

Risk of cancer in patients with medically diagnosed hay fever or allergic rhinitis

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Data on allergic conditions as risk or protective factors for cancer are controversial probably because most studies have used self-reported data on mixed groups of allergies in a case-control setting. We define cancer risks in medically diagnosed hay fever/allergic rhinitis patients in a nationwide cohort study. A total of 138,723 hay fever/allergic rhinitis patients were identified from three Swedish health care databases and standardized incidence ratios (SIRs) were calculated for subsequent cancers identified from the Swedish Cancer Registry. Overall cancer risk was not changed (SIR 1.03). For individual cancers, the highest SIR was observed for nasal cancer (SIR 2.63), followed by testicular (1.46) and endocrine tumors (1.42), and kidney (1.31), prostate (1.18) and breast (1.11) cancers. The results were consistent in the three sources of data and all SIRs were above unity, albeit mainly not statistically significant. The SIRs for nervous system tumors were above unity and of borderline significance. SIRs were decreased for esophageal (0.50), liver (0.62) and lung (0.78) cancers, and the three sources of data agreed in the direction of the effect. The increased risks for testicular, renal, prostate and endocrine cancers may be explained by immunological mechanisms. Excess risk for these cancer accounts for a significant population attributable fraction. Nervous system cancers showed a borderline increase and none of the histological types were significantly decreased, providing strong evidence against the published case-control studies, which have reported protective effects. The reasons for the reduced risks for esophageal, liver and lung cancer remain to be explained.

Allergic diseases, encompassing hay fever, allergic rhinitis, allergic asthma and atopic dermatitis, are caused by inappropriate immunological response to antigens that do not elicit response in most individuals. The incidence of allergic conditions varies between population being highest in the developed countries where the incidence has increased and some 40% of the population may have experienced some allergic conditions.¹ Allergic rhinitis is considered to be the most common allergic condition among adults affecting between 10 and 30% of the population and showing increasing prevalence rates worldwide (http://www.worldallergy.org/publications/wao_white_book.pdf). The prevalence in Sweden is in that range and the recently reported prevalence was 28%.^{2,3} The increases

in allergic conditions have been explained by “the hygiene hypothesis,” which postulates that hygienic conditions in the developed countries have reduced exposures to microbial allergens and thus, shifted immune responses from Th1 arm to an overactive Th2 arm, with propensity to allergic disease.⁴ Mechanistically, allergy may have dual functions in respect to cancer: enhanced immune surveillance may help in defense against malignant cells but chronic stimulation and inflammation may have an opposite effect.^{1,5} Although recent reviews have covered tens of papers examining cancer risks in patients suffering from allergies, most of these were case-control studies with self-reported allergies as the disease definition. For some reason, there has been a large interest to study brain tumors in relation to allergy even though the ascertainment of disease history would appear most problematic for these patients unless medical records on allergies were available; most studies have reported negative associations between allergy and glioma risk.^{1,5–7} When four genetic susceptibility loci for allergy were tested for glioma risk, only one showed a borderline association.⁸ A recent large study on medically diagnosed allergic rhinitis patients illustrate the difficulties in *a priori* mechanistic assumptions on how allergy may influence cancer: of 19 specific sites reported, eight showed a significant increase and six showed a significant decrease of cancer risk.⁹

In the present study, we focus on patients medically diagnosed with hay fever/allergic rhinitis. These are the most common allergic conditions and if they are associated with cancer

Key words: hay fever, allergic rhinitis, cancer risk, immune disturbance, standardized incidence ratio

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What's new?

While up to a third of the population in developed countries may suffer from hay fever or allergic rhinitis, studies on the associated cancer risks are few, and data on allergic conditions as risk or protective factors for cancer remain controversial. Here, the authors defined cancer risks in medically diagnosed hay fever/allergic rhinitis patients in a Swedish nationwide cohort study. Data on 138,723 allergy patients showed increased risks for testicular, renal, prostate, and endocrine cancers. Although the cancer risks were not high in this relatively young cohort, the population impact is significant because of the prevalence of hay fever/allergic rhinitis.

risk, the impact on the population at large, measured by the population attributable fraction, may be significant. Our working hypothesis was that these allergic conditions increase the risk of some cancers. Even if this is opposite to the above data on glioma, the overwhelming literature on autoimmune conditions and cancers, by us and others, suggests that dysfunctional immune function is associated with increased cancer risk.^{10–13} Yet the mechanistic underpinnings remain unclear because associations have differed even for histological types in the same organ, including those in lung cancer or adenocarcinoma and squamous cell carcinoma of the esophagus.^{11,14} The only consistent protective effect that we and others have found was between rheumatoid arthritis and colorectal cancer, assumed to be due to anti-inflammatory medication.^{15–17} In the present large-scale cohort study, we aim to comprehensively investigate the cancer risk among hay fever/allergic rhinitis patients. Data on allergic conditions were retrieved from Swedish primary health care, hospital outpatient and hospital inpatient records and linked to the National Cancer Registry data up to the year 2010. For this study, close to 140,000 allergy and 2,500 cancer patients were identified.

