

Atopic diseases, immunoglobulin E and risk of cancer of the prostate, breast, lung and colorectum

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There is increasing epidemiological evidence for a role of allergic/atopic disorders in cancer development. However, findings have been inconsistent, which may be partly due to differences in defining allergy and the associated atopic disorders. The use of a biological marker for atopy may enhance the exploration of the association with cancer risks. To examine the association of atopy with common malignancies, we compared the prevalence of atopy in 318 patients with prostate cancer, 381 patients with breast cancer, 196 patients with lung cancer, 477 patients with colorectal cancer and 4,271 controls in a case-control analysis of participants of 2 prospective studies conducted in Saarland, Germany. Data on physician-diagnosed atopy-related diseases (asthma, hay fever and atopic dermatitis) were obtained by self-administered questionnaire. Allergen-specific immunoglobulin E (IgE) was assessed among cases and controls to define atopy. We observed a significantly increased risk of prostate cancer (odds ratio (OR) 1.35, 95% confidence interval (CI) 1.00–1.83) and a tentatively, statistically not significant increased risk of breast cancer (OR 1.20, 95% CI 0.87–1.66) and lung cancer (OR 1.29, 95% CI 0.87–1.92) with specific IgE positivity. No consistent associations were found with atopy-related diseases. Our findings are consistent with other epidemiological evidence suggesting an increased risk of prostate cancer with atopy and indicate a complex association between atopy/atopy-related diseases and cancer risk that varies by type of atopy-related disorders and the particular type of cancer under consideration. The effect on cancer risk by atopy, defined by IgE reactivity, may differ from the effect by atopy-related clinically defined diseases such as asthma, hay fever and atopic dermatitis.

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There is a growing interest in a potential link between atopic disorders and cancer.¹ Atopy, as a subset of the allergic disorders, has been implicated in the risk of lymphoma,^{2–4} leukemia,^{5–7} brain tumor^{8–11} and pancreatic cancer,¹² and possibly of other solid tumors as well.¹³ Results from epidemiological studies have been conflicting, and 2 distinct and contradictory hypotheses have been raised. When atopy is regarded as a hyperreactive state of the immune system, it is usually assumed to reflect a shift in the T-lymphocyte response away from the Th1 towards a Th2 dominated activity, although coexistence of Th1-mediated diseases and Th2-induced disorders have been described.^{14,15} Theoretically, this hyperreactive state might be accompanied by an enhanced immune-surveillance, leading to better detection and destruction of malignant cells, and consequently a decreased risk of cancer. On the other hand, a higher incidence of cancer may result from repeated tissue inflammation in atopic patients, which in turn may be linked to repeated tissue damage and repair.¹⁶

The emerging picture from most of the currently available epidemiologic data indicates that the association of allergy, atopy and cancer is complex, dependent on the specific allergic condition and the particular organ site. However, the varying results may also reflect potential problems of recall bias in retrospective studies, as well as problems associated with the small number of subjects with a specific subtype of atopy and/or “allergy” and various cancer types in prospective studies. Differences in defining allergy and the associated atopic disorders are also important issues to consider in the interpretation of these findings. Use of a biological marker besides the inherently subjective questionnaire data may

help to reduce misclassification bias. The term allergy covers a wide range of symptoms, including nonatopic diseases, and also reactions that are not Immunoglobulin E (IgE) mediated. Strictly defined, atopy means a tendency to produce allergen-specific IgE to environmental agents, which can be assessed by skin-prick tests or by measuring allergen-specific IgE in serum. Only 2 studies, 1 from Sweden and 1 from Australia, used a positive skin-prick test rather than a symptom-based definition as marker for atopy in their analysis,^{17,18} and 1 recent study on glioma used total and allergen-specific IgE as biomarker.¹⁹ However, the Swedish study was hampered by the fact that there were small numbers of observed cases in specific cancer sites in the relatively young cohort.¹⁷ In the Australian study, the information on skin-prick tests was available for a relatively small subset of the cohort and did not include atopic dermatitis.¹⁸ The American glioma case-control study was the first to include food- and respiratory-specific IgE as biomarker, demonstrating a protective effect of IgE-mediated allergy.¹⁹

In this case-control analysis among participants of 2 large prospective studies, we assessed allergen-specific IgE positivity in combination with self-reported diseases that are related to atopy (asthma, hay fever and atopic dermatitis) to investigate the association with risk for prostate, breast, lung and colorectal cancers.

