Psoriasis, its Treatment, and Cancer in a Cohort of Finnish Patients

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This study was designed to estimate the relative cancer risk of patients with moderate to severe psoriasis, with reference to different treatments. A cohort of 5687 hospitalized patients with psoriasis obtained from the Finnish Hospital Discharge Register in 1973–84 was linked with the records of the Finnish Cancer Registry. Standardized incidence ratios for cancer were calculated by dividing the observed number of cases by the expected cases, which were based on the national sex-specific and age-specific cancer incidence rates. By the end of 1995, 533 cancer cases were observed in the cohort. The overall cancer incidence was increased (standardized incidence ratio 1.3, 95% confidence interval 1.2–1.4). The estimated relative risks were highest for Hodgkin's disease (standardized incidence ratio 3.3, 95% confidence interval 1.4–6.4), squamous cell skin carcinoma (standardized incidence ratio 3.2, 95% confidence interval 2.3–4.4), non-Hodgkin's lymphoma (standardized incidence ratio 2.2, 95% confidence interval 1.4–3.4), and laryngeal cancer (standardized incidence ratio 2.9, 95% confidence interval 1.5–5.0). The role of prior oral antipsoriatic medications or phototherapy on the development of these cancers was assessed in a nested case-control study, for which 67 cases and 199 sex and age matched controls were selected from the psoriasis cohort. The relative risks were estimated using conditional logistic regression analysis. Oral 8-methoxypsoralen plus ultraviolet-A radiation therapy and the use of retinoids were associated with an increased risk of squamous cell skin carcinoma (relative risk adjusted for the other treatment variables 6.5, 95% confidence interval 1.4–31, and 7.4, 95% confidence interval 1.4–40, respectively), whereas none of the treatments could be linked with the occurrence of non-Hodgkin's lymphoma. ***Key words: laryngeal cancer/lymphoma/PUVA/skin cancer. J Invest Dermatol 114:587–590, 2000***

Studies concerning cancer incidence in patients with psoriasis have most often investigated the contribution of some treatment to the cancer risk. There are two reports on the occurrence of cancer in unselected hospitalized psoriasis patients. No increase in the incidence of skin, lung, stomach, or bladder cancers was found in a Scottish follow-up of 8405 psoriasis patients (Alderson and Clarke, 1983). A Danish record linkage study, on the other hand, revealed an excess of squamous cell skin carcinoma, laryngeal cancer, lung cancer, kidney cancer, and colon cancer among 6910 patients with psoriasis. Previous antipsoriatic treatments were not investigated, but the authors noted that some of the therapies could be suspected as possible risk factors (Olsen *et al*, 1992). Oral 8-methoxypsoralen plus ultraviolet-A (PUVA) treatment (Lindelöf *et al*, 1991, 1999; Stern and Laird, 1994) and arsenic (Neubauer, 1947) have been indisputably shown to cause squamous cell skin carcinoma. The role of other therapies, some of which are potentially carcinogenic, has been debated.

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Abbreviation: SIR, standardized incidence ratio.

We aimed to clarify the cancer risk in psoriasis patients with special reference to different treatments. This was done by means of a cohort study and a nested case-control study in a population of patients with psoriasis in Finland.

MATERIALS AND METHODS

Cohort study We first identified all the records of the patients hospitalized with a diagnosis of psoriasis in the Finnish Hospital Discharge Register in 1973–84 (15,406 hospital discharges for 6024 different persons). This cohort was then linked with the Population Central Register using the personal identification codes. The 278 patients (4.6%) who were not found in the Population Central Register due to an erroneous personal identification code in the Hospital Discharge Register were excluded. The dates of death and emigration were obtained from the Population Central Register for the remaining 5746 patients. By the end of 1995, 1978 (34%) patients had died and 51 (0.9%) had emigrated.

The follow-up for cancer was performed by linking the cohort with the files of the population-based country-wide Finnish Cancer Registry, again using the personal identification code. The follow-up began 6 mo after the last day of the first hospitalization period during 1973–84 and ended on the date of emigration, death, or 31 December 1995, whichever was first. Because of the 6 mo exclusion following the first hospitalization, the final cohort comprised 5687 patients.

