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ORIGINAL CONTRIBUTIONS

Cancer Mortality among US Men and Women with Asthma and Hay Fever

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The relation between self-reported physician-diagnosed asthma and/or hay fever and cancer mortality was explored in a prospective cohort study of 1,102,247 US men and women who were cancer-free at baseline. During 18 years of follow-up, from 1982 to 2000, there were 81,114 cancer deaths. Cox proportional hazards models were used to obtain adjusted relative risks for all cancer mortality and for cancer mortality at 12 sites associated with allergy indicators. There were significant inverse associations between a history of both asthma and hay fever and 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) in comparison with persons with neither of these allergic conditions. A history of hay fever only was associated with a significantly lowered risk of pancreatic cancer mortality, and a history of asthma only was associated with a significantly lowered risk of leukemia mortality. In never smokers, these associations persisted but were no longer significant. Results for mortality from cancer at other sites were less consistent. Collectively, these results suggest an inverse association between a history of allergy and cancer mortality; however, the strength of evidence for this association is limited.

allergy and immunology; asthma; cohort studies; hay fever; mortality; neoplasms

Abbreviations: CI, confidence interval; ICD, *International Classification of Diseases*; RR, relative risk.

A number of epidemiologic studies have reported inverse associations between allergy and cancer development; however, the existence of such an association remains controversial. Inverse associations have been reported in case-control studies of glioma (1–3), pancreatic cancer (4, 5), non-Hodgkin's lymphoma (6), and leukemia (7–9). However, a history of asthma has been positively associated with lung cancer (10), and results for all cancers combined are unclear (8, 11–14). It has been suggested that persons with a history of allergy, particularly atopic disorders, may demonstrate enhanced immune function (15–18).

The vast majority of previous studies have used self-reported history of allergy, allergic conditions, or allergic symptoms for the measurement of allergy. However, since few questionnaires that have been used to measure allergic history have been validated, previous studies may have been limited by exposure misclassification. Questions on self-reported physician-diagnosed asthma and hay fever have been found to be highly specific and more reliable than symptom-based questions or questionnaires asking respondents if they have ever had the disease (19, 20). Additional limitations of previous studies have included small sample

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TABLE 1. Selected demographic characteristics (%*) of Cancer Prevention Study II participants at baseline, by asthma and hay fever status, United States, 1982

Characteristic	Asthma and/or hay fever status				
	Asthma only ($n = 26,097$)	Hay fever only ($n = 105,044$)	Both asthma and hay fever ($n = 23,902$)	Asthma and/or hay fever ($n = 155,043$)	Neither asthma nor hay fever ($n = 947,204$)
Age (years)					
<50	25.9	31.1	32.2	30.4	24.8
50–59	34.5	36.7	37.1	36.4	35.7
60–69	26.6	22.8	22.2	23.3	26.7
≥70	13.1	9.4	8.5	9.9	12.7
Education†					
Less than high school	17.3	10.2	10.3	11.5	15.0
High school graduate	24.0	20.8	19.5	21.1	26.5
Some college	28.5	30.0	30.5	29.8	28.2
College graduate	28.6	37.6	38.3	36.1	28.7
Smoking†					
Never smoker	36.1	47.7	44.7	45.2	39.9
Current smoker	20.5	14.7	14.5	15.6	21.2
Former smoker	28.5	23.6	26.4	25.0	24.1
Ever smoker	2.1	1.6	1.9	1.7	1.7
Pipe/cigar smoker	8.7	8.3	9.1	8.5	8.8
Body mass index†,‡					
<18.5	2.2	1.9	2.1	2.0	1.9
18.5–24.9	45.8	53.1	50.4	51.4	48.7
25.0–29.9	35.9	33.6	34.5	34.1	36.3
≥30.0	13.6	9.4	11.0	10.3	10.9

* Some percentages do not sum to the total because of missing data.
† Age-standardized to the age distribution of the entire cohort.
‡ Weight (kg)/height $(m)^2$.

sizes, hospital-based recruitment, limited control for confounding, and potential biases associated with participant selection and exposure measurement (8, 12, 14, 16, 21). It has been suggested that further prospective studies are needed in order to address these limitations and to more fully evaluate associations at specific cancer sites (21). We undertook an analysis of the American Cancer Society Cancer Prevention Study II cohort to further examine the association between allergy and cancer risk.

