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# Risk of Malignancies in Psoriasis Patients Treated with Cyclosporine: a 5 y Cohort Study

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**This prospective long-term cohort study investigated the incidence of malignancies in severe psoriasis patients treated with cyclosporine. A total of 1252 patients were followed prospectively for up to 5 y. Malignancies were recorded prospectively. Incidence rates for malignancies were compared with the general population using standardized incidence ratios. The effect of duration of exposure to cyclosporine and to previously administered anti-psoriatic treatments on the incidence of malignancies was investigated using Poisson regression models. The mean age of patients was 43 y and on average, patients received cyclosporine for 1.9 y. Malignancies were diagnosed in 47 patients (3.8%), 49% of them had skin malignancies. The standardized incidence ratio in the study cohort was 2.1 as compared with the general population. The higher incidence of malignancies was attributed to a 6-fold higher incidence of skin malignancies, most of which were squamous cell carcinoma. The incidence of nonskin malignancy overall was not significantly higher in this study than in the general population. Duration of exposure to cyclosporine, exposure to psoralen and ultraviolet A, exposure to methotrexate, and exposure to immunosuppressants showed a significant effect on the incidence of nonmelanoma skin malignancies. In conclusion, treatment of psoriasis with cyclosporine is associated with an increased risk of nonmelanoma skin cancer. Patients treated for more than 2 y with cyclosporine were shown to have a higher risk. In addition, exposure to psoralen and ultraviolet A and to other immunosuppressants was shown to contribute to the overall risk.** ***Key words: autoimmune diseases/immunosuppressant/skin cancer/standardized incidence ratio. J Invest Dermatol 120:211–216, 2003***

Severe psoriasis can seriously affect a patient's quality of life (Finlay and Coles, 1995) and life-long intermittent treatment with systemic therapies may often be required to control the disease (Spuls *et al*, 1997). Systemic therapies, however, can induce adverse effects that restrict their long-term use. For example psoralen and ultraviolet (UV) A (PUVA) therapy has been associated with an increased risk of skin cancer (Stern *et al*, 1984, 1997a; Lindelöf *et al*, 1991). Hepatotoxicity is a major limitation to long-term methotrexate use (Roenigk *et al*, 1998). Similarly, synthetic retinoids are highly teratogenic and are often ineffective as a monotherapy (Paul and Dubertret, 1998) and long-term treatment with cyclosporine is associated with nephrotoxicity (Grossman *et al*, 1996). In addition, long-term use of immunosuppressants such as cyclosporine is associated with a potential safety concern because an increased risk of malignancy, primarily of the skin and lymphoid tissue is observed in transplant patients treated with immunosuppressants regimens (Sloan *et al*, 1977; Cockburn and Krupp, 1989; Penn, 1994; Jonas *et al*, 1997). The risk appears to be less in patients treated with cyclosporine for autoimmune diseases (Van den Borne *et al*, 1998; Paul and Hornig, 1999). With the exception of PUVA therapy, there are scant data available on the long-term safety of systemic treatment in psoriasis. The carcinogenic risk is a concern relevant to the psoriasis population as the majority of patients with severe psoriasis may receive various carcinogenic treatments, including arsenic preparations, tar, ionizing radiation, phototherapy, and PUVA. Furthermore, several epidemiologic studies have shown that psoriasis patients have already an increased risk of malignancies primarily of the skin (Frentz and Olsen, 1999; Hannuksela-Svahn *et al*, 2000; Margolis *et al*, 2001). Consequently, there is a need to evaluate the risk of malignancies in psoriasis patients receiving cyclosporine and to identify the possible role of other risk factors in the development of malignancy. The primary objective of the present prospective cohort study was to investigate the type and incidence of malignancies that may occur in patients treated with cyclosporine for psoriasis and to identify the contributing role of duration of exposure and of other psoriasis treatments.