Patients and Methods

Patients were identified from three Swedish health care databases: Hospital Discharge Register including all hospital discharges with dates of hospitalization and diagnoses since 1964 with regional coverage and 1987 national coverage, Outpatient Registry since 2001 and Primary Health Care Registry in Stockholm (2001–2007) and Region Skane (1987–2010). These databases include all patient visits for the described periods. Practically all health care is publically funded in Sweden and is provided against a nominal charge.¹⁸ When a person was identified in multiple databases, the first visit was counted. Patients with allergies were individually linked to the Swedish Cancer Registry (1.7 million recorded primary cancer patients followed-up from year 1964 to 2010), and to national census data for individual background data. The International Classification of Diseases codes were used for hay fever and allergic rhinitis combined (because the codes were not separated; the included codes were in ICD-7 240, ICD-8 507 and ICD-9 477, ICD-10 J30.1–J30.4). Cancer codes were based on ICD-7, which was used until year 1986; the subsequent codes were translated

back to ICD-7 for uniformity. The ICD-7 codes are listed in Supporting Information Table 1.

Person-years of follow-up were calculated from date of the first medical diagnosis for allergy until diagnosis of first cancer, death, emigration or closing date of the study, December 31, 2010, whichever came first. Standardized incidence ratios (SIRs) were calculated as the ratio of observed to expected number of cancers. Expected numbers were calculated for anyone not diagnosed with allergy, that is, the Swedish population reduced by the allergy cohort. The expected numbers were calculated by applying the background population rates to the number of age (5-year groups), sex, calendar period (5-year groups), region and education-specific (*i.e.*, length and level of education) person-years in the cohort study. For breast cancer, parity was additionally considered; parity data were available for the whole population. Analyses were first conducted separately for each source of allergy data and then combined (All) by considering the first allergy diagnosis for a person that appeared in multiple sources of data. Specific analyses were conducted by follow-up time since allergy diagnosis and age at allergy diagnosis. For nervous system tumors, analysis was conducted by histology and for endocrine tumors by location. Population attributable fraction was calculated according to formula: $p(\text{SIR} - 1)$ divided by $p(\text{SIR} - 1) + 1$ where p is population prevalence of exposure, that is, allergic conditions (%).¹⁹

The study protocol was approved by the regional ethical review board at the Lund University.

Results

The total number of unique patients diagnosed with hay fever/allergic rhinitis allergy was 138,723 (Table 1). Hay fever/allergic rhinitis was most common among outpatients (81,340) and only 7,904 inpatients were identified. Curiously, more males had inpatient visits than females. A small number (18,070, 11.5%) of the patients were found in more than one source of data and thus, the three sources provided largely independent patient cohorts. This is shown in the last three lines of Table 1: for example, 49,682 patients were found only in primary health care records, whereas 17,713 were also found as outpatients and 151 as inpatients. Because data from primary health care and outpatients were available only relatively recently, 82% of the diagnoses were after year

Table 1. Source of identification of hay fever/allergic rhinitis and clinical characteristics

	Primary health care	Outpatient	Inpatient	All
	<i>N</i>	<i>N</i>	<i>N</i>	<i>N</i>
All	67,546	81,343	7,904	138,723
Sex				
Male	33,063	42,579	12,212	70,521
Female	34,483	38,764	4,395	68,202
Median age at allergy diagnosis	27	20	23	24
Median year at allergy diagnosis	2004	2005	1974	2004
Median age at cancer diagnosis	61	56	62	60
Median year at cancer diagnosis	2006	2008	1999	2006
Person-year at cancer risk	519,562	458,351	237,173	1,107,919
Source of identification				
Primary health care	49,682	17,713	151	67,546
Outpatient	17,713	63,388	242	81,343
Inpatient	151	242	7,511	7904