MATERIALS AND METHODS

Study population

Cancer Prevention Study II is a longitudinal US mortality study designed and conducted by the American Cancer Society (22). Approximately 1.2 million participants were enrolled nationwide in 1982, with the goal of examining the role of environmental and lifestyle factors in cancer etiology. Study participants were at least 30 years of age and had at least one family member aged 45 years or older. In 1982, participants completed a self-administered four-page baseline questionnaire that included questions about a range of demographic, lifestyle, medical, and other characteristics.

The vital status of study participants has been determined every 2 years—by volunteers in 1984, 1986, and 1988 and subsequently by computerized linkage to the National Death Index (23). As of December 31, 2000, 332,673 participants had died (28.1 percent), 849,019 were alive (71.7 percent), and 2,896 (0.2 percent) had had follow-up terminated in September 1988 because of inadequate information with which to link them to the National Death Index. Over 98 percent of deaths have been assigned a cause.

A total of 1,102,247 participants were retained for analysis (483,080 men and 619,167 women) following the exclusion of persons who reported prevalent cancer (except nonmelanoma skin cancer) at enrollment ($n = 82,341$). Female participants were excluded from the analysis of ovarian cancer mortality and mortality from cancer of the corpus and uterus, not otherwise specified, if they reported a previous hysterectomy or an artificial menopause ($n = 201,230$). Female participants were also excluded from analysis of ovarian cancer mortality if they reported having undergone ovarian surgery ($n = 12,395$). A total of 81,114 cancer deaths were observed (44,524 in men and 36,590 in women).

TABLE 2. Relation of cancer mortality to asthma and/or hay fever in the Cancer Prevention Study II cohort, United States, 1982–2000

Cancer site	Asthma and/or hay fever status				
	Asthma only (n = 26,097)*	Hay fever only (n = 105,044)*	Both asthma and hay fever (n = 23,902)*	Asthma and/or hay fever (n = 155,043)*	Neither asthma nor hay fever (n = 947,204)*
All cancer					
No. of deaths	1,937	6,081	1,287	9,305	71,809
Death rate†	486.64	378.33	367.30	395.08	463.12
RR‡ (95% CI‡)§	1.06 (1.02, 1.11)	0.92 (0.89, 0.94)	0.88 (0.83, 0.93)	0.94 (0.92, 0.96)	1.00
Lung cancer					
No. of deaths	611	1,279	281	2,171	18,987
Death rate	153.70	79.47	78.37	91.73	122.65
RR (95% CI)¶	1.11 (1.02, 1.20)	0.85 (0.80, 0.90)	0.73 (0.65, 0.83)	0.89 (0.85, 0.93)	1.00
Pancreatic cancer					
No. of deaths	119	373	110	602	4,557
Death rate	29.85	23.55	31.54	25.83	29.35
RR (95% CI)#	1.02 (0.85, 1.23)	0.85 (0.77, 0.95)	1.14 (0.94, 1.38)	0.93 (0.85, 1.01)	1.00
Non-Hodgkin's lymphoma					
No. of deaths	88	318	68	474	3,330
Death rate	22.09	19.75	19.65	20.25	21.47
RR (95% CI)**	1.05 (0.85, 1.30)	0.96 (0.85, 1.08)	0.94 (0.74, 1.19)	0.97 (0.88, 1.07)	1.00
Leukemia					
No. of deaths	56	294	52	402	2,978
Death rate	14.10	18.29	15.52	17.14	19.17
RR (95% CI)††	0.75 (0.58, 0.98)	1.01 (0.90, 1.14)	0.82 (0.63, 1.09)	0.94 (0.84, 1.04)	1.00
Multiple myeloma					
No. of deaths	43	159	37	239	1,684
Death rate	10.76	9.83	10.14	10.08	10.85
RR (95% CI)‡‡	1.00 (0.74, 1.36)	0.94 (0.80, 1.11)	1.02 (0.73, 1.41)	0.96 (0.84, 1.10)	1.00
Brain cancer					
No. of deaths	47	196	44	287	1,908
Death rate	11.88	12.43	11.73	11.78	12.37
RR (95% CI)§§	0.97 (0.73, 1.30)	0.96 (0.83, 1.11)	0.96 (0.71, 1.30)	0.96 (0.85, 1.09)	1.00
Colorectal cancer					
No. of deaths	221	711	130	1,062	8,279
Death rate	55.39	44.65	38.37	45.57	53.28
RR (95% CI)¶¶	1.04 (0.91, 1.19)	0.92 (0.85, 0.99)	0.76 (0.64, 0.91)	0.92 (0.86, 0.98)	1.00
Stomach cancer					
No. of deaths	34	146	32	212	1,820
Death rate	8.53	9.29	9.10	9.14	11.71
RR (95% CI)##	0.72 (0.51, 1.01)	0.91 (0.77, 1.08)	0.92 (0.65, 1.30)	0.87 (0.76, 1.00)	1.00

