



Allergy, Atopy, and Cancer: A Prospective Study of the 1981 Busselton Cohort

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The associations among certain allergic disorders, atopy upon skin-prick testing, and specific cancers were evaluated in a prospective study. Information regarding history of asthma and hay fever was collected by questionnaire from 3,308 cancer-free participants in the 1981 Busselton Health Survey. A subset of 1,005 participants also underwent skin-prick testing. The cohort was followed for a new diagnosis of cancer or death until the end of 1999. Cox proportional hazards regression analysis was used to estimate adjusted hazard ratios (relative risks) for breast, prostate, colorectal, lung, and hematologic cancers and melanoma. Having a skin reaction to house dust mites nearly tripled the risk of prostate cancer (relative risk = 2.90, 95% confidence interval: 1.26, 6.68). History of asthma and hay fever were associated with a trend toward a reduced risk of colorectal cancer and increased risk of leukemia, but these results were not statistically significant. Hay fever was associated with melanoma risk in men but not in women. No association was found between breast and lung cancers and allergic disorders or atopy.

allergy and immunology; asthma; hypersensitivity, immediate; neoplasms; skin tests

Abbreviations: ICD-10, *International Classification of Diseases*, Tenth Revision; ICDO-2, *International Classification of Diseases for Oncology*, Second Edition.

Although an association between allergic disorders and cancer risk is well supported by epidemiologic studies, the exact nature of the association remains controversial. Conflicting results have provided support for two distinct and contradictory hypotheses. Studies reporting a protective effect of allergies support an “enhanced immune surveillance theory,” with stimulated immune systems being better able to detect and destroy malignant cells (1–15). In contrast, studies reporting allergy to be associated with an increased risk of cancer support an “antigenic stimulation theory,” with chronic immune stimulation leading to random pro-oncogenic mutations in actively dividing stem cells (16–20).

There are a number of explanations for the inconsistent and contradictory results reported in the literature. Methodological issues include small numbers of subjects, lack of adjustment for confounding factors, and selection bias. It has been recognized that the association is complex, dependent on both the specific allergic condition and the particular organ site (21–23). However, studies have used different

measures of exposure (i.e., allergy) and outcome (i.e., cancers). Some studies have also examined the association with “all cancers”; results of such studies will be biased by the prevalence of specific cancers within the study and so not comparable between populations.

There have been relatively few prospective studies of the association between allergic disorders and cancer. Most studies have been cross-sectional or retrospective case-control studies (summarized by Vena et al. (15)), which may have examined effects of cancer on the immune system rather than a preexisting association. Of the eight prospective studies carried out to date, most examined only the association with a history of physician-diagnosed asthma or allergy (hay fever, allergic rhinitis, hives, urticaria, or food or drug allergy) (1, 9, 19, 20, 22, 23). Only two have examined the association of cancer with atopy, as determined by skin-prick testing (7, 21). Both of these studies were limited by small numbers of observed cancer cases, and while one (7) had inadequate data analysis, the other (21) used an

unusual interpretation of skin-prick test results. Like many of the other prospective studies (1, 9, 20, 23), they also failed to control for confounding factors.

Thus, there is a need for well-designed prospective studies examining the association between both specific allergic disorders and atopy (as defined by skin-prick testing) and specific cancers.

MATERIALS AND METHODS

Subjects

The association between allergy and atopy and cancer was studied using the 1981 Busselton Health Survey. Busselton is a coastal town in Western Australia, and it has been the site of repeated health surveys since 1966 (see the Busselton Health Study website at <http://bsn.uwa.edu.au>). The 1981 Busselton Health Survey targeted all adults registered to vote in the Shire of Busselton (registration to vote is compulsory in Australia) and consisted of a self-completed general health questionnaire and a visit to the study clinic for various measurements and tests (24). Informed written consent for participation and subsequent use of data was obtained from participants at the time of the survey. Permission to access the data was granted by the Busselton Population Medical Research Foundation. Ethical approval was obtained from the University of Western Australia Human Research Ethics Committee.