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## SUBJECTS AND METHODS

This study was designed as an open, uncontrolled, nonrandomized, multicenter, prospective observational cohort study. It was conducted in 277 centers in 11 countries: Austria, Canada, Denmark, France, Germany, Great Britain, Italy, Portugal, Spain, Switzerland, and Turkey.

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Patients with severe psoriasis treated with cyclosporine (as indicated in the product monograph) were included in the study. All patients were included in the study if they had received at least 1 mo of cyclosporine treatment and had to be followed-up for 5 y. The evaluation schedule included a baseline clinical assessment and follow-up clinical assessments at month 1, and every 6 mo thereafter until month 60. All assessments had to be performed by a dermatologist. Malignancies were monitored continuously and were recorded on a dedicated form. Data on all malignancies were verified by direct contact with the investigators.

Other safety assessments consisted of information on cyclosporine dose and duration of therapy, information on concomitant therapy received for psoriasis in addition to regular measurements of serum creatinine, blood pressure, and weight.

**Statistical analysis** All analyses were performed on the safety population, which consists of all patients who received at least one dose of cyclosporine. Incidence rate of malignancies and corresponding 95% confidence intervals (CI) were calculated separately for each year of follow-up and overall. Separate incidence rates were calculated for periods of low and high exposure to cyclosporine defined as at most 2 y and more than 2 y of cumulative treatment. For each type of malignancy, the incidence observed in the cohort was compared with the corresponding incidence in the general population using standardized incidence ratios (SIR), which represent the ratio between observed and expected number of malignancies.

The expected number of malignancies was calculated by applying the incidence rate of the general population to the study cohort. Incidence rates in the general population were taken from national or regional cancer registries in the countries participating in the study (Parkin *et al*, 1992, 1997). Attention was paid to select as reference registries including both basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Separate incidence rates for BCC and SCC were not provided in the registries. No registry was available for Portugal and Turkey. Consequently, registries for Spain (Zaragoza) and Italy (Modena) were chosen as respective references for these two countries. Strata were formed by the cross-sections of age group, sex, and country. For each patient, follow-up years were allocated to age groups based on the patient's age at the midpoint of the follow-up year. In addition, separate SIR were calculated for follow-up years with low and high exposure to cyclosporine. The influence of history of malignancy and of previous use of other psoriasis treatment (methotrexate, PUVA, retinoids, immunosuppressants, phototherapy, tar) was investigated. The effect of exposure to cyclosporine and to any of the explanatory variables listed above was investigated using Poisson regression models for the SIR, incorporating the expected number of malignancies as prior weights in the model to account for overdispersion (Breslow and Day, 1988). All models included three explanatory variables: exposure to cyclosporine, previous history of malignancy, and the respective exposure to previous treatments for psoriasis (PUVA, oral retinoids, methotrexate, other immuno-suppressants, phototherapy, tar). The significance of each effect was determined using a likelihood ratio test. Relative risks were presented together with 95% CI.

The Poisson regression was performed for all malignancies, all skin malignancies, all nonmelanoma skin malignancies, all nonskin malignancies, and for BCC and SCC. Other individual types of malignancies were not further analyzed because of the low number of events.

In the analyses of BCC and SCC, it was assumed that the proportion of BCC among nonmelanoma skin cancer in the general population is 80% for men and 86% for women. Accordingly the proportion of SCC was estimated to be 20% for men and 14% for women. These estimates are based on literature data from European countries and Canada, which showed consistent proportions of BCC and SCC across countries (Stern, 1999; Holme *et al*, 2000).

## RESULTS

**Patient disposition and follow-up** A total of 1252 patients were included in the safety population. The median duration of follow-up was 4.5 y (range 0–8.6 y) with 48% of patients having attended the month 60 final visit. The total cohort was 4440 person-years of follow-up.