Table continues

Ascertainment of allergy indicators and cancer deaths

The baseline survey listed 25 diseases or medical conditions, including asthma and hay fever, and prompted the respondent to indicate which of these conditions had ever been diagnosed by a doctor. Self-reported diagnoses of asthma and hay fever were used as indicators of allergy history. Three mutually exclusive categories were constructed to examine the independent effects of asthma only, hay fever only, and both asthma and hay fever. In addition, a fourth combined category of "any asthma and/or hay fever" was constructed. The reference category comprised persons with no asthma and no hay fever. Since persons who report multiple atopic disorders are thought to be more likely to truly be allergic (24), the best a priori classification of allergy was predicted to occur among persons with both asthma and

TABLE 2. Continued

Cancer site	Asthma and/or hay fever status				
	Asthma only ($n = 26,097$)*	Hay fever only ($n = 105,044$)*	Both asthma and hay fever ($n = 23,902$)*	Asthma and/or hay fever ($n = 155,043$)*	Neither asthma nor hay fever ($n = 947,204$)*
Prostate cancer					
No. of deaths	114	406	86	606	5,068
Death rate	68.01	71.84	69.56	70.60	75.95
RR (95% CI)***	0.92 (0.77, 1.11)	0.95 (0.86, 1.05)	0.94 (0.76, 1.17)	0.94 (0.86, 1.02)	1.00
Breast cancer (women)					
No. of deaths	128	525	100	753	4,497
Death rate	56.00	49.50	42.87	49.63	51.02
RR (95% CI)†††	1.10 (0.92, 1.31)	1.00 (0.91, 1.09)	0.86 (0.71, 1.05)	0.99 (0.92, 1.07)	1.00
Ovarian cancer					
No. of deaths	33	195	34	262	1,728
Death rate	23.20	30.82	25.78	28.79	29.48
RR (95% CI)‡‡‡	0.79 (0.56, 1.11)	1.03 (0.89, 1.20)	0.84 (0.60, 1.18)	0.97 (0.85, 1.10)	1.00
Cancer of the corpus and uterus, not otherwise specified					
No. of deaths	16	97	12	125	856
Death rate	10.87	15.05	8.89	13.45	14.12
RR (95% CI)§§§	0.74 (0.45, 1.21)	1.02 (0.83, 1.27)	0.59 (0.33, 1.05)	0.92 (0.76, 1.11)	1.00

* Ovarian cancer: $n = 9,083$ (asthma only), $n = 40,449$ (hay fever only), $n = 8,922$ (both asthma and hay fever), $n = 58,454$ (asthma and/or hay fever), and $n = 347,088$ (neither asthma nor hay fever); cancer of the corpus and uterus, not otherwise specified: $n = 9,366$ (asthma only), $n = 41,790$ (hay fever only), $n = 9,258$ (both asthma and hay fever), $n = 60,414$ (asthma and/or hay fever), and $n = 357,523$ (neither asthma nor hay fever).

† Death rate per 100,000 person-years, age-standardized to the age distribution of the entire cohort.

‡ RR, relative risk; CI, confidence interval.

§ Age-stratified and adjusted for gender, race, smoking, education, marital status, body mass index, diabetes, exercise, alcohol drinking, aspirin use, vegetable intake, and fat intake.