Material and methods

Study population

This investigation was based on the ESTHER study (“Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung”) carried out in the state of Saarland (population 1.1 million) in Southwest Germany. The ESTHER study consists of 2 substudies. ESTHER-I is a prospective cohort study on new approaches to the prevention and early detection of chronic diseases among older adults.²⁰ The study recruited 9,961 subjects who had a general health check-up by a general practitioner between June 2000 and December 2002, were between 50- and 74-years old, reside in Saarland and speak German. These health-screening examinations are offered biannually free of charge to adults aged more than 35 years by the health insurance system in Germany. ESTHER-II is a large prospective clinical study including cases with common forms of cancer, first diagnosed from January 2001 to December 2003 among 50- to 74-years old residents of Saarland. Recruitment took place in 27 hospitals and 3 oncological practices in Saarland. All cases were confirmed histologically based on surgical specimen or biopsy, and most were recruited within 3 months of diagnosis of the disease.

For this investigation, we used a case-control approach where cases were drawn from the ESTHER-II study and participants of the ESTHER-I study served as controls. The study was limited to cancers of colon/rectum ($n = 478$), lung ($n = 197$), prostate ($n =$

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TABLE I – CHARACTERISTICS OF CANCER CASES AND CONTROLS

	Control			Patients with cancer of the			
	Total	Male	Female	Colorectum	Lung	Prostate	Breast
	N = 4,271	N = 1,904	N = 2,367	N = 477	N = 196	N = 318	N = 381
Age (years)	61.8 (6.6) ¹	61.9 (6.5) ¹	61.6 (6.7) ¹	65.1 (6.3) ¹	63.8 (6.8) ¹	65.5 (5.1) ¹	62.2 (6.7) ¹
BMI (kg/m ²)	27.7 (4.3) ¹	27.8 (3.8)	27.6 (4.8)	26.5 (4.1)	25.1 (4.2)	27.0 (3.5)	27.6 (5.4)
Normal (<25)	26.7	21.1	31.2	40.3	54.8	31.6	37.3
Overweight (25–29.9)	47.7	54.6	42.2	42.4	30.9	50.0	37.3
Obese (≥30)	25.6	24.3	26.6	17.3	14.4	18.4	25.4
Education (%)							
Low	73.6	69.9	76.6	69.9	80.8	64.1	72.8
Middle	15.8	14.4	17.0	17.3	9.4	15.5	17.7
High	10.6	15.8	6.4	12.8	9.8	20.4	9.5
Family history of cancer (%)							
Colorectal	9.8			12.1			
Lung	8.3				11.2		
Prostate		3.1 ²				6.2	
Breast			7.8 ³				10.8
Smoking status (%)							
Nonsmoker	49.9	30.5	65.7	42.8	9.8	36.9	63.9
Ex-smoker	32.3	49.0	18.7	42.2	51.3	46.5	22.6
Current smoker	17.8	20.5	15.6	15.0	38.9	16.6	13.5
Alcohol consumption (g/day) (%)							
None	17.0	4.1	28.9	15.8	10.9	4.3	27.5
1–5	30.5	20.1	40.1	25.9	30.6	19.1	38.1
6–13	27.2	31.7	22.9	27.0	25.7	34.6	25.6
14+	25.4	44.1	8.1	31.3	32.8	42.0	8.8

¹Values in parentheses indicate mean SD. ²Among males. ³Among females.

