

Cancer incidence in 13811 patients skin tested for allergy

N. E. Eriksson*, Z. Mikoczy**, L. Hagmar**

* Lung and Allergy Clinic, Department of Medicine, County Hospital, Halmstad, Sweden

** Department of Occupational and Environmental Medicine, Lund University Hospital, Lund, Sweden

Abstract.

Aim. Several studies have shown a negative correlation between cancer and atopy-related diseases. There are also a few reports of a positive relationship. We wanted to further evaluate these relationships in a prospective study.

Subjects and methods. The incidence of malignant diseases among adult patients with atopy-related diseases (asthma, rhinitis, urticaria, eczema etc; n=13811), who had been skin prick tested in 1976-1999 was compared with the incidence in the general population. Expected cancer incidence from the date of skin prick testing up to 1999 was obtained from cause-, sex-, calendar-year-, and 5-year-age-group specific incidence rates for the county. These rates were calculated from cancer incidence and population counts obtained from the Swedish Cancer Register. The 95% confidence intervals (CIs) for cause-specific standardized incidence ratios (SIRs) were calculated. Skin prick tests were performed with *Dermatophagoides pteronyssinus*, horse, dog, cat, timothy, mugwort, birch, and *Cladosporium*. Patients having one or several positive skin prick test reactions ($\geq 2+$) were regarded as atopics.

Results. 119 cases of cancer occurred among 6224 atopic individuals (SIR 1.0) compared with 216 cases (SIR 0.94, CI 0.82-1.08) among 6358 non-atopics. There was a slight excess of Hodgkin's lymphoma cases among atopic men (SIR 4.03, 95% CI 1-10.3), and of non Hodgkin lymphoma cases among atopic women (SIR 4.52, 95% CI 1.23-11.6). However, a large number of comparisons were made which can have caused random findings.

Conclusions. The results showed no associations between atopy or allergic symptoms, and subsequent cancer risk, but supported the theory that type-I allergy is not related to cancer risk.

Key words. Allergy, asthma, allergic rhinitis, atopy-related diseases, cancer, malignancies, skin prick test.

Introduction

The results of the relationship between allergic conditions and cancer are contradictory. A negative relationship has been reported by several authors [1-6], whereas others have found no relationship at all [7, 8] and others still reported an increased risk of cancer in patients with allergic diseases [9-11].

The immune system is involved in cancers as well as in allergic diseases. The prevalence of some malignancies is increased in patients with depressed immunity [12]. According to the immune surveillance hypothesis, a hyperstimulated immune system in allergic patients might possibly detect and eliminate malignant cells and thus act protectively against cancers. Animal experiments suggest that IgE-mediated allergy can

inhibit tumour development (for a review, see [13]). On the other hand, it has been suggested that immune-stimulating conditions could increase the risk of cancer by chronic stimulation of cells inducing pro-oncogenic mutations. As an example, an increased risk of some malignancies has been reported in patients with autoimmune diseases [14]. The association between allergic conditions and cancer risk is in all probability complex and the risk of developing a neoplasm could depend both on the type of allergic condition and on the type of tumour.

In an earlier investigation we assessed the cancer incidence among 6593 adult subjects with asthma, allergic rhinitis or urticaria [15]. We found that the total cancer incidence did not differ from that of the general population. On the other hand there were small increases in breast cancer and malignant lymphomas in atopic patients. The cohort consisted of young patients and the

Table 1. Distribution of sex, age and clinical diagnoses with respect to outcome of skin prick testing (SPT) among 13,811 patients in the cohort.

SPT result	Females/ males	Median age at testing	Median age year 1999 ¹	Asthma	Rhinitis	Urticaria	Other diagnoses ²	Total
Non atopic	3958/2400	38	48	1955	3991	939	1737	6358
Intermediate	730/499	36	50	367	740	236	307	1229
Atopic	3150/3074	27	38	2482	5175	646	1116	6224
Total	7838/5973	32	43	4804	9906	1821	3160	13811

¹ End of follow-up period

² Mainly eczema

cancers were few. In the present investigation the same study design was used to further evaluate possible relationships between atopic diseases and cancer in a larger study group. The present study group comprised 13811 patients tested for atopy due to asthma, rhinitis, urticaria or eczema, including the 6593 individuals who participated in our previous study.

