History of Allergy and Reduced Incidence of Colorectal Cancer, Iowa Women's Health Study

Anna E. Prizment,[1] Aaron R. Folsom,[1,3] James R. Cerhan,[4] Andrew Flood,[1,3] Julie A. Ross,[2,3] and Kristin E. Anderson[1,3]

[1]Division of Epidemiology and Community Health, School of Public Health, [2]Division of Epidemiology/Clinical Research, Department of Pediatrics, and [3]Cancer Center, University of Minnesota, Minneapolis, Minnesota and [4]Mayo Clinic College of Medicine, Rochester, Minnesota

Abstract

Previous epidemiologic studies have reported that a history of allergy is associated with reduced risk of colorectal cancer and other malignancies. We studied the association between allergy history and incident colorectal cancer (n = 410) prospectively in 21,292 Iowa women followed for 8 years. Allergy was defined from four self-reported questions about physician-diagnosed asthma (a), hay fever (b), eczema or allergy of the skin (c), and other allergic conditions (d). A history of any allergy was inversely associated with incident colorectal cancer: after multivariate adjustment, the hazard ratio (HR) was 0.74 [95% confidence interval (95% CI), 0.59-0.94]. Compared with women with no allergy, women reporting only one of the four types of allergy and women reporting two or more types had HRs of 0.75 (95% CI, 0.56-1.01) and 0.58 (95% CI, 0.37-0.90), respectively (P trend = 0.02). The inverse association persisted in analyses restricted to any type of nonasthmatic allergy (HR, 0.73; 95% CI, 0.56-0.95). HRs were similar for rectal and colon cancers as well as for colon subsites: proximal and distal (HRs for any allergy ranged from 0.63 to 0.78 across these end points). Allergy history, which may reflect enhanced immunosurveillance, is associated with a reduced risk of colorectal cancer. (Cancer Epidemiol Biomarkers Prev 2007;16(11):2357–62)

Introduction

Allergy, a hypersensitivity reaction initiated by immunologic mechanisms (1), has long been hypothesized to influence carcinogenesis. Two contradictory theories have been proposed: the theory of immune surveillance suggests that allergic conditions could reduce cancer risk by enhancing the ability of the immune system to detect and remove malignant cells, whereas another theory argues that allergy is accompanied by repeated tissue inflammation, damage, and repair, which increases the risk of cancer (2, 3). A 2005 review, which analyzed epidemiologic literature since 1985, concluded that atopy (immunoglobulin E–mediated allergy) is associated with decreased overall cancer risk with consistent findings for childhood leukemia and brain and pancreatic cancers (4).

We were interested in the possible relationship between allergy and colorectal cancer, the second most common malignancy in the United States (5). In spite of all prevention strategies, 153,760 incident cases and >52,180 deaths are estimated to occur in 2007 (6). So, identifying risk factors for colorectal cancer and elucidating mechanisms of carcinogenesis are important for colorectal cancer prevention.

Several case-control studies that have analyzed allergy suggested that it might play a protective role in the carcinogenesis of the colon and rectum (7-9). Data reported by cohort studies are inconsistent (10-14). The largest prospective study published to date, the Cancer Prevention Study II, reported an inverse association between colorectal cancer mortality and a history of ''asthma and hay fever'' [relative risk, 0.76; 95% confidence interval (95% CI), 0.64-0.91] compared with those who did not have any of these allergic conditions (15). Our a priori hypothesis for the present analysis was that allergy is inversely associated with colorectal cancer incidence.

Materials and Methods

In 1986, the Iowa Women's Health Study (IWHS) mailed a baseline questionnaire to 98,030 women ages 55 to 69 years, randomly selected from the Iowa driver's license list. The 41,836 women who completed the questionnaire (42.7%) constituted the cohort. Responders and nonresponders to the baseline questionnaire had similar demographic characteristics and incidence rates of colorectal cancer (16). Five follow-up questionnaires were mailed to cohort subjects to update vital status, residence, and exposure information; the response rates were 91% in 1987, 90% in 1989, 83% in 1992, 79% in 1997, and 70% in 2004. Data from follow-up surveys indicated that the migration rate from Iowa among cohort members is <1% annually, allowing nearly complete follow-up for cancer incidence end points (16).

