

Original article

Allergy and cancer

Background: Conflicting results have provided support for two distinct and contradictory hypotheses: (i) allergy has a protective effect against cancer by enhanced immune surveillance, and (ii) allergy is associated with an increased risk of cancer by chronic immune stimulation. We therefore aimed us to perform a large epidemiological study with a defined allergic disease cohort.

Methods: During the years 1988–2000, 70 136 patients tested for total serum immunoglobulin E (IgE) and 57 815 tested with Phadiatop for diagnosing allergic disease at Karolinska University Hospital, Stockholm, Sweden, were linked with the Swedish Cancer Registry for a virtually complete follow up with regard to cancer.

Findings: The total number of observed cancers was normal in the total serum IgE-cohort; standardized incidence ratio (SIR) = 0.98 (95% CI: 0.92–1.04) and in the Phadiatop-cohort: SIR = 0.99 (0.92–1.06) independent of the level of IgE and positive or negative Phadiatop. Specific analysis was done for cancer of the lung, cervix, pancreas, lymphoma, and nonmelanoma skin cancer. None of these forms of cancer had increased risks.

Interpretation: The study does not support the hypothesis that allergy has a protective effect against cancer, nor does it support an increased risk.

**B. Lindelöf¹, F. Granath²,
M. Tengvall-Linder³, A. Ekbom²**

¹Unit of Dermatology and Venereology, ²Unit of Clinical Epidemiology and ³Unit of Clinical Allergy Research, Department of Medicine, Karolinska University Hospital and Institute, Stockholm, Sweden

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B. Lindelöf MD
Department of Dermatology
Karolinska University Hospital
S-171 76 Stockholm
Sweden

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Patients with allergies have hypothetically an overactivity of their immunological mechanisms and thus the presence of clinical allergy might be protective with regard to the development of cancer. To date, a number of studies have reported a protective effect (1–27) but other studies have found allergy to be a risk factor for cancer (28–33) and some have found no correlation or conflicting results (34–43). Many of these studies have had the major drawback of not surveying large enough populations, or defining their patients with allergies from data derived from interviews or questionnaires.

There are few large epidemiological studies (21, 33, 36, 37, 40, 42, 43) with different definitions of allergy: positive skin prick test (37), hospital discharge for asthma (21, 40), insurance institutions file of asthma (36), positive patch tests (32), self-reported atopic dermatitis (42) and self-reported allergies (43). In general, these studies found the association between allergy and cancer to be more complex.

The present knowledge might indicate that the 'hyper-immune' theory of allergic response forward a protective effect against cancer under certain circumstances, but allergy can also be considered as a failure of the immune system, and thus predispose for cancer, especially in the immune system itself.

Today many people are allergic, and therefore an allergic predisposition might have some advantages in an evolutionary perspective. This observation, in combina-

tion with the fact that the interpretation of the available data is extremely difficult, have aimed us to perform a large epidemiological study, with a defined allergic disease cohort with virtually complete follow up with regard to cancer.

Methods

This study was approved by the Ethics Committee at the Karolinska Institute, Stockholm, Sweden.

Study population

During the years 1988–2000, 71 525 patients at the Department of Clinical Immunology, Karolinska University Hospital, Stockholm, Sweden, were tested for total serum immunoglobulin E (Total-IgE) for diagnosing allergic disease. 1274 were excluded because of an earlier malignancy and 115 (0.16%) were excluded due to errors in the database registration. Thus, 70 136 patients tested for Total-IgE were included in the study. 28 669 (40.9%) were men and 41 467 (59.1%) were women. The number of patients in different age groups were as follow: 0–19 years: 19 186 (27.4%), 20–39 years: 26 334 (37.5%), 40–59 years: 19 102 (27.2%) and ≥60 years: 5514 (7.9%). Mean age: 31.8 years (range: 1–89). Total follow-up time = 462 738 person-years.

A total of 58 818 patients were tested with Phadiatop. 934 patients were excluded because of an earlier malignancy and 69 (0.12%) were excluded due to errors in the database registration. Thus, 57 815 Phadiatop-tested patients were included in the study.

23 669 (40.9%) were men and 44 851 (58.5%) were women. The number of patients in different age groups were as follow: 0–19 years: 17 080 (29.5%), 20–39 years: 20 921 (36.2.5%), 40–59 years: 15 174 (26.3%) and ≥60 years: 4640 (8.0%). Mean age: 31.6 years (range: 1–89). Total follow-up time = 291 661 person-years.

IgE-testing

Total-IgE concentrations were determined by using Pharmacia CAP System™ (Pharmacia Diagnostics AB, Uppsala, Sweden). Concentrations were expressed as kU/l and levels are characterized and defined in Table 1. 74.2% of the patients had normal, 18.5% had slightly elevated and 7.3% had highly elevated levels of Total-IgE. 86.3% of the patients were tested only once. The level of Total-IgE for the first test was used in the analysis when multiple testing.