A total of 3,940 adults participated in the 1981 survey—a response rate of 64 percent. Twenty subjects were excluded because of a prior diagnosis of malignancy. After the exclusion of subjects with missing values on key variables, the resulting cohort consisted of 3,308 subjects: 1,522 men and 1,786 women. One third of participants (five consecutive subjects from every 15 with the same appointment time) were asked to undergo skin-prick testing. Of the 1,313 subjects asked, 1,172 (89 percent) agreed to be tested. After exclusion of those who failed to react to the positive control and those who were missing data on key variables, 463 men and 542 women with useful data on skin-prick testing were included.

Allergy and atopy

Allergy was defined as a history of physician-diagnosed asthma or hay fever on the basis of a positive response to the question “Has a doctor ever told you that you had asthma?” or “Has a doctor ever told you that you had hay fever?”. Atopy was defined as a positive reaction to one or more allergens upon skin-prick testing, performed using the method of Pepys (25). Allergens known to cause symptoms in southwestern Australia were tested: house dust mites, cat dander, cattle dander, two molds (*Aspergillus fumigatus* and *Alternaria tenuis*), and seven local pollens (rye grass, barley, capeweed, orchard grass, plantago, peppermint tree, couchweed grass, and wild oat). All tests were conducted between 7:30 a.m. and 1:00 p.m. and were completed during a 2-week period to include the height of the pollen season. Histamine at 1 mg/ml was used as a positive control, and saline at 0.9 percent was used as a negative control. Fifteen

minutes after pricking, two perpendicular diameters of wheals were measured and the mean of the two diameters was recorded. After the size of the negative control was subtracted, having a wheal of 3 mm or more was defined as a positive response to an allergen.

Follow-up and cancer outcomes

The cohort was followed to the end of 1999. Linkage to death registrations was used to identify deaths occurring within Western Australia. Information obtained from relatives and linkage to electoral rolls was used to determine whether and when a participant had left Western Australia. Approximately 3 percent of survey participants left the state during the follow-up period.

Incident cancer endpoints were determined via linkage to the West Australian Cancer Registry. This population-based cancer registry receives mandatory notification from pathologists, hematologists, and radiation oncologists. Data are collected on incident malignant primary cancer cases and death from cancer. Primary endpoints were prostate cancer (*International Classification of Diseases*, Tenth Revision (ICD-10) code C61.9), breast cancer (ICD-10 codes C50.0–C50.9), colorectal cancer (ICD-10 codes C18.0–C20.9), leukemia (*International Classification of Diseases for Oncology*, Second Edition (ICDO-2) codes 9800–9948), lymphoma (ICDO-2 codes 9590–9729), melanoma (ICD-10 codes C44.0–C44.9), and lung cancer (ICD-10 codes C34.0–C34.9).

Statistical analysis

The survival time variable calculated for each member of the cohort was time from the survey to diagnosis of first cancer (if a cancer diagnosis was recorded) or time from the survey to the date on which the subject was last known to be alive in Western Australia (if no diagnosis of cancer occurred). For each type of cancer, a subject was considered a case if his or her first cancer was of that type. Cox proportional hazards regression was used to investigate the relation between allergy and atopy and the cancer endpoints. The underlying proportionality assumption was tested by examining the effect of adding an interaction with the natural log of time into the model.

Separate regression analyses were performed for each cancer outcome with the following allergy and atopy variables: asthma; hay fever; any atopy (yes/no); and specific atopies that were sufficiently common to allow meaningful analysis (sensitization to house dust mites and pollens from rye grass, barley, orchard grass, and wild oats). Analyses were performed for males and females separately and were adjusted for age. The models for prostate cancer, breast cancer, colorectal cancer, leukemia, lymphoma, and lung cancer also included smoking status at the time of the 1981 survey (current smoker, ex-smoker, and never smoker); the models for prostate cancer and colorectal cancer also included body mass index (weight (kg)/height (m)²); and the model for breast cancer also included body mass index, menopausal status, and number of pregnancies.