**Baseline demographics and background disease characteristics (Table I)** The study population had an age range from 9 to 88 y with an average age of 43 y. Sixty-eight percent of the patients were male and 95% of the patients were aged between 20 and 75 y. On average, patients had suffered from psoriasis for 16 y and the mean age at onset of psoriasis was 27 y. A total of 7% of patients suffered from psoriatic arthropathy. The most commonly used prior therapies for psoriasis were PUVA (47%), retinoids (45%), methotrexate (28%), phototherapy (19%), tar (8%), cyclosporine (8%), and other immunosuppressants (6%). There was no noteworthy difference in the demographic characteristics observed between the patient group that received more than 2 y of cyclosporine (high exposure group) and the patient group that received less than 2 y (low exposure group) during the study. The proportion of patients previously exposed to PUVA, retinoids, and methotrexate was slightly higher in the high cyclosporine exposure group as compared with the low exposure group (**Table I**).

**Table I. Baseline characteristics of the patients**

| | Total (n = 1252) | Patients with at most 2 y of cyclosporine (n = 781) | Patients with more than 2 y of cyclosporine (n = 471) |
|---|---|---|---|
| Age (y) | | | |
| Mean ± SD | 43.3 ± 14.0 | 44.0 ± 14.3 | 42.3 ± 13.4 |
| Range | 9–88 | 9–88 | 11–80 |
| Sex (% male/female) | 68/32 | 70/30 | 65/35 |
| Weight (kg) | | | |
| Mean ± SD | 76.9 ± 16.6 | 76.7 ± 16.4 | 77.3 ± 16.9 |
| Range | 26–174 | 26–174 | 30–147 |
| Duration of psoriasis (y) | | | |
| Mean ± SD | 16.2 ± 11.2 | 15.8 ± 11.5 | 16.8 ± 10.7 |
| Age at onset of psoriasis (y) | | | |
| Mean ± SD | 27.1 ± 14.3 | 28.2 ± 14.6 | 25.3 ± 13.6 |
| Previous systemic therapy of psoriasis (% of patients receiving therapy) | | | |
| PUVA | 47 | 45 | 49 |
| Retinoids | 45 | 41 | 51 |
| MTX | 28 | 25 | 33 |
| UVB/UVA | 19 | 21 | 17 |
| Tar | 8 | 9 | 8 |
| Cyclosporine | 8 | 8 | 8 |
| Immuno. | 6 | 4 | 8 |
| Fumaric a. | 2 | 2 | 1 |
| Arsenic | < 1 | < 1 | < 1 |
| Ioniz. rad. | < 1 | < 1 | < 1 |

MTX, methotrexate; ioniz. rad., ionizing radiation; immuno., immunosuppressant w/o cyclosporine; fumaric a., fumaric acid.

**Exposure to cyclosporine and other systemic psoriasis treatments** The mean daily starting dose of cyclosporine was 3 mg per kg, starting doses higher than 3.5 mg per kg were taken by 20% of patients. Thereafter, the mean daily dose decreased over time from 3.1 mg per kg at month 6 to 2.7 mg per kg at the end of month 54. At each time point, between 18 and 28% of patients received daily doses between 3.5 mg per kg and 5 mg per kg. Doses of more than 5 mg per kg were taken by 3–4% of patients. Approximately 40% of all patients received cyclosporine intermittently, whereas the remaining 60% received it continuously until they ceased cyclosporine treatment permanently. The mean duration of cyclosporine therapy was 1.9 y with 471 (38%) patients receiving it for more than 2 y and 201 patients (16%) receiving it for more than 4 y. During the follow-up period, 34% of patients received other systemic therapy for psoriasis. These consisted primarily of methotrexate and retinoids, which were received by 20% of patients. PUVA and

phototherapy were received by 13% and 10% of patients, respectively.

