

Incidence of Cancer Among Patients With Atopic Dermatitis

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Objective: To assess the risk of skin cancer and other cancers among patients with atopic dermatitis.

Design: Register-based retrospective cohort study.

Setting: Sweden.

Patients: A total of 15 666 hospitalized patients identified in the national Inpatient Register as having discharge diagnoses of atopic dermatitis between January 1, 1965, and December 31, 1999.

Interventions: The National Swedish Cancer Register coded malignant neoplasms during the entire period of study. Follow-up time was calculated from the date of entry in the cohort until the occurrence of a first cancer diagnosis, emigration, death, or the end of the observation period, whichever occurred first.

Main Outcome Measures: Follow-up by means of record linkages to several nationwide registers, among them the National Swedish Cancer Register. Standardized incidence ratios (SIRs) (the ratios of numbers of observed patients with cancer to expected numbers of incident cases of cancer) estimated the risk of developing cancer rela-

tive to the risks in the age-, sex-, and calendar year-matched general Swedish population.

Results: After excluding the first year of follow-up, the risk of developing any cancer was increased by 13% (95% confidence interval [CI] of SIR, 1.01-1.25, based on 311 observed patients with cancer). Excess risks were observed for cancers of the esophagus (SIR, 3.5; 95% CI, 1.3-7.7; 6 patients), pancreas (SIR, 1.9; 95% CI, 1.0-3.4; 11 patients), brain (SIR, 1.6; 95% CI, 1.1-2.4; 27 patients), and lung (SIR, 2.0; 95% CI, 1.3-2.8; 31 patients) and for lymphoma (SIR, 2.0; 95% CI, 1.4-2.9; 29 patients). There was a nonsignificant 50% excess risk for nonmelanoma skin cancer (SIR, 1.5; 95% CI, 0.8-2.6; 12 patients), seemingly confined to men and to the first 10 years of follow-up. Malignant melanoma did not occur more often than expected.

Conclusions: The observed risk elevations, all of borderline statistical significance, should be interpreted cautiously. We could not control for possible confounding by cases of cancer caused by smoking, and the combination of multiple significance testing and few observed patients may have generated chance findings.

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ATOPIC DERMATITIS (AD) IS A common, often chronic, inflammatory disease that causes itching and affects widespread areas of the skin. Several immunological aberrations, both humoral and cellular, are found in patients with AD.¹ Nonetheless, the pathogenesis is not fully understood.¹ Also, many of the treatments for the disease affect the immunosurveillance of the skin, which might conceivably increase the risk for skin cancer, although this has not been confirmed.² On theoretical grounds, the risk caused by treatment is considered to be small, at least for treatment by UV-B,³ but firm epidemiological data are lacking. In a recent case-control study that used a mailed survey, patients with a history of AD did not seem more at risk to develop nonmelanoma skin cancers than patients with other dermatologic conditions.⁴ A few case reports have described patients who developed cutaneous lymphoma after having

long-standing disease.^{5,6} In an attempt to assess the risk of developing skin cancer for patients with AD, we performed a retrospective cohort study of patients hospitalized for AD in Sweden from 1965 to 1999. The risk of developing cancers other than skin cancer was also investigated because an impaired immune system, microbial infections or colonizations, a long-standing inflammation, or treatments for these conditions might conceivably increase the risk of malignant transformation in organs other than the skin. The patients were observed for up to 31 years to assess subsequent risks for cancer.

METHODS

STUDY COHORT

In 1964-1965, Sweden's National Board of Health and Welfare began to collect data on individual hospital discharges in a national register, called the Inpatient Register.⁷ This register attained complete nationwide coverage in

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Table 1. Characteristics of the Cohort of Patients Hospitalized for Atopic Dermatitis From 1965 to 1999 in Sweden

Characteristic	Female (n = 8031)	Male (n = 7635)	Total (N = 15 666)
Age at entry into study, y			
Mean age	18.5	12.7	15.7
0-1	1370	2442	3812
2-9	2085	2429	4514
10-19	1459	890	2349
20-39	2062	1159	3221
40-59	655	410	1065
≥60	400	305	705
Calendar year at entry, mean	1983	1983	1983
Years of follow-up, mean	15.6	15.2	15.4
Person-years at risk*	117 480	108 916	226 396
No. of cancers*	190	141	331
Average age at diagnosis of cancer, y	53.0	54.9	53.8
Some groups of codiagnosis			
Lung disease	1883	2512	4395
Other skin disease	2087	2075	4162
Infectious disease	1878	1997	3875

*Person-years and cancers accrued during first year of follow-up were excluded.