¶ Age-stratified and adjusted for gender, race, smoking, education, marital status, body mass index, occupational exposures, beer, wine, and liquor consumption, chronic bronchitis, emphysema, tuberculosis, intakes of vegetables, fruit, fiber, and fat, and passive smoking.

Age-stratified and adjusted for gender, race, smoking, education, body mass index, alcohol drinking, diabetes, gallstones, family history of pancreatic cancer, and consumption of vegetables, red meat, and fruit.

** Age-stratified and adjusted for gender, race, smoking, body mass index, education, and family history of non-Hodgkin's lymphoma.

†† Age-stratified and adjusted for gender, race, smoking, education, and family history.

‡‡ Age-stratified and adjusted for gender, race, smoking, and education.

§§ Age-stratified and adjusted for gender, race, smoking, body mass index, education, vegetable intake, and family history of brain cancer.

¶¶ Age-stratified and adjusted for gender, race, smoking, education, body mass index, exercise, alcohol drinking, aspirin use, intakes of vegetables, red meat, and fiber, multivitamin use, and family history.

Age-stratified and adjusted for gender, race, smoking, education, body mass index, aspirin use, intakes of vegetables, fruit, and fiber, number of siblings, and family history.

*** Age-stratified and adjusted for gender, race, smoking, education, body mass index, exercise, alcohol drinking, family history of prostate cancer, and consumption of vegetables, fat, and red meat.

††† Age-stratified and adjusted for gender, race, smoking, education, body mass index, exercise, alcohol drinking, use of oral contraceptives, estrogen replacement therapy, age at first birth, age at menarche, age at menopause, height, and family history of breast cancer.

‡‡‡ Age-stratified and adjusted for gender, race, smoking, education, body mass index, exercise, parity, age at menarche, age at menopause, use of oral contraceptives, estrogen replacement therapy, tubal ligation, and family history of breast or ovarian cancer.

§§§ Age-stratified and adjusted for gender, race, smoking, education, body mass index, parity, diabetes, estrogen replacement therapy, use of oral contraceptives, age at menarche, age at menopause, exercise, and hypertension.

hay fever. Conversely, the greatest amount of misclassification was predicted to occur in the asthma-only category because of difficulties in distinguishing between asthma and other chronic lung diseases, as well as the variable etiology of asthma, which may involve a number of immunologic and nonimmunologic factors, including allergy (25).

Cancer deaths were classified by the underlying cause of death according to *International Classification of Diseases* (ICD) codes (26, 27). The Ninth Revision of the ICD (ICD-9) was used through the end of 1998, and the Tenth Revision (ICD-10) was used from 1999 to 2000. The following ICD-9/-10 codes were used to define cancer deaths

TABLE 3. Relation of cancer mortality to asthma and/or hay fever among never smokers in the Cancer Prevention Study II cohort, United States, 1982–2000

