

Allergy and Risk of Cancer

A Prospective Study Using NHANESI Followup Data

WILLIAM P. McWHORTER, MD, MPH

The First National Health and Nutrition Examination Survey (NHANESI), conducted in 1971–1975, included a cohort of 6913 adults for whom history of smoking, allergies, and other factors was obtained. These persons were traced (with 93% success) approximately 10 years later by the NHANESI Epidemiologic Followup Survey, and incidence of malignancy in the interim period was determined. Primary allergy variables were physician-diagnosed asthma, hay fever, hives, food allergy, or other allergies. Excluded were persons with a prior history of cancer and cases of nonmelanoma skin cancer. After adjustment by logistic regression for age, sex, race, and smoking history, allergic history was found to increase the risk of subsequent malignancy (risk odds ratio = 1.40, 95% confidence interval = 1.10–1.77). The specific allergy type with the strongest cancer risk was hives. The cancer group with the strongest allergy association was lymphatic–hematopoietic (leukemia, lymphoma, myeloma). The risk odds ratio of developing leukemia, lymphoma, or myeloma for persons with hives history was 7.89 (95% CI = 3.13–19.89). These findings suggest that a history of allergy does not protect against subsequent cancer, and may be a risk factor. The possibility is raised that a history of hives may be a particular risk factor for lymphatic–hematopoietic malignancies.

Cancer 62:451–455, 1988.

A NUMBER of studies of the association of allergic diseases and symptoms with malignancy have been reported over the past three decades.^{1–18} Of these, 13 reported allergy to be protective,^{1–13} three found no association,^{14–16} and two found allergy to be a risk factor.^{17,18} The hypothesis often given to explain a protective effect is that individuals with allergies may have hyperstimulated immune systems, which are better able to detect and eliminate incipient malignancies. A recent summary was published by Vena *et al.*¹³ Of note is the lack of a prospective study controlling for known cancer risk factors such as age, sex, race, and smoking. This

report describes a prospective study of the relationship of allergic history to subsequent malignancy using the First National Health and Nutrition Examination Survey (NHANESI), conducted by the National Center for Health Statistics in 1971–1975, and the NHANESI Epidemiologic Followup Survey, conducted in 1982–1984.

Materials and Methods

NHANESI was a national probability sample of the US population conducted in 1971–1975 by examination teams in mobile units, and included 23,808 persons ages 1 through 74 years. Details of the survey methods are available from the National Center for Health Statistics.^{19,20} The current study was limited to the 6913 adults (age range, 25 to 74 years) who were given supplemental medical questionnaires that included smoking history; smoking history was not asked of the other subjects. Although NHANESI oversampled children, aged, poor, and women of childbearing age, this was not true of the supplemental sample used for this cohort.

The NHANESI Epidemiologic Followup Survey was conducted in 1982–1984; details have been published.²¹ Individual interviews were conducted, with proxies answering for disabled or deceased persons. Diagnostic information was gathered from hospital and nursing home records and coded by trained personnel using standard

From the Division of Cancer Prevention and Control, National Cancer Institute, Bethesda, Maryland.

The author would like to acknowledge the assistance of Drs. David Poskanzer, Philip Taylor, Yvonne Jones, and Arthur Schatzkin (all of the Division of Cancer Prevention and Control) and Helen Barbano of the National Center for Health Statistics.

Address for reprints: William P. McWhorter, MD, MPH, National Cancer Institute/DCPC, Blair 4A01, Bethesda, MD 20892-4200.

The NHANESI Epidemiologic Followup Survey was conducted by the National Center for Health Statistics in conjunction with the National Institute on Aging, the National Cancer Institute, the National Institute of Allergic and Infectious Diseases, the National Heart, Lung, and Blood Institute, the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, the National Institute of Mental Health, the National Institute of Alcohol Abuse and Alcoholism, and the National Institute of Neurological and Communicative Disorders and Stroke.

Accepted for publication January 4, 1988.

National Center for Health Statistics criteria. All records were sought from any institution reported. Date and cause of death were verified with searches of death certificate files. Copies of discharge summaries for selected cases were made available by the National Center for Health Statistics for review.

