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Research Article

Hay Fever and Asthma as Markers of Atopic Immune Response and Risk of Colorectal Cancer in Three Large Cohort Studies

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Abstract

Background: In a previous analysis of 12 cancers in the Cancer Prevention Study II (CPS-II) cohort including follow-up from 1982–2000, having both hay fever and asthma was associated with lower colorectal cancer mortality. The combination of these allergic conditions may be a marker for allergy-related immune responses that could inhibit colorectal carcinogenesis.

Methods: We examined the association of having both hay fever and asthma with colorectal cancer mortality among 1,023,191 participants in CPS-I, followed from 1959–1972, and 1,102,092 participants in CPS-II, now followed from 1982–2008. We also examined associations with colorectal cancer incidence among 174,917 participants in the CPS-II Nutrition Cohort, a subgroup of CPS-II followed from 1992–2007. During the follow-up, there were 5,644 colorectal cancer deaths in CPS-I, 13,558 colorectal cancer deaths in CPS-II, and 3,365 incident colorectal cancer cases in the CPS-II Nutrition Cohort. Cox proportional hazards regression was used to calculate multivariable-adjusted relative risks (RR) and 95% confidence intervals (CI).

Results: RRs for colorectal cancer mortality associated with having both asthma and hay fever, compared with neither condition, were 0.90 (95% CI, 0.74–1.09) in CPS-I, 0.79 (95% CI, 0.69–0.91) in CPS-II, and 0.83 (95% CI, 0.74–0.92) when results from both cohorts were combined in a meta-analysis. The corresponding RR for colorectal cancer incidence in the CPS-II Nutrition Cohort was 0.90 (95% CI, 0.71–1.14).

Conclusion: These results support an association between having both hay fever and asthma and modestly lower colorectal cancer mortality.

Impact: Research examining other potential markers of allergy-related immune response in relation to colorectal cancer is warranted. *Cancer Epidemiol Biomarkers Prev; 22(4); 661–9. ©2013 AACR.*

Introduction

Hay fever (also known as allergic rhinitis) and asthma are both allergy-related conditions (1–3). Associations of hay fever and asthma with mortality from 12 cancers were examined in a previous analysis of the Cancer Prevention Study II (CPS-II; ref. 4). In that analysis, individuals who reported diagnoses of both hay fever and asthma had significantly lower overall cancer mortality [relative risk (RR) = 0.88; 95% confidence interval (CI), 0.83–0.93] and colorectal cancer mortality (RR = 0.76; 95% CI, 0.64–0.91) than those who reported neither hay fever nor asthma. Hay fever alone was associated with only slightly lower colorectal cancer mortality (RR = 0.92; 95% CI, 0.85–0.99), whereas no association was observed with asthma alone (RR = 1.04; 95% CI, 0.91–1.19).

A potential biologic explanation for lower colorectal cancer mortality among individuals with both hay fever and asthma is that these individuals are more likely than others to have atopy, a general predisposition to develop immunoglobulin E (IgE)-mediated (allergic) immune reactions (3), and therefore to develop IgE-mediated immune reactions against colorectal neoplasia. IgE-mediated immune reactions have been hypothesized to play an important role in immune surveillance against cancer in general (5) and could be important in inhibiting colorectal carcinogenesis in particular. In mice, treatment with IgE monoclonal antibodies that were specific for a colorectal tumor antigen inhibited the growth of human colorectal tumor xenografts (6). Recruitment of eosinophils to allergic sites is a key feature of IgE-mediated immune reactions (7), and eosinophils may have important antitumor effects (8), including cytotoxic effects on colorectal cancer cells (9). Eosinophil infiltration of colorectal adenomas is

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common and is associated with smaller size and less aggressive characteristics (10). Eosinophil infiltration of colorectal cancers is associated with better prognosis, independent of stage and grade (11, 12). The potential importance of eosinophils is also suggested by a recent cohort study showing an association between blood eosinophil count (typically elevated in atopic individuals; ref. 13) and substantially lower colorectal cancer incidence (14).

Epidemiologic studies to date have provided only limited support for an association between allergic conditions and lower risk of colorectal cancer. Other than CPS-II (4), only the Iowa Women's Health Study (IWHS; ref. 15), examined the association between having 2 or more allergic conditions and colorectal cancer risk. In the IWHS (15), having 2 or more allergic conditions was associated with approximately 40% lower colorectal cancer incidence. Although some studies of individual allergic conditions found associations with modestly lower risk of colorectal cancer (15–18), others did not (19–25), or found lower risk of rectal cancer, but not colon cancer (26).

Confirmation of the association of having both hay fever and asthma with lower risk of colorectal cancer mortality observed in CPS-II (4) is important given that it was observed in an analysis of multiple cancer outcomes, which raises the possibility that it could have been at least partly due to chance. In addition, results from other studies of allergic conditions and colorectal cancer are inconsistent. Confirmation of this association would also provide support for the hypothesis that IgE-mediated immune reactions can inhibit the development or progression of colorectal cancer. This in turn could have implications for research on vaccinations to stimulate or enhance IgE-mediated immune reactions against colorectal neoplasia (5).

