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PUVA TREATMENT AND SKIN CANCER: A FOLLOW-UP STUDY

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Abstract. Altogether 525 PUVA-treated psoriatics were re-examined. The mean follow-up period since the beginning of PUVA therapy was 2.1 years (range 1–3.6 years). In 107 cases (20%) the total UVA dose was below 100 J/cm² and in 20 (4%) over 1 000 J/cm². During PUVA treatment or at re-examination 14 of the 525 patients (3%) were found to have skin lesions suspected of being malignant. A total of 23 biopsies were taken and in one case a basal-cell carcinoma was histologically verified. This had almost certainly been present before the beginning of the PUVA therapy. Two other patients, both previously treated with methotrexate, had reversible lesions with Bowenoid histology. Both these patients had received a total UVA dose of more than 1 000 J/cm². The incidence of skin carcinomas in the present PUVA-treated series was lower than that in hospitalized psoriatics treated with regimens other than PUVA and was not higher than the incidence in the age-matched general population in Finland.

Key words: Photochemotherapy; Skin carcinoma

There are sufficient published data to establish oral psoralen plus long-wave ultraviolet light (PUVA) as being an effective treatment for psoriasis (5, 6, 7, 10). Patients tolerate PUVA quite well and the therapy rarely has to be discontinued because of acute side-effects such as severe phototoxicity, nausea or pruritus. However, there are still some possible long-term effects, such as cutaneous aging, cataracts and carcinogenicity, which must be considered when evaluating the benefits and risks of PUVA treatment (1, 2). It is well known that solar ultraviolet light seems to be the major factor in the pathogenesis of basal-cell and squamous-cell carcinomas in man (8). However, various artificial ultraviolet light sources have been used for years, either alone or together with such potential carcinogens as coal tar, for the treatment of psoriasis, without any observed increase in the frequency of skin cancer (2).

Recent reports from the USA and West Germany (3, 9) show that certain groups of psoriatics may develop skin cancer during or after PUVA treatment. In order to evaluate this risk in another population we re-examined 525 PUVA-treated Finnish psoriatics. The results were compared with the incidence of skin carcinomas in psoriatics treated with regimens other than PUVA and with the incidence of skin carcinomas in the general population of Finland.

PATIENTS AND METHODS

PUVA therapy has been used in Helsinki since May, 1976, at three different clinics under the supervision of the authors. The same PUVA cabin was used (PUVA-22, Airam Ltd, Helsinki, Finland) at all three clinics. An oral dose of approximately 0.6 mg/kg of 8-methoxypsoralen was given 2 hours before the UVA radiation. The initial UVA dose was about the same in all cases (1–1.5 J/cm²) and was usually increased gradually at weekly intervals. The maximum dose used was 14 J/cm². After the psoriatic lesions had cleared up the majority of patients continued on maintenance therapy given either once a week or twice a month. As a rule the patients were seen by the supervising dermatologist before the treatment, about once a month during the therapy and then at the end of it. When PUVA therapy was introduced in Finland it was generally agreed that no patients with a history of earlier skin carcinomas should receive this therapy, thus all such patients and also patients highly sensitive to sunlight were excluded from PUVA treatment.

All 568 patients with psoriasis who had received their first course of PUVA treatment before the end of 1978 were invited to take part in the study. The re-examination was carried out between October 1979 and February 1980. During this period 119 patients still on PUVA therapy and 406 other patients no longer on PUVA participated. Some of the remaining 43 patients could not be traced, others did not want to take part in the examination and a few had died from unrelated diseases. Therefore, altogether 525 (92%) of the 568 psoriatics were re-examined and included in the present study. The re-examination was carried out in all cases by one of authors. Special attention was paid to all skin lesions suspected of being malignant. All such lesions were excised and examined by light microscopy.

Since 1953 all cases of cancer in Finland have been reported to the Finnish Cancer Registry—the institute for statistical and epidemiological cancer research. The re-

Table I. *Clinical data of 525 PUVA-treated patients*

Males	274 (52.2%)
Females	251 (47.8%)
Mean age	43.2 years
Mean duration of psoriasis	16.9 years
Skin type I or II	41 (7.8%)
Skin type III or IV	484 (92.2%)
Earlier arsenic treatment	108 (20.6%)
Earlier ionizing radiation	19 (3.6%)
Earlier methotrexate treatment	9 (1.7%)

ported incidences of basal-cell and squamous-cell carcinomas in 1976 (Publication no. 27, Cancer Society of Finland, Helsinki, 1979) were used for comparison in the present study. The year 1976 was chosen because that was the year PUVA therapy was introduced in Finland. In 1976, a total of 1 033 psoriatics received hospital treatment for their skin disease in Finland. The hospital records of these patients were examined for the presence of either basal-cell or squamous-cell carcinoma. As all these patients were treated with methods other than PUVA and they serve as a control patient population at the start of PUVA therapy in Finland.