TABLE 1. Characteristics of the study subjects at baseline in 1981, Busselton Health Survey, Busselton, Western Australia*

Variable	All subjects		Subjects with skin-prick testing	
	Men (n = 1,522)	Women (n = 1,786)	Men (n = 463)	Women (n = 542)
Asthma	124 (8.1%)	155 (8.7%)	78 (16.8%)	107 (19.7%)
Hay fever	197 (12.9%)	400 (22.4%)	75 (16.2%)	155 (28.6%)
Atopy				
Any atopy			228 (49.2%)	239 (44.1%)
House dust mites			163 (35.2%)	149 (27.5%)
Rye grass pollen			101 (21.8%)	138 (25.5%)
Barley pollen			88 (19.0%)	117 (21.6%)
Orchard grass pollen			95 (20.5%)	126 (23.2%)
Wild oat pollen			87 (18.8%)	112 (20.7%)
Mean age (years)	50.7 (16.7)†	50.0 (16.6)	49.0 (16.6)	47.8 (16.3)
Mean body mass index‡	26.0 (3.3)†	24.9 (4.3)	26.0 (3.5)	24.8 (4.1)
Menopause		984 (55.1%)		279 (51.5%)
No. of pregnancies				
0		216 (12.1%)		61 (11.2%)
1		126 (7.0%)		47 (8.7%)
2		403 (22.6%)		129 (23.8%)
3		402 (22.5%)		110 (20.3%)
4		304 (17.0%)		93 (17.2%)
5		154 (8.6%)		55 (10.1%)
≥6		181 (10.1%)		47 (8.7%)
Smoking				
Never smoker	539 (35.3%)	1,131 (63.3%)	176 (38.0%)	356 (65.7%)
Ex-smoker	623 (40.9%)	364 (20.4%)	171 (36.9%)	103 (19.0%)
Current smoker	360 (23.6%)	291 (16.3%)	116 (25.0%)	83 (15.3%)

* Numbers and percentages are shown unless mean values and standard deviations are specified.

† Numbers in parentheses, standard deviation.

‡ Weight (kg)/height (m)².

RESULTS

The prevalence of allergy and atopy and the characteristics of the study sample and the subset with atopy data are shown in table 1. Female members of the cohort reported a higher prevalence of asthma and hay fever than male members. More men than women were current smokers.

Those subjects who participated in skin-prick testing were slightly younger, on average, than the entire cohort, and they had a slightly higher prevalence of allergies. They were similar to the entire cohort with regard to the other characteristics. Male members of the cohort had a greater prevalence of any atopy than females, with 49.2 percent of males being atopic upon skin-prick testing compared with 44.1 percent of females. Results for the common allergens with an overall prevalence of 20 percent or more upon skin-prick testing are presented.

As expected, there was an association between atopy and allergy in the subjects. Asthma was reported by 29 percent of atopic subjects and 9 percent of nonatopic subjects, while 35

percent of atopic subjects and 12 percent of nonatopic subjects reported having hay fever. These proportions were similar in males and females.

A total of 343 incident cancers were observed during follow-up of the cohort, including 86 prostate cancers, 65 breast cancers, 67 colorectal cancers, 28 lung cancers, 68 melanomas, 15 lymphomas, and 14 leukemias. Of these 343 cancers, only 16 were recorded within 2 years of the survey. There were 100 cancers among the subjects who had undergone skin-prick testing.

A significantly increased risk of prostate cancer was found for history of asthma, any atopy, and reaction to house dust mites (table 2). After adjustment for asthma, the risks were similar—2.25 (95 percent confidence interval: 0.92, 5.47) for atopy and 2.55 (95 percent confidence interval: 1.04, 6.27) for sensitization to house dust mites.

No association was found between asthma or hay fever and breast cancer among female members of the cohort (table 3). While sensitization to house dust mites was associated with nearly double the risk of breast cancer, this was not

TABLE 2. Risk of prostate cancer in relation to allergy and atopy, Busselton Health Survey, 1981–1999

	HR*,†	95% CI*
<i>Allergy (86 cases)</i>		
Asthma	1.89	1.00, 3.60
Hay fever	1.06	0.56, 2.01
<i>Atopy (23 cases)</i>		
Any atopy	2.49	1.04, 5.93
House dust mites	2.90	1.26, 6.68
Rye grass pollen	0.47	0.11, 2.05
Barley pollen	1.14	0.38, 3.46
Orchard grass pollen	0.85	0.25, 2.96
Wild oat pollen	0.81	0.23, 2.81

* HR, hazard ratio; CI, confidence interval.