To clarify whether having both hay fever and asthma is associated with colorectal cancer mortality, we examined this association in CPS-I, a large prospective study similar in design to CPS-II. In addition, we reexamined this association in CPS-II after extending follow-up from 16 years to 24 years, thereby adding more than 4,000 colorectal cancer deaths to the analysis. Finally, we examined the association between having both hay fever and asthma and colorectal incidence in the CPS-II Nutrition Cohort to explore whether the association previously observed for colorectal cancer mortality might also be apparent for colorectal cancer incidence.

Materials and Methods

Analyses of colorectal cancer mortality or incidence were conducted in 3 American Cancer Society prospective cohort studies, CPS-I, CPS-II, and the CPS-II Nutrition Cohort, a subgroup of CPS-II. Hereafter, the larger "parent" CPS-II cohort will be referred to as the CPS-II Mortality Cohort. Each of these cohorts is described in more detail below.

CPS-I

CPS-I included 1,051,031 participants (456,487 men and 594,544 women) from 25 U.S. states who were at least 30 years of age at enrollment in 1959 (27, 28). Participants were enrolled by American Cancer Society volunteers who asked their friends and neighbors to complete a self-administered questionnaire that included information on demographic, medical, and lifestyle factors. Those who self-reported any cancer other than nonmelanoma skin cancer at enrollment ($N = 27{,}840$) were excluded, leaving 1,023,191 participants (449,320 men and 573,871 women) in the analysis.

Hay fever and asthma were self-reported on the 1959 baseline questionnaire. A list of medical conditions including "hay fever" and "asthma" was provided, and participants were asked to "mark each of the following diseases you have ever had."

Follow-up for cancer mortality was based on ascertainment of vital status by volunteers and subsequent verification based on review of death certificates (27). For the first 6 years of CPS-I, volunteers made personal inquiries annually to determine the vital status of the participants they had enrolled. Follow-up by the volunteers was done again during 1971 and 1972 (27). After 13 years of follow-up, 731,273 participants (69.6%) were still living, 188,056 (17.9%) had died, 75,934 (7.2%) were lost to follow-up, and 55,768 (5.3%) had follow-up truncated in 1965 because of the inability of the American Cancer Society volunteer organizations in some locations to continue the study. Death certificates or multiple causes of death codes were obtained for 97% of known deaths. Colorectal cancer deaths were those assigned codes 153 and 154 using the International Classification of Diseases, Seventh Revision (ICD-7; ref. 29). Among participants included in this analysis, 5,644 deaths from colorectal cancer were identified during follow-up through September 30, 1972.

CPS-II Mortality Cohort

The CPS-II Mortality Cohort was similar in design to CPS-I and included 1,184,418 participants (508,237 men and 676,181 women) from 50 U.S. states, the District of Columbia and Puerto Rico, who were at least 30 years of age at enrollment in 1982 (30). Participants were enrolled by American Cancer Society volunteers who asked their friends and neighbors to complete a 4 page self-administered questionnaire that included information on demographic, medical, and lifestyle factors. Those who self-reported any cancer other than nonmelanoma skin cancer at enrollment in 1982 ($N = 82{,}326$) were excluded, leaving 1,102,092 participants (483,005 men and 619,087 women) in the analysis.

Hay fever and asthma were self-reported on the 1982 baseline questionnaire. A list of medical conditions, including "hay fever" and "asthma," was provided, and the participants were asked to mark diseases or conditions "for which you have ever been diagnosed by a doctor."

To ascertain the vital status of CPS-II Mortality Cohort participants, American Cancer Society volunteers made

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personal inquiries in September 1984, 1986, and 1988 to determine whether the participants they had enrolled were alive or dead, and recorded the dates and places of deaths. Reported deaths were verified by obtaining death certificates. At completion of the 1988 follow-up, vital status was known for 98.2% of the cohort. Linkage to the National Death Index was used to identify deaths that occurred between September 1988 and December 2008 and to identify deaths among 21,704 participants lost to follow-up between 1982 and 1988 (31). Death certificates or codes for the cause of death were obtained for more than 99% of all known deaths. The underlying cause of death was defined according to the ICD-9(32) for deaths occurring from 1982 through 1998 and the ICD-10 (33) for deaths occurring from 1999 through 2008. Colorectal cancer deaths were defined as ICD-9 codes 153 (colon) and 154 (rectal), or as ICD-10 codes C18 (colon) and C19, C20 (rectal). Among participants included in this analysis, 13,558 deaths from colorectal cancer were identified during follow-up through December 31, 2008. Of these, 9,404 occurred during follow-up from 1982 through 2000, the follow-up period included in the previous analysis (4), and 4,154 occurred during follow-up from 2001 through 2008.