**Incidence of malignancies and distribution across the follow-up period** Malignancies were diagnosed in 47 patients (3.8%). The corresponding yearly incidence density rate was 10.8 per 1000 person-years of follow-up. Forty-nine percent of the malignancies were skin cancers. The number and percentage of patients with the most frequent malignancies and corresponding incidence-density rates are displayed in **Table II**. The proportion of SCC to BCC was 3 : 1. All patients with BCC and/or SCC had previously received PUVA therapy. The yearly incidence density rate of malignancies was equally distributed across years of follow-up and ranged from 10.2 to 12.5 per 1000 person-years for follow-up years 1–5. There was no trend towards an increased incidence of malignancies over time within the cohort. In 30 of the 47 patients (64%) malignancies occurred while patients were on cyclosporine. The mean duration of cyclosporine treatment at the time the first malignancy was diagnosed was 22 mo (range 0.4–55 mo). In the remaining 17 patients (36%) malignancies were diagnosed after cyclosporine had been stopped, which on average was 19.6 mo after last administration.

**Table II. Number (%) of patients with malignancies by selected category of malignancy, and corresponding incidence density rates with 95% CI**

| | Patients | | Person-Years[b] | Per 1000 person-years Incidence rate | 95% CI |
|---|---|---|---|---|---|
| | N | (%) | | | |
| Any malignancy | 47 | 3.8 | 4340 | 10.8 | 8.0–14.4 |
| Skin malignancies | 23 | 1.8 | 4377 | 5.3 | 3.3–7.9 |
| BCC | 5 | 0.4 | 4426 | 1.1 | 0.4–2.6 |
| SCC | 15 | 1.2 | 4401 | 3.4 | 1.9–5.6 |
| Melanoma | 2 | 0.2 | 4431 | 0.5 | 0.1–1.6 |
| Porocarcinoma | 1 | 0.1 | 4439 | 0.2 | 0.0–1.3 |
| Nonskin malignancies[a] | 24 | 1.9 | 4404 | 5.4 | 3.5–8.1 |
| Colon cancer | 3 | 0.2 | 4435 | 0.7 | 0.1–2.0 |
| Leukemia | 3 | 0.2 | 4440 | 0.7 | 0.1–2.0 |
| Lymphoma | 2 | 0.2 | 4437 | 0.5 | 0.1–1.6 |
| Lung cancer | 2 | 0.2 | 4439 | 0.5 | 0.1–1.6 |
| Esophageal cancer | 2 | 0.2 | 4434 | 0.5 | 0.1–1.6 |
| Breast cancer | 2 | 0.2 | 4437 | 0.5 | 0.1–1.6 |
| Gastric cancer | 2 | 0.2 | 4435 | 0.5 | 0.1–1.6 |

[a]Also including malignancies experienced by one patient only, these are not displayed separately in this table
[b]Numbers are different because patients are censored at the time they experience a malignancy.

**Comparison of the incidence of malignancies with the general population and effect of duration of exposure to cyclosporine** **Table III** shows the SIR and 95% CI by malignancy and exposure to cyclosporine. The overall incidence of malignancies was significantly higher in the cohort as compared with the general population. The 2-fold higher incidence of malignancy was mainly caused by a 6-fold higher incidence of skin malignancies most of which were nonmelanoma skin cancers. The incidence of nonmelanoma skin cancer was higher during high-exposure follow-up years, which is reflected in the increased value of the high-exposure SIR compared with the low-exposure SIR. The increase in the incidence of nonmelanoma skin cancer was mainly driven by a 24.6-fold increase in the incidence of SCC in the cohort.

The incidence of nonskin malignancies was not significantly increased as compared with the general population (SIR: 1.3; 95% CI: 0.8–1.9). Among nonskin malignancies, only the SIR for leukemia was significantly elevated in the cohort (SIR: 7.3; 95% CI: 1.5–21.5). CI were generally large, however, due to a low observed number of events of individual types of nonskin malignancies (**Table III**).