Phadiatop® (a mixture of 11 airborne allergens) was determined by using Pharmacia CAP System™. A value of 0.35 kU/l or more was considered positive. 38 643 (66.8%) of the patients had negative and 19 172 (33.2%) had positive Phadiatop test.

A total of 99 598 patients were tested, of which 28 353 (28.5%) were tested with both Total-IgE and Phadiatop test, 41 783 (42%) were tested only for Total-IgE, and 29 462 (29.5%) were tested only with Phadiatop.

The Swedish Cancer Registry and Cause-of-death Registry

Information from the Swedish Cancer Registry from 1958 to 2000 was correlated with the records of the 70 136 Total-IgE tested and the 57 815 Phadiatop-tested patients to identify those with cancer. Only cancer-free patients at first test were included and the first year of the observation period was disregarded. A separate analysis of all cancers occurring in childhood (0–14 years of age) was performed, where children with a positive Phadiatop and/or elevated IgE were classified as positive. Also in this analysis we started the follow up 1-year after the test, in the case where children had undergone both types of test, the follow up started 1 year after the last test was performed.

Nationwide information on the incidence of cancer in Sweden is available for all the years since 1958, when compulsory registration began (44). The cancer registry collects information on diagnosed cancers from clinicians and pathologists. If a person has more than one cancer, each one is registered separately. The completeness of registration is close to 100% for all cancers.

The Cause-of-death Registry includes information on all deceased persons listed in the parish registers, whether they died in Sweden or abroad. The underlying cause of death is generally determined from

data on medical death certificates, which were designed in accordance with the internationally established norm.

The individually unique 10 digit national registration number ascribed to every Swedish citizen, ensures accurate identification and follow up of each patient.

Analysis and statistics

Expected number of cancers were calculated by multiplying the age, gender, and calendar-year-specific risk time by the corresponding cancer incidence rates of the general Swedish population. The standardized incidence ratio (SIR); the ratio of the observed to the expected number of incident cancers, was used to estimate the relative risk of tumours for different categories. We only counted first cancers after the test-situation, and disregarded multiple cancers and cancers detected incidentally at autopsy, both in the cohort and in the expected rates. The first year of observation following the first test was excluded in order to reduce screening bias. Confidence intervals of SIR were calculated assuming that the observed number of events followed a Poisson distribution (45).

Results

Tables 2 and 3 provide summary information on the results of the study. The number of observed cases of total cancer was normal in the Total-IgE-tested patients SIR: 0.98 (95% CI: 0.92–1.04) as well as in the Phadiatop-tested patients SIR: 0.99 (95% CI: 0.92–1.06). This finding was independent of the level of Total-IgE (normal, slightly or highly elevated), Phadiatop result (positive or negative), sex and age at first testing.

The same SIR analysis was carried out also for the following specific cancers: lung, cervix, pancreas, lymphoma and nonmelanoma skin cancer. None of these forms of cancer had increased or decreased risks.

We also performed a separate analysis of the follow up during childhood, i.e. up to 14 years of age. Fifteen cancer cases were observed, SIR: 1.42 (95% CI: 0.79–2.34). Eleven of these cases were observed among those

Table 1. Total-IgE (definitions)

Age of patients	IgE range (kU/l)		
	Normal	Slightly elevated	Highly elevated
>20 years	<122	122–500	>500
6–20 years	<263	263–500	>500
10 months to 5 years	<22.3	22.3–200	>200
3–9 months	<16.3	16.3–100	>100
6–12 weeks	<4.9	6–100	>100
<6 weeks	<1.3	1.3–100	>100

Total-IgE, total serum immunoglobulin E.

Table 2. Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) of total cancers amongst 70 136 total-IgE-tested patients according to age, sex and level of IgE

	Observed	SIR	95% CI
Total cancers	1158	0.98	0.92–1.04
Females	735	0.97	0.90–1.04
Males	423	1.00	0.90–1.10
Age (year)			
0–19	27	1.08	0.71–1.57
20–39	125	0.76	0.64–0.91
40–59	584	1.00	0.92–1.08
>60	422	1.03	0.94–1.13
IgE			
Normal	923	0.98	0.92–1.04
Slightly elevated	173	0.95	0.82–1.11
Highly elevated	62	1.07	0.82–1.37

Total-IgE, total serum immunoglobulin E.

Table 3. Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) of total cancers amongst 57 815 Phadiatop-tested patients according to age, sex and positive or negative test

	Observed	SIR	95% CI
Total cancers	757	0.99	0.92–1.06
Females	488	0.99	0.91–1.08
Males	269	0.99	0.87–1.11
Age (year)			
0–19	19	1.36	0.82–2.12
20–39	86	0.88	0.70–1.09
40–59	346	0.95	0.85–1.05
>60	306	1.07	0.95–1.19
Phadiatop			
Negative	601	1.00	0.92–1.08
Positive	156	0.97	0.82–1.14

with elevated Total-IgE and/or positive Phadiatop, SIR: 2.62 (95% CI: 1.31–4.69). Six of these 11 cases were brain cancers. The negative cohort showed no elevated cancer risk, SIR: 0.63 (95% CI: 0.17–1.61).