† Adjusted for age, smoking status, and body mass index.

statistically significant. No other sensitizations showed evidence of an association with breast cancer.

Most of the associations between colorectal cancer and history of allergy or atopy were negative (protective), but none had confidence intervals that excluded 1 (table 4).

For hematologic malignancies (table 5), the results were based on small numbers and should be interpreted with caution. The presence of allergic disorders tended to show nonsignificant increased risks of leukemia. Associations between allergies and atopy and lymphoma were inconsistent.

There were no significant associations between allergy or atopy and lung cancer (table 6).

The risk of melanoma was significantly increased among males with a history of hay fever (table 7), but this was not seen among females. In males, those subjects with any atopy were approximately three times more likely to develop melanoma, but the confidence interval included 1. Further investigation of specific atopies revealed a significantly higher

TABLE 3. Risk of breast cancer in relation to allergy and atopy, Busselton Health Survey, 1981–1999

	HR*,†	95% CI*
<i>Allergy (65 cases)</i>		
Asthma	1.13	0.49, 2.64
Hay fever	0.94	0.51, 1.73
<i>Atopy (21 cases)</i>		
Any atopy	1.44	0.61, 3.41
House dust mites	1.94	0.81, 4.67
Rye grass pollen	1.11	0.40, 3.09
Barley pollen	0.93	0.31, 2.81
Orchard grass pollen	0.89	0.30, 2.69
Wild oat pollen	0.66	0.19, 2.29

* HR, hazard ratio; CI, confidence interval.

† Adjusted for age, smoking status, body mass index, number of pregnancies, and menopausal status.

TABLE 4. Risk of colorectal cancer in relation to allergy and atopy, by sex, Busselton Health Survey, 1981–1999

	Men		Women	
	HR*,†	95% CI*	HR†	95% CI
<i>Allergy</i>				
	33 cases		34 cases	
Asthma	0.44	0.06, 3.23	0.39	0.05, 2.84
Hay fever	0.79	0.23, 2.72	1.08	0.46, 2.50
<i>Atopy</i>				
	5 cases		10 cases	
Any atopy	0.32	0.03, 2.84	1.42	0.41, 4.95

* HR, hazard ratio; CI, confidence interval.

† Adjusted for age, smoking status, and body mass index.

risk of melanoma among the 40 men with allergy to capeweed pollen (hazard ratio = 7.38, 95 percent confidence interval: 2.40, 22.69), although numbers were small in this group.

DISCUSSION

As with other prospective studies, in this study we were able to examine the associations between preexisting allergy and subsequent malignancy. This contrasts with retrospective studies, which may be examining the effects of malignancy per se on the immune system. However, ours is one of the few prospective studies (7, 21) to have examined the association of both allergy and atopy (as determined by skin-prick testing) with specific malignancies.

Our findings, like those of a number of other prospective studies (21–23), show the association of allergy, atopy, and cancer to be complex, dependent on the type of allergic disorder, the specific allergen(s), and the particular type of cancer under consideration.

There is a substantial body of evidence to support the role of cellular (type 1) immunity—characterized by the production of γ -interferon—as the dominant adaptive immune response to neoplasia. This includes the predisposition to malignancies found in murine models of γ -interferon-deficient mice (26) and in patients with congenital and acquired immunodeficiencies (27), the prognostic value of the presence of lymphocytes within early lesions of tumors (28, 29), and the ability of adoptively transferred CD8+ T lymphocytes to mediate tumor killing (30). On the other hand, atopy and allergic diseases, including asthma and allergic rhinitis, are associated with type 2 immune responses, which is characterized by the production of interleukins 4, 5, 9, and 13 (31).