Cancer site	Asthma and/or hay fever status				
	Asthma only ($n = 9,461$)*	Hay fever only ($n = 49,933$)*	Both asthma and hay fever ($n = 10,630$)*	Asthma and/or hay fever ($n = 70,024$)*	Neither asthma nor hay fever ($n = 378,586$)*
All cancer					
No. of deaths	484	2,259	438	3,181	19,907
Death rate†	317.71	295.41	277.95	296.59	311.22
RR‡ (95% CI‡)§	1.01 (0.92, 1.11)	0.97 (0.93, 1.02)	0.91 (0.83, 1.00)	0.97 (0.93, 1.01)	1.00
Lung cancer					
No. of deaths	35	156	26	217	1,322
Death rate	23.06	20.79	15.55	20.30	20.62
RR (95% CI)¶	1.11 (0.79, 1.56)	1.02 (0.86, 1.21)	0.83 (0.56, 1.22)	1.00 (0.86, 1.16)	1.00
Pancreatic cancer					
No. of deaths	42	150	32	224	1,548
Death rate	27.57	20.40	19.97	21.43	24.15
RR (95% CI)#	1.13 (0.83, 1.53)	0.84 (0.71, 1.00)	0.86 (0.60, 1.22)	0.89 (0.77, 1.02)	1.00
Non-Hodgkin's lymphoma					
No. of deaths	32	149	26	207	1,280
Death rate	20.66	19.52	16.29	19.48	20.01
RR (95% CI)**	1.06 (0.74, 1.50)	0.99 (0.83, 1.17)	0.84 (0.57, 1.23)	0.98 (0.84, 1.13)	1.00
Leukemia					
No. of deaths	15	125	25	165	1,037
Death rate	9.85	16.66	16.62	15.69	16.17
RR (95% CI)††	0.62 (0.37, 1.02)	1.04 (0.87, 1.26)	1.02 (0.69, 1.52)	0.98 (0.83, 1.16)	1.00
Multiple myeloma					
No. of deaths	19	66	16	101	700
Death rate	12.50	8.31	9.19	9.13	10.95
RR (95% CI)‡‡	1.13 (0.72, 1.78)	0.79 (0.61, 1.01)	0.94 (0.58, 1.55)	0.86 (0.69, 1.06)	1.00
Brain cancer					
No. of deaths	23	96	21	140	765
Death rate	15.35	11.87	12.60	12.40	12.06
RR (95% CI)§§	1.28 (0.84, 1.93)	0.98 (0.79, 1.21)	1.01 (0.65, 1.56)	1.02 (0.85, 1.22)	1.00
Colorectal cancer					
No. of deaths	83	314	54	451	3,021
Death rate	53.91	41.42	36.94	42.78	47.10
RR (95% CI)¶¶	1.14 (0.91, 1.41)	0.94 (0.84, 1.06)	0.78 (0.60, 1.02)	0.95 (0.86, 1.05)	1.00
Stomach cancer					
No. of deaths	13	57	10	80	547
Death rate	8.49	7.84	6.53	7.76	8.51
RR (95% CI)##	0.95 (0.55, 1.65)	0.97 (0.74, 1.27)	0.83 (0.44, 1.55)	0.94 (0.75, 1.20)	1.00

Table continues

by site: all cancer, 140–195 and 199–208/C00–C76 and C80–C97; lung cancer, 162/C33 and C34; colorectal cancer, 153 and 154/C18–C21; breast cancer (women), 174/C50; prostate cancer, 185/C61; pancreatic cancer, 157/C25; non-Hodgkin's lymphoma, 200 and 202/C82–C85; leukemia, 204–208/C91–C95; brain cancer, 191/C71; multiple myeloma, 203/C88 and C90; stomach cancer, 151/C16; ovarian cancer, 183/C56; and cancer of the corpus and uterus, not otherwise specified, 182 and 179/C54 and C55.

Statistical analysis

Death rates per 100,000 person-years were calculated according to asthma and/or hay fever status and were directly age-standardized to the age distribution of the entire

TABLE 3. Continued

Cancer site	Asthma and/or hay fever status				
	Asthma only ($n = 9,461$)*	Hay fever only ($n = 49,933$)*	Both asthma and hay fever ($n = 10,630$)*	Asthma and/or hay fever ($n = 70,024$)*	Neither asthma nor hay fever ($n = 378,586$)*
Prostate cancer					
No. of deaths	26	147	30	203	1,290
Death rate	64.44	77.04	75.13	74.83	75.22
RR (95% CI)***	0.87 (0.59, 1.29)	1.04 (0.88, 1.24)	1.06 (0.74, 1.53)	1.02 (0.88, 1.18)	1.00
Breast cancer (women)					
No. of deaths	61	305	56	422	2,335
Death rate	55.16	51.21	44.72	51.07	50.16
RR (95% CI)†††	1.10 (0.86, 1.43)	1.05 (0.93, 1.18)	0.92 (0.70, 1.20)	1.04 (0.93, 1.15)	1.00
Ovarian cancer					
No. of deaths	15	114	20	149	932
Death rate	22.20	32.13	29.56	30.24	30.20
RR (95% CI)‡‡‡	0.74 (0.44, 1.24)	1.06 (0.87, 1.29)	0.93 (0.60, 1.45)	1.00 (0.84, 1.19)	1.00
Cancer of the corpus and uterus, not otherwise specified					
No. of deaths	12	53	8	73	522
Death rate	17.09	14.68	11.48	14.51	16.40
RR (95% CI)§§§	0.98 (0.55, 1.74)	0.88 (0.66, 1.17)	0.65 (0.32, 1.31)	0.86 (0.68, 1.10)	1.00