The numbers of observed cases and the person-years at risk were calculated separately for three calendar periods (1973–80, 1981–88, and 1989–95) by gender and 5 y age groups. The expected numbers of cases for overall cancer and for specific cancer types were calculated by multiplying the number of person-years in each sex/age group by the corresponding

Table I. Case-control study: characteristics of cancer cases and controls and the prevalence of different treatments in these groups

	SCC[a]		NHL[a]		Laryngeal cancer	
	Cases	Controls	Cases	Controls	Cases	Controls
n (sex: F/M)	30 (8/22)	137 (46/91)	19 (9/10)	110 (54/56)	11 (1/10)	85 (14/71)
Year of birth, mean (range)	1920 (1901–1956)	1918 (1899–1956)	1919 (1900–1941)	1918 (1899–1943)	1923 (1902–1939)	1920 (1900–1941)
Duration between onset of psoriases and dg of cancer in respective cases (years)	28 (1–72)	28 (1–72)	29 (4–54)	27 (2–68)	28 (6–64)	25 (3–66)
Psoriasis treatments:	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
oral 8-methoxypsoralen PUVA	12 (40)	14 (10)	1 (5)	9 (8)	2 (18)	10 (12)
8-methoxypsoralen bath PUVA	2 (7)	8 (6)	–	6 (6)	–	1 (1)
trioxsalen bath PUVA	10 (33)	27 (20)	6 (32)	25 (23)	1 (9)	19 (22)
UVB	21 (70)	63 (46)	3 (16)	52 (47)	6 (55)	32 (38)
Goeckerman regimen[b]	12 (43)	33 (24)	2 (11)	32 (29)	4 (36)	19 (22)
arsenic	5 (17)	10 (7)	1 (5)	10 (9)	–	13 (15)
retinoids	13 (43)	19 (14)	2 (11)	18 (16)	2 (18)	10 (12)
methotrexate	5 (17)	11 (8)	–	8 (7)	3 (27)	8 (9)
cyclosporine	1 (3)	–	–	2 (2)	–	–
other cytostates	2 (7)	1 (1)	–	–	–	1 (1)
grenz rays	–	3 (2)	–	2 (2)	1 (9)	4 (5)

[a]SCC, squamous cell skin carcinoma; NHL, non-Hodgkin's lymphoma.
[b]Including its modifications.

sex-specific and age-specific cancer incidence rates in the whole Finnish population during the period of observation according to standard procedures (Rothman and Greenland, 1998). A further division was made by the time that had elapsed since the start of follow-up. The cancer types analyzed in the study included all the common cancer types and potential treatment-related cancers selected *a priori*. The category of ''other nonmelanoma skin cancers'' (ICD-9 code 173) includes squamous cell skin carcinoma in 85% of the cases. The next largest single tumor types in the category are Kaposi's sarcoma and fibrosarcoma, which comprise 3% of the tumors each. The term squamous cell skin carcinoma was chosen to represent the whole category in this paper. The registration of basal cell skin carcinomas is kept separate from the other cutaneous as well as noncutaneous malignancies.

The standardized incidence ratio (SIR) was calculated by dividing the observed number of cases by the expected number (Rothman and Greenland, 1998). The exact 95% confidence intervals (CI) for the SIR were calculated assuming that the observed number of cases followed a Poisson distribution (Gardner and Altman, 1989).

Nested case-control study The incidences of squamous cell skin carcinoma, non-Hodgkin's lymphoma, and laryngeal cancer were found to be increased in the cohort. The role of prior exposure to different psoriasis treatments was investigated in a nested case-control study, for which 34 incident cases of squamous cell skin carcinoma, 21 of non-Hodgkin's lymphoma, and 12 of laryngeal cancer were selected. The control subjects were chosen from the psoriasis cohort using the density sampling principle (Rothman and Greenland, 1998). They were matched for sex and year of birth ($\pm$ 2 y), being alive at the time of the cancer diagnosis of the case. A total of 199 such controls were found. The treatment data on the patients were searched for from the central and university hospitals in Finland. The last home address and the hospital code in the Hospital Discharge Register denoted the hospitals where enquiries about the patients were made. Information was requested from one to four different hospitals per patient, but it was usually found from one or two hospitals. The patients were not contacted. Data on the treatments given outside hospitals, e.g., in private dermatological clinics, could not be obtained. The permission to collect data was granted by the Ministry of Health and Social Affairs. Of the 67 cases, two patients with non-Hodgkin's lymphoma and one with laryngeal carcinoma were dropped because no information on the patients' medical histories was found. Three cases of squamous cell skin carcinoma were excluded because psoriasis was not mentioned in the patient history and one case was excluded because the patient had pustulosis palmoplantaris instead of psoriasis. Of the 199 controls, three were dropped due to a lack of any information on their medical histories and 12 because psoriasis was not mentioned in the patient history. Four controls were excluded because the respective cases were not found. A hundred and twenty-four of the controls were shared by two or three different cases from different cancer groups. There were 1–16 controls per case. The final case-control groups were as follows: 30 cases of squamous cell skin carcinoma and 137 controls, 19 cases of non-Hodgkin's lymphoma and 110 controls, and 11 cases of laryngeal cancer and 85 controls. Some of their characteristics are shown in **Table I**.

