The Risk of Cancer Among Patients Previously Hospitalized for Atopic Dermatitis

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In treatment of severe atopic dermatitis, drugs with carcinogenic potentials are used to manage the disease. We therefore analyzed whether patients having severe atopic eczema had an increased cancer risk. The study population included all individuals hospitalized in Denmark with a primary diagnosis of atopic dermatitis during 1977–1996. Follow-up was conducted in 1996 in the Danish Cancer Register. A total of 6275 persons were included. Among 2030 adult patients, an increased risk of cancer was observed, standard morbidity ratio (SMR) = 1.5 (95% CI: 1.2–1.9). Half the excess cases of cancer was keratinocyte carcinomas of the skin diagnosed within the first 9 y of follow–up, SMR = 2.4 (95% CI: 1.4–3.9). For men, SMR = 2.7 (95%CI: 1.2–5.4). In conclusion, earlier hospitalized adult atopic dermatitis patients had an increased risk of cancer. Half the excess cases of cancer were keratinocyte carcinomas. This may be a result of a detection bias or due to the carcinogenic potentials of some of the therapies of severe atopic dermatitis.

Key words: atopic dermatitis/keratinocyte carcinomas/standard morbidity ratio
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Atopic dermatitis is a common chronic disease among children in industrialized countries (Olesen *et al*, 1997; Laughter *et al*, 2000; Mortz *et al*, 2001). The immune activation in atopic dermatitis has been intensively studied (Thestrup-Pedersen, 1997; Thestrup-Pedsersen *et al*, 1997; Vestergaard *et al*, 2000; Volke *et al*, 2000; Bang *et al*, 2001; Higashi *et al*, 2001; Ringer *et al*, 2001). Recently, it was observed that blood and skin-homing lymphocytes in adults with atopic dermatitis had telomere erosion together with increased telomerase activity of their T lymphocytes (Wu *et al*, 2000), findings that are known to be associated with almost 90% of all cancers of the hematopoietic system (Shay and Bacchetti, 1997) including cutaneous T cell lymphoma (Wu *et al*, 1999). Also, immunosuppressive therapies such as ultraviolet (UV) light therapy, tar, and cyclosporine, a calcineurin inhibitor immunosuppressant used for a variety of skin diseases including atopic dermatitis, may increase the risk of cancer (Stern *et al*, 1979; Stern and Laird, 1994; Marcil and Stern, 2001; Paul *et al*, 2003). We therefore asked if atopic dermatitis is associated with an increased risk of cancer later in life.

Results

The cohort consisted of 6275 persons eligible for follow-up for a first cancer. In this group, 4245 were children (<18 y of age) and 2030 were adults (Table I). Among the children, only four were found to later develop cancer (none skin cancers), whereas 9.2 cancers were expected. The reduced cancer prevalence among children with atopic dermatitis was not statistically significant. The cohort of children was therefore not analyzed further. The adults, 779 men and 1251 women, could be followed in the Cancer Register for 6908 and 11,559 y, respectively. Table I shows the adult atopic dermatitis cohort regarding gender, age, and diagnosis period.

Table II shows the results for observed *versus* expected cancers and the types of cancers. Persons previously admitted for atopic dermatitis had a significant increased risk of cancer development standard morbidity ratio (SMR) = 1.5 (95% CI: 1.2–1.9). Half of the excess cancers were skin cancer. We observed 16 skin cancer cases *versus* 6.6 expected, SMR = 2.4 (95% CI: 1.4–3.9). Eight men developed skin cancer *versus* 2.9 expected, SMR = 2.7 (95% CI: 1.2–5.4), whereas eight women developed skin cancer *versus* 3.7 expected, SMR = 2.2 (95% CI: 0.9–4.3). The increased risk for development of skin cancer was statistically significant 5–9 y after discharge, but decreased to an insignificant level thereafter (Table III). All skin cancers were biopsy-proven keratinocyte carcinomas. Table IV shows characteristics of these individuals. Among men, six cases of basal cell carcinomas and two cases of squamous cell carcinomas were found. Among women, seven cases of basal cell carcinomas and one case of squamous cell carcinoma were observed. No cases of melanoma were observed in the adult cohort *versus* 2.4 expected.