**Effect of exposure to other systemic psoriasis treatments on the incidence of malignancies** Estimated relative risks for each factor, adjusted for the other factors in the model are presented together with 95% CI in **Table IV**. The duration of exposure to cyclosporine showed a significant effect on the incidence of malignancies of any type, on the incidence of skin malignancies, and on the incidence of nonmelanoma skin malignancies, whereas no significant increased risk of nonskin malignancies was observed. The relative risk was 3.3 for nonmelanoma skin malignancies (95% CI 1.3–8.4) and 1.5 for nonskin malignancies (95% CI 0.6–3.5).

Aside from exposure to cyclosporine, the following factors showed a significant effect on the incidence of malignancies of any type. Previous exposure to PUVA (relative risk 3.5; 95% CI: 1.8–7.2), previous exposure to retinoids (relative risk 2.9; 95% CI: 1.5–6.3) and previous exposure to immunosuppressants (relative risk 2.0; 95% CI: 1.0–3.7) significantly increased the risk of malignancies. Similarly these effects were mainly driven by a higher risk of developing skin malignancies, especially nonmelanoma skin malignancies, as compared with the general population. The highest increase in the risk of skin malignancies

**Table III. SIR and 95% CI[b] by malignancy and exposure to cyclosporine**

| | Overall | | | Low exposure | | | High exposure | | |
|---|---|---|---|---|---|---|---|---|---|
| | Person-years[a] | SIR | 95% CI | Person-years | SIR | 95% CI | Person-years | SIR | 95% CI |
| Any malignancy | 4294 | 2.1 | 1.6–2.9 | 3280 | 1.8 | 1.2–2.6 | 1014 | 3.3 | 1.9–5.3 |
| Any skin malignancy | 4330 | 6.1 | 3.8–9.1 | 3300 | 4.8 | 2.6–8.1 | 1029 | 10.1 | 4.6–19.2 |
| Nonmelanoma skin malignancy | 4339 | 6.2 | 3.8–9.5 | 3310 | 4.6 | 2.4–8.1 | 1029 | 11.4 | 5.2–21.7 |
| BCC | 4379 | 1.8 | 0.6–4.1 | 3338 | 0.9 | 0.1–3.3 | 1041 | 4.6 | 0.9–13.3 |
| SCC | 4354 | 24.6 | 13.8–40.7 | 3317 | 19.2 | 8.8–36.5 | 1037 | 42.7 | 15.7–93.2 |
| Malignant melanoma | 4384 | 4.7 | 0.6–17.0 | 3336 | 6.2 | 0.8–22.5 | 1048 | 0.0 | |
| Any nonskin malignancy | 4357 | 1.3 | 0.8–1.9 | 3324 | 1.2 | 0.7–1.9 | 1033 | 1.7 | 0.7–3.5 |
| Lymphoma | 4390 | 2.0 | 0.2–7.2 | 3342 | 1.3 | 0.0–7.2 | 1048 | 4.3 | 0.1–23.9 |
| Lung cancer | 4393 | 0.6 | 0.1–2.2 | 3344 | 0.8 | 0.1–2.8 | 1048 | 0.0 | |
| Esophageal cancer | 4387 | 5.1 | 0.6–18.4 | 3342 | 6.7 | 0.8–24.1 | 1045 | 0.0 | |
| Leukemia | 4393 | 7.3 | 1.5–21.5 | 3345 | 9.5 | 2.0–27.7 | 1048 | 0.0 | |
| Colon cancer | 4388 | 2.1 | 0.4–6.1 | 3343 | 0.9 | 0.0–5.0 | 1045 | 6.3 | 0.8–22.8 |
| Breast cancer | 4390 | 1.2 | 0.1–4.2 | 3345 | 0.0 | | 1045 | 4.2 | 0.5–15.2 |
| Gastric cancer | 4388 | 2.1 | 0.3–7.5 | 3340 | 1.3 | 0.0–7.3 | 1048 | 5.1 | 0.1–28.6 |