320) and female breast ($n = 381$), which were the most frequent cancer sites in the ESTHER-II study. Out of the participants of the ESTHER-I study, a total of 5,040 subjects were randomly selected for specific IgE measurement. We excluded 324 of these individuals for whom no serum sample was available, leaving 4,716 persons. Of these, we also excluded subjects who reported a history of malignant disease ($n = 305$) and subjects with missing information for this question ($n = 140$). Therefore, our control group consisted of 4,271 persons. For the analysis on breast cancer, we restricted our control group to the 2,367 females in this control group. For the analysis on prostate cancer, we used only the 1,904 males as control group.

Data collection

Both cases and controls completed a self-administered questionnaire that collected information on demographic variables, education level, general lifestyle habits, such as smoking, alcohol and coffee consumption, selected occupational exposures and level of physical activity. The medical part of the questionnaire asked for information on the history of a series of physician-diagnosed diseases and conditions. With regard to family history of cancer, subjects were asked whether any first-degree blood relatives ever had cancer, and if so, to specify the type of neoplasm. For women, reproductive history was obtained by asking for the number of live births, the age at first regular menstrual period, the age at first birth and the age when the menstrual cycles ceased, if applicable. We also recorded history of hysterectomy/oophorectomy, use of oral contraceptives and hormone replacement.

Assessment of atopy

Questionnaire. Respondents were classified as having a history of atopy-related disease if they gave a positive answer when asked if they “ever had” any of the following diseases diagnosed by a physician: asthma, hay fever and atopic dermatitis. Subjects who reported such a physician-diagnosed positive history were asked to provide information on age at onset.

Allergen-specific IgE measurement. Atopy was assessed by allergen-specific IgE measurement. All participants from the ESTHER-I and II study were asked to donate a blood specimen. Blood samples were mailed to the laboratory of the German Cen-

ter for Research on Aging (DZFA), where serum was extracted and stored at -80°C until analysis. A serum sample was not available for 2 prostate cancer cases, 1 colorectal cancer case and 1 lung cancer case.

Measurements of serum-specific IgE were carried out using the SX1 version of the UniCAP Phadiatop test (Pharmacia and Upjohn diagnostics, Uppsala, Sweden). The measurements were performed following the instructions of the manufacturer, and all measurements were done in blinded way. By this fluoroenzyme immunoassay, the presence of specific serum IgE was detected against the following common inhalant allergens: pollen of timothy, rye, birch and mugwort, house-dust mite, cat, dog and clado-sporium. It is assumed that these allergens include 90% of all relevant inhalation allergens in Western Europe. The percentage binding was determined, and the results were classified in a semiquantitative way as CAP classes. The cut-off value for positivity of the specific IgE assay was 0.35 KU/L, where 1U of IgE equals 2.42 ng of the World Health Organization IgE standard 75/502. Positivity for allergen-specific IgE was defined as atopy; a participant having allergen-specific IgE positivity was defined as being atopic. Throughout this article, we use the term atopy for allergen-specific IgE positivity, and the term atopy-related diseases for asthma, hay fever and atopic dermatitis.

Statistical analysis

Main characteristics of the study population were described. Analysis of the association between cancer risk and atopy and atopy-related diseases was carried out using unconditional logistic regression. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated for risks of cancers of the breast, prostate, lung and colorectum.²¹ Separate regression analyses were performed for each cancer outcome (dependent variable) with each of the following independent variables: asthma, hay fever, atopic dermatitis, history of any atopy-related disease and atopy defined as allergen-specific IgE positivity (dichotomous; yes vs. no).

Covariates were included as potential confounders if described in the literature or were found to be associated with the risk of the respective cancer in bivariate analysis. For all cancer sites, the variables included in the model as potential confounders were age (as continuous variable), education level (low (<10 years of school

education), middle and high (>12 years)), body mass index (BMI) (kg/m² defined using the WHO classification, <25, 25.0–29.9, ≥30 kg/m²), family history (first degree relative) of cancer (dichotomous; yes vs. no), cigarette smoking (never, ex- and current smoker) and alcohol consumption (g ethanol/day, in quartiles defined by using the distribution among controls). The model for breast cancer also included menopausal status, use of hormone replacement and age at first full-term pregnancy. Statistical analysis was carried out using the SAS software version 9 (SAS institute, Cary, NC).

