total
	<1	1–2	3–5	>5	
Asthma					
Yes	77.4	14.5	5.3	2.8	100
No	69.1	18.5	6.8	5.6	100
Hay fever					
Yes	76.8	15.8	4.4	3.0	100
No	68.1	18.8	7.2	5.9	100
Reaction to medications					
Yes	80.6	13.2	3.8	2.4	100
No	67.3	19.3	7.3	6.0	100
Reaction to chemicals					
Yes	79.5	13.3	4.1	3.1	100
No	69.2	18.5	6.8	5.5	100
Reaction to bee stings					
Yes	77.3	15.6	4.1	3.1	100
No	69.2	18.4	6.9	5.6	100
Reaction to poisonous plants					
Yes	74.0	16.9	5.6	3.5	100
No	68.6	18.6	7.0	5.9	100
History of any allergy					
Yes	74.8	16.4	5.2	3.4	100
No	65.0	19.9	8.0	7.1	100

that surveillance bias may explain the results of other investigations of this issue.

Because screening for ovarian neoplasms and the lymphatic and hematopoietic neoplasms is not feasible or common, however, it is unlikely that surveillance bias could explain the associations observed between allergies and these types of neoplasms. Indeed, recent evidence suggests that immunoregulation may play an important role in the etiology of tumors characterized by a high degree of antigenicity (23) and some evidence indicates that ovarian cancers of epithelial origin display such a high degree of antigenicity (24). This may explain the suggestive decreased risk of ovarian cancer associated with heightened allergic response observed in this study.

Conversely, risks of the lymphatic and hematopoietic tumors and sarcomas were generally elevated in association with allergic history. This is interesting in that the lymphatic and hematopoietic malignancies have previously been associated not with heightened immuno-competence but with decreased immuno-competence (e.g., 8). These conflicting results await clarification in additional studies of these tumor types.

Risk of multiple myeloma was generally elevated in association with allergic history in this study, a finding consistent with one previous case-control study (4) but not another (3). Treatment of persons suffering from allergies with hyposensitization agents has been noted in previous studies to be associated with subsequent multiple myeloma (25–28). It is unclear whether the associations in the present study were due to allergic symptoms or their treatment. No data are available regarding type of treatment, although all of the reported allergies must have been sufficiently serious to require a physician's attention.

The associations reported here were observed in a special, low-risk population which is generally more highly educated than the general population and which has a greater awareness of personal health because of their religious beliefs. Adventists have better access to and utilization of high quality medical resources and this may in part explain the associations noted herein.

For example, although the prevalence of asthma in this population was similar to that found in the first National Health and Nutrition Survey (NHANES I) (6.7 and 5.7 percent, respectively), the prevalence of hay fever was 18.3 percent among Adventists in California in 1976, whereas it was only 10.8 percent in the NHANES I in 1971. This difference in prevalence of hay fever may be related to the fact that this study was limited to California residents, while NHANES I was a national sample. However, the difference may also reflect differences in utilization of health care resources between Adventists and non-Adventists and this possibility should be carefully considered when interpreting the associations observed in this population.

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