Seven percent of the 6913 subjects (503 persons) were lost to follow-up (vital status unknown). Persons who reported a history of cancer at NHANESI (an additional 174 subjects) were excluded from the cohort. Either smoking or allergic status was unknown for an additional 128 persons. The analyses in this report were based on the remaining 6108 subjects.

The primary cancer endpoint was a cancer diagnosis (ICD9 code numbers 140–208) listed on hospital or nursing home records, or on death certificate if hospital record of cancer was not present. Incidence date was considered the date of first admission to hospital with a cancer diagnosis, or date of death for those cases with death certificate diagnosis of cancer only. Nonmelanoma skin cancers and diagnoses listed as questionable were not included as cancer cases. A separate analysis was done using an expanded definition of cancer and included as cases those subjects who reported having a physician-diagnosed cancer occur during the follow-up period, but diagnosis could not be verified in the medical record.

Persons were considered to have a history of allergy if they reported on NHANESI interview that they had previously been told by a doctor that they had any of the following; asthma, hay fever, hives, food allergy, or other allergy. Other allergy, not clarified by further questions, would have included drug allergy. A separate analysis was done in which allergic conditions diagnosed within the prior 5 years were excluded. A question on hives history that did not specifically require a doctor's diagnosis was available from a different section of the questionnaire and was used in further analyses.

History of smoking was considered positive if subjects reported that they were smoking cigarettes at the time of the NHANESI interview, or had been regular smokers within the prior 5 years. In further analyses, smoking was considered as a continuous variable of lifetime pack-years of cigarettes smoked prior to NHANESI.

Adjusted estimated risk odds ratios (ROR) were calculated using both logistic regression and Cox proportional hazards models, the latter to account for possible distortions due to differential follow-up times. The programs LOGIST and PHGLM from the statistical software package SAS were used.²² Adjusting variables included age at NHANESI, sex, race, and the smoking variables, except that female breast cancer, uterus, cervix, and ovarian cancers were also adjusted for number of pregnancies and Quetelet's index (weight/height²) at

TABLE 1. Adjusted Risk of Developing Cancer for Persons With Any Allergy: Stratified Analysis by Cancer Type*

Outcome cancer type (no. of cases)	Estimated ROR (95% CI)
Larynx and lung (73)	1.19 (0.71–2.01)
Colon and rectum (45)	1.69 (0.92–3.11)
Female breast (34)	1.20 (0.60–2.43)
Prostate (34)	1.32 (0.62–2.80)
Uterus, cervix, and ovary (27)	1.62 (0.75–3.51)
Lymphoma, leukemia, and myeloma (20)	3.84 (1.55–9.51)
Kidney, bladder (17)	1.11 (0.39–3.19)
Pancreas (11)	1.69 (0.49–5.83)
All other sites (80)	1.05 (0.64–1.73)

ROR: risk odds ratio; CI: confidence interval.

* Adjusted by logistic regression for age, race, sex, and smoking status. Female breast and uterus, cervix, and ovary were also adjusted for number of pregnancies and Quetelet's index. Any allergy pertains to doctor-diagnosed asthma, hay fever, hives, food allergy, or other allergy. Reference categories are persons without that type of cancer, persons without history of any allergy. Nonmelanoma skin cancer was not considered.

NHANESI. Age was considered both as a continuous variable and as 10-year age groups.

Results

During the follow-up period, 341 patients developed cancer based on hospital, nursing home, and death records. Fifty-seven of these cases had death certificate diagnosis data only. An additional 53 cases were reported on follow-up questionnaire, but records could not be found. Frequencies of major cancer sites are noted in Table 1.

Persons with history of any allergy comprised 30.1% of the cohort; considering only those with more than a 5-year history dropped this only slightly, to 26.3%. Frequencies of the five specific allergy types are noted in Table 2. Some subjects reported more than one type of allergy; consequently, the specific types sum to more than 30.1%. Self-reported hives (not requiring a doctor's

TABLE 2. Adjusted Risk of Developing Any Cancer for Persons With Allergy: Stratified Analysis by Allergy Type*

Allergy type (% of cohort)	Estimated ROR (95% CI)
Hives (7.9)	1.50 (1.03–2.17)
Asthma (5.7)	1.02 (0.63–1.65)
Hay fever (10.8)	1.18 (0.82–1.70)
Food allergy (5.6)	1.43 (0.92–2.23)
Other allergy (15.4)	1.38 (1.02–1.86)

ROR: risk odds ratio; CI: confidence interval.