The IWHS was conducted under a protocol approved for human subjects research by the University of Minnesota

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Requests for reprints: Kristin E. Anderson, Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, 1300 2nd Street South, Suite 300, Minneapolis, MN 55455. Phone: 612-626-8568; 612-624-0315. E-mail: ander116@umn.edu

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Institutional Review Board. The return of baseline and follow-up questionnaires was considered consent.

Four questions about history of allergy were asked during the 1997 follow-up survey, which comprised the start date for the present analysis. Participants were asked if they had been diagnosed by physician with asthma (*a*), hay fever (*b*), eczema or allergy of the skin (*c*), or other allergic conditions (*d*). Women were defined as having allergy if they answered ''yes'' to any of these questions and not having allergy if they answered ''no'' to all of these questions.

Information on sociodemographic characteristics and lifestyle behaviors, including education, residence, occupation, smoking status, number of pack-years, and regular physical activity, was collected in 1986. Participants also completed a diet assessment in 1986 that included a 126-item food frequency questionnaire, which collected information on food consumption, alcohol intake, and vitamin and supplement use (17). Intakes of calcium and vitamin E were calculated as sums of corresponding nutrients from food and supplements.

Participants self-reported height and weight in 1986 and weight at each follow-up. Body mass index (BMI) was calculated as weight (in kilograms) divided by baseline height squared (in meters). For these analyses, we used weight from the 1997 follow-up survey to calculate BMI. In 1986, the waist/hip circumference ratio was also obtained. Self-reported medical histories of hormone replacement therapy (HRT) use and diabetes mellitus were obtained from the 1986 questionnaire and each follow-up. Information about nonsteroidal anti-inflammatory drugs and family history of colon cancer in first-degree relatives was assessed in the 1992 follow-up survey.

For this analysis, we excluded women who in 1986 self-reported cancer other than nonmelanoma skin cancer (n = 3,830), those who had ≥30 missing values on the food questionnaire or had a total energy intake of <600 kcal/d or >5,000 kcal/d (n = 2,785), those who did not respond to the 1997 survey (n = 9,947), and those who developed cancer between 1986 and 1997 (n = 2,334). This resulted in 22,940 women. After exclusion of women with unknown/missing information about allergy (n = 1,648), there were 21,292 left for the analysis.

Incident cases of colorectal cancer were identified between 1997 and 2004 through annual linkage to the State Health Registry of Iowa, part of the Surveillance, Epidemiology, and End Results Program. Name, address, maiden name, birth date, and social security number were used for linkage. The International Classification of Diseases for Oncology, Second Edition codes were used to classify incident cases of colon (18.0-18.9) and rectal (19.9 and 20.9) cancers. Proximal and distal colon cancers were defined by codes 18.0 to 18.5 and 18.6 to 18.7, respectively.

All analyses were done using Statistical Analysis System (version 8.1; SAS Institute, Inc.). Characteristics of women with and without allergy were compared using the general linear model or χ^2 test for continuous and categorical variables, respectively. Nutritional factors, including red meat, calcium, and vitamin E, were adjusted for total energy intake. Person-years were calculated from the date of the follow-up survey in 1997 until one of the following: date of the first colorectal cancer diagnosis, date of death (if death occurred in Iowa), date of migration out of Iowa (if known), midpoint of the interval between the last follow-up contact and December 31, 2004 (if date of emigration was unknown), the midpoint of the interval between the last contact and date of death (if women died outside of Iowa), or December 31, 2004. We computed age-adjusted incidence rates of colorectal cancer per 100,000 person-years for women with known and unknown/missing allergy status.

Cox proportional hazards regression was used to calculate age-adjusted and multivariate-adjusted hazard ratios (HR) of colorectal cancer and 95% CIs. Analyses were conducted to estimate the association between allergy, in general, and its specific types with the incidence of colorectal cancer and its anatomic subtypes. Women without any allergy were the reference category in all analyses. We tested the assumptions of proportional hazards regression and found they were not violated.