Results

General characteristics of cases and controls

Main socio-demographic and lifestyle characteristics of the study population are shown in Table I. With the exception of breast cancer, cases tended to be slightly older than controls.

TABLE II – HISTORY OF ATOPY (ALLERGEN-SPECIFIC IgE POSITIVITY) BY SELECTED CHARACTERISTICS AMONG CONTROLS

	Atopy	
	N	Percentage
Age at recruitment		
≤54	213	28.3
55–59	224	27.7
60–64	249	20.5
65–69	148	16.5
≥70	92	15.4
p-Value	<0.001	
Gender		
Male	470	24.7
Female	456	19.3
p-Value	<0.001	
Education		
Low	623	20.3
Middle	165	25.0
High	127	28.8
p-Value	<0.001	
BMI (Kg/m ²)		
Normal (<25)	240	21.6
Overweight (25–29.9)	431	21.7
Obese (≥30)	231	21.7
p-Value	0.99	
Smoking		
Nonsmoker	472	22.7
Ex-smoker	277	20.6
Current smoker	159	21.4
p-Value	0.34	
Alcohol consumption (g/day)		
0	110	17.4
1–5	214	18.9
6–13	230	22.8
14+	268	28.4
p-Value	<0.001	

Fewer cases tended to be overweight or obese. Cases with prostate cancer were more likely to be highly educated when compared to controls, while the reverse was true for cases with lung cancer. A higher proportion of cases than controls reported having a first degree relative with the index cancer. Cases with lung cancer were markedly more likely to be smokers (ex-smoker and current smoker). The cases and controls had comparable distributions of alcohol consumption.

Atopy and demographic variables among controls

Table II shows the distribution of atopy (allergen-specific IgE positivity) among controls by selected characteristics. The prevalence of atopy significantly decreased with age. Atopy was more common among males when compared with females. The proportion of allergen-specific IgE positivity among people with a high level of education, which is commonly used as indicator of socioeconomic status, was much higher than among those with a low level of education. There was no difference in prevalence of atopy according to BMI. The prevalence of atopy was slightly lower in both ex-smokers and current smokers when compared with non-smokers. The proportion of allergen-specific IgE was lowest among people who did not drink alcohol, and increased with the amount of alcohol consumption.

Atopy compared with self-reported atopy-related diseases among controls

Among controls, allergen-specific IgE was positive in 43.6% of those who reported a history of asthma when compared to 20.3% among those who did not. Prevalence of atopy was 75.1 and 16.8% among controls with and without physician-diagnosed hay fever, but was only slightly higher among controls with atopic eczema (23.8%) than the other controls (21.4%).

Prostate cancer

The proportion of prostate cancer cases with allergen-specific IgE positivity was 29.6% when compared with 24.7% among controls (Table III). The adjusted OR for this allergen-specific IgE positivity was 1.35 (95% CI 1.00–1.83), indicating a significantly elevated risk. There was no significant association with asthma (OR 1.09, 95% CI 0.61–1.94) or hay fever (OR 0.90, 95% CI 0.53–1.52). Conversely, men who reported atopic dermatitis were at decreased risk of prostate cancer, although the CI was wide and included 1 (OR 0.56, 95% CI 0.20–1.58). There was no association of the combined atopy-related diseases with the risk of prostate cancer.

Breast cancer

Respondents with allergen-specific IgE positivity comprised 23.1% of breast cancer cases and 19.3% of controls; the adjusted OR was 1.20 (95% CI 0.87–1.66) (Table IV). Most of the associations between breast cancer and atopy-related diseases were positive, but all CIs included 1. Women reporting atopic dermatitis did not have an increased risk when compared with those without history of atopic dermatitis.