1987. Each record—corresponding to 1 hospitalization—contains the patient's National Registration Number (NRN) (a unique personal identifier assigned to all Swedish residents) and administrative and medical data such as hospital department and discharge diagnoses. The diagnoses are coded according to the *International Classification of Diseases (ICD), Seventh Revision (ICD-7)*, through 1968; the *Eighth Revision (ICD-8)* through 1987; the *Ninth Revision (ICD-9)* through 1996; and the *Tenth Revision (ICD-10)* thereafter.

All patients recorded in the Inpatient Register with a discharge diagnosis of AD (ICD-7 code 244.99; ICD-8 code 691.00; ICD-9 code 691W; and ICD-10 codes L20.0, L20.8, and L20.9) were initially selected for inclusion in the study. A total of 16 381 unique NRNs were registered at least once with this diagnosis between 1965 and 1999.

The NRNs are used for individual identity in all health registers in Sweden, and they are thus critical identifiers in all record linkages. To remove records with incorrect NRNs, which would otherwise add unnecessary time for follow-up of individuals who are at no risk of cancer or death, we linked the cohort file to computerized nationwide registers of the total population, deaths, and emigrations.^{8,9} If an NRN could not be found in any of these registers, we concluded that it did not correspond to an existing person. Accordingly, we excluded 463 records from the cohort. Because we counted only first cancers, we excluded 137 patients with cancers diagnosed prior to cohort entry and 115 patients with inconsistencies uncovered during the subsequent record linkages. Thus, a total of 15 666 patients—8031 female and 7635 male—were entered into the study cohort, which is described in **Table 1**. The most common non-AD diagnoses were also registered.

FOLLOW-UP

Record linkage of the study cohort to the registers of cancer, deaths, and emigration provided follow-up information through 1999. The general method has been described in detail previ-

ously.¹⁰ The National Swedish Cancer Register, in operation since 1958 and close to 98% complete,¹¹ coded malignant neoplasms according to the ICD-7 classification during the entire period of study. Follow-up time (in person-years) was calculated from the date of entry into the cohort (date a patient was first discharged from a hospital with a diagnosis of AD) until a first primary cancer diagnosis, emigration, death, or the end of the observation period (December 31, 1999), whichever occurred first. To avoid possible ascertainment bias associated with different autopsy rates of the cohort members and the general population, we did not count cancers found incidentally at autopsy in the cohort rate or in the population rate.

STATISTICAL ANALYSIS

The relative risk of cancer was estimated by the standardized incidence ratio (SIR), defined as the ratio of the observed number of patients with cancer to the expected number of patients with cancer. The expected number of patients with cancer was calculated by multiplying the number of observed person-years, divided into age- (in 5-year groups), sex-, and calendar year-specific strata, by the corresponding cancer incidence rates. These incidence rates, derived from the relevant strata in the entire Swedish population and aggregated in 5-year periods to avoid instability in rates of rare cancers, were calculated by dividing the number of first primary cancers, excluding those discovered incidentally at autopsy, by person-years at risk (the mid-year population of individuals without any previously reported cancer). The 95% confidence interval (CI) of the SIR was calculated on the assumption that the observed numbers follow a Poisson distribution.¹² For selected cancer sites, stratified analyses were also performed to detect differences in risk pattern across sex and length of follow-up. An approximate χ^2 test was used to evaluate the difference between 2 SIRs.¹³ Stratified analyses by age at entry in cohort, year of discharge from hospital, comorbidity, and type of hospital department that gave the diagnosis of AD (dermatology department vs others) was not completed because of small numbers of patients. In our main analyses, we excluded cancers and person-years accumulated during the first year of follow-up to minimize the possible impact of selection bias. Such bias occurs because patients with AD and subclinical cancers are more likely to be hospitalized than those without such cancers, and therefore these cancers are most likely to be diagnosed within the first year of follow-up.