Material and methods

Cohort

The cohort consisted of a consecutive series of patients, 5 years of age or older, skin prick tested in 1976-1999 at the Lung and Allergy Clinic of County Hospital in Halmstad, Sweden. The number of residents in the catchment area is about 120000. Altogether, 14399 patients were examined but 98 were excluded as their unique 10-digit personal identification code could not be retrieved and another 317 were excluded because no information on their diagnosis was available in the medical records. Finally, 173 patients were excluded as they had been diagnosed with cancer before skin prick testing. Thus, the final cohort consisted of 13811 patients, 7838 of whom were women. The median age at skin prick testing was 32 years (10th percentile 18 and 90th percentile 57 years).

Skin prick tests and definition of atopy

Skin prick tests (SPT) were performed as a part of the routine work at the clinic with the following inhalant allergens: Dermatophagoides pteronyssinus, horse, dog, cat, timothy, mugwort, birch, and Cladosporium. During the years 1977-1979, 1:100 (w/v) extracts produced at Sahlgrenska Hospital, Gothenburg, Sweden, were used.

In 1980, 5000 PNU/ml Neohelisen (Allergopharma, Reinbeck, Germany) and in 1981-1999 biologically standardized Soluprick extracts (ALK, Copenhagen, Denmark) were used. The strength of the Soluprick extracts was 1 HEP (Histamine Equivalent Prick) in 1981-1982, 5 HEP in 1983-1985, 3 HEP in 1986-1987, and 10 HEP in 1988-1999. Test results were recorded according to the Nordic Guidelines [16]. An allergen-induced wheal of the same size as that induced by the positive control (histamine 1 g/l in 1977-1985, 3 g/l in 1986-1987, and 10 g/l in 1988-1999) was recorded as 3+ and a wheal half the size of 3 + was recorded as 2+. Subjects with a positive SPT ($\geq 2+$) with one or several of the allergens were defined as atopic. Those with completely negative SPT results for all allergens were defined as non-atopic, and those with intermediate test results (1+) constituted an intermediate group. In the cohort, 6220 patients were atopic, 1229 had intermediate results in the SPT, and 6358 were non-atopic.

Clinical diagnoses

The definitions of airway diseases were those used in clinical practice. Patients reporting symptoms such as dyspnoea or wheezing on exposure to allergens, unspecific irritants, or exercise, or showing reversible airway obstruction on spirometry, were regarded as having bronchial asthma. Patients with continuous or intermittent blockage of the nose, sneezing, running, or itching, or with symptoms of conjunctivitis not caused by infection, were regarded as having rhinitis. Patients having a history of chronic, acute, or recurrent attacks of itching with erythematous cutaneous elevations were regarded as having urticaria. The cohort, broken down by atopy and clinical diagnoses, is displayed in Table 1. Patients could be classified as having more than one disorder.

Follow up of cancer incidence

Vital status in the cohort was determined as of December, 31, 1999 (Table 2), that was the end of the follow-up period. Information on tumours (coded according to the International Classification of Diseases [ICD] 7th revision) diagnosed from 1976 to 1999 in the cohort was obtained from the Swedish National Cancer Registry. Date of skin prick test (SPT) was used as start of follow up, and dates of death, tumour diagnosis or emigration, whichever occurred first, were used as individual end points for follow up. The median age at the end of follow-up was 43 years (10th percentile 26 years, 90th percentile 67 years) and the median length of follow-up was 9.5 years (10th percentile 1.5 years, 90th percentile 20 years). Expected cancer was calculated

Table 2. Vital status as of December, 31, 1999 in a cohort of 13811 patients skin prick tested for allergy 1976-1999.

Vital status	N
Living in Sweden	13239
Dead	483
Emigrated	89
Total	13811

from cause-, sex-, calendar-year-, and 5-year- age-group-specific incidence rates for the county, obtained from the Swedish National Cancer Registry, by means of the SYDCAP cohort program. The 95 % confidence intervals (CI's) for cause-specific standardized cancer incidence ratios (SIRs) were calculated by treating the observed number as a Poisson variable, or a normal variable if the observed value was greater than 10.

Results

The overall SIR for the 13811 subjects was close to unity (Table 3). There were 401 incident cases of cancer observed compared to 408 expected cases, which yielded a SIR of 0.98 (95% CI 0.89-1.08). There was no obvious discrepancy in overall cancer incidence with respect to atopy test result. Moreover, in none of the sub-cohorts the incidence of specific malignant neoplasms differed from unity. However, when performing gender-stratified analyses, an increased incidence of Hodgkin's lymphoma, based on four cases, was observed among atopic men (SIR 4.03, 95% CI 1.00-10.3) and an increased incidence of non-Hodgkin's lymphoma (NHL), also based on four cases, was observed among atopic women (SIR 4.52, 95 % CI 1.23-11.6).