In our study, preexisting asthma, atopy, and sensitization to house dust mites were associated with 2–3 times the risk of prostate cancer. Other prospective studies have reported an increased risk of prostate cancer with asthma (19, 23), but their findings were nonsignificant at the 5 percent level. One prospective study reported an inverse (protective) association with prostate cancer (9). However, this was presented as a standardized mortality ratio, unadjusted for confounding

TABLE 5. Risk of leukemia and lymphoma in relation to allergy and atopy, by sex, Busselton Health Survey, 1981–1999

	Leukemia				Lymphoma			
	Men		Women		Men		Women	
	HR*,†	95% CI*	HR†	95% CI	HR‡	95% CI	HR‡	95% CI
<i>Allergy</i>								
	7 cases		7 cases		9 cases		6 cases	
Asthma			2.13	0.25, 17.79	1.67	0.21, 13.37		
Hay fever	1.23	0.14, 10.63	3.62	0.79, 16.47	0.86	0.11, 6.94	0.88	0.10, 7.63
<i>Atopy</i>								
	2 cases		1 case		3 cases		2 cases	
Any atopy	1.32	0.08, 21.54			0.52	0.05, 5.77	1.27	0.08, 20.45

* HR, hazard ratio; CI, confidence interval.

† Adjusted for age and smoking status.

‡ Adjusted for age.

factors and open to both surveillance and treatment bias. The increased risk found with sensitization to house dust mites has not previously been reported, with either no observed cases of prostate cancer (21) or no analysis for prostate cancer (7) appearing in previous prospective studies. Cellular immunity is likely to be important in the body's defense against prostate cancer, with lymphocyte infiltration being demonstrable within tumors following androgen ablative therapy (32). It is possible that the bias to type 2 immune responses found in atopic and allergic patients may predispose them to the development of prostate cancer.

Our study failed to show an association of breast cancer with either allergy or atopy. This is surprising given others' findings of an increased but nonsignificant risk associated with allergy (19, 22). Another prospective study with a similar number of breast cancer cases also found atopy to be associated with a significantly increased risk (21).

The nonsignificant but consistently protective association between allergies and colorectal cancer is supported by some prospective studies (9, 22) but not others (19, 23). To our knowledge, only two other prospective studies have examined atopy and colorectal cancer. One contained only one case of colorectal cancer and used all cancers as an endpoint

(7). The other used an unusual classification of skin-prick test results, making interpretation of the findings difficult (21). Although cellular immunity is also likely to be important in the body's defense against colorectal cancers, other genetic and environmental factors are more important in defining the risk of this malignancy—factors that were not accounted for in our model (33).

The small number of hematologic malignancies in our cohort makes caution necessary when interpreting these results. The only other prospective study examining these specific outcomes with any history of allergy reported findings similar to ours for leukemia but not lymphoma (22). However, those investigators reported a protective effect of hay fever for leukemia (both sexes combined), which contrasts with the nonsignificant increased risk for leukemia seen among women in our study. To our knowledge, this is the first prospective study to have examined atopy (as determined by skin-prick testing) and hematologic malignancies.

After adjusting for smoking, we did not find lung cancer to be associated with either allergy or atopy, but our result was based on quite small numbers of cases. Several previous studies also found no association (9, 19, 21, 22). Investigators in two of these studies (19, 22) were able to adjust for

TABLE 6. Risk of lung cancer in relation to allergy and atopy, by sex, Busselton Health Survey, 1981–1999

	Men		Women	
	HR*,†	95% CI*	HR†	95% CI
<i>Allergy</i>				
	15 cases		13 cases	
Asthma	1.18	0.15, 9.06	0.96	0.12, 7.48
Hay fever	0.64	0.08, 4.87	1.45	0.40, 5.30
<i>Atopy</i>				
	6 cases		3 cases	
Any atopy	0.28	0.03, 2.49	0.87	0.08, 9.89

* HR, hazard ratio; CI, confidence interval.

† Adjusted for age and smoking status.