* Ovarian cancer: $n = 4,260$ (asthma only), $n = 22,687$ (hay fever only), $n = 4,691$ (both asthma and hay fever), $n = 31,638$ (asthma and/or hay fever), and $n = 181,820$ (neither asthma nor hay fever); cancer of the corpus and uterus, not otherwise specified: $n = 4,379$ (asthma only), $n = 23,362$ (hay fever only), $n = 4,861$ (both asthma and hay fever), $n = 32,602$ (asthma and/or hay fever), and $n = 186,716$ (neither asthma nor hay fever).

† Death rate per 100,000 person-years, age-standardized to the age distribution of the entire cohort.

‡ RR, relative risk; CI, confidence interval.

§ Age-stratified and adjusted for gender, race, education, marital status, body mass index, diabetes, exercise, alcohol drinking, aspirin use, vegetable intake, and fat intake.

¶ Age-stratified and adjusted for gender, race, education, marital status, body mass index, occupational exposures, beer, wine, and liquor consumption, chronic bronchitis, emphysema, tuberculosis, intakes of vegetables, fruit, fiber, and fat, and passive smoking.

Age-stratified and adjusted for gender, race, education, body mass index, alcohol drinking, diabetes, gallstones, family history of pancreatic cancer, and consumption of vegetables, red meat, and fruit.

** Age-stratified and adjusted for gender, race, body mass index, education, and family history of non-Hodgkin's lymphoma.

†† Age-stratified and adjusted for gender, race, education, and family history.

‡‡ Age-stratified and adjusted for gender, race, and education. Significant gender interaction with asthma only (for men, RR = 2.57, 95 percent CI: 1.50, 4.42; for women, RR = 0.44, 95 percent CI: 0.18, 1.07; $p < 0.001$).

§§ Age-stratified and adjusted for gender, race, body mass index, education, vegetable intake, and family history of brain cancer.

¶¶ Age-stratified and adjusted for gender, race, education, body mass index, exercise, alcohol drinking, aspirin use, intakes of vegetables, red meat, and fiber, multivitamin use, and family history.

Age-stratified and adjusted for gender, race, education, body mass index, aspirin use, intakes of vegetables, fruit, and fiber, number of siblings, and family history.

*** Age-stratified and adjusted for gender, race, education, body mass index, exercise, alcohol drinking, family history of prostate cancer, and consumption of vegetables, fat, and red meat.

††† Age-stratified and adjusted for gender, race, education, body mass index, exercise, alcohol drinking, use of oral contraceptives, estrogen replacement therapy, age at first birth, age at menarche, age at menopause, height, and family history of breast cancer.

‡‡‡ Age-stratified and adjusted for gender, race, education, body mass index, exercise, parity, age at menarche, age at menopause, use of oral contraceptives, estrogen replacement therapy, tubal ligation, and family history of breast or ovarian cancer.

§§§ Age-stratified and adjusted for gender, race, education, body mass index, parity, diabetes, estrogen replacement therapy, use of oral contraceptives, age at menarche, age at menopause, exercise, and hypertension.

cohort. Cox proportional hazards regression models (28) were used to determine the independent effects of asthma and/or hay fever on cancer mortality while adjusting for other cancer site-specific covariates. Covariates included in the cancer site-specific multivariable models were chosen on the basis of associations previously reported in this study population or other study populations. Follow-up time since baseline (1982) was used as the time axis. The survival times of persons who were still alive were censored at the end of follow-up. Age adjustment was achieved by stratifying the baseline hazard of each proportional hazards regression model by 1-year age categories.

Smoking is an important risk factor for cancer. Persons with asthma or allergy have been reported to be less likely to smoke (17, 29). In addition, greater misclassification of asthma may occur among persons who smoke, since symptoms of other chronic respiratory diseases may mimic those of asthma (10). Therefore, we further evaluated cancer mortality among 448,610 never smokers (23,088 cancer deaths) in order to obtain a relative risk estimate that was largely free of potential residual confounding by smoking status, and to reduce potential misclassification of asthma.