Information on topical psoriasis treatments, Goeckerman therapy and its modifications, ultraviolet-B irradiation and PUVA treatments, grenz rays, and systemic psoriasis treatments such as arsenic, retinoids (etretinate and acitretin), methotrexate, hydroxyurea, cyclosporinee, and azathioprine as well as radiation therapy and cytostatics used for other diseases were collected from the patient files. This was done by the first author, who was not aware at that time whether or not the patient was a case or a control, or what kind of cancer he/she had. Only the data from the period between the onset of psoriasis (different for each patient) and the diagnosis of cancer (for controls until the time of cancer diagnosis of the respective case) were included in the final analysis. Topical treatments were not included in the analysis.

The relative risks associated with all treatment types, adjusted for other treatments, sex, year of birth, and the period between the onset of psoriasis and the cancer diagnosis, e.g., the duration of psoriasis (for controls until the cancer diagnosis of the respective cases), were estimated and the asymptotic 95% CI were calculated by fitting the conditional logistic regression model (Breslow and Day, 1980) using the Stata (Statacorp, 1997) software. In this model all the treatment variables were dichotomous (given *versus* not). The year of birth and the duration of psoriasis were treated as continuous variables. Due to the relatively scant data, the software was unable to calculate the asymptotic CI of some treatment factors for the relative risks with point estimates 0 or ∞.

RESULTS

Cohort study The study population consisted of 3132 men and 2555 women. The total person-years were 41,685 and 35,893, respectively (**Table II**). The mean length of follow-up was thus 14 y. During the follow-up, 533 cancers were observed in psoriasis patients *versus* 426 expected (**Table III**), the SIR being 1.3 (95% CI 1.2–1.4). There was a particularly pronounced excess of squamous cell skin carcinoma (nonmelanoma skin cancer, SIR 3.2), laryngeal cancer (SIR 2.9), non-Hodgkin's lymphoma (SIR 2.2), and Hodgkin's disease (SIR 3.3) (**Table III**). Lung cancer (SIR 1.5) (**Table III**) and liver cancer in men (SIR 2.7, 95% CI 1.3–5.0) showed a moderate increase in incidence. The risks of cutaneous malignant melanoma and basal cell carcinoma were not increased (**Table III**).

Nested case-control study The use of oral 8-methoxypsoralen PUVA was associated with a greatly elevated risk of squamous cell

Table II. Number of patients with psoriasis under follow-up and number of person-years at risk in 1973–95, by sex and age

	Men		Women	
Age	N[a]	Person-years	N[a]	Person-years
0–14	94	407	198	836
15–29	600	4591	629	7374
30–44	918	12,559	419	8767
45–59	860	13,165	534	6836
60–74	544	8919	573	8159
≧76	116	2044	202	3921
Total	3132	41,685	2555	35,893

[a]Age at the beginning of the follow-up.

Table III. Observed (Obs) and expected (Exp) numbers of cancer and standardised incidence ratios (SIR) with 95% confidence intervals (95% CI) among 5687 Finnish patients with psoriasis in 1973–95, by site

Primary site	Obs	Exp	SIR	95% CI
All sites[a]	533	425.8	1.3	1.2–1.4
Mouth	1	1.6	0.7	0.0–3.6
Pharynx	3	2.2	1.3	0.3–3.9
Oesophagus	7	5.7	1.2	0.5–2.5
Stomach	34	30.8	1.1	0.8–1.5
Colon	20	23.5	0.9	0.5–1.3
Liver	11	5.9	1.9	0.9–3.3
Pancreas	26	17.2	1.5	1.0–2.2
Larynx	12	4.2	2.9	1.5–5.0
Lung, bronchus	101	68.0	1.5	1.2–1.8
Breast	37	43.4	0.9	0.6–1.2
Kidney and renal pelvis	12	15.1	0.8	0.4–1.4
Bladder, ureter, and urethra	25	17.8	1.4	0.9–2.1
Skin melanoma	8	10.3	0.8	0.3–1.6
Non-melanoma skin ca[a]	40	12.4	3.2	2.3–4.4
Nervous system	14	12.7	1.1	0.6–1.9
Non-Hodgkin's lymphoma	21	9.6	2.2	1.4–3.4
Hodgkin's disease	8	2.5	3.3	1.4–6.4