Discussion

Evaluation of the relationship between allergy and cancer on the basis of prior studies is difficult because of differences in definition of allergy, specific types of cancers studied, and methodological limitations. The nature of this relationship has therefore been controversial since the reporting started in the 1960s.

Recently, the development of cancer in immunosuppressed patients, suggesting a direct relation between the immune system and malignancies, has reactivated our interest in this area (46, 47).

In this, to our knowledge the largest study so far, we have been able to a more precise quantification of risks of cancer of the patients in general, but also in separate analyses of several anatomic sites and different age groups. Furthermore, in contrast to previous studies, the present study was based on consecutive patients tested for Total-IgE and Phadiatop in order to diagnosing allergic disease, and different levels of Total-IgE (normal/slightly elevated/highly elevated) enabled us to perform a trend analysis.

At present, no single laboratory test can define a patient being an allergic individual. Rather, the diagnosis usually is based on accumulated evidence of the patient's history and *in vivo* and *in vitro* diagnostic procedures. Many studies have shown that Total-IgE concentrations tend to be higher in allergic compared with nonallergic individuals, but the diagnostic value of Total-IgE, as a single test, is considered to be limited. There are difficulties in defining normal limits (48), because Total-IgE levels vary widely. A number of nonallergic factors affect Total-IgE, i.e. infection, parasites, renal and liver disease, and IgE myeloma.

In contrast to the limited specificity of Total-IgE in diagnosing allergic disease, the detection and titration of allergen-specific IgE determined by the Phadiatop test is of great clinical importance. In a study comparing the results of Phadiatop testing with the clinical diagnosis of atopy in patients with rhinoconjunctivitis and asthma, a specificity of 0.91–0.94 and a sensitivity of 0.89–0.96 was found for the test (49).

Our study did not support the reported decreased risk of cancer in allergic patients, nor did it support an increased risk. The overall risk of cancer was not elevated in the Total-IgE or in the Phadiatop-cohort, independent of the level of Total-IgE or negative/positive Phadiatop. However, we had no information on the patients symptoms or allergic disease diagnoses. Therefore, we found no association between atopy rather than allergy and the risk of cancer. There are some literature data, which suggest that this different approach may be important for the final conclusions (37).

Epidemiological studies are subject to many biases and are often difficult to interpret. In multiple statistical tests, one can always expect some of the factors tested to show statistical significance.

Also many confounders must be considered when interpreting the available studies. In this study, we had no control of confounders such as smoking and alcohol consumption. Atopy is less frequent in smokers (50) and since smokers are at increased risk of, e.g. lung cancer, smoking may be a confounder. Thus, this study tends to underestimate a possible positive association between atopy and lung cancer. Similarly, alcohol consumption is associated with increased levels of Total-IgE (51) and may also be related to some cancers.

We also analysed several cancer sites previously reported to have an association with allergy either protective or with an increased risk. None of these sites: lung (15, 18, 33, 36, 40), cervix (15, 32), pancreas (25) and lymphoma (14, 35, 37) had an association with allergy in our study. Also, we found no increased risk for nonmelanoma skin cancer, which is in line with a recent study (42). The elevated risk of childhood cancer among those having a positive test, has to be interpreted with caution. First, it is a small number of observed cases and the finding may be due to chance. Secondly, there may be a potential for surveillance bias where children with a positive allergy test have earlier diagnoses. Thirdly, the power of this study is limited for childhood cancer and a second follow up of this database in 5 or 10 years would be important.

There are a number of explanations for the inconsistent and contradictory results reported in the literature; methodological issues include small numbers of patients, lack of adjustments for confounding (i.e. smoking and occupation) and selection bias. This study comprises a large number of patients with defined allergic disease in the form of a specific biological marker, IgE, measuring the degree of atopy in our patients. Furthermore, the follow up with regard to cancer is virtually complete

owing to the accurate registration in the Swedish Cancer Registry. By disregarding the cancers appearing the first year of follow up after test, we reduced much of the screening bias that can occur because patients with yet undetected subclinical cancer are more likely to be examined with different tests, i.e. Total-IgE or Phadiatop. The present study was not community based, but was based on consecutive patients allergy tested in a hospital laboratory. This may cause some selective effects. The cohorts probably comprised relatively more subjects with strong than weak allergy reactions, when compared with the general population in the catchment area. This is, however, not a problem, as it adds to the precision of the

study without compromising its validity. Moreover, comparison of cancer incidence were not made only with the general population, but also between subjects with and without positive Phadiatop test and with different levels of Total-IgE.

In conclusion, this study does not support the hypothesis that allergy has an impact on cancer development.

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