CPS-II Nutrition Cohort

The CPS-II Nutrition Cohort is a prospective study of cancer incidence, established in 1992, which includes 184,188 CPS-II Mortality Cohort participants from 21 U.S. states (34). At enrollment in 1992 or 1993, participants completed a mailed self-administered questionnaire including information on demographic, medical, and lifestyle factors. Follow-up questionnaires were sent in 1997 and every 2 years thereafter to update health-related information and ascertain newly diagnosed cancers. The response rate for each follow-up questionnaire was at least 87%. This analysis excludes participants with a history of colorectal cancer at enrollment ($N = 2,894$), those who were lost to follow-up before contributing any person-time to the analysis (alive at the time of the first follow-up questionnaire in 1997, but did not complete the 1997 or any subsequent follow-up questionnaire, $N = 6,170$), and those who self-reported a colorectal cancer on the first follow-up survey that could not be verified through medical records or cancer registry linkage ($N = 207$), leaving 174,917 participants (81,574 men and 93,343 women) in this analysis. Follow-up time began at enrollment in 1992 or 1993 and continued until diagnosis with colorectal cancer, return date of the last completed follow-up questionnaire, death, or the end of the study follow-up period on June 30, 2007.

There were no questions about hay fever or asthma on the 1992 enrollment questionnaire or on later follow-up questionnaires. Hay fever and asthma status are therefore based on what participants reported on the 1982 CPS-II Mortality Cohort questionnaire, as described above.

Of the 3,365 incident colorectal cancer cases included in this analysis, 2,729 were initially identified by self-report on the follow-up questionnaires and were subsequently verified by obtaining medical records, or through linkage with state cancer registries when complete medical records could not be obtained (34). Ascertainment of cancer by self-report is estimated to have a sensitivity of 93% in the Nutrition Cohort (35). An additional 636 cases of colorectal cancer were identified through linkage with the National Death Index (31), of which 492 were verified through subsequent linkage with state cancer registries. Both the CPS-II Nutrition Cohort and the CPS-II Mortality Cohort have been approved by the Emory University Institutional Review Board (Atlanta, GA).

Statistical analyses

A variable for allergic conditions was created that included 4 categories, no hay fever or asthma (the referent group), hay fever only, asthma only, and both hay fever and asthma. Cox proportional hazards modeling was used to estimate RR while adjusting for potential confounders. Time since enrollment was used as the underlying time axis. All multivariable models were adjusted for age, sex, race, education, body mass index (BMI), physical activity, smoking, and use of aspirin. In the CPS-II Nutrition Cohort, analyses were also adjusted for history of colorectal endoscopy. However, because information on endoscopy was first collected on the 1997 follow-up questionnaire, rather than at enrollment in 1992, only follow-up time after completion of the 1997 questionnaire could be adjusted for this factor. Age was adjusted for using the stratified Cox procedure (36) with one-year strata. Aspirin use was categorized as never, seldom, or often in CPS-I (the categories provided on the questionnaire) or as unknown, as no regular use, occasional use, 1 to 14, 15 to 29, 30 times or more per month or unknown in the CPS-II Mortality Cohort, and as no regular use, 1 to 14, 15 to 29, 30 to 59, 60 pills or more per month or unknown in the CPS-II Nutrition Cohort. All other covariates were modeled using the categories shown in Table 1. Further adjustment for alcohol use, diabetes, vegetable intake (in all 3 cohorts), red and processed meat intake, and use of oral contraceptives and postmenopausal hormones (assessed only in CPS-II and the CPS-II Nutrition Cohort) had negligible impact on risk estimates, and these factors were not included in the final multivariable models.

In selected analyses, associations with colorectal cancer mortality in CPS-I and the CPS-II Mortality Cohort were combined in a meta-analysis. A fixed-effects model was used because of the similar design of these 2 cohorts (37).

Because IgE-mediated immune reactions may differ by age (38) and sex (39), and because self-reported asthma in smokers might reflect smoking-related respiratory problems, possible differences in the association of having both asthma and hay fever with risk of colorectal cancer by attained age, sex, and smoking status were examined. We modeled multiplicative interaction terms between a dichotomous variable for having both hay fever and asthma, and attained age (modeled as a continuous

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Table 1. Baseline characteristics by asthma and hay fever status in CPS-I, the CPS-II Mortality Cohort, and the CPS-II Nutrition Cohort[a]