Among women with asthma or rhinitis, the incidence of acute myeloid leukemia (AML) was increased (five cases, SIR 4.38, 95% CI 1.42-10.2), but the risk increase was seen only among non-atopic women (four cases SIR 7.31, 95% CI 1.99-18.7). Among men with rhinitis, the incidence of rectal cancer was increased (12 cases, SIR 2.19, 95 % CI 1.11-3.82), but the risk increase was observed only among non-atopic subjects (seven cases, SIR 2.49, 95% CI 1.00-5.14). Finally, the risk excess for malignant melanoma was restricted to women with urticaria (6 cases, SIR 2.78, 95 % CI 1.02-6.05), but the risk increase was again observed only among non-atopic subjects or subjects with intermediate atopy (six cases, SIR 3.80, 95% CI 1.39-8.27).

Discussion

The main finding of our study was that atopy did not predict overall cancer risk and there was no coherent risk pattern for specific neoplasms. Increased tumour risks related to clinical symptoms were observed only among subjects who had proved non-atopic at testing.

The present study was based on consecutive patients skin prick tested at an allergy clinic, which may have led to the cohort probably including relatively more subjects with strong allergic reactions, as compared with the total group of allergic subjects from the general population in the catchment area. This is, however, not a problem, but rather an advantage, as it adds to the precision of the study without compromising its validity. Neither is there any concern of a misclassification bias in the present study as the definition of atopy was based on a well-standardized SPT procedure and there was a complete follow-up against the Swedish Cancer Register, which has a very high diagnostic accuracy [17]. Approximately 97% of the cases are morphologically verified.

Unfortunately, no information on smoking habits was available for the subjects in the present cohort, but a Swedish cross-sectional study showed that in adults there is an association between current exposure to tobacco smoke and a low prevalence of atopic disorders [18]. The prevalence of allergic rhino-conjunctivitis was 25.1% among non-smokers and 12.8% among those who smoked at least 20 cigarettes per day. Thus, we cannot exclude that when comparing cancer incidence between atopic subjects in the cohort and the general population, there were a slight negative confounding for tobacco related tumours.

Despite the relatively large cohort, we still consider the main limitation of the study to be a lack of statistical power for assessing the association between atopy and rarely occurring tumours. Most of the examined subjects in the cohort are still young, and if atopy predicts cancer risk mainly occurring late in life, it may still be too early for a proper evaluation. Another aspect is that the present study design can give no clues to whether atopy may increase or decrease the risk of childhood cancers.

Table 3. Cancer incidence 1976-1999 in atopic, intermediate atopic and non-atopic patients. Obs=Number of observed cases, Exp=Number of expected cases, SIR=Standardized incidence ratio, 95% CI=95% confidence interval.

ICD-7	Cancer	Non-atopy (n=6358)					Intermediate atopy (n=1229)					Atopy (n=6224)				
		Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI	Obs	Exp	SIR
140-209	All types	216	229	0.94	0.82-1.08	66	60.3	1.09	0.85-1.39	119	119	1.00	0.83-1.20			
145-148	Pharynx	0	1.58	0.00	0.00-2.34	1	0.39	2.54	0.06-14.1	0	1.02	0.00	0.00-3.63			
151	Stomach	4	5.44	0.74	0.20-1.88	1	1.62	0.62	0.02-3.43	5	2.26	2.21	0.72-5.16			
153	Colon	13	16.1	0.81	0.43-1.38	7	4.50	1.56	0.63-3.21	5	7.04	0.71	0.23-1.66			
154	Rectum	12	11.0	1.09	0.56-1.91	4	2.85	1.40	0.38-3.59	6	5.40	1.11	0.41-2.42			
157	Pancreas	4	5.41	0.74	0.20-1.89	2	1.48	1.35	0.16-4.89	2	2.78	0.72	0.09-2.60			
161	Larynx	1	0.58	1.73	0.04-9.64	1	0.19	5.37	0.14-29.9	0	0.23	0.00	0.00-16.1			
162.0-162.1	Lung and trachea	15	16.7	0.90	0.50-1.49	1	4.20	0.24	0.01-1.33	5	7.91	0.63	0.21-1.47			
170	Breast	40	40.5	0.99	0.71-1.34	13	10.1	1.28	0.68-2.19	21	19.9	1.06	0.65-1.62			
172	Corpus uteri	8	9.34	0.86	0.37-1.69	1	2.34	0.43	0.01-2.38	3	3.85	0.78	0.16-2.27			
174	Uterus Unspecified	1	1.63	0.61	0.02-3.42	0	0.39	0.00	0.00-9.36	2	0.81	2.48	0.30-8.97			
175	Ovaric	9	9.60	0.94	0.43-1.78	4	2.40	1.66	0.45-4.26	4	4.94	0.81	0.22-2.07			
177	Prostate	21	18.2	1.15	0.71-1.76	3	5.20	0.58	0.12-1.68	7	6.40	1.09	0.44-2.25			
180	Kidney	5	4.85	1.03	0.33-2.41	2	1.28	1.56	0.19-5.64	0	3.04	0.00	0.00-1.21			
181	Bladder	6	8.27	0.73	0.27-1.58	5	2.24	2.24	0.73-5.22	2	3.62	0.55	0.07-1.99			