RESULTS

PUVA-treated patients

The clinical data obtained from the 525 PUVA-treated psoriatics in the present study are given in Table I and data regarding their PUVA therapy are shown in Table II. The series included almost equal numbers of males and females, whose mean age was 43 years. One of the patients had earlier had a carcinoma of the prostate and another a carcinoma of the breast, but both had been successfully treated more than 5 years before their PUVA treatment began. Only a small proportion of the patients (8%) had skin of type I or II, which is typical of very blond or red-haired individuals who tan poorly and sunburn easily. One-fifth of the patients had earlier received one or several courses of arsenic and in 19 cases there was a history of exposure to Grenz-rays 15–30 years before PUVA. According to patient histories X-rays had not been used for the treatment of psoriasis in any of the present cases. Methotrexate has been used very sparingly for the treatment of psoriasis in Finland and only 9 of the present patients had previously been on such therapy. The mean follow-up period since the beginning of PUVA treatment was 26 months (range 12–43 months). The total UVA dose was below 100 J/cm² in 107 patients and over 1 000 J/cm² in 20 patients (Table II).

During PUVA treatment or at re-examination, skin lesions suspected of being malignant were observed in 14 (3%) of the 525 patients. From these 14 patients a total of 23 biopsies were taken for microscopical examination (Table III). One of the lesions was a basal-cell carcinoma. The patient was a 75-year-old man who had had psoriasis for 7 years. He had never been treated with arsenic, ionizing radiation or methotrexate. The tumour was observed on the bald scalp of the patient after 33 sessions of PUVA treatment over 5 months (a total UVA dose of 234 J/cm²) when his psoriasis had completely cleared up. According to the patient the lesions had been present for several years and had obviously remained undetected at the beginning of PUVA therapy because of a thick, uniform psoriasis lesion covering his scalp. The patient has now been followed up for 16 months without PUVA and no further skin malignancies have been detected.

Two patients, 38- and 48-year-old males, had a similar clinical picture of solar keratosis on their trunk with ephelides-like spots as well as hypopigmented areas (Fig. 1). They had both been on long-term PUVA therapy with high UVA doses (a total of 268 and 287 UVA doses, 1916 and 2612 J/cm², respectively). The microscopical examination revealed foci of atypical epidermal cells with large vacuolated and prominent polymorphic nuclei (Fig. 2). There was also disarrangement of cells in the lower and middle parts of the Malphigian layers. The picture resembled that described by Hofmann

Table II. *Data on PUVA treatment*

	Number of treatments				Total UVA dose (J/cm²)				
	≤20	21–50	51–100	>100	≤100	101–200	201–500	501–1 000	>1 000
Number of patients (n=525)	72	255	147	51	107	137	187	74	20

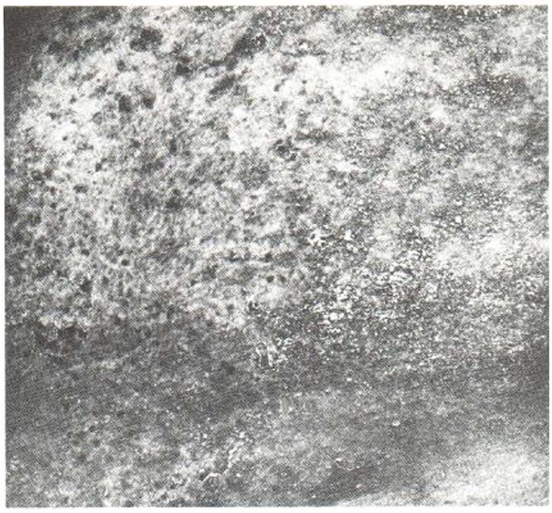

Fig. 1. Dirty-brown-coloured scales and hyperpigmented spots on the skin of the left shoulder in a 48-year-old man.

et al. (3) who designated it as a Bowenoid lesion. PUVA therapy was terminated in both cases and oral retinoid (RO 10-9359) was started, with doses ranging from 60–20 mg/day. Three months later a complete normalization of the epidermal changes was observed. Neither of these two patients had earlier been treated with arsenic or ionizing radiation but both had been treated with methotrexate for 6–12 months in the past. Both patients and the one with basal-cell carcinoma had skin of type III or IV. Skin biopsies were also taken from 11 other patients but revealed only benign lesions such as nevi, fibromas, warts, etc. (Table III).