Because many women reported having more than one type of allergy, we examined a trend in the association between colorectal cancer and the number of different allergy types reported by each person as an ordinal variable. For this analysis, only women who answered all four specific allergy questions were included. In addition, we conducted a supplemental analysis after excluding women with asthma because some types of asthma have a nonallergic etiology.

The following variables were included as confounders: age (continuous), BMI (continuous), pack-years of smoking (continuous), multivitamin use (yes/no), total energy intake (continuous), calcium intake (continuous), red meat intake (continuous), and history of HRT use (yes/no) and diabetes mellitus (yes/no). Other variables that were checked as potential confounders but were not retained in the final model were waist/hip circumference ratio, education, physical activity, smoking status, living on a farm and working on a farm, as well as intakes of vitamin E, fat, fiber, alcohol, and vegetables and fruits. To test for confounding by nonsteroidal anti-inflammatory drug use and family history of colon cancer (reported in 1992 only), we reanalyzed data by including only those women who responded to both follow-ups in 1992 and 1997. Finally, because both allergy (18, 19) and colorectal cancer risk could be related to smoking (20, 21), we ran a supplemental analysis restricted to never smokers.

Results

At the beginning of follow-up in 1997, the mean age of the 22,940 women at risk was 72.1 years. There were 6,765 (30%) women with history of allergy, 14,527 (63%) without allergy, and 1,648 (7%) women who did not know their allergy status or did not answer questions about allergy. The prevalence of asthma was ~7%, hay fever was 8%, eczema and skin allergies was 11%, and other allergies was 17%. These cohort data correspond well with results of the 1999 National Health Interview Survey that reported prevalences of 7.1% for asthma and 6.7% for hay fever among 65- to 74-year-old adults (22). The age-adjusted incidence rate of colorectal cancer for women with unknown/missing allergy status was 298 per 100,000 person-years of observation (95% CI, 218-410) versus 249 per 100,000 person-years (95% CI, 226-276) for

those who answered the allergy questions. These incidence rates were not statistically significantly different, and data for women with missing allergy information were not included in the tables. During 8 years of follow-up, among those who answered questions about allergy, 410 women were diagnosed with colorectal cancer: colon cancer (n = 345), rectal (n = 69), and both rectal and colon cancer (n = 4).

Women with allergy were somewhat more likely to be obese, have higher waist-to-hip ratios, have education beyond high school, and be smokers (Table 1). More women with allergies had ever used HRT, reported diabetes, or ever used nonaspirin nonsteroidal anti-inflammatory drugs. Alcohol consumption and intake of multivitamins, calcium, and vitamin E were also slightly higher for women with allergies. Aspirin use was slightly lower among those with allergies. Red meat intake, physical activity level, and family history of colon cancer were similar across the allergy categories.

Incident colorectal cancer was inversely associated with any allergy (yes/no): the age-adjusted HR for those with versus those without self-reported allergies was 0.73 (95% CI, 0.58-0.91; Table 2). The HR was 0.74 (95% CI, 0.59-0.94) after multivariate adjustment for age, pack-years of smoking, total energy intake, red meat, calcium, multivitamin use, BMI, diabetes, and HRT use. Compared with women with no allergy, the adjusted HR of colorectal cancer for women reporting only one of the four types of allergy was 0.75 (95% CI, 0.56-1.01), and for women with two or more types of allergy, it was 0.58 (95% CI, 0.37-0.90; P trend = 0.02). After exclusion of women reporting asthma, the inverse association held for women having any type of nonasthmatic allergy versus those without any allergy (HR, 0.73; 95% CI, 0.56-0.95). Similar associations were observed for specific types of allergy but not all HRs were statistically significant (Table 2).

The associations were similar across the various colorectal cancer sites and subsites. For women with allergies versus those without allergy, the HRs by site were as follows: rectal cancer, 0.63 (95% CI, 0.36-1.12); colon cancer, 0.77 (95% CI, 0.60-0.99); proximal colon, 0.78 (95% CI, 0.58-1.05); and distal colon, 0.76 (95% CI, 0.45-1.26; Table 3).