	CPS-I 1959				CPS-II Mortality Cohort 1982				CPS-II Nutrition Cohort 1992			
	No asthma or hay fever $N = 883,389$ (%)	Asthma only $N = 27,732$ (%)	Hay fever only $N = 87,560$ (%)	Hay fever and asthma $N = 24,510$ (%)	No asthma or hay fever $N = 947,073$ (%)	Asthma only $N = 26,094$ (%)	Hay fever only $N = 105,028$ (%)	Hay fever and asthma $N = 23,897$ (%)	No asthma or hay fever $N = 148,709$ (%)	Asthma only $N = 3,690$ (%)	Hay fever only $N = 18,160$ (%)	Hay fever and asthma $N = 4,358$ (%)
Age, y												
30–39	8.1	6.5	10.3	9.7	4.6	5.6	6.1	6.5	0.0	0.0	0.0	0.0
40–49	30.7	26.5	35.5	34.9	20.2	20.3	25.1	25.7	1.1	1.5	1.4	1.6
50–59	34.1	33.3	33.7	32.9	35.8	34.5	36.7	37.1	28.0	28.6	32.4	33.2
60–69	18.7	22.2	14.9	16.1	26.7	26.6	22.8	22.2	53.4	53.8	51.5	51.3
70–79	6.9	9.5	4.7	5.4	10.6	11.0	8.1	7.2	17.1	15.5	14.4	13.7
≥80	1.5	2.0	0.9	1.0	2.1	2.1	1.3	1.3	0.5	0.6	0.3	0.2
Sex												
Female	55.8	50.7	59.5	59.0	55.5	55.2	61.4	60.4	52.9	51.4	56.6	56.8
Male	44.2	49.3	40.5	41.0	44.5	44.8	38.6	39.6	47.1	48.6	43.4	43.2
Race												
White	96.5	96.2	96.3	97.0	93.3	91.1	92.6	93.7	97.5	96.8	96.6	96.8
Black	2.4	2.7	2.6	1.9	4.5	6.0	4.5	4.0	1.4	1.7	1.4	1.2
Other or unknown	1.2	1.1	1.1	1.1	2.3	3.0	2.8	2.3	1.2	1.5	2.0	2.0
Education												
Less than high school	40.8	47.5	33.0	33.6	15.0	17.2	10.2	10.3	7.0	6.7	3.9	3.1
High school graduate	22.7	20.3	21.6	20.9	26.5	23.9	20.8	19.5	26.8	24.6	19.2	18.3
Some college	19.6	18.3	23.1	23.2	28.2	28.6	30.1	30.6	28.8	29.7	29.0	29.7
College graduate	15.9	12.8	21.4	21.5	15.5	14.6	19.2	18.9	19.4	19.2	23.9	23.2
Graduate school[b]	–	–	–	–	13.3	14.0	18.4	19.3	17.3	19.0	23.5	25.3
Unknown	1.0	1.1	0.8	0.9	1.6	1.7	1.3	1.4	0.7	0.8	0.5	0.4
BMI (kg/m^2)												
<22.5	25.3	25.9	28.6	27.8	24.9	23.7	27.9	26.5	19.6	19.9	22.5	22.0
22.5–<25.0	26.1	23.8	27.5	26.2	25.6	24.4	27.1	26.0	24.4	24.4	26.5	25.8
25.0–<27.5	23.8	22.4	22.6	22.8	24.6	23.8	23.2	23.2	25.4	23.7	24.9	24.5
27.5–<30.0	10.2	10.8	8.9	9.4	11.7	12.0	10.3	11.2	14.1	13.7	12.3	12.1
≥30.0	7.6	9.9	6.1	7.3	10.9	13.6	9.4	11.0	14.9	16.9	12.7	14.2
Unknown	7.0	7.2	6.3	6.5	2.3	2.5	2.0	2.0	1.5	1.4	1.2	1.5
Physical activity[c]												
None	2.3	3.2	2.0	2.6	2.2	3.2	1.9	2.6	10.8	12.0	8.8	11.0
Slight	16.6	18.9	18.6	19.8	22.6	26.2	23.7	26.2	29.6	29.8	29.0	30.7
Moderate	67.0	63.1	67.4	65.1	64.8	60.9	65.3	62.3	47.6	46.0	49.9	47.2
Heavy	11.6	12.7	10.1	10.8	8.7	7.9	7.5	7.3	10.3	10.4	10.8	10.1
Unknown	2.5	2.1	1.9	1.8	1.7	1.8	1.5	1.6	1.6	1.8	1.4	1.1
Cigarette smoking												
Never	50.8	40.9	55.5	53.6	43.5	39.7	51.3	48.5	42.8	39.9	50.2	47.9
Former	10.9	13.0	12.2	13.6	27.5	32.1	27.1	30.3	46.7	50.6	42.5	45.1
Current	35.6	42.9	29.6	30.0	22.5	21.5	15.6	15.4	9.1	8.2	6.0	5.9
Unknown	2.6	3.1	2.7	2.9	6.5	6.6	6.0	5.8	1.3	1.2	1.3	1.1

[a]All percentages standardized to the age and sex distribution of each study cohort.

[b]Information on graduate school education not collected in CPS-I.

[c]Categories as worded on the CPS-I and CPS-II questionnaires. For the CPS-II Nutrition Cohort, levels correspond to 0, <7, 7 –<28, and ≥28 METs (metabolic equivalents) per week.

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variable), sex, and smoking status (never, former, current) and calculated a *P* value for interaction by comparing the likelihood ratio statistic from models with and without interaction terms.