2000. The total number of person-years at risk for cancer was 1.1 million and the mean follow-up time was 8 years.

Cancer risks after hay fever/allergic rhinitis are shown in Table 2 for 25 cancer types. A total of 34 cancer sites were analyzed but because for rare cancers the case numbers were below 20 and the SIRs were not significant they are not shown. Overall (including the sites that were not shown), the SIR was 1.03 (95%CI 0.99–1.07) and it was not statistically significant for any of the sources of allergy patients. For “all” patients, that is, combined unique hay fever/allergic rhinitis patients defined by the first diagnosis, the SIRs were increased most for nasal cancer (SIR 2.63, 1.19–5.01), followed by testicular (1.46, 1.10–1.89) and endocrine tumors (1.42, 1.10–1.80), and kidney (1.31, 1.02–1.67), prostate (1.18, 1.06–1.30) and breast (1.11, 1.01–1.21) cancers. Importantly, for all these cancers, the results were consistent in the three sources (*i.e.*, internal validation) and all SIRs were above unity, *albeit* mostly not significant. The SIRs for squamous cell skin cancer and nervous system tumors were above unity and of borderline significance. SIRs were decreased for esophageal (0.50, 0.21–0.99), liver (0.62, 0.40–0.92), lung (0.78, 0.64–0.93) and, of borderline significance, bladder (0.79, 0.62–1.00) cancers, and the three sources of data agreed in the direction of the effect, except for bladder cancer.

In Table 3, the risk was analyzed by follow-up time, <1, 2–3 and ≥4 years. The overall SIRs were stable, 1.04, 1.06 and 1.04, respectively. For nasal cancer, there was a vastly increased risk of 10.69 (2.02–31.64) within the first year ($n = 3$). Also, the risk of testicular cancer was increased within the first year (3.15, 1.62–5.52) and the subsequent period (2.44, 1.44–3.86). Risk of skin cancer was increased (2.15, 1.44–3.09) in the second follow-up period. For prostate and endocrine cancers, the increase was significant in the last follow-up period, as it was of borderline significance for

breast and kidney cancers. The decreased risks of esophageal, liver and lung cancer were noted only in the last period. The total case number is 51 patients less in Table 3 than in Table 2 because of uncertain follow-up time.

Because of the abundance of literature of nervous system cancers in allergy patients, a detailed analysis of nervous system tumors was conducted (Table 4). Meningioma was the most common type with a SIR of 1.15 (0.80–1.60); for high and low grade gliomas, the SIRs were 1.00 and 1.39 (0.86–2.13), respectively, although not significant.

Endocrine tumors are found at many organ sites (Table 5). Even though the SIRs were above unity for all organs sites, the only significant increase (1.48, 1.06–2.01) was for the most common nonthyroid endocrine neoplasm, parathyroid tumor.

Some additional analyses are shown in Supporting Information Tables. In Supporting Information Table 1, cancer risk is analyzed by age at allergy diagnosis. The groups were selected based on median diagnostic ages from Table 1; nevertheless most cancers were found in those diagnosed at age 30+ years. The reason for this was the fact that 82% of patients were diagnosed after year 2000 whereby young allergy patients did not reach the age when cancers were common. Because of the large numbers in the age 30+ group, most significant increases were observed in these patients. However, the risk of melanoma was 1.69 (1.11–2.46) in those diagnosed for allergy at age <20 years, and only increased in this age group. Sex-specific analysis is shown in Supporting Information Table 2. All significant effects were observed for men only, except for endocrine tumors, which were increased and leukemia, which were decreased in women; lung cancer was decreased in men and women. In Supporting Information Table 3, data are stratified by comorbidity with chronic obstructive pulmonary lung disease