In analyses limited to never smokers, a statistically significant inverse association was observed among women with allergies (HR, 0.74; 95% CI, 0.56-0.98). Finally, after additional adjustment for aspirin and other nonsteroidal anti-inflammatory drugs and for family history of colon cancer in a subcohort of women who responded to the 1992 and 1997 surveys, the colorectal cancer risk was 0.79 (95% CI, 0.61-1.02) when women with versus without allergies were compared (data not presented in the table).

Discussion

We found an inverse association between self-reported allergy history and colorectal cancer in older women in the IWHS cohort. The associations were similar for rectal and colon cancers and for proximal and distal colon subsites; these associations remained after adjustment for multiple colorectal cancer risk factors. A trend of decreasing risk with increasing number of allergies was observed. The statistically significant association persisted for never smokers. The associations behaved similarly for specific allergy types.

Our results are consistent with findings of three case-control studies (7-9). However, three other case-control studies (4, 23, 24) did not observe significant associations between colorectal cancer and allergy. Findings from cohort studies are inconsistent: four studies did not find any significant associations (3, 10-12), one study (13)

Table 1. Characteristics (%) of IWHS participants across allergy categories

Characteristics	Allergy	
	No (n = 14,527)	Yes (n = 6,765)
Mean age in 1997, y (SE)	72.1 (0.03)	72.0 (0.05)
Mean age at diagnosis of colon cancer, y (SE)	77.7 (0.28)	77.0 (0.43)
Mean age at diagnosis of rectal cancer, y (SE)	75.7 (0.7)	78.2 (1.45)
BMI in 1997 (≥30 kg/m^2)	22.5	26.5
Waist-to-hip ratio,† ≥0.8606 (highest tertile)	32.6	34.9
Education (more than high school)†	41.1	46.3
Ever smoked†	29.4	35.4
≥40 pack-years of smoking†	5.9	8.1
Regular physical activity† (yes)	42.9	42.1
Energy intake† (≥1,722.8 cal/d*)	48.6	53.1
Calcium† (≥1,046.3 mg/d*)	48.9	52.8
Red meat† (≥5 servings/wk*)	56.8	56.3
Vitamin E† (≥9.8 mg/d*)	48.2	53.2
Multivitamins† (yes)	31.7	37.2
Alcohol intake† (ever)	47.0	48.1
Diabetes mellitus before 1997	9.3	10.8
HRT use before 1997	44.3	53.9
Aspirin use‡ (ever)	73.6	70.8
Nonaspirin NSAID use‡ (ever)	37.9	44.3
Family history of colon cancer‡	5.0	5.3

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.
*Cut point is the cohort median. Calcium, red meat, and vitamin E were adjusted for total energy intake.
†Information about these characteristics was obtained in 1986.
‡Analyses limited to the responders to the 1992 and 1997 surveys.

Table 2. Age- and multivariate-adjusted HRs for incident colorectal cancer in relation to history of allergy, IWHS 1997-2004

Allergy characteristics	No. cases	Person-years	Age-adjusted HR (95% CI)	Multivariate-adjusted* HR (95% CI)
No allergy	309	109,252	1 (reference)	1 (reference)
Allergy	101	49,678	0.73 (0.58-0.91)	0.74 (0.59-0.94)
Except asthma	71	36,222	0.70 (0.54-0.91)	0.73 (0.56-0.95)
Asthma	25	11,658	0.77 (0.51-1.15)	0.77 (0.50-1.16)
Hay fever	29	12,908	0.82 (0.56-1.19)	0.81 (0.54-1.20)
Skin allergies	37	19,943	0.68 (0.48-0.96)	0.70 (0.49-0.98)
Other allergies	51	27,910	0.66 (0.49-0.98)	0.69 (0.51-0.92)
No. allergies in a person †				
0	309	109,252	1 (reference)	1 (reference)
1	54	26,712	0.73 (0.54-0.97)	0.75 (0.56-1.01)
≥2	22	13,832	0.58 (0.38-0.89)	0.58 (0.37-0.90)
P trend			0.01	0.02