TABLE III – ODDS RATIOS AND CONFIDENCE LIMITS FOR PROSTATE CANCER IN RELATION TO ATOPY¹ AND ATOPY-RELATED DISEASES²

	Prostate cancer (n = 318)		Controls (n = 1,904)		Adjusted OR ³	95% CI	p-Value
	N	%	N	%			
No atopy ⁴	201	63.2	1,248	65.6	1.00	(Reference)	
Atopy ¹	94	29.6	470	24.7	1.35	1.00–1.83	0.05
Asthma	17	5.4	98	5.2	1.09	0.61–1.94	0.77
Hay fever	22	6.9	157	8.3	0.90	0.53–1.52	0.68
Atopic dermatitis	5	1.6	57	3.0	0.56	0.20–1.58	0.27
Any atopy-related diseases ²	41	12.9	278	14.6	0.98	0.66–1.45	0.91

¹Defined by allergen-specific IgE positivity. ²Asthma, hay fever and atopic dermatitis. ³Adjusted for age, education, body mass index, family history of cancer (first degree), smoking status and alcohol consumption. ⁴Persons without any atopy-related diseases and without allergen-specific IgE positivity.

TABLE IV – ODDS RATIOS AND CONFIDENCE LIMITS FOR BREAST CANCER IN RELATION TO ATOPY¹ AND ATOPY-RELATED DISEASES²

	Breast cancer (n = 381)		Controls (n = 2,367)		Adjusted OR ³	95% CI	p-Value
	N	%	N	%			
No atopy ⁴	258	67.7	1,673	70.7	1.00	(Reference)	
Atopy ¹	88	23.1	456	19.3	1.20	0.87–1.66	0.44
Asthma	21	5.5	122	5.2	1.24	0.69–2.22	0.31
Hay fever	40	10.6	189	8.0	1.18	0.75–1.84	0.56
Atopic dermatitis	14	3.7	90	3.8	0.95	0.49–1.85	0.92
Any atopy-related diseases ²	65	17.1	342	14.5	1.13	0.79–1.62	0.61

¹Defined by allergen-specific IgE positivity. ²Asthma, hay fever and atopic dermatitis. ³Adjusted for age, education, body mass index, family history of cancer (first degree), smoking status and alcohol consumption. ⁴Persons without any atopy-related diseases and without allergen-specific IgE positivity.

TABLE V – ODDS RATIOS AND CONFIDENCE LIMITS FOR LUNG CANCER IN RELATION TO ATOPY¹ AND ATOPY-RELATED DISEASES²

	Lung cancer (n = 196)		Controls (n = 4,271)		Adjusted OR ³	95% CI	p-Value
	N	%	N	%			
No atopy ⁴	131	66.8	2,921	68.4	1.00	(Reference)	
Atopy ¹	48	24.5	926	21.7	1.29	0.87–1.92	0.20
Asthma	13	6.6	220	5.2	1.40	0.71–2.77	0.33
Hay fever	3	1.5	346	8.1	0.34	0.11–1.10	0.07
Atopic dermatitis	5	2.6	147	3.5	1.00	0.38–2.57	0.98
Any atopy-related diseases ²	19	10.0	620	15.1	0.85	0.50–1.47	0.56

¹Defined by allergen-specific IgE positivity. ²Asthma, hay fever and atopic dermatitis. ³Adjusted for age, gender, education, body mass index, family history of cancer (first degree), smoking status and alcohol consumption. ⁴Persons without any atopy-related diseases and without allergen-specific IgE positivity.

TABLE VI – ODDS RATIOS AND CONFIDENCE LIMITS FOR COLORECTAL CANCER IN RELATION TO ATOPY¹ AND ATOPY-RELATED DISEASES²

	Colorectal cancer (n = 477)		Controls (n = 4,271)		Adjusted OR ³	95% CI	p-Value
	N	%	N	%			
No atopy ⁴	322	67.5	2,921	68.4	1.00	(Reference)	
Atopy ¹	106	22.2	926	21.7	1.03	0.80–1.34	0.80
Asthma	29	6.1	220	5.2	1.25	0.81–1.93	0.31
Hay fever	31	6.5	346	8.1	0.88	0.58–1.35	0.57
Atopic dermatitis	9	1.9	147	3.4	0.64	0.32–1.28	0.20
Any atopy-related diseases ²	62	13.0	620	14.5	0.99	0.73–1.35	0.96

¹Defined by allergen-specific IgE positivity. ²Asthma, hay fever and atopic dermatitis. ³Adjusted for age, gender, education, body mass index, family history of cancer (first degree), smoking status and alcohol consumption. ⁴Persons without any atopy-related diseases and without allergen-specific IgE positivity.