Neither men nor women had an increased risk of other cancers including lymphoma.

Abbreviation: SMR, standard morbidity ratio

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Table I. Demographic data for persons in the Danish atopic dermatitis (AD) cohort 1977–1996, 18 y or older at first hospitalization

	No. men (%) 779 (100.0)	No. women (%) 1251 (100.0)
Age at AD		
18–29	456 (58.5)	859 (68.7)
30–39	142 (18.2)	200 (16.0)
40–49	78 (10.0)	107 (8.6)
50–59	38 (4.9)	45 (3.6)
60–69	37 (4.7)	24 (1.9)
70+	28 (3.6)	16 (1.3)
Period of AD		
1977–1981	163 (20.9)	249 (19.9)
1982–1986	193 (24.8)	324 (25.9)
1987–1991	231 (29.7)	385 (30.8)
1992–1996	192 (24.6)	293 (23.4)

Discussion

The main finding of this study is that adults previously admitted to hospital with atopic dermatitis had an increased risk of cancer mostly ascribed to a significant increase of keratinocyte carcinomas among men diagnosed within 9 y after discharge of the hospital. No cases of malignant melanoma nor lymphomas were observed. Children admitted for atopic dermatitis had no increased risk of any cancer.

The risk of cancer among atopic dermatitis patients has not been intensively studied, but a recent case–control study has observed a lack of relationship between atopic dermatitis and non-melanoma skin cancer (Ming *et al*, 2004). This study was based on selecting both cases and controls among dermatological patients, and a direct comparison of the results is not possible. The increased risk of cancer among our population of patients hospitalized for atopic dermatitis is consistent with the observed increased risk of cancer among patients hospitalized for psoriasis in Sweden (Boffetta *et al*, 2001). The increased risk of cancer in patients with psoriasis, however, covered several malignancies, whereas the increase in keratinocyte carcinomas of the skin contributed to half of the excess number of cancers among atopic dermatitis patients in Denmark.

Table II. Number of observed and expected first cancers and standard morbidity ratio (SMR) with 95% confidence intervals in Danish adult atopic dermatitis cohort, 1977–1996

	Observed	Expected	SMR (95% CI)
All cancer	67	44.3	1.5 (1.2–1.9)
Digestive organs	7	6.4	1.1 (0.4–2.2)
Respiratory system	8	4.6	1.7 (0.7–3.4)
Breast cancer	10	6.9	1.4 (0.7–2.7)
Female genital organs	10	4.6	2.2 (1.0–4.0)
Male genital organs	6	2.6	2.3 (0.8–5.0)
Keratinocyte carcinomas	16	6.6	2.4 (1.4–3.9)
Lymphatic and hematopoitic tissue	4	2.9	1.4 (0.4–3.5)
Other cancer	6	9.7	0.6 (0.2–1.3)

Table III. Relative risk of keratinocyte carcinomas by follow-up time in the Danish cohort of adult atopic dermatitis patients, 1977–1996

Follow-up time (y)	Observed	Expected	Relative risk	95% CI
0–4	6	2.4	2.5	0.9–5.5
5–9	8	2.1	3.8	1.6–7.4
$\geq$ 10	2	2.1	0.9	0.1–3.4

The increased risk of keratinocyte carcinomas may have several explanations. One obvious reason is the carcinogenic potentials of a variety of different treatments that hospitalized patients with severe atopic dermatitis receive. The squamous cell carcinomas among our cases occurred on sites different from the normally sun-exposed areas of the body which indicate a causative role of earlier immunosuppressive therapy, i.e., UV light treatments and/or tar bath treatments that are frequently used in Denmark. Only one study has previously looked at risks for skin cancer among patients with atopic dermatitis treated with coal tar and UV light (Goeckerman therapy). The follow-up period for the 426 patients was 25 y, and no increase of skin cancer was observed compared with the background population (Maughan *et al*, 1980).