[a]Excludes basal cell carcinoma: Obs, 98; Exp, 81.1; SIR, 1.2; 95% CI, 1.0–1.5.

skin carcinoma when it was analyzed by conditional logistic regression jointly with all the other treatment variables, duration of psoriasis, sex, and age (adjusted relative risk 6.5, 95% CI 1.4–31) (**Table IV**). The use of retinoids (etretinate and acitretin) also appeared to have a high relative risk of squamous cell skin carcinoma (adjusted relative risk 7.4, 95% CI 1.4–40), when analyzed similarly with all the other variables (**Table IV**).

The patients with squamous cell skin carcinoma had been exposed to higher doses of retinoids and oral 8-methoxypsoralen PUVA than their controls. The cases received a mean of 127 PUVA treatments (range 4–314), whereas the controls were treated 59 times on average (range 6–193). Four cases but none of the controls received more than 200 PUVA treatments. Retinoids were administered for a mean of 41 mo (range 1–140) in the cases and for a mean of 22 mo (range 1–121) in the controls. The cases received a mean of 2.8 different psoriasis therapies, whereas the controls had been treated with 1.4 different therapies on average.

There was no significant association between any of the different psoriasis treatments and non-Hodgkin's lymphoma (**Table IV**). Data for the cases with laryngeal cancer and their controls were mainly collected for information to be used in an eventual meta-analysis.

Table IV. Estimated relative risks (RR) with asymptotic 95% confidence intervals (CI)[a] for the different treatment factors associated with squamous cell carcinoma (SCC) and non-Hodgkin's lymphoma (NHL)

	SCC[b]		NHL[b]	
	RR	95% CI	RR	95% CI
Birthyear	0.7	0.4–1.5	0.6	0.3–1.2
Oral 8-methoxypsoralen PUVA	6.5	1.4–31.4	1.1	0.0–23.8
8-methoxypsoralen bath PUVA	0.2	0.0–2.9	0	
Trioxsalen bath PUVA	0.8	0.2–3.8	4.2	0.8–21.5
UVB	1.6	0.4–6.4	0.1	0.0–0.8
Goeckerman regimen	1.5	0.3–7.3	1.2	0.1–16.8
Arsenic	2.7	0.6–13.1	1.2	0.0–33.1
Retinoids	7.4	1.4–39.9	0.3	0.0–2.4
Methotrexate	0.4	0.1–1.9	0	
Cyclosporine	∞		0	
Other cytostatics	13.8	0.3–548	–	–
Grenz rays	0	.	0	.

[a]Asymptotic confidence intervals could not be calculated when the point estimate was either 0 or ∞.

[b]SCC, 30 cases and 137 controls; NHL, 19 cases and 110 controls; calculated by fitting the conditional logistic regression model, including all treatment factors, age, sex and duration of psoriasis.

DISCUSSION

An increased total incidence of cancers was found among 5687 psoriasis patients after a mean follow-up of 14 y. This excess was largely attributable to squamous cell skin carcinoma, non-Hodgkin's lymphoma, and Hodgkin's lymphoma as well as laryngeal cancer.

An excess of lymphoma in psoriasis patients has been expected but until now not reported in any larger psoriasis cohort. The incidence of non-Hodgkin's lymphoma has increased in the whole Finnish population in a similar fashion as in the other parts of the world. Increased exposure to recreational sunlight has been postulated to play a role (Adami *et al*, 1995; Levi *et al*, 1996) partly because of the statistically significant association between squamous cell skin carcinoma and non-Hodgkin's lymphoma found in many countries, including Finland (Teppo *et al*, 1985). Chronic primary or secondary immunosuppression is considered a major risk factor of non-Hodgkin's lymphoma. Phototherapies and many of the antipsoriatic oral medications are immunosuppressive. The results of this study, however, did not show any significant association between therapeutic ultraviolet-B or PUVA and non-Hodgkin's lymphoma.