[a]Person-years of follow-up;
[b]95% CI for SIR

**Table IV. Adjusted relative risks and 95% CI**

| | | 95% CI |
|---|---|---|
| All malignancies | | |
| Exposure to cyclosporine (high/low) | 2.0 | 1.1–3.8 |
| Exposure to PUVA (some/none) | 3.5 | 1.8–7.2 |
| Exposure to retinoids (some/none) | 2.9 | 1.5–6.3 |
| Exposure to methotrexate (some/none) | 1.8 | 1.0–3.2[a] |
| Exposure to immunosuppressant (some/none) | 2.0 | 1.0–3.7 |
| Exposure to phototherapy (some/none) | 1.2 | 0.6–2.3 |
| Exposure to tar (some/none) | 2.1 | 0.9–4.5 |
| All skin malignancies | | |
| Exposure to cyclosporine (high/low) | 2.7 | 1.1–6.4 |
| Exposure to PUVA (some/none) | 5.8 | 2.0–25.0 |
| Exposure to retinoids (some/none) | 4.5 | 1.5–19.5 |
| Exposure to methotrexate (some/none) | 2.1 | 0.9–5.3 |
| Exposure to immunosuppressant (some/none) | 2.9 | 1.2–6.8 |
| Exposure to phototherapy (some/none) | 0.7 | 0.2–1.8 |
| Exposure to tar (some/none) | 2.4 | 0.7–6.6 |
| All nonmelanoma skin malignancies | | |
| Exposure to cyclosporine (high/low) | 3.3 | 1.3–8.4 |
| Exposure to PUVA (some/none) | 7.3 | 1.3–134.5 |
| Exposure to retinoids (some/none) | 4.6 | 0.9–86.1 |
| Exposure to methotrexate (some/none) | 2.7 | 1.1–7.3 |
| Exposure to immunosuppressant (some/none) | 3.5 | 1.4–8.4 |
| Exposure to phototherapy (some/none) | 0.5 | 0.1–1.5 |
| Exposure to tar (some/none) | 1.9 | 0.4–5.7 |
| All BCC | | |
| Exposure to cyclosporine (high/low) | 4.9 | 0.8–36.9 |
| Exposure to PUVA (some/none) | Not estimable | |
| Exposure to retinoids (some/none) | Not estimable | |
| Exposure to methotrexate (some/none) | 2.5 | 0.4–18.7 |
| Exposure to immunosuppressant (some/none) | 3.3 | 0.4–19.6 |
| Exposure to phototherapy (some/none) | 2.3 | 0.1–24.0 |
| Exposure to tar (some/none) | 6.5 | 0.9–39.4 |
| All SCC | | |
| Exposure to cyclosporine (high/low) | 3.3 | 1.0–10.6[b] |
| Exposure to PUVA (some/none) | 4.4 | 0.7–84.7 |
| Exposure to retinoids (some/none) | 2.6 | 0.4–50.7 |
| Exposure to methotrexate (some/none) | 2.5 | 0.8–8.6 |
| Exposure to immunosuppressant (some/none) | 4.0 | 1.3–11.5 |
| Exposure to phototherapy (some/none) | 0.6 | 0.1–2.7 |
| Exposure to tar (some/none) | 1.5 | 0.1–9.3 |
| All nonskin malignancies | | |
| Exposure to cyclosporine (high/low) | 1.5 | 0.6–3.5 |
| Exposure to PUVA (some/none) | 2.5 | 1.1–6.5 |
| Exposure to retinoids (some/none) | 2.1 | 0.9–5.4 |
| Exposure to methotrexate (some/none) | 1.3 | 0.6–3.1 |
| Exposure to immunosuppressant (some/none) | 1.3 | 0.4–3.2 |
| Exposure to phototherapy (some/none) | 1.6 | 0.6–3.8 |
| Exposure to tar (some/none) | 1.5 | 0.4–4.5 |

Results of Poisson regressions with SIR as outcome variable and previous history of malignancy, exposure to cyclosporine, and exposure to respective previous therapy as explanatory variables.