Psoriasis patients have been more intensively studied for development of skin cancer. Several studies have observed an increased risk of non-melanoma skin cancer, especially squamous cell carcinomas associated with the use of UV light and PUVA as therapeutic modalities, with an anatomical distribution different from the background population (Stern *et al*, 1979, 1998; Stern and Laird, 1994; Frentz *et al*, 1999; Frentz and Olsen, 1999; Hannuksela-Svahn *et al*, 2000; Marcil and Stern, 2001; Margolis *et al*, 2001). UV-light therapy is increasingly being used in patients with atopic dermatitis, but it has not been associated with increased risk of skin cancer (Jekler, 1992).

It is known from patients in immunosuppressive therapy with calcineurin-inhibitor immunosupressants following organ transplantation or as a treatment for psoriasis that skin cancer is a very common event, developing within 5–10 y after initiation of the therapy (Birkeland *et al*, 1995; Bouwes Bavinck *et al*, 1996; Ong *et al*, 1999; Winkelhorst *et al*, 2001; Paul *et al*, 2003). This demonstrates that immune surveillance mechanisms are important for resistance toward development of skin cancer. Studies among children and adults in immunosuppressive therapy following organ transplantation indicate that those developing skin cancers have a history of sun-damaged skin, meaning that the rise of skin cancer is a consequence of a carcinogenic impact followed

Table IV. Types of skin cancer and location in Danish adult atopic dermatitis patients

Patient	Gender	Age at cancer (y)	Time[a] (mo)	Diagnosis[b]	Tumor location
1	F	55	98	BCC	Trunk
2	F	45	50	BCC	Trunk
3	F	39	154	BCC	Lip
4	F	53	32	BCC	Lip
5	F	51	61	BCC	Face
6	F	49	194	BCC	Multiple sites
7	F	57	67	BCC	Multiple sites
8	M	59	102	BCC	Face
9	M	74	13	BCC	Face
10	M	60	77	BCC	Face
11	M	44	40	BCC	Face
12	M	49	118	BCC	Face
13	M	48	79	BCC	Face
14	F	53	3	SCC	Upper limb
15	M	60	88	SCC	Trunk
16	M	52	18	SCC	Multiple sites

[a]Time from admission to hospital with atopic dermatitis to diagnosis of skin cancer.
[b]Biopsy proven.
M, male; F, female; BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

by immunosuppression (Birkeland *et al*, 1995; Bouwes Bavinck *et al*, 1996; Ong *et al*, 1999; Winkelhorst *et al*, 2001).

The increased risk of keratinocyte carcinomas among the Danish adult patients hospitalized with atopic dermatitis may be due to the carcinogenic potential of immunosuppressive therapies that they have received over the years. But, we lack information on the treatments the individual patients in this cohort underwent.

Detection bias is another plausible explanation of the increased risk of non-melanoma skin cancer observed among atopic dermatitis patients. The skin of a patient with chronic relapsing atopic dermatitis is often examined by a phycisian trained in discovering skin cancer, which increases the chance of discovering cancer of the skin compared with individuals of the general population.

Diagnostic misclassification might be another problem. The Danish National Hospital register recieves information from the hospital departments and out-patient clinics every month (Andersen *et al*, 1999). We included the patients with a primary diagnosis of atopic dermatitis all hospitalized in dermatological or pediatric departments, and we therefore suspect that misclassification is a minor problem.

The results are not applicable to all atopic dermatitis patients as the majority of patients are not hospitalized because of their skin disease. In Denmark, admission to a hospital for atopic dermatitis is free of charge for the patient, but it can only take place after referral by a doctor. It is most likely that the adult patients with atopic dermatitis included in our study represent severe chronical cases, whereas hospitalization of infants and children with atopic dermatitis may have a variety of reasons like anxiety and compliance problems of the parents.

Two case reports have described non-Hodgkin lymphoma (Lange-Vejlsgaard *et al*, 1989), and Sézary's syndrome (Van Haselen *et al*, 1999) in patients with severe atopic dermatitis. Despite the findings that lymphocytes among this group of patients show telomere erosion (Wu *et al*, 2000), we found no increased risk for lymphoma.