Results

The prevalence of having both hay fever and asthma was similar across the cohorts included in this analysis (Table 1). In the CPS-I cohort, 2.4% reported having both hay fever and asthma, whereas 85.9% reported having neither allergic condition. Similarly, in the CPS-II Mortality Cohort and the CPS-II Nutrition Cohort, 2.2% and 2.5% reported having both hay fever and asthma, whereas 85.9% and 85.0% reported having neither allergic condition, respectively. In each of the cohorts, participants were predominantly White, aged 40 years or older at enrollment, and slightly more than half were women (Table 1). Compared with participants with neither asthma nor hay fever, those with both asthma and hay fever were more likely to be well educated and less likely to be current smokers. BMI and physical activity were generally similar to asthma and hay fever status, although participants with asthma only were more likely than other participants to be obese. In the CPS-II Nutrition Cohort, the prevalence of a history of colorectal endoscopy in 1997 (the year this was first reported) was slightly higher among individuals with asthma and hay fever (59.9%) than among those with neither condition (55.3%).

Having both asthma and hay fever, compared with having neither, was associated with nonstatistically significantly lower colorectal cancer mortality in CPS-I (RR = 0.90; 95% CI, 0.74–1.09) and statistically significantly lower colorectal cancer mortality in the CPS-II Mortality Cohort (RR = 0.79; 95% CI, 0.69–0.91; Table 2). This association did not differ between CPS-I and the CPS-II Mortality Cohort ($P = 0.28$ for heterogeneity). In a meta-analysis of results from CPS-I and the CPS-II Mortality Cohort, having both hay fever and asthma was associated with statistically significantly lower colorectal cancer mortality (RR = 0.83; 95% CI, 0.74–0.92).

In the CPS-II Nutrition Cohort, having both hay fever and asthma was associated with nonstatistically significantly lower incidence of colorectal cancer (RR = 0.90; 95% CI, 0.71–1.14). We also examined associations with colorectal cancer mortality within the CPS-II Nutrition Cohort to determine whether associations with colorectal cancer mortality might be stronger than those with colorectal incidence within the same study population. Having both hay fever and asthma was not associated with colorectal cancer mortality within the CPS-II Nutrition Cohort although statistical precision was limited (RR = 0.99; 95% CI, 0.69–1.44, in analyses including 29 deaths among participants with both conditions).

In each of the 3 cohorts in this analysis, multivariable-adjusted RRs for having both hay fever and asthma (shown in Table 2) were slightly closer to the null than results adjusted only for age and sex. RRs for having both hay fever and asthma, adjusted for only age and sex, were 0.89 (95% CI 0.74–1.08) in CPS-I, 0.75 (95% CI 0.65–0.86) in the CPS-II Mortality Cohort, and 0.84 (95% CI 0.67–1.07) in the CPS-II Nutrition Cohort.

Because the association between hay fever and asthma and colorectal cancer mortality during the first 18 years of follow-up of the CPS-II Mortality Cohort has been previously reported (4), we examined this association separately during follow-up time included in the previous report (1982–2000) and during more recent follow-up (2001–2008). The RR of colorectal cancer mortality associated with having both hay fever and asthma during follow-up from 1982–2000 was 0.77 (95% CI 0.65–0.91), nearly identical to that previously reported (4). The

Table 2. Colorectal cancer incidence or mortality by asthma and hay fever status, in CPS-I, the CPS-II Mortality Cohort, and the CPS-II Nutrition Cohort

	CPS-I Mortality, 1959–72			CPS-II Mortality Cohort Mortality, 1982–2008			CPS-II Nutrition Cohort, Incidence, 1992–2007		
	Deaths	Person-years	RR (95% CI)[a]	Deaths	Person-years	RR (95% CI)[a]	Cases	Person-years	RR (95% CI)[b]
Asthma and hay fever status									
No asthma or hay fever	4,965	9,864,615	1.00 (ref)	11,976	20,086,992	1.00 (ref)	2,923	1,801,429	1.00 (ref)
Asthma only	154	287,454	0.97 (0.82–1.14)	302	522,659	1.01 (0.90–1.13)	65	44,228	0.92 (0.72–1.18)
Hay fever only	417	998,750	0.97 (0.88–1.07)	1,078	2,354,617	0.92 (0.86–0.98)	307	227,878	0.95 (0.85–1.07)
Hay fever and asthma	108	275,117	0.90 (0.74–1.09)	202	529,567	0.79 (0.69–0.91)	70	54,525	0.90 (0.71–1.14)

[a]RR for colorectal cancer mortality adjusted for age, sex, race, education, BMI, physical activity, smoking, and aspirin use.
[b]RR for incident colorectal cancer, adjusted for age, sex, race, education, BMI, physical activity, smoking, aspirin use, and history of colorectal endoscopy.