Non-PUVA-treated patients and controls

In 1976 a total of 1 033 patients with psoriasis were treated in Finnish hospitals with regimens other than PUVA. According to the hospital records none of them had squamous-cell carcinoma but 4 of them (0.4%) had basal-cell carcinoma. All 4 were above the age of 50. Three of them had single, deep basal-cell corcinomas on their face. They had never been treated with arsenic, ionizing radiation or methotrexate. The fourth patient had multiple, superficial basal-cell carcinomas on the trunk and had been repeatedly treated with arsenic 20–30 years earlier.

In 1976, 1796 new cases of either basal-cell or squamous-cell carcinoma were reported in Finland. In this year the whole population was 4.7 million, which means a skin carcinoma frequency of 0.04%.

One of the present 525 PUVA-treated psoriatics was found to have skin carcinoma during a mean follow-up period of 2.2 years. The expected value calculated from the age-matched general population was 0.5 (Table IV). This difference is not significant. The expected value for psoriatics treated in hospital in 1976 with regimens other than PUVA was 0.7. This is significantly ($p<0.01$) lower than the observed value (Table IV).

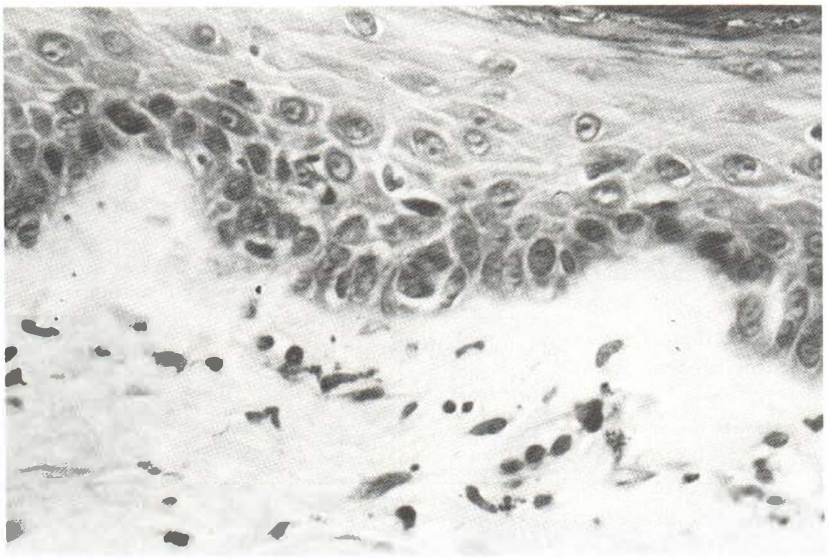

Fig. 2. Biopsy of hyperpigmented spot (Fig. 1). Foci of large vacuolated cells with prominent and polymorphic nuclei. Frequent mitoses (H & E, ×240).

Table III. *Histopathological findings in 14 PUVA-treated patients suspected of having malignant skin lesions*

	Number of lesions ($n=23$)	Number of patients ($n=14$)
Basal-cell carcinoma	1	1
Bowenoid lesions	7	2
Seborrhoeic keratosis	4	2
Benign nevi	5	4
Warts	1	1
Various benign lesions	5	4

DISCUSSION

The results of the present study indicated that PUVA therapy does not increase the risk of skin carcinomas over a relatively short follow-up period. Only one of the 525 patients examined was found to have skin carcinoma during or after PUVA treatment. The result is in contrast to that presented by Stern et al. (9), who found during an equally long follow-up period that 30 out of 1373 patients developed skin carcinomas. Obviously these contradictory results are due to differences between the two PUVA-treated patient populations. Stern et al. (9) found the highest risk of skin carcinomas in patients who had already had a skin carcinoma before PUVA treatment. According to our primary selection there were no such patients in our series. Another significant risk factor in the series of Stern et al. (9) was previous treatment with ionizing radiation. 27% of their patients had previously received such treatment, compared with only 4% of our cases. The third main risk factor found by Stern et al. (9) was skin of type I or II. Due to primary selection only 8% of our patients had such a sensitive skin. In agreement with the present study Stern et al. (9) did not observe any statistical increase in the frequencies of skin carcinomas in PUVA-treated psoriatics who had no previous history of skin carcinomas or treatment with ionizing radiation. Thus, it seems probable that with the same pre-selection of patients as in our study their results would have been quite similar to the present findings.