This study was approved by the ethics committee of Karolinska University Hospital Huddinge, Stockholm, Sweden.

RESULTS

On average, patients with AD were followed up for 15.4 years, yielding 241 867 accumulated patient-years at risk, 15 471 of which were during the first year. After excluding this first year of observation, during which 1 case of squamous cell carcinoma of the skin occurred, we ascertained a total of 331 cases of cancer (190 in women, 141 in men). The average age at diagnosis of cancer was 53.0 years for women and 54.9 years for men (Table 1). The incidence of any cancer (all sites) was increased by 13% (95% CI, 1%-25%), compared with the age- and sex-matched general Swedish population (**Table 2**).

The estimated relative risks for cancer sites with at least 6 observed patients are listed in Table 2. There was a statistically nonsignificant risk elevation for nonmelanoma skin cancer (SIR, 1.5; 95% CI, 0.8-2.6; 12 patients) but a decreased risk for melanoma (SIR, 0.6; 95%

Table 2. Standardized Incidence Ratio (SIR) and 95% Confidence Interval (CI) for Major Cancer Types Among Patients Hospitalized for Atopic Dermatitis From 1965 to 1999 in Sweden*

Cancer Type	ICD-7 Code	No. of Patients Observed	SIR (95% CI)
All-site	140-209	331	1.13 (1.01-1.25)
Sex†			
Male		141	1.30 (1.10-1.54)
Female		190	1.02 (0.88-1.88)
Length of follow-up, y‡			
1-9		149	1.19 (1.01-1.40)
≥10		182	1.08 (0.93-1.24)
Cancers of the skin			
Nonmelanoma	191	12	1.5 (0.8-2.6)
Sex§			
Male		8	2.0 (0.9-4.0)
Female		3	1.0 (0.3-2.5)
Length of follow-up, y‡			
1-9		7	2.0 (0.8-4.1)
≥10		5	1.0 (0.4-2.6)
Melanoma‡	190	10	0.6 (0.3-1.2)
Cancers other than skin			
Buccal	140-148	9	1.7 (0.8-3.2)
Esophagus	150	6	3.5 (1.3-7.7)
Sex§			
Male		3	2.8 (0.6-8.1)
Female		3	4.9 (1.0-14.3)
Length of follow-up, y‡			
1-9		3	4.0 (0.8-11.7)
≥10		3	3.2 (0.7-9.2)
Stomach	151	9	1.1 (0.5-2.1)
Colon	153	13	0.7 (0.4-1.3)
Rectum	154	10	1.0 (0.5-1.8)
Pancreas	157	11	1.9 (1.0-3.4)
Liver, biliary	155	6	1.2 (0.4-2.6)
Lung	162, 163	31	2.0 (1.3-2.8)
Sex§			
Male		15	1.8 (1.0-2.9)
Female		16	2.2 (1.3-3.6)
Length of follow-up, y‡			
1-9		14	2.1 (1.2-3.6)
≥10		17	1.9 (1.1-3.0)
Breast	170	44	0.8 (0.6-1.1)
Cervix	171	10	1.1 (0.5-2.0)
Endometrial	172	10	1.2 (0.6-2.1)
Prostate	177	19	0.9 (0.6-1.5)
Kidney	180	11	1.6 (0.8-2.9)
Brain	193	27	1.6 (1.1-2.4)
Sex§			
Men		11	1.5 (0.7-2.7)
Women		16	1.7 (1.0-2.8)
Length of follow-up, y‡			
1-9		14	1.8 (1.0-3.0)
≥10		13	1.5 (0.8-2.5)
Lymphoma	200-202	29	2.0 (1.4-2.9)
Sex§			
Male		17	2.4 (1.4-3.8)
Female		12	1.7 (0.9-3.0)
Length of follow-up, y‡			
1-9		20	3.3 (2.0-5.1)
≥10		9	1.1 (0.5-2.1)
Leukemia	204-205	6	0.6 (0.2-1.3)

Abbreviation: ICD-7, *International Classification of Diseases, Seventh Revision*.

*Data exclude the first year of follow-up; selected cancer types are stratified by sex and length of follow-up.