[a]CI includes 1.0.

[b]CI does not include 1.0.

was obtained with PUVA exposure. Exposure to PUVA was estimated to increase the risk of nonmelanoma skin cancer by factor 7.3 (95% CI 1.3–134.5). Exposure to methotrexate, immunosuppressants as well as high *vs* low exposure to cyclosporine were also significant risk factors for nonmelanoma skin cancers in the cohort. Exposure to tar, phototherapy alone, and retinoids showed no significant effect. The results of the separate analyses for SCC and BCC were consistent with the results of the analysis of nonmelanoma skin cancer, although the CI were larger due to low number of events. With regard to nonskin malignancies, the only significant factor in the multivariate Poisson regression model was previous exposure to PUVA (relative risk: 2.5; 95% CI: 1.1–6.5).

## DISCUSSION

The analysis of the cyclosporine long-term cohort study provides important information on the long-term safety of cyclosporine in the treatment of psoriasis. The total cohort was almost 4500 person-years of follow-up. This represents to our knowledge the largest prospective cohort of psoriatic patients after the PUVA cohort study from the U.S.A. (Stern *et al*, 1984). The majority of patients had previously received UV therapy for psoriasis (including UVB, PUVA, or combination therapy) or systemic therapy, including methotrexate, other immunosuppressants, or retinoids. Indirectly, this reflects the nature of the population receiving cyclosporine treatment as consisting of patients with severe psoriasis. The overall incidence of malignancies was about twice as high in this cohort of patients with severe psoriasis than in the general population. The higher incidence of malignancies of any type in the cohort was mainly caused by a 6-fold higher incidence of skin malignancies, mostly nonmelanoma skin malignancies. Nonskin malignancies overall were not significantly more frequent in this cohort than in the general population. A significantly higher incidence of leukemia was observed in the cohort as compared with the general population. Three patients developed leukemia after a relatively short exposure to cyclosporine and with no apparent relationship to the duration of exposure. Given the small size of the cohort and the absence of relationship to exposure, the results should be interpreted with caution and further studies are needed to confirm these findings. The SIR for lymphoma is 2 with a wide CI. This SIR is similar to the one observed in a cohort of patients with moderate to severe psoriasis reported before the introduction of cyclosporine (Hannuksela-Svahn *et al*, 2000).

There are many factors influencing the risk of malignancies in severe psoriasis patients (Murphy, 1999). The contributing role of PUVA, cyclosporine, and methotrexate to the increased risk of skin cancer in the psoriasis population has been demonstrated, although few studies have assessed simultaneously the respective contribution of individual psoriasis therapies (Stern *et al*, 1984; Lindelöf *et al*, 1999; Hannuksela-Svahn *et al*, 2000; Marcil and Stern, 2001).

In this study, previous history of malignancy, high exposure to cyclosporine, and previous exposure to PUVA, methotrexate, and immunosuppressants were associated with an increased risk of nonmelanoma skin malignancies. The contribution of the role of retinoids that were identified as being a significant risk factor for malignancies overall and skin malignancies should be interpreted with caution because of possible confounding. Retinoids are frequently used in combination with PUVA and it may be difficult to separate the individual contribution of retinoids in the model. Moreover, use of retinoids has been advocated in patients experiencing SCC to prevent recurrence suggesting a possible confounding by indication when assessing risk of skin cancer in patients treated with retinoids (Hannuksela-Svahn *et al*, 2000).