Table 2. Cancer risk among patients diagnosed with hay fever/allergic rhinitis

Cancer site	Primary health care				Outpatient				Inpatient				All			
	N	SIR	95%CI		N	SIR	95%CI		N	SIR	95%CI		N	SIR	95%CI	
Upper aerodigestive tract	15	0.69	0.39	1.15	11	0.86	0.43	1.55	16	0.97	0.56	1.59	40	0.84	0.60	1.15
Esophagus	5	0.67	0.21	1.59	2	0.52	0.05	1.92	2	0.35	0.03	1.28	8	0.50	0.21	0.99
Stomach	19	1.06	0.64	1.66	6	0.69	0.25	1.51	23	1.28	0.81	1.92	45	1.06	0.77	1.42
Colon	61	0.84	0.64	1.08	28	0.73	0.49	1.06	50	0.97	0.72	1.27	134	0.87	0.73	1.03
Rectum	34	0.87	0.60	1.22	13	0.62	0.33	1.07	29	0.99	0.66	1.42	75	0.89	0.70	1.12
Liver	10	0.56	0.27	1.04	6	0.67	0.24	1.46	10	0.63	0.30	1.17	25	0.62	0.40	0.92
Pancreas	17	0.88	0.51	1.42	7	0.70	0.28	1.45	12	0.72	0.37	1.27	33	0.76	0.52	1.07
Nose	4	2.53	0.66	6.54	3	3.21	0.61	9.51	2	1.76	0.17	6.47	9	2.63	1.19	5.01
Lung	62	0.87	0.66	1.11	33	0.88	0.61	1.24	30	0.57	0.38	0.81	119	0.78	0.64	0.93
Breast	243	1.06	0.93	1.20	169	1.19	1.02	1.38	139	1.06	0.89	1.25	519	1.11	1.01	1.21
Cervix	22	0.94	0.59	1.43	10	0.67	0.32	1.23	17	1.32	0.77	2.12	47	0.99	0.73	1.32
Endometrium	26	0.75	0.49	1.09	21	1.12	0.69	1.71	20	0.81	0.49	1.25	63	0.85	0.65	1.09
Ovary	24	0.92	0.59	1.37	9	0.59	0.27	1.13	25	1.26	0.82	1.87	56	0.98	0.74	1.27
Prostate	195	1.19	1.03	1.36	92	1.06	0.85	1.29	137	1.20	1.01	1.42	404	1.18	1.06	1.30
Testis	27	1.38	0.91	2.00	24	1.55	0.99	2.31	10	1.22	0.58	2.26	57	1.46	1.10	1.89
Kidney	29	1.28	0.86	1.85	19	1.47	0.88	2.30	24	1.24	0.79	1.85	68	1.31	1.02	1.67
Urinary bladder	44	1.08	0.78	1.45	10	0.49	0.23	0.91	22	0.68	0.42	1.03	70	0.79	0.62	1.00
Melanoma	81	1.11	0.88	1.38	47	0.97	0.71	1.29	50	1.26	0.94	1.67	163	1.10	0.93	1.28
Skin, squamous cell	63	1.38	1.06	1.77	29	1.32	0.89	1.90	25	0.88	0.57	1.30	110	1.21	1.00	1.46
Nervous system	60	1.21	0.92	1.55	38	1.06	0.75	1.46	33	1.13	0.78	1.59	122	1.15	0.96	1.37
Thyroid gland	19	1.21	0.73	1.89	11	0.98	0.49	1.77	7	0.92	0.36	1.90	37	1.17	0.82	1.61
Endocrine glands	35	1.62	1.13	2.25	18	1.32	0.78	2.08	18	1.17	0.69	1.86	67	1.42	1.10	1.80
Non-Hodgkin lymphoma	49	1.03	0.76	1.36	24	0.86	0.55	1.28	35	1.07	0.74	1.48	102	1.00	0.82	1.22
Myeloma	12	0.97	0.50	1.70	8	1.22	0.52	2.41	10	1.04	0.50	1.92	29	1.08	0.72	1.55
Leukemia	19	0.72	0.43	1.12	14	0.72	0.39	1.21	15	1.03	0.57	1.70	46	0.82	0.60	1.09
All	1,210	1.04	0.98	1.10	679	0.99	0.92	1.07	789	1.02	0.95	1.09	2,535	1.03	0.99	1.07

N = number of cancer cases, SIR = standardized incidence ratio; 95%CI = 95% confidence interval.
 Bolding shows that 95%CI's do not overlap with 1.00.

(COPD) as a proxy for heavy smoking. SIRs for all smoking related cancers (lung, upper aerodigestive tract, esophagus, pancreas, kidney and bladder) were lower among COPD patients, *albeit* the confidence intervals overlapped with SIRs for patients not diagnosed with COPD. A similar analysis was conducted for persons diagnosed with alcoholism but not more than 57 combined cancers (SIR 0.99, 0.75–1.29) were diagnosed in these individuals and the results were non-informative on specific cancers.

Discussion

The strengths of the present study included medical diagnosis of allergy and, additionally, cohort design and nationwide coverage of a large population. We had three, largely independent sources of data, which helped to assess internal consistency. Michelle Turner reviewed recently 55 epidemiological studies on various kinds of allergy and cancer, which included only three cohort studies covering all

cancers alike the present study.⁵ A vast majority of the reviewed 55 studies were based on self-reported allergies in case-control studies. Reporting bias is a problem in all case-control studies but it is most serious in recurring common diseases, such as hay fever or allergic rhinitis. Many persons with allergies do not seek medical care and thus, in the present study the reference population is not completely disease-free, which decreases the power of detection and underestimates true risks. The weakness of the present approach was that most allergy diagnoses were recent and only 18% of the diagnoses were rendered before year 2000. Even though the mean follow-up time was 8 years, the follow-up was largely at a relatively young age, early for risk age for cancer. Essentially only inpatient data were available from an extended period. However, allergies are chronic conditions and many patients may have had their first diagnosis well before the start of our follow-up. The patient clientele can be expected to be different in primary and hospital care,

Table 3. Cancer risk among patients diagnosed with hay fever/allergic rhinitis by follow up time