† $P < .05$.

‡ P value for trend not significant.

§ P value was not significant.

||Person-years and cancers accrued during the first year of entry were excluded. An approximate χ^2 test was used to evaluate the difference between 2 SIRs. In cancer types where the total number was less than 10, no stratified analyses were made.

CI, 0.3-1.2; 10 patients). Increased risks were noted for cancer of the esophagus (SIR, 3.5; 95% CI, 1.3-7.7; 6 patients), lung (SIR, 2.0; 95% CI, 1.3-2.8; 31 patients), and brain (SIR, 1.6; 95% CI, 1.1-2.4; 27 patients) and for lymphoma (SIR, 2.0; 95% CI, 1.4-2.9; 29 patients). A 1.9-fold excess risk of pancreatic cancer was of borderline statistical significance.

COMMENT

To our knowledge, this is the first large-scale follow-up study of patients with AD with cancer as the outcome. There was a statistically significant 13% overall excess risk, driven mainly by excesses of lung and brain cancers and lymphoma. Risk elevations were noted also for esophageal and pancreatic cancers. We also observed a 2-fold elevation of risk for nonmelanoma skin cancer 1 to 35 years after entry into the study among men but not among women and only during the first 10 years of follow-up. With only 12 observed patients with nonmelanoma skin cancer, however, both the overall excess and the sex difference could be a chance finding. Our findings are in contrast with those of a recent case-control study⁴ that used a mailed survey and found that 254 patients with a history of AD did not seem to develop nonmelanoma skin cancers more often than patients with other dermatologic conditions.

Skin tumors, in contrast to tumors of internal organs, are readily observable. For example, prevalent but undiagnosed skin tumors may be detected in connection with hospital care for AD. However, neither patients with basal cell carcinoma nor those with actinic keratosis are reported in the National Swedish Cancer Register. Thus, the nonmelanoma skin cancer category includes only patients with squamous cell carcinoma and not those with squamous intraepidermal neoplasia or Bowen disease. If a skin tumor was diagnosed during the first hospitalization and recorded in the Inpatient Register, the affected patient would not be included in our cohort. Consequently, our cohort members had, in effect, been screened for skin tumors before inclusion. Therefore, the rate of skin tumors diagnosed during the ensuing years was probably somewhat lower than in an unscreened population, at least in the older age groups (10 years or older) in whom skin tumors are not exceedingly rare. This hypothetical incidence deficit is expected to be balanced by a bias toward increased detection during follow-up as a result of closer dermatological surveillance linked to the presence of any chronic skin disorder. As the initial screening effect wears off, the presumed detection bias will dominate the findings. The net effect on overall skin cancer risk is difficult to predict, but because the cohort, as it is aging, is slowly moving from lower to higher absolute risk, any bias will have greater impact during the last years of follow-up. Hence, it is likely that overestimation of the incidence resulting from detection bias will dominate. The shift from underestimation (resulting from initial screening) to overestimation (resulting from detection bias during follow-up) is expected to lead to spurious impressions of an increasing relative risk over the follow-up period. Al-

though the small numbers of patients observed hamper the interpretation of our data, the observed decrease in relative risk with increasing follow-up time is probably not the effect of screening or detection bias. Instead, it creates skepticism about the biological relevance of the nonsignificant 50% overall excess risk of nonmelanoma skin cancer in our cohort, seemingly confined to the first 9 years of follow-up.

Because no laboratory marker for AD exists, the diagnosis is based on major and minor clinical criteria, of which the major features are pruritus, typical morphologic traits and distribution of the lesions, chronic relapsing course, and personal and family history of atopic disease (asthma, hay fever, or AD).¹⁴ The pathogenesis is not fully understood, but several immunological aberrations are found in AD, including impaired cellular mediated immunity, elevated serum IgE and eosinophil levels, and IgE-bearing Langerhans cells.¹ Furthermore, colonization of the more-or-less chronically inflamed lesions by microbes—most important, the yeast *Malassezia* (formerly *Pityrosporum*) *orbiculare* and the bacterium *Staphylococcus aureus*—may contribute to the perpetuation of the lesions. Chronic inflammation and microbial colonization or infection in combination with the immune impairments (primary infection or adverse effects of treatment) may lead to proliferative epidermal changes; hence, the suspicion of a link to cancer development. Both sexes are affected by AD; among adults, more women than men have the disease.¹⁵ However, among children 12 years or younger, more boys have it than girls. The reason for this sex difference is unclear. Because in Sweden the onset of AD begins, on average, earlier among men than among women, the duration of the chronic disease at any given age has generally been longer in men.¹⁶ In children, it also seems as if boys have a more severe disease than girls.¹⁶ Therefore, it is not inconceivable that there might be sex differences in risks of adverse long-term consequences of the disease.