We entered an interaction term into the multivariate models to examine whether the association between history of asthma and/or hay fever and cancer mortality was modified by gender. We calculated two-sided p values to assess the significance of the interaction terms at the $p < 0.01$ level using the likelihood ratio statistic. We tested the proportional hazards assumption by assessing the significance of an interaction term between asthma and/or hay fever and follow-up time. All analyses were conducted using SAS, version 8.2 (30).

RESULTS

A history of asthma was reported in 4.5 percent of participants, and a history of hay fever was reported in 11.7 percent. A history of asthma only, without a history of hay fever, was reported in 2.4 percent of participants, and a history of hay fever only, without a history of asthma, was reported in 9.5 percent. A history of both asthma and hay fever was reported in 2.2 percent of participants. On average, participants with asthma and/or hay fever tended to be younger and more likely to be never or former smokers than those with neither condition and had attained a higher level of education (table 1).

A small but statistically significant inverse association was observed for all cancer mortality in participants with histories of hay fever only (relative risk (RR) = 0.92, 95 percent confidence interval (CI): 0.89, 0.94), both asthma and hay fever (RR = 0.88, 95 percent CI: 0.83, 0.93), and asthma and/or hay fever (RR = 0.94, 95 percent CI: 0.92, 0.96) (table 2). This effect appeared to be driven largely by significant inverse associations with lung and colorectal cancer mortality. A history of hay fever only was associated with a significantly lowered risk of pancreatic cancer mortality (RR = 0.85, 95 percent CI: 0.77, 0.95), and a history of asthma only was associated with a significantly lowered risk of leukemia mortality (RR = 0.75, 95 percent CI: 0.58, 0.98). A history of asthma only was also associated with a significantly increased risk of lung cancer mortality (RR = 1.11, 95 percent CI: 1.02, 1.20).

In never smokers (table 3), the inverse associations observed for lung cancer mortality and overall cancer mortality among persons with histories of hay fever only and asthma and/or hay fever disappeared. Point estimates of the relative risk remained less than 1 for overall cancer mortality and colorectal cancer mortality associated with a history of asthma and hay fever, pancreatic cancer mortality associated with a history of hay fever only, and leukemia mortality associated with a history of asthma only, but they were no longer significant. Reduced point estimates were also observed for cancer mortality at other sites; however, none were significant.

A statistically significant interaction by gender was observed in never smokers with a history of asthma only for multiple myeloma mortality (for men, RR = 2.57, 95 percent CI: 1.50, 4.42; for women, RR = 0.44, 95 percent CI: 0.18, 1.07; $p < 0.001$).

DISCUSSION

In this study, we found significantly lowered risks of approximately 10 percent for overall cancer mortality and 20 percent for colorectal cancer mortality among persons with a history of both asthma and hay fever. A history of hay fever only was associated with a significantly lowered risk of pancreatic cancer mortality, and a history of asthma only was associated with a lowered risk of leukemia mortality. These associations persisted upon restriction to never smokers but were no longer significant.

Several other large cohort studies have also recently examined the association between allergic status and cancer risk. A record-linkage study of 64,346 people treated in hospital for asthma in Sweden found significantly lowered risks of all cancers and site-specific cancers (12). However, another cohort study linking 77,952 people who had received reimbursement for asthma medication with the Finnish Cancer Registry showed a significantly increased risk of all cancer in men but not in women (8). The remaining cohort studies revealed no significant associations between allergy and overall cancer occurrence (13, 29, 31, 32), including three small prospective studies that used skin tests as an indicator of allergic status (11, 16, 33).

An increasing body of evidence has suggested that asthma patients experience an increased risk of lung cancer (10). Recently, a meta-analysis estimated a combined odds ratio of 1.8 (95 percent CI: 1.3, 2.3) from previous case-control studies that evaluated the association between asthma and lung cancer risk in never smokers (10). Combining the results from all case-control and cohort studies that controlled for smoking history in the analysis yielded a relative risk of 1.7 (95 percent CI: 1.3, 2.2). However, potential misclassification and differential recall bias in previous studies are still of concern (10). In contrast, we observed a much more modest increase in risk for lung cancer mortality in participants with asthma only (RR = 1.11). To our knowledge, the present study is the first large prospective study of never smokers to evaluate this association.