*Adjusted for age, pack-years, total energy intake, calcium, red meat, and multivitamin use in 1986, BMI in 1997, and diabetes and HRT use before 1997.
†For this analysis, only women who answered all four specific allergy questions were included.

observed an increased risk of colon cancer for patients with asthma (standardized incidence ratio, 1.17; 95% CI, 1.02-1.33), whereas another study (14) reported a statistically significant inverse association between asthma and cancers of colon (standardized incidence ratio, 72; 95% CI, 65.2-79.4) and rectum (standardized incidence ratio, 59; 95% CI, 51.6-68.5). The inconsistency in the cohort study results could be explained by the small number of cases [67 in an Australian cohort (3), 45 in National Health and Nutrition Examination Survey (10), and 47 in a Swedish cohort (12)], different allergic conditions under study, absence of uniform definition of allergy, and failure to control for confounders (12-14).

The findings of Cancer Prevention Study II cohort with 1,102,247 participants agree with our results: after adjustment for confounders, subjects with asthma and hay fever had an ~20% decrease in risk of colorectal cancer mortality compared with those without these conditions (15).

Advantages of our study include a large population-based prospective cohort with practically complete follow-up, reliable ascertainment of colon and rectal cancer cases, and detailed information about cancer risk factors. Although exposure information was self-reported, participants were asked to report allergy conditions diagnosed by physician, which is considered to be more reliable that recalling of events by participants (25, 26). Of note, the prevalence of allergic conditions reported by IWHS participants was similar to those reported from a U.S. population survey of 65- to 74-year-old adults (22). However, some allergy cases could be missed in our cohort if women with mild symptoms had not contacted their physicians. Misclassification of the exposure could also occur because some types of asthma are not allergy related and hay fever and skin diseases could be confused with nonallergic diseases having similar clinical presentation. Although misclassification of exposure is possible, we found that, first, after exclusion of women with asthma, the association between colorectal cancer and allergy persisted. Second, we observed the lowest HR of colorectal cancer for women with two or more allergies (i.e., women who were ''more likely to be truly allergic''; ref. 15). Third, the associations of colorectal cancer with allergy, in general, and its specific subtypes behaved in similar ways.

A potential limitation in this and other cohort studies is that exposures may change over time. In this study, some covariates were measured in 1986, whereas follow-up began in 1997. Of note, the covariates we examined

Table 3. Multivariate-adjusted HRs (95% CI) for subtypes of incident colorectal cancer in relation to history of allergy, IWHS 1997-2004

Allergy characteristics	No. cases	Colon cancer,* HR † (95% CI)	No. cases	Proximal colon cancer,* HR † (95% CI)	No. cases	Distal colon cancer,* HR † (95% CI)	No. cases	Rectal cancer,* HR † (95% CI)
No allergy	259	1 (reference)	186	1 (reference)	65	1 (reference)	53	1 (reference)
Allergy	86	0.77 (0.60-0.99)	64	0.78 (0.58-1.05)	20	0.76 (0.45-1.26)	16	0.63 (0.36-1.12)
Except asthma	57	0.71 (0.53-0.95)	37	0.63 (0.43-0.90)	18	0.94 (0.55-1.60)	14	0.78 (0.43-1.41)
Asthma	24	0.90 (0.59-1.39)	22	1.13 (0.72-1.75)	2	0.33 (0.08-1.37)	2	0.32 (0.08-1.31)
Hay fever	26	0.88 (0.58-1.34)	20	0.92 (0.57-1.50)	4	0.58 (0.21-1.61)	3	0.46 (0.14-1.47)
Skin allergies	31	0.70 (0.48-1.03)	23	0.71 (0.45-1.10)	8	0.79 (0.38-1.65)	6	0.60 (0.26-1.41)
Other allergies	43	0.71 (0.51-0.98)	31	0.71 (0.48-1.04)	11	0.75 (0.39-1.42)	8	0.54 (0.26-1.15)
No. allergies in a person ‡								
0	259	1 (reference)	186	1 (reference)	65	1 (reference)	53	1 (reference)
1	44	0.74 (0.54-1.03)	29	0.67 (0.45-1.00)	14	0.98 (0.55-1.75)	11	0.82 (0.43-1.58)
≥2	19	0.61 (0.38-0.99)	13	0.57 (0.32-1.03)	5	0.68 (0.27-1.71)	3	0.41 (0.13-1.33)
P trend		0.04		0.06		0.42		0.14