Lung cancer

A total of 48 cases of lung cancer (24.5%) and 926 (21.7%) controls had allergen-specific IgE positivity (Table V). The estimated OR was 1.29 (95% CI 0.87–1.92) after adjustment for potential confounders. Asthma was associated with an increased risk of lung cancer, although the risk estimate did not reach statistical significance (OR 1.40, 95% CI 0.71–2.77). No association was seen between the risk of lung cancer and atopic dermatitis. The risk of lung cancer tended to be slightly lower in subjects who had a history of any atopy-related disease. Interestingly, a non-significant decreased OR of lung cancer was observed for hay fever (OR 0.34, 95% CI 0.11–1.10).

Colorectal cancer

The proportion of subjects having allergen-specific IgE positivity was similar between cases of colorectal cancer and controls (22.2% vs. 21.7%) (Table VI). Atopy did not show an association with colorectal carcinoma risk after adjustment for potential confounders (OR 1.03, 95% CI 0.80–1.34). Similarly, the risk associated with any atopy-related disease was 0.99 (95% CI 0.73–1.35). There was a tendency to a higher risk of colorectal cancer with

having asthma (OR 1.25, 95% CI 0.81–1.93). A slightly lower risk of colorectal cancer was observed with hay fever (OR 0.88, 95% CI 0.58–1.35). Atopic dermatitis was associated with a reduced risk of colorectal cancer (OR 0.64, 95% CI 0.32–1.28), but none of these associations were statistically significant.

Discussion

In this investigation, we evaluated the associations of common atopy-related diseases and atopy (defined by allergen-specific IgE positivity) with the risk of colorectal, lung, prostate and breast cancer in a case-control approach. Allergen-specific IgE positivity was associated with a moderately increased risk of prostate cancer. Tentative but statistically not significant positive associations with atopy were also seen with the risk of breast cancer and lung cancer.

The overall pattern of atopy (specific IgE positivity) among controls was as one would expect from data reported in the literature: the prevalence was higher for males when compared to females, decreased with age and increased with level of education.²² It has been reported that cigarette smoking and alcohol consumption may influence serum IgE levels.²³ In our study, the controls showed for

smoking and alcohol a pattern that was also similar to the pattern reported elsewhere: allergen-specific IgE levels were increasing with alcohol consumption²⁴ and were decreased among smokers.²⁵

A major strength of our study, in addition to the large numbers of cases and controls, is the careful assessment of atopy by specific IgE measurement. To our knowledge, there is only 1 recent study that explored the association between cancer risk and atopy defined by allergen-specific IgE positivity.¹⁹ Only 2 earlier studies have used skin-prick test positivity as a biomarker of atopy.^{17,18}

The most prominent finding in our study is the positive association between prostate cancer and atopy, which is in agreement with data from prospective studies.^{18,26–29} An earlier study using data of the first National Health and Nutrition Examination Survey (NHANES I) reported that the risk of prostate cancer was increased in those with a history of any type of “allergy.”²⁶ Another cohort study on more than 34,000 Seventh-day Adventists in California found positive, albeit statistically nonsignificant, associations of several “allergies” with prostate cancer.²⁷ A Finnish cohort study of 78,000 asthmatic patients demonstrated a slightly increased risk of prostate cancer.²⁸ Atopy, defined by skin-prick testing, was associated with a significant elevation in the risk of prostate cancer among participants of the follow-up study of the Busselton Health Survey.¹⁸ In that study, sensitization to house dust mite was associated with a nearly 3-fold higher risk of prostate cancer. In a letter to the editor, Ohrui *et al.* reported a very high relative risk of 22.8 (95% CI 5.48–94.7) for prostate cancer in 486 nonsmoking male patients with asthma.²⁹ On the other hand, 1 retrospective study suggested that the risk of prostate cancer was slightly lower among participants with a history of asthma, hay fever or any “allergic” disease.³⁰ Our study is the first to show that allergen-specific IgE positivity is associated with an increased risk of prostate cancer.