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Table 3. Colon and rectal cancer incidence or mortality by asthma and hay fever status, in CPS-I, the CPS-II Mortality Cohort, and the CPS-II Nutrition Cohort

	CPS-I Mortality, 1959–72			CPS-II Mortality Cohort Mortality, 1982–2008			CPS-II Nutrition Cohort, Incidence, 1992–2007		
	Deaths	Person-years	RR (95% CI)[a]	Deaths	Person-years	RR (95% CI)[a]	Cases	Person-years	RR (95% CI)[b]
Colon									
No asthma or hay fever	3,895	9,864,615	1.00 (ref)	10,396	20,086,992	1.00 (ref)	2,182	1,801,429	1.00 (ref)
Asthma only	110	287,454	0.89 (0.74–1.07)	260	522,659	1.00 (0.88–1.13)	44	44,228	0.84 (0.62–1.13)
Hay fever only	339	998,750	1.00 (0.89–1.12)	951	2,354,617	0.93 (0.87–1.00)	235	227,878	0.97 (0.84–1.11)
Hay fever and asthma	91	275,117	0.96 (0.78–1.18)	171	529,567	0.77 (0.66–0.90)	55	54,525	0.94 (0.72–1.23)
Rectal									
No asthma or hay fever	1,070	9,864,615	1.00 (ref)	1,580	20,086,992	1.00 (ref)	741	1,801,429	1.00 (ref)
Asthma only	44	287,454	1.24 (0.92–1.68)	42	522,659	1.07 (0.79–1.46)	21	44,228	1.17 (0.76–1.80)
Hay fever only	78	998,750	0.87 (0.69–1.09)	127	2,354,617	0.82 (0.69–0.99)	72	227,878	0.91 (0.71–1.16)
Hay fever and asthma	17	275,117	0.68 (0.42–1.09)	31	529,567	0.92 (0.65–1.32)	15	54,525	0.78 (0.47–1.30)

[a]RR for colorectal cancer mortality adjusted for age, sex, race, education, BMI, physical activity, smoking, and aspirin use.
[b]RR for incident colorectal cancer, adjusted for age, sex, race, education, BMI, physical activity, smoking, aspirin use, and history of colorectal endoscopy.

corresponding RR during follow-up from 2001–2008 was similar in magnitude, although not statistically significant (RR = 0.83; 95% CI, 0.66–1.06).

Because the CPS-II Nutrition Cohort is a subgroup of the CPS-II Mortality Cohort, results from analyses of these 2 cohorts are not statistically independent. A total of 950 individuals were included as both incident cases of colorectal cancer in the CPS-II Nutrition Cohort and colorectal cancer deaths in the CPS-II Mortality Cohort. We conducted a sensitivity analysis censoring participants from the CPS-II Mortality Cohort on the date they entered the Nutrition Cohort analysis to obtain a statistically independent risk estimate. Results of this sensitivity analysis were similar to those from the main CPS-II Mortality Cohort analysis (RR = 0.78; 95% CI, 0.67–0.90 for having both hay fever and asthma compared with neither).

Associations with having both hay fever and asthma seemed generally similar for colon cancer and rectal cancer (Table 3). Having hay fever alone was much more common than having both hay fever and asthma and therefore could be examined with more statistical power in subsite analyses. Having hay fever alone was associated with lower risk of rectal cancer mortality (RR = 0.84; 95% CI, 0.73–0.97 in a meta-analysis of CPS-I and the CPS-II Mortality Cohort) but was not associated with colon cancer mortality (RR = 0.95; 95% CI, 0.89–1.01). Associations of having both asthma and hay fever with colorectal cancer mortality or incidence seemed similar in analyses stratified by attained age, sex, and smoking status (Table 4).

Discussion

In combined analyses of CPS-I and the CPS-II Mortality Cohort that included more than 19,000 colorectal cancer deaths, having both hay fever and asthma, a potential marker of atopy, was associated with approximately 17% lower colorectal cancer mortality. Our results continue to support the association reported in an earlier analysis of the CPS-II Mortality Cohort (4) that included slightly less than half of the colorectal cancer deaths included in the current analysis. It should be noted, however, that our results suggest that the reduction in colorectal cancer mortality associated with having both hay fever and asthma may be smaller than the 24% lower colorectal mortality observed in the earlier CPS-II Mortality Cohort analysis (4). Having both hay fever and asthma was not associated with statistically significantly lower colorectal cancer incidence in the CPS-II Nutrition Cohort (RR = 0.90; 95% CI, 0.71–1.14), although our results are compatible with slightly lower risk.