*Total number of women with colon and rectal cancers ($n = 414$) is larger than the number of women with colorectal cancer ($n = 410$) because 4 women had both colon and rectal cancers. Colon cancer ($n = 345$) includes proximal ($n = 250$), distal ($n = 85$), not otherwise specified ($n = 7$), and overlapping lesion of colon ($n = 3$).
†Adjusted for age, pack-years, total energy intake, calcium, red meat, and multivitamin use in 1986, BMI in 1997, and diabetes and HRT use before 1997.
‡For this analysis, only women who answered all four specific allergy questions were included.

did not substantially change the HR (i.e., the age- and multivariate-adjusted HRs were very similar; Table 2). Another limitation of this study is potential confounding by colorectal cancer screening (27-29), which could arise if women with physician-diagnosed allergies are those with better access to health care and more likely to visit physicians. However, when we adjusted for surrogate measures related to colorectal cancer screening, such as education, living in rural area, and family history of colon cancer, the association between allergy and colorectal cancer did not change.

The observed inverse associations, if causal, may reflect enhanced immunosurveillance in allergic participants (i.e., the enhanced ability of the immune system to detect and eliminate cancer cells before they become clinically manifest). This hypothesis is consistent with findings in other epidemiologic studies that showed decreased risk estimates for various cancers, such as pancreatic cancer, liver cancer, glioma, and breast cancer, associated with a history of allergy (30-35). The hypothesis that allergies lead to enhanced immunosurveillance is supported by laboratory studies that show that allergy is accompanied by immunoglobulin E production, a significant decrease in tumor occurrence and growth, and an increase in survival time in sensitized mice (36-38).

A precise mechanism for the immunosurveillance hypothesis in humans has not been established. Most allergies involve the production of immunoglobulin E antibody driven by antigen-specific T-helper 2 cells. T-helper 2 cells directly recognize the allergen peptides and at the same time release interleukins, which account for the B-cell production of immunoglobulin E antibodies, mast cells, and eosinophil granulocytes during allergic inflammation. It is known that eosinophil granule proteins are highly tumor cytotoxic at least *in vitro* (39). Moreover, eosinophil-derived peroxidase can synergize with macrophages to kill tumor cells or catalyze the oxidation of nitrite to produce additional cytotoxic radicals (40). In colon cancer patients, it has been shown that atopic dermatitis is accompanied by up-regulation of cytokines that simulate eosinophilic and T-cell infiltration against colon tumor cells (41). Moreover, it was shown that high counts of eosinophils and mast cells predict better survival in colorectal cancer patients (42, 43). Other studies indicated that patients with atopic dermatitis have increased numbers of T-helper ($CD4^+$) cells and of $CD8^+$ T cells compared with nonatopic individuals (44, 45). Infiltration of colorectal cancer cell nests by $CD8^+$ T cells was found to be associated with longer survival of colorectal cancer patients (46, 47). Furthermore, it was shown recently (48) that type and density of T cells near tumor cells was a better predictor of survival in colorectal cancer patients than traditional histopathologic methods based on staging. Viewed together, such data suggest that allergy characterized by abnormal production of interleukins and eosinophils could result in an increased immune response against carcinogenesis.

Recently, another explanation for a protective role of allergy in carcinogenesis has been suggested (49, 50). The ''toxin-pathogen hypothesis'' contends that in allergic individuals mutagenic toxins and foreign particles are bound with mucous and eliminated before they can trigger mutagenesis especially in tissues routinely exposed to environmental toxins and particulates. Such a mechanism could be plausible in colorectal cancer tissues.

It will be of interest for cohort studies with prediagnostic specimens to evaluate the potential relationship between allergy and colorectal cancer risk using biomarkers for allergy status.

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