One limitation of this study is that the incidence of malignancies had to be compared with the general population. This is a common limitation of most cohort studies investigating the risk of malignancies in psoriasis patients (Stern *et al*, 1984; Lindelöf *et al*, 1991; Frentz and Olsen, 1999a,b; Hannuksela-Svahn *et al*, 2000). Problems may arise from different sources. First, psoriasis *per se* is associated with an increased risk of malignancies. An increased risk of nonskin malignancies has been observed in psoriasis in some studies, but no consistent pattern was found across studies (Stern *et al*, 1997b; Frentz and Olsen, 1999a,b; Hannuksela-Svahn *et al*, 2000; Margolis *et al*, 2001). Secondly, skin cancers are more likely to be detected and reported in

patients followed up by dermatologists. This detection bias may have produced an overestimation of the risk of skin cancer in the cohort. Thirdly, perfect matching between the study population and cancer registries is not possible because cancer registries do not exist in all countries. This is relevant to this study, which includes patients from a very large geographic background.

It is noteworthy that the risks estimated from this study are very close to those of a recent study in severe psoriasis patients from an administrative database (Margolis *et al*, 2001). In this study, the relative risk for all malignancies in patients with severe psoriasis was 1.78 and the risk of nonmelanoma skin cancer was 4.15 as compared with 2.1 and 6.1 in the present cohort. The risk of nonmelanoma skin malignancies observed in this study is also close to the one observed in cohorts of severe psoriasis patients from northern Europe showing relative risk of nonmelanoma skin cancers varying from 2.6 to 4.83 (Frentz and Olsen, 1999a,b; Hannuksela-Svahn *et al*, 1999). High exposure to cyclosporine as defined by more than 2 y of treatment was estimated to increase the risk of nonmelanoma skin cancer by a factor of 3.3 compared with low exposure. Among previous therapies, the most important factor influencing the risk of nonmelanoma skin cancer was found to be PUVA with a relative risk of 7.3. Among the 21 patients who developed nonmelanoma skin cancer 20 (95%) had previously received PUVA. This is in line with the results of a recent meta-analysis that indicated PUVA is the major skin carcinogen in psoriasis patients; high exposure being associated with a 14-fold higher incidence of SCC (Stern and Lunder, 1998).

As in other studies, it might have been interesting to analyze the effect of cyclosporine dose instead of the duration of treatment as risk factor. Significant effect of the dose of cyclosporine on the incidence of skin malignancies was shown in a cohort study in transplantation (Dantal *et al*, 1998). Such an analysis was not performed, however, as the use of cyclosporine in psoriasis is associated with frequent changes in doses of study medication for each patient depending upon the clinical outcome. In addition, many psoriasis patients receive intermittent treatment with cyclosporine as opposed to transplant patients who receive it continuously (Berth-Jones *et al*, 1997; Ho *et al*, 1999, 2001). Long-term studies in transplantation have shown that duration of exposure to immunosuppressants is an important factor influencing the risk of malignancies (Sheil, 2001). Therefore duration of exposure was chosen as the relevant parameter for categorization of exposure in the study population. Similarly, it would have been useful to have more detailed information on previous exposure to other anti-psoriatic drugs, such as duration and dose, as it is common practice to rotate treatment in psoriasis. In a study of this size and duration, however, it was decided to take a pragmatic approach and not record such data as such details are known to be highly variable in the individual patient. Lastly the duration of follow-up in the cohort is relatively limited and does not allow a precise estimate of incidence rates of individual types of nonskin cancers. Studies with longer follow-up, including larger groups of patients will be required to assess more precisely the effect of cyclosporine treatment on the risk of nonskin malignancies.

In conclusion, the risk of malignancy associated with cyclosporine treatment in psoriasis appears to be significantly increased with more than 2 y of cumulative treatment as compared with less than 2 y. This is mainly due to an increase in risk of nonmelanoma skin cancers, mostly SCC. The contributing role of previous exposure to PUVA, methotrexate, and other immunosuppressants was demonstrated. The incidence of nonskin cancer does not appear to be significantly increased overall. For individual types of nonskin malignancies, however, the cohort is not large enough to provide a precise estimate of incidence. The increased incidence of nonmelanoma skin cancers in the cohort is in line with published literature in psoriasis patients, which thus provides confidence with regard to the validity of the results.

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