Our findings of an increased (albeit statistically nonsignificant) risk of breast cancer associated with atopy is consistent with data from other publications,^{17,18,26,27} such as McWhorter's, which reports a similar relative risk estimate of 1.2 for a history of any allergy.²⁶ Two prospective studies, which used positive skin-prick testing as criterion for atopy, also reported a higher risk of breast cancer. This is at variance with some reports that suggested that the risk may be lower among people with a history of atopy.^{13,31}

The OR for lung cancer, although not statistically significant, points towards a higher risk in participants with asthma as well as atopy. Most epidemiologic studies published so far indicate an elevated lung cancer risk with asthma.^{1,16} In a review by Santillan *et al.*, the pooled relative risk estimates were 1.8 for studies limited to nonsmokers and 1.7 for studies that controlled for smoking history.¹⁶ We found an inverse association between lung cancer and hay fever, although not statistically significant. As the numbers underlying the estimates are small, they should be interpreted with caution. Nevertheless, we note that this is consistent with previous reports of a protective effect of hay fever on lung cancer.^{17,18,32–35} Osann reported a 50% reduction in risk of lung cancer among nonsmoker women with a history of asthma and hay fever combined.³² The OR for rhinitis (OR 0.46, 95% CI 0.01–2.5) pointed to a protective effect in a Swedish study that was a follow-up of skin-prick tested individuals.¹⁷ The Busselton cohort study indicated that the risk of lung cancer in males seemed to be decreased (OR 0.6, 95% CI 0.1–4.9) with hay fever.¹⁸ Recently, a prospective analysis focusing on cancer mortality among US men and women showed a significant inverse association between a history of hay fever and lung cancer mortality (RR 0.85, 95% CI 0.80–0.90).³³ The recently published case-control studies in Texas reported that hay fever had a significant protective effect on lung cancer (OR 0.58, 95% CI 0.48–0.70),³⁴ also among never smokers (OR 0.57, 0.35–0.92).³⁵

We did not find any association of colorectal cancer with either atopy or the atopy-related diseases combined. This is consistent with results of a cohort study from the USA,²⁷ but contrary to those of other case-control studies that suggest a protective effect of atopy on the risk of colorectal cancer.^{36–39} In our study, we

detected a statistically nonsignificant reduction of 40% in the risk of colorectal cancer among participants with atopic dermatitis.

Immunological explanations for the postulated relationship between atopy and cancer risk are still very speculative. In the consistently shown protective effect of atopy on glioma, a role of eosinophils and IL-13 produced by eosinophils is postulated.¹⁹ For the atopy-related increased risk of prostate cancer, it is suggested that an imbalance in the Th1 *versus* the Th2 cytokines (which is a feature of atopy) and the asthma-related macrophage inhibitory factor may play a role.^{29,40} Three plausible biological mechanisms are proposed to explain the increased lung cancer risk among asthmatic patients: the increased asthma-associated risk may be due to the chronic state of inflammation of the airways in combination with reduced free radical/reactive oxygen species scavenging; it may be due to impaired clearance of inhaled toxic agents in asthmatics; or it may be due to inhibition of apoptosis by corticosteroid treatment.¹⁶ The protective effect of hay fever on lung cancer might be due to enhanced immune surveillance resulting in a stimulated immune system. Anti-inflammatory agents to treat hay fever could also contribute to this protection. The ambiguous epidemiological findings in breast cancer reflect the absence of a plausible theory. In the colon, upregulation of cytokines that stimulate eosinophilic infiltration was demonstrated in patients with atopic dermatitis.⁴¹ This phenomenon might confer enhanced immune-surveillance against tumor cells in the colon, which may be an explanation of the tentative protective effect of atopic dermatitis in our study population.