Cancer site	≤1 year				2–3 years				≥4 years			
	N	SIR	95%CI		N	SIR	95%CI		N	SIR	95%CI	
Upper aerodigestive tract	3	0.81	0.15	2.39	3	0.41	0.08	1.21	31	0.89	0.60	1.26
Esophagus	0				3	1.27	0.24	3.76	5	0.42	0.13	0.99
Stomach	1	0.32	0.00	1.82	7	1.14	0.45	2.36	37	1.18	0.83	1.62
Colon	9	0.77	0.35	1.47	16	0.69	0.39	1.12	105	0.93	0.76	1.13
Rectum	4	0.63	0.16	1.63	8	0.64	0.27	1.26	62	1.00	0.77	1.28
Liver	4	1.32	0.34	3.42	5	0.85	0.27	2.00	16	0.53	0.30	0.87
Pancreas	2	0.62	0.06	2.28	3	0.47	0.09	1.40	28	0.87	0.58	1.26
Nose	3	10.69	2.02	31.64	1	1.84	0.00	10.54	5	2.02	0.64	4.76
Lung	9	0.77	0.35	1.47	27	1.18	0.78	1.72	80	0.71	0.56	0.88
Breast	42	1.05	0.76	1.42	96	1.23	0.99	1.50	367	1.10	0.99	1.22
Cervix	2	0.43	0.04	1.59	9	1.02	0.46	1.95	34	1.06	0.73	1.48
Endometrium	5	0.87	0.28	2.05	13	1.15	0.61	1.98	42	0.77	0.55	1.04
Ovary	5	1.04	0.33	2.44	6	0.65	0.23	1.42	43	1.05	0.76	1.41
Prostate	29	1.14	0.77	1.64	53	1.05	0.78	1.37	315	1.24	1.10	1.38
Testis	12	3.15	1.62	5.52	18	2.44	1.44	3.86	26	0.99	0.64	1.45
Kidney	4	0.99	0.26	2.56	12	1.54	0.79	2.69	50	1.32	0.98	1.74
Urinary bladder	7	1.06	0.42	2.20	4	0.31	0.08	0.79	57	0.87	0.66	1.13
Melanoma	13	1.01	0.54	1.73	24	0.94	0.60	1.41	121	1.15	0.96	1.38
Skin, squamous cell	6	0.91	0.33	2.00	29	2.15	1.44	3.09	75	1.12	0.88	1.40
Nervous system	11	1.07	0.53	1.92	24	1.25	0.80	1.86	84	1.17	0.93	1.45
Thyroid gland	4	1.31	0.34	3.40	6	1.02	0.37	2.22	26	1.21	0.79	1.78
Endocrine glands	6	1.49	0.54	3.27	10	1.29	0.61	2.38	49	1.45	1.07	1.92
Non-Hodgkin lymphoma	9	1.08	0.49	2.05	15	0.92	0.52	1.53	76	1.04	0.82	1.30
Myeloma	1	0.50	0.00	2.84	4	1.00	0.26	2.58	23	1.15	0.73	1.73
Leukemia	3	0.53	0.10	1.57	11	1.05	0.52	1.89	32	0.86	0.59	1.21
All	208	1.04	0.90	1.19	418	1.06	0.96	1.17	1,848	1.04	1.00	1.09

Bolding shows that 95%CI's do not overlap with 1.00.

Table 4. Nervous system cancer risk by histology among patients diagnosed with hay fever/allergic rhinitis

Cancer site	N	SIR	95%CI	
Meningioma	35	1.15	0.80	1.60
High grade glioma	28	1.00	0.66	1.44
Low grade glioma	21	1.39	0.86	2.13
Neurinoma	12	1.15	0.59	2.01
Hemangioma	6	2.53	0.91	5.54
Ependymoma	4	1.23	0.32	3.19
Medulloblastoma	1	0.70	0.00	4.02
Neuroblastoma	1	0.63	0.00	3.63
Others	1	3.12	0.00	17.88

N = number of cancer cases, SIR = standardized incidence ratio; 95%CI = 95% confidence interval.

and we thus, considered important to first consider results from each source separately before combining the data. Despite these differences, we found fairly consistent results

even in the source-specific analyses. Misclassification and possible changes in diagnostic practice over time are issues that would have reduced risk estimates. However, as 82% of the allergy diagnoses were since year 2000 calendar time-dependent changes should be of minor concern.