To our knowledge, only one other study (15) has examined the association between having 2 allergic conditions and risk of colorectal cancer. In an analysis of the IWHS that included 410 incident colorectal cancer cases, having 2 or more allergy-related conditions (potentially including asthma) was associated with considerably lower incidence of colorectal cancer (RR = 0.58; 95% CI, 0.37–0.90; ref. 15). Variation in results in the IWHS and the CPS-II Nutrition Cohort analyses of colorectal cancer incidence could be due to chance or to differences in the information

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Table 4. Colorectal cancer incidence or mortality associated with asthma and hay fever status, by age, sex, and smoking status in CPS-I, the CPS-II Mortality Cohort, and the CPS-II Nutrition Cohort

	CPS-I Mortality, 1959–72			CPS-II Mortality Cohort Mortality, 1982–2008			CPS-II Nutrition Cohort, Incidence, 1992–2007		
	Deaths	Person-years	RR (95% CI)[a]	Deaths	Person-years	RR (95% CI)[a]	Cases	Person-years	RR (95% CI)[b]
Age < 70 years									
No asthma or hay fever	2,751	8,389,693	1.00 (ref)	3,427	11,599,057	1.00 (ref)	1,062	904,787	1.00 (ref)
Asthma only	68	236,865	0.83 (0.65–1.05)	100	316,244	1.08 (0.89–1.32)	25	23,206	0.94 (0.63–1.40)
Hay fever only	247	887,407	0.93 (0.81–1.06)	330	1,461,652	0.88 (0.78–0.98)	108	123,110	0.85 (0.69–1.03)
Hay fever and asthma	64	242,931	0.87 (0.68–1.12)	57	338,216	0.65 (0.50–0.85)	26	30,132	0.83 (0.56–1.22)
Age ≥ 70 years									
No asthma or hay fever	2,214	1,474,921	1.00 (ref)	8,549	8,487,935	1.00 (ref)	1,861	896,642	1.00 (ref)
Asthma only	86	50,590	1.12 (0.90–1.39)	202	206,414	0.98 (0.85–1.12)	40	21,022	0.92 (0.67–1.25)
Hay fever only	170	111,342	1.04 (0.89–1.22)	748	892,966	0.94 (0.87–1.01)	199	104,767	1.02 (0.89–1.19)
Hay fever and asthma	44	32,186	0.94 (0.69–1.26)	145	191,351	0.86 (0.73–1.01)	44	24,393	0.95 (0.71–1.28)
$P_{interaction}$[c]			*0.83*			*0.10*			*0.89*
Men									
No asthma or hay fever	2,374	4,233,190	1.00 (ref)	6,074	8,432,777	1.00 (ref)	1,627	816,578	1.00 (ref)
Asthma only	93	135,875	1.11 (0.90–1.36)	150	222,298	1.00 (0.85–1.17)	36	20,771	0.92 (0.66–1.28)
Hay fever only	206	388,657	1.04 (0.90–1.20)	476	868,136	0.90 (0.82–0.99)	148	94,757	0.93 (0.79–1.11)
Hay fever and asthma	44	106,957	0.81 (0.60–1.09)	89	200,398	0.76 (0.62–0.94)	35	22,633	0.92 (0.66–1.28)
Women									
No asthma or hay fever	2,591	5,631,425	1.00 (ref)	5,902	11,654,214	1.00 (ref)	1,296	984,851	1.00 (ref)
Asthma only	61	151,580	0.82 (0.63–1.05)	152	300,361	1.02 (0.87–1.20)	29	23,457	0.94 (0.65–1.37)
Hay fever only	211	610,093	0.91 (0.79–1.05)	602	1,486,482	0.94 (0.86–1.02)	159	133,120	0.99 (0.84–1.17)
Hay fever and asthma	64	168,159	0.97 (0.76–1.25)	113	329,169	0.82 (0.68–0.98)	35	31,893	0.90 (0.64–1.26)
$P_{interaction}$[c]			*0.26*			*0.66*			*0.99*
Never smoker									
No asthma or hay fever	2,504	4,580,901	1.00 (ref)	4,399	8,364,584	1.00 (ref)	1,009	746,143	1.00 (ref)
Asthma only	67	111,639	0.98 (0.77–1.25)	110	201,520	1.06 (0.87–1.28)	22	16,872	0.98 (0.64–1.50)
Hay fever only	210	497,073	0.95 (0.82–1.09)	480	1,145,024	0.95 (0.87–1.05)	128	109,487	0.96 (0.80–1.15)
Hay fever and asthma	65	133,796	1.06 (0.82–1.35)	93	242,000	0.89 (0.73–1.10)	27	24,503	0.89 (0.60–1.30)
Former smoker									
No asthma or hay fever	500	914,174	1.00 (ref)	3,439	5,411,919	1.00 (ref)	1,392	777,121	1.00 (ref)
Asthma only	13	31,205	0.67 (0.38–1.16)	88	161,631	0.89 (0.72–1.10)	30	20,985	0.82 (0.57–1.18)
Hay fever only	50	107,792	0.98 (0.74–1.32)	306	631,797	0.92 (0.82–1.03)	147	90,787	1.02 (0.86–1.21)
Hay fever and asthma	9	32,948	0.57 (0.29–1.10)	57	158,607	0.71 (0.55–0.92)	33	23,041	0.91 (0.64–1.28)
Current smoker									
No asthma or hay fever	1,124	3,224,821	1.00 (ref)	2,489	4,098,268	1.00 (ref)	274	144,225	1.00 (ref)
Asthma only	47	109,356	1.09 (0.82–1.46)	61	102,513	1.10 (0.85–1.42)	8	3,191	1.33 (0.66–2.70)
Hay fever only	86	285,309	0.97 (0.78–1.21)	156	345,655	0.86 (0.73–1.01)	19	12,481	0.88 (0.55–1.41)
Hay fever and asthma	22	78,365	0.91 (0.60–1.39)	31	77,124	0.79 (0.56–1.13)	1	3,044	0.21 (0.03–1.47)
$P_{interaction}$[c]			*0.17*			*0.42*			*0.15*