The risk analysis of the different antipsoriasis therapies in skin cancer showed a clear association between oral 8-methoxypsoralen PUVA and squamous cell skin carcinoma. This result is in good agreement with the latest large-scale PUVA studies, which showed a 6- to 12-fold increase in the incidence of squamous cell skin carcinoma in patients exposed to oral 8-methoxypsoralen PUVA (Lindelöf *et al*, 1991, 1999; Stern and Laird, 1994). The number of patients needed to be treated with PUVA to result in one extra case of squamous cell skin carcinoma in this study was 3030, keeping in mind, however, that the skin cancer risk associated with PUVA is dose-dependent.

Quite opposite was the finding that the use of retinoids was much more common among the cases than among the controls. Retinoids are frequently used in the chemoprevention of squamous cell skin carcinoma (Kelly *et al*, 1991; Bouwes Bavinck *et al*, 1995; Hudson-Peacock *et al*, 1996). They are believed to prevent skin carcinomas through their ability to stimulate epithelial differentiation and restore normal growth (Craven and Griffiths, 1996). The present result suggests, however, that retinoid treatment did not prevent development of squamous cell skin carcinoma in these

patients. The result may be a chance finding, because many exposures were evaluated simultaneously. Residual confounding related to PUVA might be one explanation, but the fact that point estimates of relative risk and respective standard errors did not materially change when PUVA was removed from the model suggests that it cannot be a major factor.

Trioxsalen bath PUVA, ultraviolet-B, and the Goeckerman regimen with its modifications were not associated with an increased risk of squamous cell skin carcinoma in this study. These results are consistent with earlier reports on these treatments (Maughan *et al*, 1980; Pittelkow *et al*, 1981; Larkö and Swanbeck, 1982; Stern and Laird, 1994; Hannuksela-Svahn *et al*, 1999). The role of cyclosporinee and grenz rays could not be assessed due to the small number of patients exposed to these treatments. Only few patients had received 8-methoxypsoralen bath PUVA therapy and methotrexate, warranting careful interpretation of the results. Arsenic often causes multiple basal and squamous cell skin carcinomas (Neubauer, 1947). In our study it did not increase the risk of squamous cell skin carcinoma. The information gathered from the patient records contained no data on multiple skin carcinomas in patients who had received arsenic.

The two most important risk factors in laryngeal cancer are tobacco smoking and alcohol consumption (Cattaruzza *et al*, 1996). Data on drinking and smoking habits were not obtained in this study. Other studies from Finland, however, have shown that patients with psoriasis smoke (Poikolainen *et al*, 1994) and drink (Poikolainen *et al*, 1990) more than other dermatological patients. These lifestyle factors may also explain the modest increase in lung cancer as well as liver cancer in men.

Cancer registration in Finland is virtually complete (over 99% of malignancies are registered) (Teppo *et al*, 1994), and the computerized record linkage procedure is precise (Pukkala, 1992). Therefore, technical deficiencies did not bias the results. Exposure data may lack some information due to the retrospective design of the study. Data were collected from the hospitals only, as we were not allowed to contact the patients. Also some patients had already passed away. There should be no reason to believe, however, that the cases were more often treated outside the hospitals before they were diagnosed with cancer than the controls or vice versa. If the skin cancer cases had more severe disease and a higher number of treatments than the controls, they might have been scrutinized more carefully for skin cancer than the controls. Unfortunately, it was not possible to record the number of skin checks for cancer in relation to the severity of psoriasis and to the number of treatments. We have no reason to doubt, however, that the results would have been influenced by surveillance bias.

The patients in this study were likely to have more severe psoriasis than psoriatics in general, because they needed dermatological consultation. A direct consequence of this would be that they also received more potent therapies. Although only oral 8-methoxypsoralen PUVA clearly increased the occurrence of squamous cell skin carcinoma, it is probable that the other immunosuppressive or potentially carcinogenic treatments also contributed to the cancer development. The risk of cutaneous cancer would thus correlate indirectly with the severity of psoriasis. The results of this study are therefore not necessarily applicable to all patients with psoriasis. Squamous cell carcinoma is a fairly rare cancer in Finland (six cases per 100,000 person-years) with a very good prognosis. A 3-fold increase in the low squamous cell skin carcinoma risk thus does not mean much difference per person. The association of lymphoma with psoriasis is more alarming and warrants careful attention.

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