Overall there was no excess risk of cancer in hay fever/allergic rhinitis patients and the SIR was 1.03. Unfortunately, there is only one study reporting similar data, the Taiwanese allergy study on 3,191 cancers in patients with allergic rhinitis.⁹ In that study, the overall cancer risk was 1.02. In an earlier Swedish follow-up study on asthma patients, the overall risk was significantly increased to 1.36.²⁰ The present highest risk was for nasal cancer (2.63), which is probably mainly due to diagnostic bias resulting from nasal examination and detection of early lesions; accordingly, the risk was highest within the first year of follow-up. The risk was almost identical (2.74) in the Taiwanese study.⁹ The present borderline risk of skin cancer may also be related to diagnostic bias because of skin testing. However, for the other sites with

Table 5. Endocrine glands tumor risk among patients diagnosed with hay fever/allergic rhinitis

Site	N	SIR	95%CI	
Parathyroid	41	1.48	1.06	2.01
Pituitary	13	1.35	0.71	2.31
Adrenal gland	8	2.06	0.88	4.07
Thymus	3	1.67	0.32	4.95

N = number of cancer cases, SIR = standardized incidence ratio; 95%CI = 95% confidence interval.

Bolding shows that 95%CI's do not overlap with 1.00.

increasing risks, including endocrine, renal, prostate and breast cancer no such simple explanation can be offered and the increases may be mechanistically related to allergy, particularly, as above unity SIRs were observed for patients from each of the three data sources. These results would support the primary hypothesis assuming that dysfunctional immune system predisposes to cancer. However, the present data do not allow exclusion of an alternative hypothesis that the increases were due to medication. The risk was very high (2.64) for renal cancer in the Taiwanese study. Breast cancer was also increased in that study (1.20): among endocrine cancer only thyroid data were reported and the SIR was increased (1.47). No data on testicular or prostate cancers were reported.

In the present study, the SIR (1.15) for all nervous system tumors was of borderline significance, supported by each of the three datasets and by the Taiwan data (1.53). Our more detailed analysis by histological types showed that the SIRs were 1.00 or higher for all common histological types. These data lend no support to the results of case-control studies showing protective effects of allergies.^{1,5-7} These data are also supported by a study on asthma patients which showed an SIR of 1.29 for nervous system tumors and an SIR of 1.58 for those hospitalized for asthma more than five times, assumed to include severely ill patients.²⁰ In the large US Cancer Prevention Study II, the overall mortality in cancer showed a relative risk of 0.91 among nonsmoking persons with hay fever and the mortality was unchanged in any of the listed cancer sites.²¹ The data on hay fever were self-reported with a specification whether the diagnosis was rendered by a doctor. A recent update of that study with an additional cohort focused

on colorectal cancer and found no differences in mortality or incidence among hay fever patients.²²

The present study showed clearly decreased risk for esophageal, liver and lung cancers with SIRs ranging from 0.50 to 0.78. A likely explanation for lung cancer and partially for esophageal cancer would be a lower frequency of smoking or smokers among allergy patients which may be due to selection.²¹⁻²³ Another mechanism applying to all these cancers is that heavy smokers and alcohol users may be reluctant users of health care services compared to the population at large. In support, the SIRs for all smoking related cancer were lower in COPD patients than in those without COPD. In the Taiwanese study, esophageal cancer was also decreased (0.68), lung cancer showed no change (1.05) and no data were given for liver cancer; urinary bladder cancer showed a borderline increase (1.23).⁹

As up to 30% of the population may suffer or may have suffered from hay fever/allergic rhinitis, the population attributable fraction of this predisposing factor may be large if the observed risks were causally related to the underlying allergy. For testicular cancer, the calculation will yield 12.1%, for renal cancer 10.2% and for prostate cancer 5.1%. To put these figures in perspective, for prostate and testicular cancers no prevalent environmental risk factors have been identified but familial risk accounts for population attributable fractions of 13.9 and 1.6% for these cancers.²⁴ Family history accounts for only 1.7% for renal cancer but overweight/obesity and tobacco smoking each account for 24%.²⁵

In conclusion, the present data showed increased risks mainly for testicular, renal, prostate and endocrine cancers with probably associations to immunological mechanisms. Each of these would assume a significant population attributable fraction. Nervous system cancers showed a borderline increase and none of the histological types were decreased providing strong evidence against the published case-control studies that have reported protective effects. The reduced risks for esophageal, liver and lung cancers remain to be explained if mechanisms other than avoidance of smoking or medical contacts would be involved. Most of the present results apply to a relatively young population, and the results may change when a large proportion of the population can be followed-up for cancer to an old age.