In contrast to PUVA-treated patients there was a significantly increased frequency of skin carcinomas in psoriatics who had been treated with methods other than PUVA in hospital in 1976. However, this difference is probably not real, but due rather to the fact that basal-cell carcinomas are often overlooked, except in individuals closely examined by dermatologists, as was the case with the present psoriatics treated in hospital. On the other hand, our findings do not support the concept of Kocsard (4), according to which psoriatics have a decreased tendency to develop skin malignancies.

Two of our patients developed Bowenoid lesions of the same type as described by Hofmann et al. (3). Both had earlier been treated with methotrexate, which was unusual in the present series. This indicates that previous methotrexate treatment may be a risk factor in PUVA therapy. However, Stern et al. (9) were unable to observe any correlation between methotrexate treatment and an increased risk of skin carcinomas during or after PUVA treatment. Both our patients with Bowenoid lesions belonged to the small group which had received the highest UVA doses. This may be the real explanation for this type of lesion, which in our cases was fortunately reversible. Although one-fifth of the present patients had been treated with arsenic in the past, the one patient with basal-cell carcinoma and two with Bowenoid lesions had never received arsenic. Stern et al. (9) did not mention how many of their patients had received arsenic but Hofmann et al. (3) reported Bowenoid lesions in one and Bowen's disease in another arsenic-treated patient during PUVA therapy. Their observations suggest that earlier intake necessitates close control during and after PUVA treatment.

In conclusion, the present study suggests that if the selection of psoriasis patients is careful, PUVA therapy involves no increased short-term risk of

Table IV. *Observed and expected skin carcinomas in PUVA-treated and in non-PUVA-treated psoriatics*

Patients	Carcinomas: Observed	Carcinomas: Expected[a]	*P*-value (Poisson distribution)
PUVA-treated psoriatics ($n=525$)	1[b]	0.5	n.s
Non-PUVA-treated psoriatics (in 1976, $n=1033$)	4	0.7	<0.01

[a] Calculated from age-matched incidences in Finland in 1976.
[b] During a mean follow-up period of 2.2 years.

developing skin carcinoma. However, a prospective study is needed to evaluate the long-term risks which PUVA and other therapeutic modalities of psoriasis may imply.

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REFERENCES

1. Bridges, B. & Strauss, G.: Possible hazards of photochemotherapy for psoriasis. Nature *283:* 523, 1980.
2. Epstein, J. H.: Risks and benefits of the treatment of psoriasis. New Engl J Med *300:* 852, 1979.
3. Hofmann, C., Plewig, G. & Braun-Falco, O.: Bowenoid lesions, Bowen's disease and keratoacanthomas in long-term PUVA-treated patients. Br J Dermatol *101:* 685, 1979.
4. Kocsard, E.: The rarity of solar keratoses in psoriatic patients: preliminary report. Austr J Dermatol *17:*65, 1976.
5. Parrish, J. A., Fitzpatrick, T. B., Tanenbaum, L. & Pathak, M. A.: Photochemotherapy of psoriasis with oral methoxsalen and longwave ultraviolet light. New Engl J Med *291:* 1207, 1974.
6. Roenigk, H. H., Jr, Farber, E. M., Lobitz, W., Stewart, W., Kligman, A., Petrozzi, J., Dobson, R., Robinson, H. L., Harber, L., Muller, S. A., Cram, D. L., Frost, P., Gladstein, A. & Levy, J.: Photochemotherapy for psoriasis: A clinical cooperative study of PUVA-48 and PUVA-64. Arch Dermatol *115:* 576, 1979.
7. Rogers, S., Marks, J., Shuster, S., Briffa, D. V., Warin, A. & Greaves, M.: Comparison of photochemotherapy and dithranol in the treatment of chronic plaque psoriasis. Lancet *i:* 455, 1979.
8. Scotto, J., Kopf, A. W. & Urbach, F.: Non-melanoma skin cancer among Caucasians in four areas of the United States. Cancer *34:* 1333, 1974.
9. Stern, R. S., Thibodeau, L. A., Kleinerman, R. A., Parrish, J. A., Fitzpatrick, T. B. et al.: Risk of cutaneous carcinoma in patients treated with oral methoxsalen photochemotherapy for psoriasis. New Engl J Med *300:* 809, 1979.
10. Wolff, K., Fitzpatrick, T. B., Parrish, J. A., Gschnait, F., Gilchrest, B., Hönigsmann, H., Pathak, M. A. & Tanenbaum, L.: Photochemotherapy for psoriasis with orally administered methoxsalen. Arch Dermatol *112:* 943, 1976.

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