The lack of melanoma among atopic dermatitis patients may be due to a chance finding; however, it is consistent with the finding by Birkeland *et al* (1995) on transplant patients and Broberg and Augustsson (2000), who observed significantly fewer nevi among atopic patients compared with non-atopic controls (Broberg and Augustsson, 2000). The mechanisms behind this observation are so far unknown.

In conclusion, adult atopic dermatitis patients had an increased risk of cancer. Half the excess cases of cancer were keratinocyte carcinomas diagnosed within 9 y of discharge from hospital. This may be due to the carcinogenic potentials of the therapies used for severe atopic dermatitis or to a detection bias. We plan to perform a comparative 10-y follow-up study of hospitalized adult atopic dermatitis patients, and suggest further studies of the cancer risk among atopic dermatitis patients, including detailed information on the clinical aspects of the disease and the treatments the individual underwent.

Subjects and Methods

Participants The study cohort consisted of all patients hospitalized at least once in Denmark between 1977 and 1996, inclusive of a primary diagnosis of atopic dermatitis. The patients were identified in the Danish National Hospital Register (Andersen *et al*,

1999) and followed up for cancer in the Danish Cancer Register (Storm *et al*, 1997), and for emigration, disappearance, and death in the Central Population Register (CPR) through 1996. Since April 1, 1968, all residents in Denmark have been assigned a unique personal identification number by CPR. Every branch of the public administration is obliged to use this number and it serves as an efficient key for linkage of data for the individual.

Trial registries: This study was approved by the Ethics Committee of the County of Aarhus, Lyseng Allé 1, DK-8000 Aarhus C, Denmark; Ref number: 2000-2.0/3 and by the Danish Data Protection Agency, Christians Brygge 28, 1559 Copenhagen V, Denmark; Ref number: 1999-1200-563.

The Danish National Hospital Register holds information on all discharges from Danish somatic hospitals from 1977 onward. Information includes identity of the patient by CPR number, date of discharge, primary diagnosis and supplementary diagnoses during the hospital stay, and identification of the department in the hospital (Andersen *et al*, 1999).

Since 1943, practically all cancer cases in Denmark have been notified in the Danish Cancer Register, and the register is considered to be 95%–98% complete (Storm *et al*, 1997).

A total of 10,398 admissions of 6563 individuals took place from 1977 to 1996, with the primary diagnosis of atopic dermatitis. The primary diagnosis indicates the cause of admission to the hospital, and the disease is diagnosed by specialists in Dermatology or Paediatrics. From 1977 to 1993, these patients were coded in the Danish National Hosptial Register according to the ICD-8 classification and according to the ICD-10 classification from 1994 onwards. Persons recorded with an invalid personal registration number or not living in Denmark were excluded, leaving 6305 persons to be followed up in the Danish Cancer Register. The observation period for cancer development for each patient started from the first admission with atopic dermatitis and the persons were followed to the first event of cancer, emigration, or death, on December 31, 1996. A total of 30 persons were already registered in the Cancer Register before their admission for atopic dermatitis and nine of these had skin cancer. These patients were omitted for further analysis. We restricted the detailed analysis to the adult cohort: 2030 persons aged 18 y or above at the first hospitalization with atopic dermatitis.

Statistical analysis For this cohort, the observed and the expected number of cancer cases were calculated, in addition to the ratio between the observed and the expected, hereafter called the SMR. The expected numbers of cancer cases were estimated by summing up the years under risk of cancer in the cohort and multiplying these with the incidence rates of cancer for the Danish population in 5-y age- and period-specific groups for each sex. Further analysis of the relative risk of keratinocyte carcinomas for the cohort compared with the risk in the Danish population used Poisson regression methods to analyze the SMR as a function of age, calendar period, and time since the first hospital diagnosis of atopic dermatitis, with the number of cases of keratinocyte carcinomas as the outcome and the logarithm of the expected number as the offset.

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