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Supplementary Tables

RISK OF CANCER IN PATIENTS WITH MEDICALLY DIAGNOSED HAY FEVER OR ALLERGIC RHINITIS

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Supplementary Table 1. Cancer risk among patients diagnosed with hay fever/allergic rhinitis by age at allergy diagnosis

Cancer site	ICD7-code	<20				20-29				30+			
		O	SIR	95%CI		O	SIR	95%CI		O	SIR	95%CI	
Upper aerodigestive tract	140,141,143-148,161	2	0.55	0.05	2.04	4	0.84	0.22	2.18	34	0.80	0.55	1.12
Oesophagus	150	0				1	0.83	0.00	4.74	7	0.45	0.18	0.93
Stomach	151	2	1.24	0.12	4.57	1	0.34	0.00	1.94	42	1.10	0.79	1.48
Colon	153	9	1.18	0.53	2.25	11	1.04	0.52	1.87	114	0.82	0.68	0.99
Rectum	154 (except 1541)	2	0.64	0.06	2.35	1	0.17	0.00	0.98	72	0.94	0.74	1.19
Anus	1541	0				0				4	0.64	0.17	1.66
Liver	155-156	1	0.58	0.00	3.35	1	0.39	0.00	2.24	23	0.63	0.40	0.94
Pancreas	157	1	0.69	0.00	3.98	4	1.41	0.37	3.66	28	0.70	0.47	1.02
Nose	160	1	3.53	0.00	20.21	1	2.65	0.00	15.17	7	2.46	0.98	5.10
Lung	162-163	2	0.37	0.03	1.36	6	0.49	0.18	1.08	111	0.69	0.57	0.83
Breast	170	16	0.73	0.42	1.19	56	1.31	0.99	1.71	447	1.08	0.99	1.19
Cervix	171	7	1.43	0.57	2.96	16	1.49	0.85	2.42	24	0.74	0.47	1.10
Endometrium	172	1	0.66	0.00	3.80	4	0.92	0.24	2.39	58	0.86	0.65	1.11
Ovary	175	5	1.29	0.41	3.03	6	1.03	0.37	2.27	45	0.95	0.69	1.27
Prostate	177	14	1.54	0.84	2.60	27	1.22	0.81	1.78	363	1.15	1.04	1.28
Testis	178	16	1.13	0.64	1.84	22	1.76	1.10	2.67	19	1.46	0.88	2.29
Kidney	180	2	0.61	0.06	2.24	3	0.71	0.13	2.09	63	1.37	1.06	1.76
Urinary bladder	181	3	0.89	0.17	2.62	5	0.81	0.26	1.90	62	0.74	0.56	0.94
Melanoma	190	27	1.69	1.11	2.46	21	0.93	0.57	1.42	115	1.06	0.87	1.27
Skin, squamous cell	191	6	1.96	0.70	4.29	1	0.21	0.00	1.22	103	1.23	1.00	1.49
Nervous system	193	24	1.04	0.66	1.55	12	0.77	0.40	1.36	86	1.25	1.00	1.54
Thyroid gland	194	6	1.02	0.37	2.23	10	1.48	0.70	2.73	21	1.05	0.65	1.61
Endocrine glands	195	6	1.05	0.38	2.29	6	1.00	0.36	2.19	55	1.48	1.11	1.93
Connective tissue	197	1	0.22	0.00	1.25	3	1.17	0.22	3.45	12	0.95	0.49	1.67

Non-Hodgkin lymphoma	200,202	14	1.34	0.73	2.25	11	1.11	0.55	2.00	77	0.92	0.73	1.16
Hodgkin's disease	201	9	0.95	0.43	1.81	6	1.06	0.38	2.33	8	1.14	0.49	2.26
Myeloma	203	2	1.97	0.19	7.26	1	0.58	0.00	3.35	26	1.06	0.69	1.55
Leukemia	204-209	15	1.07	0.60	1.78	3	0.50	0.09	1.48	28	0.75	0.50	1.09
All		200	1.06	0.92	1.21	249	1.04	0.92	1.18	2086	1.00	0.95	1.04

Supplementary Table 2. Cancer risk among patients diagnosed with hay fever/allergic rhinitis by gender