TABLE 7. Risk of melanoma in relation to allergy and atopy, by sex, Busselton Health Survey, 1981–1999

	Men		Women	
	HR*,†	95% CI*	HR†	95% CI
<i>Allergy</i>				
	27 cases		41 cases	
Asthma	0.47	0.06, 3.46	1.25	0.44, 3.51
Hay fever	2.39	1.00, 5.70	1.02	0.48, 2.17
<i>Atopy</i>				
	13 cases		11 cases	
Any atopy	2.90	0.89, 9.47	1.30	0.37, 4.49

* HR, hazard ratio; CI, confidence interval.

† Adjusted for age.

smoking. In a case-control study, Vena et al. (15) reported a positive association between asthma and lung cancer and a negative association between hives and lung cancer after adjustment for smoking. In a Finnish study (23), people who had filled prescriptions for bronchial asthma medication were significantly more likely to develop lung cancer. This result was not adjusted for smoking, but the authors argued that any confounding effect was likely to have been small.

In males, we found melanoma risk to be associated with hay fever but not with other allergies. The only atopic sensitization significantly associated with melanoma in males was capeweed. In a prospective study, Mills et al. (22) found no association with hay fever in an analysis adjusted for sex, while Vena et al. (15), in their case-control study, found a nonsignificant slight increase among males with hay fever. Asthma has been reported as being protective against melanoma (9) or as having no association with melanoma (15, 21, 23). We had no information on other risk factors for melanoma, such as skin type, number of nevi, or sun exposure. Cellular immunity is important in the control of melanoma (28). People with atopy and allergy have a tendency to have type 2 immune responses, and this may predispose them to melanoma. The bias toward males may be explained by the differences in exposure to ultraviolet radiation between males and females in this rural population.

Our study had a number of advantages over previous studies. Our cohort was community-based, which helped us avoid the selection bias evident in other case-control studies and prospective studies using registry- and hospital-based cohorts (9, 15, 21). Unlike researchers in most other prospective studies (1, 7, 9, 20, 21, 23), we were able to adjust our estimates for multiple confounders using information collected at the initial survey. Follow-up of our cohort gave us over 62,000 person-years at risk, resulting in reasonably large numbers of observed cancer cases. This was less true for participants undergoing skin-prick testing. Although our study had much larger numbers of observed cancer cases than other prospective studies of atopy (7, 21), small numbers hampered examination of associations of specific allergic disorders and atopic sensitizations and may explain why some results failed to reach statistical significance.

By 1981, the Busselton population and their general practitioners were well used to being surveyed. This should have minimized respondent error and reduced the need to account for surveillance bias due to allergic subjects' having greater physician contact. The prevalence of asthma in our cohort was 8.5 percent, corresponding to the 9 percent prevalence of self-reported asthma among Australian adults in the 1989/1990 National Health Survey (34). Like investigators in most other studies (15, 19, 22), we used a physician diagnosis of allergic conditions that was not validated (e.g., by bronchial provocation tests), which may have resulted in the inclusion of asthma with a nonallergic basis. However, follow-up studies on subsamples of the 1981 Busselton cohort found a history of physician-diagnosed asthma to be significantly associated with bronchial responsiveness to inhaled beta-agonists, histamine (35), and methacholine (36). Furthermore, reporting of nonallergic asthma is unlikely to differ between participants with and without a subsequent malignancy. This would result in a nondifferen-

tial source of bias and lead to underestimation of any existing associations.

As was done in many other studies of allergy and cancer (15, 19, 21, 22), we performed a relatively large number of statistical tests. Although our search for associations was targeted (as opposed to examining all possible associations), it is still possible that some of the findings were due to chance. Associations that are consistently observed across studies (especially prospective studies) are more likely to be real.

In conclusion, a history of asthma doubled the risk of prostate cancer; and allergic disorders and atopy were associated with trends toward a reduced risk of colorectal cancer and an increased risk of leukemia, but the latter results were not statistically significant. Specific allergic disorders and atopy were associated with risk of melanoma, but those findings were inconsistent between genders. No association was found between breast and lung cancers and allergic disorders or atopy.

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