ICD-7	Cancer	Non-atopy (n=6358)			Intermediate atopy (n=1229)			Atopy (n=6224)					
		Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95% CI
190	Melanoma of skin	19	12.2	1.56	0.94-2.43	5	3.05	1.64	0.53-3.83	9	9.07	0.99	0.45-1.88
191	Other skin	10	6.51	1.54	0.74-2.82	1	1.91	0.52	0.01-2.91	3	2.33	1.29	0.27-3.76
193	Brain and other nervous system	7	9.22	0.76	0.31-1.56	1	2.30	0.43	0.01-2.42	6	6.22	0.96	0.35-2.10
194	Thyroid gland	2	1.38	1.45	0.18-5.25	1	0.37	2.69	0.07-15.0	2	1.16	1.73	0.21-6.25
195	Other endocrine	6	4.43	1.36	0.50-2.95	0	1.06	0.00	0.00-3.47	2	2.70	0.74	0.09-2.67
197	Connective tissue	0	2.06	0.00	0.00-1.79	0	0.53	0.00	0.00-6.90	0	1.40	0.00	0.00-2.64
200+202	Non-Hodgkin's lymphoma	7	6.40	1.09	0.44-2.25	1	1.75	0.57	0.01-3.19	6	3.36	1.78	0.66-3.88
201	Hodgkin's disease	1	1.37	0.73	0.02-4.07	0	0.37	0.00	0.00-10.1	4	1.47	2.73	0.74-6.99
203	Multiple myeloma	2	2.82	0.71	0.09-2.56	1	0.79	1.26	0.03-7.04	2	1.00	2.00	0.24-7.21
204.0	Acute lymphatic leukemia	0	0.11	0.00	0.00-34.6	0	0.03	0.00	0.00-114	1	0.12	8.05	0.20-44.8
205.0	Acute myeloid leukemia	4	1.39	2.88	0.78-7.37	1	0.35	2.83	0.07-15.8	1	0.89	1.12	0.03-6.23
205.1	Chronic myeloid leukemia	0	0.39	0.00	0.00-9.45	1	0.14	7.17	0.18-40.0	0	0.15	0.00	0.00-25.0

The present finding of a near uniform risk for overall cancer, corroborating the finding in our previous less informative study [15], supports previous observations that there may be no relationship between atopy or allergic conditions and overall cancer risk [7, 8], and speaks against both increased [9-11] and decreased [1-6] cancer risks previously observed.

Results from our previous cohort study indicated atopy to be a risk factor for breast cancer in women, based on 7 incident cases [15]. The present results, based on 21 incident cases, give no support at all to such a risk increase. It should be noted that there is an overlap between the two studies; all patients from the previous study are also included in the present one, containing a much larger number of cases. The previous study indicated that there was an about four-fold risk increase for all malignant lymphomas among atopic subjects [15]. This was of some interest because e.g. NHL is associated with immune deficiency [12] as well as with autoimmune diseases [14]. Significant NHL subtype-specific associations for allergies to insects (immunoblastic) and chemicals (diffuse and small cell lymphocytic) has been reported [19], but on the other hand also an association between allergy to plants, bee and wasp stings and a decreased risk of NHL [20]. Moreover, no association at all was found between allergic symptoms and NHL in some studies [21-23]. To a certain extent, the risk pattern for malignant lymphomas remains in the present study, but the risk increase for NHL was only seen among atopic women and the risk increase for Hodgkin's lymphomas was only seen among atopic men. We have no biologically based explanation for this gender-specific risk pattern. This inconsistency illustrates that we have made a large number of statistical analyses in the study base and that some of the results may therefore be caused by simultaneous inference and represent random findings.

In conclusion, in a large prospective cohort study of patients tested for allergy, we have not seen any convincing associations between atopy or allergic symptoms, and subsequent cancer risk. In contrast to both the immune surveillance hypothesis and the antigenic stimulation hypothesis, our results add support to the idea that type-I allergy is not related to cancer risk.