Cancer site	Male				Female			
	O	SIR	95%CI		O	SIR	95%CI	
Upper aerodigestive tract	20	0.63	0.38	0.97	20	1.05	0.64	1.62
Esophagus	5	0.41	0.13	0.96	3	0.58	0.11	1.73
Stomach	24	0.99	0.63	1.48	21	1.12	0.70	1.72
Colon	58	0.84	0.64	1.09	76	0.87	0.68	1.09
Rectum	39	0.87	0.62	1.19	36	0.89	0.62	1.24
Liver	6	0.31	0.11	0.68	19	0.88	0.53	1.37
Pancreas	13	0.66	0.35	1.13	20	0.82	0.50	1.27
Nose	5	2.58	0.81	6.06	4	2.56	0.66	6.61
Lung	58	0.70	0.53	0.91	61	0.63	0.48	0.81
Breast	2	1.15	0.11	4.22	517	1.09	1.00	1.19
Cervix	0				47	0.97	0.71	1.30
Endometrium	0				63	0.86	0.66	1.10
Ovary	0				56	0.98	0.74	1.27
Prostate	404	1.17	1.06	1.29	0			
Testis	57	1.44	1.09	1.86	0			
Kidney	39	1.30	0.92	1.78	29	1.24	0.83	1.78
Urinary bladder	48	0.73	0.54	0.97	22	0.79	0.50	1.20
Melanoma	70	1.14	0.89	1.44	93	1.08	0.87	1.33
Skin, squamous cell	55	1.17	0.88	1.52	55	1.23	0.93	1.61
Nervous system	56	1.18	0.89	1.53	66	1.10	0.85	1.40
Thyroid gland	11	1.48	0.73	2.66	26	1.03	0.67	1.52
Endocrine glands	15	1.01	0.57	1.68	52	1.52	1.14	2.00
Non-Hodgkin lymphoma	52	0.94	0.70	1.23	50	1.04	0.77	1.37
Myeloma	15	1.07	0.60	1.78	14	1.05	0.57	1.76
Leukemia	29	0.99	0.66	1.43	17	0.61	0.35	0.98
All	1129	1.02	0.96	1.08	1406	1.00	0.94	1.05

Supplementary Table 3. Cancer risk among patients diagnosed with hay fever/allergic rhinitis stratified by chronic obstructive pulmonary disease (COPD)

Cancer site	COPD-				COPD+				All			
	O	SIR	95%CI		O	SIR	95%CI		O	SIR	95%CI	
Upper aerodigestive tract	35	0.86	0.60	1.19	5	0.49	0.16	1.16	40	0.79	0.56	1.07
Esophagus	7	0.53	0.21	1.09	1	0.24	0.00	1.40	8	0.46	0.20	0.91
Stomach	37	1.02	0.72	1.41	8	1.21	0.52	2.39	45	1.05	0.77	1.41
Colon	120	0.91	0.76	1.09	14	0.57	0.31	0.95	134	0.86	0.72	1.02
Rectum	63	0.86	0.66	1.10	12	0.98	0.50	1.72	75	0.88	0.69	1.10
Liver	20	0.58	0.35	0.90	5	0.77	0.24	1.82	25	0.61	0.40	0.90
Pancreas	30	0.81	0.54	1.15	3	0.44	0.08	1.30	33	0.75	0.52	1.05
Nose	9	2.98	1.35	5.69	0				9	2.57	1.16	4.89
Lung	87	0.73	0.58	0.90	32	0.54	0.37	0.76	119	0.67	0.55	0.80
Breast	453	1.09	0.99	1.20	66	1.06	0.82	1.35	519	1.09	1.00	1.19
Cervix	42	0.98	0.71	1.33	5	0.89	0.28	2.09	47	0.97	0.71	1.30
Endometrium	54	0.84	0.63	1.10	9	0.97	0.44	1.84	63	0.86	0.66	1.10
Ovary	49	0.98	0.72	1.29	7	1.01	0.40	2.09	56	0.98	0.74	1.27
Prostate	363	1.20	1.08	1.33	41	0.97	0.69	1.32	404	1.17	1.06	1.29
Testis	55	1.50	1.13	1.95	2	0.67	0.06	2.46	57	1.44	1.09	1.86
Kidney	59	1.32	1.01	1.71	9	1.02	0.46	1.94	68	1.27	0.99	1.62
Urinary bladder	61	0.82	0.63	1.06	9	0.46	0.21	0.88	70	0.75	0.58	0.94
Melanoma	153	1.12	0.95	1.31	10	0.90	0.43	1.67	163	1.11	0.94	1.29
Skin, squamous cell	93	1.19	0.96	1.46	17	1.25	0.73	2.00	110	1.20	0.99	1.45
Nervous system	115	1.20	0.99	1.44	7	0.59	0.23	1.23	122	1.13	0.94	1.35
Thyroid gland	33	1.15	0.79	1.62	4	1.03	0.27	2.66	37	1.13	0.80	1.57
Endocrine glands	52	1.25	0.93	1.64	15	2.04	1.14	3.37	67	1.37	1.06	1.74
Non-Hodgkin lymphoma	84	0.94	0.75	1.17	18	1.24	0.73	1.96	102	0.98	0.80	1.19
Myeloma	23	0.99	0.62	1.48	6	1.48	0.53	3.25	29	1.06	0.71	1.52
Leukemia	39	0.78	0.56	1.07	7	0.97	0.39	2.01	46	0.81	0.59	1.07
All	2216	1.03	0.99	1.08	319	0.85	0.76	0.95	2535	1.01	0.97	1.05