* Adjusted by logistic regression for age, sex, race, and smoking status. Reference categories are all persons without cancer and all persons without history of that type of doctor-diagnosed allergy. Outcome pertains to any cancer except nonmelanoma skin cancer. The source was the hospital, nursing home, and death certificate records.

TABLE 3. Description of Cohort*

Variable category	No. of persons in category	% with any allergy	% developing any cancer
Age at NHANESI (yr)			
25-34	1306	32.1	0.7
35-44	1080	30.6	1.9
45-54	1456	29.6	4.4
55-64	1187	31.0	8.3
65-74	1079	27.1	13.9
Sex			
M	2835	25.5	6.8
F	3273	34.1	4.6
Race			
White	5369	31.5	5.5
Black	739	20.4	6.2
Smoking status			
Smoker	2743	28.1	5.9
Nonsmoker	3365	31.8	5.4

NHANESI: National Health and Nutrition Examination Survey.

* Any allergy pertains to history of doctor-diagnosed asthma, hay fever, hives, food allergy, or other allergy. Outcome refers to any malignancy except nonmelanoma skin cancer.

diagnosis) was positive in 8.3% of a somewhat smaller cohort.

Those persons excluded from the analysis (lost to follow-up, history of prior cancer, or incomplete data) had approximately the same allergy characteristics (total allergy, 32.7%; hives, 9.1%) as the final cohort.

The unadjusted figures showed that persons with a history of any allergy were more likely to develop a malignancy in the follow-up period, but the confidence interval (CI) was not high. Of 4268 persons without allergic history, 225 subsequently developed a malignancy; of 1840 persons with allergic history, 118 developed a malignancy. The ROR was 1.23, and the 95% CI was 0.98-1.55.

TABLE 4. Adjusted Risk of Developing Any Cancer for Persons With History of Any Allergy*

Cancer outcome (no. of cases)	Allergy type (% of cohort)	Estimated ROR (95% CI)
Any cancer (341)	Any allergy (30.1)	1.40 (1.10-1.77)
Any cancer, including 53 self-reports (394)	Any allergy (30.1)	1.37 (1.10-1.71)
Any cancer (329)	More than 5-year history of any allergy (26.3)	1.47 (1.14-1.88)
Any Cancer incident in last 5 follow-up years only (180)	Any allergy (30.0)	1.40 (1.01-1.92)

* Adjusted by logistic regression for age, race, sex, and smoking status at NHANESI. Reference categories are all persons without cancer and all persons without history of asthma, hay fever, hives, food allergy, or other allergy. Outcome refers to any cancer except nonmelanoma skin cancer. The source was the hospital, nursing home, and death certificate records.

TABLE 5. Adjusted Risk of Developing Lymphoma, Leukemia, or Myeloma for Persons With History of Hives*

Hives history at NHANESI (% of cohort)	Estimated ROR (95% CI)
Doctor-diagnosed hives (7.9%)	7.89 (3.13-19.89)
Doctor-diagnosed hives more than 5-year history (6.5%)	9.33 (3.69-23.57)
Any hives not requiring doctor diagnosis (8.3%)	7.45 (2.61-21.26)

ROR: risk odds ratio; CI: confidence interval; NHANESI: National Health and Nutrition Examination Survey.

* Adjusted by logistic regression for age, race, sex, and smoking status. Outcome is taken from the hospital, nursing home, or death certificate record of lymphoma, leukemia, or myeloma (20 cases). Reference categories are all persons without leukemia, lymphoma, or myeloma and all persons without that type of hives history.

However, persons with allergic history were more likely to be white, female, younger, and nonsmokers compared to those without allergic history. These are the groups that developed fewer cancers as expected. The comparisons are given in Table 3.

Simultaneous adjustment by logistic regression for these four potentially confounding variables resulted in a highly significant positive association between history of any allergy and development of any cancer (ROR = 1.40; 95% CI = 1.10-1.77). These results were little affected, either when the definition of cancer was expanded to include subject reports, hospital, nursing home, and death records, when the definition of allergy was restricted to a greater than 5-year history, or when considering only cancer cases incident in the latter 5 years of the follow-up period. These results are summarized in Table 4.