Acknowledgments

The study was supported by the County of Halland and The Swedish Cancer and Allergy Fund

References

1. Johnson K.J. The relation of cancer to allergy. *Lancet* 1966; 86: 5-11.
2. Allegra J., Lipton A., Harvey H., Luderer J., Brenner D., Mortel R., Demers L., Gillin M., White D., Trautlein J. Decreased prevalence of immediate hypersensitivity (atopy) in a cancer population. *Cancer Res* 1976; 36: 3225-6.

3. Cockcroft D.W., Klein G.J., Donevan R.E., Copland G.M. Is there a negative correlation between malignancy and respiratory atopy? *Ann Allergy* 1979; 43: 345-7.
4. Vena J.E., Bona J.R., Byers T.E., Middleton E., Jr., Swanson M.K., Graham S. Allergy-related diseases and cancer: an inverse association. *Am J Epidemiol* 1985; 122: 66-74.
5. Källén B., Gunnarskog J., Conradson T.B. Cancer risk in asthmatic subjects selected from hospital discharge registry. *Eur Respir J* 1993; 6: 694-7.
6. Petroianu A., Chaves D.N., De Oliveira O., Jr. Comparative incidence of allergy in the presence or absence of cancer. *J Int Med Res* 1995; 23: 358-63.
7. Hughes W.F., Raitz R.L. A comparison of cancer occurrence in allergic and nonallergic populations. *Ann Allergy* 1979; 43: 163-4.
8. Shapiro S., Heinonen O.P., Siskind V. Cancer and allergy. *Cancer* 1971; 28: 396-400.
9. Robinette C.D., Fraumeni J.F., Jr. Asthma and subsequent mortality in World War II veterans. *J Chronic Dis* 1978; 31: 619-24.
10. Mills P.K., Beeson W.L., Fraser G.E., Phillips R.L. Allergy and cancer: organ site-specific results from the Adventist Health Study. *Am J Epidemiol* 1992; 136: 287-95.
11. McWhorter W.P. Allergy and risk of cancer. A prospective study using NHANESI followup data. *Cancer* 1988; 62: 451-5.
12. Penn I. Depressed immunity and the development of cancer. *Cancer Detect Prev* 1994; 18: 241-52.
13. Jui S., Zhang Y.H. On the relationship between type I hypersensitivity and cancer: a review. *Asian Pac J Allergy Immunol* 1990; 8: 61-4.
14. Kinlen L.J. Malignancy in autoimmune diseases. *J Autoimmun* 1992; 5 Suppl A: 363-71.
15. Eriksson N.E., Holmen A., Högstedt B., Mikoczy Z., Hagmar L. A prospective study of cancer incidence in a cohort examined for allergy. *Allergy* 1995; 50: 718-22.
16. Aas K., Belin L. Standardization of diagnostic work in allergy. *Int Arch Allergy Appl Immunol* 1973; 45: 57-60.
17. Mattson B., Wallgren A. Completeness of the Swedish Cancer Register. Non-notified cancer cases recorded on death certificates in 1978. *Acta Radiol Oncol* 1984; 23: 305-13.
18. Hjern A., Hedberg A., Haglund B., Rosen M. Does tobacco smoke prevent atopic disorders? A study of two generations of Swedish residents. *Clin Exp Allergy* 2001; 31: 908-14.
19. Briggs N.C., Levine R.S., Brann E.A. Allergies and risk of non-Hodgkin's lymphoma by subtype. *Cancer Epidemiol Biomarkers Prev* 2002; 11: 401-7.
20. Holly E.A., Lele C., Bracci P.M., McGrath M.S. Case-control study of non-Hodgkin's lymphoma among women and heterosexual men in the San Francisco Bay Area, California. *Am J Epidemiol* 1999; 150: 375-89.
21. Franceschi S., Serraino D., Bidoli E., Talamini R., Tirelli U., Carbone A., La Vecchia C. The epidemiology of non-Hodgkin's lymphoma in the north-east of Italy: a hospital-based case-control study. *Leuk Res* 1989; 13: 465-72.
22. La Vecchia C., Negri E., Franceschi S. Medical history and the risk of non-Hodgkin's lymphomas. *Cancer Epidemiol Biomarkers Prev* 1992; 1: 533-6.
23. Doody M.M., Linet M.S., Glass A.G., Friedman G.D., Pottern L.M., Boice J.D., Jr., Fraumeni J.F., Jr. Leukemia, lymphoma, and multiple myeloma following selected medical conditions. *Cancer Causes Control* 1992; 3: 449-56.

Dr. Nils E. Eriksson

Gaggegatan 17b - SE-30237 Halmstad
E-mail: eriksson.035129150@telia.com
Fax: +46 35 130397