The atopic disease triad consists of hay fever, asthma, and AD. Over the life span, an individual with atopic disease may suffer from 1, 2, or all 3 of the manifestations. The connection between AD and lung disease was also manifested in our cohort, where lung disease (mainly asthma) was the most commonly found non-AD diagnosis, followed by other skin diseases and infectious diseases. Although little is known about associations between cancer and hay fever, patients with asthma seem to be at increased risk for lung cancer,¹⁷⁻²⁰ although contradicting results have been reported.²¹⁻²³ Because no risk elevations for esophageal cancer were observed in a cohort of hospitalized patients with asthma in a previous study,²⁴ the excess of this cancer among patients with AD in our study is unlikely to be an unspecific phenomenon linked to the need for hospitalization. Among other allergic manifestations investigated for cancer risks, positive epicutaneous tests were reportedly linked to an overall increased risk of cancer within 20 years of follow-up in men but not in women.²⁵ No risk elevations were found among 1155 patients with chronic urticaria observed for up to 27 years.²⁶

The excess of lung, esophageal, and pancreatic cancers in our cohort is consistent with confounding by smok-

ing and alcohol consumption. We have no information about these habits among our cohort members. According to epidemiological data, cigarette smoking seems to be associated with many skin diseases, as reported previously.²⁷ Although smoking is believed to trigger or worsen AD,²⁸ Mills et al²⁹ found no significant difference in smoking habits of patients with AD and matched controls. Smoking and alcohol abuse may still have contributed to a biased selection in our cohort of hospitalized patients. Most patients with AD are treated on an outpatient basis, and those who are hospitalized may have less healthy lifestyles.

The major strength of our study is its internal validity; that is, its cohort design has no risk for recall bias, almost no patients lost to follow-up, and virtually complete cancer ascertainment. Our cohort comprised all hospitalized Swedish patients with AD, thus ensuring external validity in relation to all hospitalized patients. The relevance of our results for outpatients with AD is less obvious. The study's restriction to patients admitted to hospitals probably reduced misclassification of AD, in any case. Several limitations should also be noted in the interpretation of our findings. In addition to the possible selection biases associated with the need for hospitalization (more severe AD is associated with increased comorbidity), scarcity of information regarding potential confounding factors (notably smoking), and the possibility of detection bias, the small numbers of expected cases of some cancers in this cohort make the risk estimates highly sensitive to chance effects. Moreover, the most established criteria for a diagnosis of AD were published in 1980,¹⁴ 15 years after our cohort began to accrue. However, we assume that even before 1980 an experienced dermatologist or pediatrician easily diagnosed AD (such as Besnier prurigo [atopic dermatitis]). In this cohort, dermatologists made the diagnoses in 38% of the cases, and other physicians, most often pediatricians, made the diagnoses in 62% of the cases.

In conclusion, a slight excess of malignant neoplasms was noted among patients with AD. The greatest relative excesses were for cancers of the esophagus, lung, brain, and pancreas and lymphoma. Confounding by smoking and alcohol abuse, however, cannot be excluded. The risk elevations, all of which are of borderline statistical significance, should be interpreted with caution. The combination of multiple significance testing and few observed patients may have generated chance findings. Because (1) the cohort has a high proportion of young patients, who are not yet in the age groups most at risk for developing cancer, and (2) the frequency of occurrence of most types of cancer increases with age, future follow-ups of our cohort would be interesting. Furthermore, this study of a cohort of patients with AD may be of value for future independent evaluation of the relationship between skin cancer development and recent new treatment with 2 different topical calcineurin-inhibitor immunosuppressants.⁴

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