The allergy sufferers were followed for essentially the same amount of time as the nonallergic group; mean follow-up time to death or follow-up interview was 8.97 years and 8.93 years, respectively ($P = 0.48$). Regression using the Cox proportional hazards model resulted in essentially the same results as the logistic model; the adjusted hazard ratio of developing any cancer for those with any allergy was 1.38 (95% CI = 1.10-1.73). The Z:PH tests for nonuniformity of hazard ratios over time were nonsignificant (less than 1.96).

A family history of allergy was also found to be a risk factor for subsequent malignancy (ROR = 1.96; 95% CI = 1.00-3.86).

Each variable was checked for effect modification by stratified analyses; a separate regression was done within each category of adjusting variable (each age group, sex, race, and smoking status separately). No significant effect modification was found. The ROR of developing any cancer for persons with any allergy history was greater than 1 within each variable category except for the ages 25 to 44 years, which included very few cancer

cases. The 95% CI around these estimated ROR all overlapped 1.40, and tests for inequality of the ROR were not significant.

Separate regressions were done within each of the five allergy variables, as shown in Table 2. The strongest cancer association was with hives.

The cancer cases were divided into the eight most frequent cancer sites, and separate regression analyses were done with each, as shown in Table 1. The strongest association was with lymphatic and hematopoietic malignancies, which included leukemias, lymphomas, and myelomas.

As shown in Table 5, the adjusted risk of developing a lymphatic-hematopoietic malignancy for persons with hives was particularly strong, with a ROR greater than 7. These results were little affected, either when the diagnosis of hives was restricted to more than 5 years duration at NHANESI or when nonspecific hives history was used (not specifically requiring a doctor's diagnosis).

The proportional hazards model yielded similar results; the hazard ratio of developing a lymphatic-hematopoietic malignancy for persons with hives, adjusted by Cox regression for age, race, sex, and smoking, was 7.93 (95% CI = 2.99–21.07).

As another check to confirm this finding, an analysis was done using the full NHANESI adult cohort, including those persons for whom smoking history was unknown. Based on 51 cases of lymphatic-hematopoietic malignancies developing in 12,968 persons, the ROR for those with hives, adjusted by logistic regression for age, race, and sex, was 4.03 (95% CI = 2.03–8.02).

As a further check, discharge summaries of all persons diagnosed with lymphatic-hematopoietic malignancies were reviewed. Only three cases were questionable, either for insufficient documentation of diagnosis or possible presence prior to NHANESI. Excluding these cases did not affect the results; the ROR of developing a lymphatic-hematopoietic malignancy for those with hives was 7.74 (95% CI = 2.90–20.72).

Using different adjusting variables also had little effect on the analyses, such as adding household income, using lifetime pack-years smoked as a continuous smoking variable rather than the dichotomous smoker/non-smoker, or using age as a continuous variable rather than as 10-year age groups.

Discussion

These results differ from most prior studies, which have shown a history of allergy to be protective against cancer. This difference appears to be partially explained by the confounding factors of age, sex, smoking, and race. The present study is the first prospective one that controls for each of these factors. Another strength of

the present study is the representative nature of the study cohort, which was based on a national probability sample; this may have avoided some possible biases.

A spurious positive association would result if undiagnosed cancer was causing allergic-type symptoms. This problem was addressed in several ways: (1) restricting the diagnosis of allergy to more than 5 years before the initial interview, (2) restricting incident cancers to more than 5 years after the interview, and (3) excluding persons with a prior history of cancer.

This study was limited by small numbers of subjects with specific allergy and cancer types. Although the risk of hives for lymphatic-hematopoietic malignancies was strong and highly significant statistically, there were relatively few cases involved.

The question could be raised whether the confounding effects of the adjusting variables are due to underreporting of true allergic symptoms in groups with high cancer risk. Is questionnaire history an adequate measure of allergic diathesis? The analysis that did not restrict hives history to physician-diagnosed conditions was an attempt to minimize diagnostic access bias, a part of this problem. However, all studies using questionnaires or prior clinical diagnoses as the basis for allergy variables have the same possible weakness. This difficulty can be resolved only with studies using more precise and objective measures of allergic diathesis, such as laboratory determinations of humoral and cell-mediated immunity.