[a]RR for colorectal cancer mortality adjusted for age, sex, race, education, BMI, physical activity, smoking, and aspirin use.

[b]RR for incident colorectal cancer, adjusted for age, sex, race, education, BMI, physical activity, smoking, aspirin use, and history of colorectal endoscopy.

[c]Interaction with having both hay fever and asthma compared with neither, as described in Materials and Methods.

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collected on allergic conditions. The IWHS asked about other allergic conditions, such as skin allergies, in addition to hay fever and asthma. However, hay fever and asthma were among the most common allergic conditions in IWHS and had similar associations with colorectal cancer incidence as other allergic conditions. The inverse association between having both hay fever and asthma and colorectal cancer mortality observed in CPS-I and the CPS-II Mortality Cohort, based on relatively large numbers, is compatible with results from the IWHS.

The absence of any important association between either hay fever alone or asthma alone, and colorectal cancer incidence or mortality in this analysis is generally consistent with the results of most previous studies that examined individual allergic conditions, rather than combinations of allergic conditions. A large Taiwanese record linkage study found inverse associations between having either asthma or hay fever and rectal cancer incidence, but no associations with colon cancer incidence (26). Results from that Taiwanese study are consistent with the inverse association between hay fever alone and rectal cancer mortality, but not colon cancer mortality, observed in our analysis. Future analyses of markers of atopy should carefully examine associations by colorectal subsite. Large European record linkage studies comparing colorectal cancer incidence in patients with asthma with that in the underlying general population reported lower risk (16), higher risk (19, 20), and no association (21). Of 6 other studies (1 cohort and 5 case-control) that examined associations with allergic conditions and included at least 100 cases of incident colorectal cancer, 4 reported no association (22–25), 1 reported significantly lower risk with a history of any allergic condition (defined as including asthma; ref. 17), and 1 reported a marginally statistically significant reduction in risk with a history of allergies (not including asthma; ref. 18). The absence of inverse associations with individual allergic conditions in most studies could reflect a weak association between having only one allergic condition and general atopy.

Important strengths of this analysis include its prospective design and large study size. Because of the large size, we were able to examine risk associated with a plausible marker of atopy, having both asthma and hay fever, even though having both conditions is relatively rare. In addition, we were able to adjust for potential confounders, including education and smoking status and to examine results by age, sex, smoking, and colorectal subsite. Several limitations should also be noted. First, analyses of colorectal cancer incidence included considerably less outcomes than analyses of colorectal cancer mortality, limiting our ability to quantify associations with colorectal cancer incidence. Second, asthma and hay fever were self-reported, although CPS-II participants were asked to report physician-diagnosed asthma and hay fever. Asthma and hay fever status may sometimes be misreported, and asthma and hay fever reported, but not diagnosed by a physician, may be less severe than physician-diagnosed asthma or hay fever. Misclassification of asthma and hay fever status could have attenuated our results, particularly in CPS-I, which did not specify that these conditions be physician-diagnosed. In addition, no information was available about age at onset of hay fever or asthma, or about new diagnoses of hay fever or asthma during follow-up. Finally, although analyses were adjusted for multiple colorectal cancer risk factors, we cannot rule out the possibility that the modestly lower risk of colorectal cancer mortality among participants with asthma and hay fever in our study might have been due to residual confounding by health-related behaviors.

In conclusion, results of this analysis of 2 large prospective studies indicate that having both asthma and hay fever, a potential marker of atopy, is associated with modestly lower colorectal cancer mortality. Whether having both hay fever and asthma is associated with colorectal cancer incidence remains unclear. Future research examining associations between colorectal cancer and other potential markers of atopy, such as IgE levels or eosinophil count in prospectively collected blood samples, could clarify the potential importance of IgE-mediated immune reactions in inhibiting colorectal carcinogenesis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: E.J. Jacobs, P.T. Campbell
Development of methodology: P.T. Campbell
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S.M. Gapstur, P.T. Campbell
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): E.J. Jacobs, C.C. Newton, M.C. Turner, P.T. Campbell
Writing, review, and/or revision of the manuscript: E.J. Jacobs, S.M. Gapstur, C.C. Newton, M.C. Turner, P.T. Campbell
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): P.T. Campbell

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