An important limitation of this study is the use of self-reported history of physician-diagnosed asthma or hay fever. Although these questions have not been validated in this cohort, it has been previously reported that asthma and hay fever questions of this type are reliable and that they have higher specificities (0.99 for asthma, 0.93 for hay fever) and positive predictive values (0.82 for asthma, 0.76 for hay fever) than symptom-based questions or questions asking people if they have ever had the disease (19, 20). However, such questions may exclude persons with mild symptoms who do not seek medical assistance (19, 24,

34). The prevalences of asthma and hay fever in this study were similar to those found in other surveys of US adults (17, 35). Information on age at diagnosis and change in allergic status since baseline was not collected in this study. Overall, misclassification of asthma or hay fever status would likely result in a bias of the association estimate towards the null. Misclassification of asthmatic status in smokers, however, may be more complex.

We evaluated cancer mortality in a subgroup of never smokers. The inverse associations observed for lung cancer mortality in the overall population were likely due to residual confounding by cigarette smoking or a potential self-selection bias associated with smoking behavior.

Smoking status was measured only at baseline. Although it is unlikely that study participants who had never smoked would begin smoking cigarettes (the average age of the study participants at baseline was 57 years) (32), persons with a history of allergy may be more likely to quit smoking (36). It might be expected, then, that the risk of smoking-related cancers among persons with asthma and/or hay fever could decline over time (10). Although a departure from the proportional hazards assumption was not observed, the potential for such a dependency of hazard ratios over time further supports the estimation of risk in never smokers for smoking-related cancers (10).

This study was based on cancer mortality, which is determined by both cancer incidence and survival. Inferences about the association between allergy and cancer risk from mortality-based studies may be more reliable with highly lethal cancers, such as pancreatic cancer and lung cancer, than with cancers for which survival rates are high, such as prostate cancer and breast cancer. Screening and treatment can affect survival rates, with earlier detection and improved treatment increasing survival. For example, 5-year survival rates for colorectal cancer improve from 9.2 percent with a distant stage at diagnosis to 90.1 percent with a local stage at diagnosis (37). Few studies examining differential cancer prognosis or survival due to the presence of asthma or hay fever have been reported to date (38–41).

There remains the possibility that other unmeasured traits among persons with a history of allergy may explain the inverse associations observed between allergic status and cancer mortality. Although asthma and allergy medications (rather than the underlying disease) could be related to cancer risk, there is little empirical support for such a relation (2, 5, 42–52). Information on use of allergy medication was not collected in this study. It is also possible that a self-selective reduction in exposure to other unmeasured environmental carcinogens or other lifestyle behaviors in persons with a history of asthma and/or hay fever may explain the inverse associations observed, such as avoidance of certain allergy triggers, including occupational carcinogens, air pollutants, or dietary constituents (53–56).

The present large-scale population-based study had a number of advantages, including 1) evaluation of the association between asthma and/or hay fever and overall cancer mortality and cancer mortality at 12 different sites and 2) the opportunity to examine persons with both asthma and hay fever, who may be more likely to be truly allergic than persons with asthma or hay fever alone (24). The prospective nature of this study and the exclusion of persons with prevalent cancer at baseline helped us avoid limitations in self-reported ascertainment of asthma and/or hay fever and the potential biases of previous case-control studies. Detailed information on important covariates that can affect cancer risk was also collected at baseline.

Overall, this study found a significantly lowered risk for overall cancer mortality in participants with a history of both asthma and hay fever. Inverse associations between cancer mortality at specific sites and certain indicators of allergic status were also observed; however, the results were not entirely consistent, and there were few significant findings. Collectively, these results suggest an association between a history of allergy and cancer mortality; however, the strength of the evidence for this association is limited. Additional large-scale prospective studies incorporating better indicators of history of allergy and focusing on cancer incidence are needed to better characterize this association.

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