The current study presents evidence that a history of allergy is not protective against cancer, and that the hypothesis of a hyperstimulated, cancer-protective immune system in allergic individuals is unlikely. The positive associations described here are intriguing, especially the ones between hives and lymphatic-hematopoietic malignancies. This association is particularly suggestive because hives is probably the most specific adult allergy symptom (with fewer mimicking conditions), and because lymphatic-hematopoietic malignancies have frequently been cited as being associated with decreased immune competence. These findings are compatible with the hypothesis that an allergic diathesis, particularly when manifested as hives, is accompanied by an abnormal immune system rather than a hyper-competent one. Further research along these lines should be interesting.

REFERENCES

1. Fisherman EW. Does the allergic diathesis influence malignancy? *J Allergy Clin Immunol* 1960; 31:74–78.
2. Johnson KJ. The relation of cancer to allergy. *Lancet* 1966; 86:5–11.
3. Mackay WD. The incidence of allergic disorders and cancer. *Br J Cancer* 1966; 20:434–437.

4. Ure DMJ. Negative association between allergy and cancer. *Scott Med J* 1969; 14:51-54.
5. Gabriel R, Dudley BM, Alexander WD. Lung cancer and allergy. *Br J Clin Pract* 1972; 26:202-204.
6. Meers PD. Allergy and cancer. *Lancet* 1973; 1:884-885.
7. Alderson M. Mortality from malignant disease in patients with asthma. *Lancet* 1974; 2:1475-1477.
8. Allegra J, Lipton A, Harvey H *et al*. Decreased prevalence of immediate hypersensitivity (atopy) in a cancer population. *Cancer Res* 1976; 36:3225-3226.
9. Ford RM. Primary lung cancer and allergy. *Ann Allergy* 1978; 49:240-242.
10. Hughes WF, Raitz RL. A comparison of cancer occurrence in allergic and nonallergic populations. *Ann Allergy* 1979; 43:163-164.
11. Cockcroft DW, Klein GH, Donevan RE *et al*. Is there a negative correlation between malignancy and respiratory atopy? *Ann Allergy* 1979; 43:345-347.
12. Rozenzweig R. Allergies: Protective against cancer but predisposing to heart disease. *Postgrad Med* 1982; 72:42.
13. Vena JE, Bona JR, Byers TE *et al*. Allergy-related diseases and cancer: An inverse association. *Am J Epidemiol* 1985; 122:66-74.
14. Dworin M, Diamond HD, Craver LF. Hodgkin's disease and allergy. *Cancer* 1955; 8:128-131.
15. McKee WD, Arnold CA, Perlman MD. A double-blind study of the comparative incidence of malignancy and allergy. *J Allergy* 1967; 39:294-301.
16. Shapiro S, Heinonen OP, Siskind V. Cancer and allergy. *Cancer* 1971; 28:396-400.
17. Logan J, Saker D. The incidence of allergic disorders in cancer. *NZ Med J* 1953; 52:210-212.
18. Robinette CD, Fraumeni JF Jr. Asthma and subsequent mortality in World War II veterans. *J Chronic Dis* 1978; 31:619-624.
19. National Center for Health Statistics. Plan and Operation of the Health and Nutrition Examination Survey, United States 1971-1973. Hyattsville, MD: National Center for Health Statistics, 1973. (Vital and Health Statistics: Series 1, Programs and Collection Procedures; No. 10a) (DHEW Publication; (PHS) 79-1310).
20. National Center for Health Statistics. HANESI Augmentation Survey of Adults 25-74 Years, United States 1974-1975. Hyattsville, MD: National Center for Health Statistics, 1978. (Vital and Health Statistics: Series 1, Programs and Collection Procedures; No. 14) (DHEW Publication; (PHS) 78-1314).
21. Cornoni-Huntley J, Barbano HE, Brody JA *et al*. National Health and Nutrition Examination I: Epidemiologic Followup Survey. *Public Health Rep* 1983; 98:245-251.
22. SAS Institute Inc. SUGI Supplemental Library User's Guide, 1983 Edition. Cary, NC: SAS Institute Inc, 1983.