The limitations of our study and their bearing on the results should be borne in mind. Recall and reporting bias by subjects is an inherent concern in studies relying on self-reported history of disease. However, the purported link between atopy and cancer is not common knowledge. Misclassification may arise from the imprecision in the questionnaire-based diagnosis of the atopy-related diseases due to the varying clinical presentation of atopic conditions. This misclassification is likely to be nondifferential. Atopic dermatitis is a disease of childhood, which may be forgotten by those who had mild or moderate symptoms. Persons who ascribe their rhinitis or conjunctivitis to “hay fever,” or ascribe their respiratory symptoms to “asthma,” may have diseases that are not atopy-related (such as chronic obstructive pulmonary disease or recurrent viral rhinitis with nonspecific hyperreactivity for example). We have attempted to avoid this by asking the participants whether their diagnosis had been made by a physician.

As in any study, there is a possibility of selection bias. It is possible that participants who refused to participate in the study may have a different prevalence rate of atopy. Controls were obtained from people who attended a health check-up facility; they may have a greater awareness of personal health. However, the prevalences of several common chronic diseases (hypertension, hyperlipidaemia and diabetes) and risk factors (smoking and obesity) in the ESTHER-I study were consistent with the prevalences found in the German National Health Interview and Examination Survey and the KORA/MONICA register, which are considered representative for the German general population.²⁰ The ESTHER-I study was also found to be representative for the general population with regard to a broad variety of sociodemographic characteristics.²⁰ Likewise, the age and sex distribution of cases was very similar to the distribution found in the population and cancer registry of Saarland.⁴²

Another limitation arises from the fact that we did not collect information on treatments associated with prior medical conditions. Current treatments for allergies may include antihistamines, corticosteroids and desensitization vaccinations.⁴³ However, adjustment for self-reported use of antiallergic drugs in a large international study had little effect on the relative risk estimates.⁸

In our analysis, we controlled for multiple confounders such as education, smoking status and alcohol consumption, but it is possible that unmeasured and yet unrecognized lifestyle factors that differ between atopic patients and nonatopic patients confounded our

results. This (confounding by unmeasured yet unrecognized risk factors) may explain in part the weak association between atopy and prostate cancer risk observed in the present study. We collected information on other risk factors (e.g. body weight) at the time of cancer diagnosis. It could argue that there might be some mistake to use such information to represent premorbid status. However, it was not possible to ascertain body weight retrospectively at the time of diagnosis among cases. As body weight was entirely unrelated to atopy, confounding by this variable and hence potential residual confounding by controlling for an imperfect indicator of body weight is of limited concern in this data analysis. When looking at the results, it has to be kept in mind that we used different atopy-related diseases in the various study population and did not adjust for multiple comparisons.

We also faced the limitation that blood samples were obtained from the cases after the diagnosis of cancer. It is unlikely that this would have an effect on the risk estimate. Most cases were recruited into the study within 3 months of diagnosis. There could be a possible effect on a biomarker by the cancer when this bio-

marker was assessed during or just preceding the diagnosis. However, we are unaware of any study documenting a rise/decrease in allergen-specific IgE because of a cancerous process. To the best of our knowledge, it is also biologically unlikely. In a population-based case-control study on glioma, Wiemels *et al.* did not find a depression of IgE by the glioma or its treatment.¹⁹ Their study showed that there was no significant effect on IgE levels by several factors: type of surgical intervention, radiation therapy, chemotherapy, medication use and the time from surgical intervention to blood draw.

In summary, our results add to existing evidence by showing the complexity of the association of allergy, atopy and cancer. This association seems to be dependent on the type of atopy-related disorder and the particular type of cancer under consideration. It is possible that IgE reactivity exerts a different effect on cancer, separate from the clinically manifest inflammatory diseases such as asthma, or hay fever, or atopic dermatitis. Advances in the understanding of cancer and immunology may give further clues to the role of atopic disorders in the risk of some types of cancer.

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