Trioxsalen bath PUVA did not increase the risk of squamous cell skin carcinoma and cutaneous malignant melanoma in a joint analysis of 944 Swedish and Finnish patients with psoriasis

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Summary
It has been suggested that trioxsalen bath and ultraviolet (UV) A (PUVA) is associated with a very low or no risk of non-melanoma skin cancer, but the numbers of patients in individual studies have been limited. In order to attain statistically relevant information about the cancer risk associated with trioxsalen bath PUVA, two follow-up studies were combined and the joined cancer incidence was analysed among 944 Swedish and Finnish patients with psoriasis. The mean follow-up time for skin cancer was 14.7 years. Standardized incidence ratios (SIR) were calculated as a ratio of observed and expected numbers of cases. The expected numbers of cases were based on the national cancer incidence rates in the respective countries. There was no excess of squamous cell skin carcinoma [SIR 1.1, 95% confidence interval (CI) 0.2-3.2] or malignant melanoma (SIR 0.9, 95% CI 0.1-3.2) in the combined cohort. Basal cell skin carcinoma was not studied. The incidence of all non-cutaneous cancers was not increased (SIR 1.1, 95% CI 0.8-1.4). A threefold excess risk of squamous cell skin carcinoma after trioxsalen bath PUVA could therefore be excluded, which is a markedly lower risk than that associated with oral 8-methoxypsoralen PUVA. The result needs to be confirmed in a future follow-up, however, as the number of patients with high PUVA exposures was low.

Psoralen plus ultraviolet A (PUVA) is frequently used in psoriasis. 4,5,8-trimethyl-psoralen, i.e. trioxsalen bath PUVA is as effective as systemic 8-methoxypsoralen PUVA or 8-methoxypsoralen bath PUVA. It is 10–15 times more phototoxic than 8-methoxypsoralen, but seldom causes phototoxic burns. The incidence of cutaneous squamous cell carcinoma has been shown to be six to 12 times higher in patients treated with systemic 8-methoxypsoralen PUVA than in the general population. The risk is dose-dependent, being about 30-fold in the high-dose group.1,2 Trioxsalen bath PUVA, on the other hand, has not been found to be associated with non-melanoma skin cancer.1-6 The incidence of squamous cell skin carcinoma was not found to be increased among 597 Swedish trioxsalen bath PUVA patients in a 9-year follow-up,5 nor among 527 Finnish patients in an 11-year follow-up.6 The purpose of this study was to evaluate with greater statistical precision the risk of squamous cell skin carcinoma after trioxsalen bath PUVA for psoriasis by combining the results of the Swedish and Finnish trioxsalen bath PUVA follow-up studies with updated cancer incidence rates.

Materials and methods
The observed and expected numbers of cancers in the Swedish and Finnish trioxsalen bath PUVA follow-up studies were added up, and the observed numbers of cases were divided by the expected ones to obtain standardized incidence ratios (SIR). The expected numbers of cases were based on the national cancer incidence rates in the respective countries. The 95% confidence intervals (95% CI) for the SIRs were defined assuming that the observed number followed the Poisson distribution.7

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As most of the tumours in the category of ‘other malignant neoplasm of skin’ (ICD-9 code 173) are squamous cell skin carcinomas, the term ‘squamous cell skin carcinoma’ has been chosen to represent the whole category in this article. All the observed non-melanoma skin tumours were squamous cell skin carcinomas. Basal cell skin carcinoma was not included in this joint analysis, because it is not registered in the Swedish Cancer Registry.

Trioxsalen bath PUV A treatment is given in the same way in both countries and has been described in detail elsewhere.5,6,8

The Swedish follow-up study

The original study consisted of 597 patients from the Uppsala University Hospital treated with trioxsalen bath PUV A for the first time during 1975–85. For the present analysis, we excluded 180 patients with dermatoses other than psoriasis. The records of the remaining 244 men and 173 women with psoriasis were linked with the Swedish Cancer Registry. Incidences of skin cancer and common internal cancers were studied. The cancer follow-up for the internal cancers was started from the first trioxsalen bath PUV A treatment in 1975–85 and ended on 31 December 1987 giving a mean follow-up time of 9 years. The follow-up for skin cancers was expanded up to 31 December 1994 for the present study (results of the updated Swedish PUVA follow-up study will be published in toto elsewhere). The mean follow-up time for squamous cell skin carcinoma and cutaneous malignant melanoma was 16.9 years.

The Swedish Cancer Registry has been collecting cancer incidence data since 1958. The registry covers 96–97% of all types of cancer occurring in Sweden.9 The record linkage is performed automatically by using personal identification numbers.

The mean age at the first trioxsalen bath PUVA treatment was 43 years, range 14–88 years. Most patients were of skin types II or III. Data on PUVA and other psoriasis treatments were collected from the patients’ records till 31 December 1985. By then, 18 patients had received more than 200 treatments and three patients more than 400 J/cm² UV A. The mean cumulative UV A dose was 33 J/cm² and the average number of treatments was 55. None of the patients had received systemic 8-methoxypsoralen PUVA. UV A light was given with three UV A sources: PUV A 22 (Airam, Helsinki, Finland) and Waldmann UV 8001 K (Herbert Waldmann GmbH & Co.) emitting an average of 11.0 mW/cm² of UV A at the treatment distance were used for inpatients throughout the study period and for outpatients from 1990 onwards. Metec Helarium (Metec-Medizin-Technische Gmbh, Munich, Germany) with irradiance from 0.012–0.04 J/cm² up to 1.0 J/cm². The minimal phototoxic dose was not tested for the initial dose. No maintenance therapy was given.

The Finnish follow-up study

A cohort of 337 male and 190 female psoriatic patients from the Oulu University Hospital treated with trioxsalen bath PUVA initially during 1977–88 was linked with the Finnish Cancer Registry till 31 December 1995 (updated by 2 years since the original study6). The mean length of follow-up was now 12.4 years.

The Finnish Cancer Registry founded in 1952 runs cancer registration in Finland. Over 99% of malignancies are recorded.10 The computerized record linkage procedure uses personal identification numbers (assigned to all Finnish residents since 1 January 1967) as a key, and it has been found to be very reliable.11

The mean age at the first bath PUVA treatment was 44 years, range 14–88 years. Most patients were of skin types II or III. Data on PUVA and other psoriasis treatments were collected from the patients’ records till 31 December, 1993. By then, 65 patients had received more than 200 treatments and 17 patients more than 400 J/cm² UV A. The mean cumulative UV A dose was 65 J/cm² and the average number of treatments was 112. None of the patients had received systemic 8-methoxypsoralen PUVA. UVB radiation treatment was given to 320 of the patients. The exact cumulative UVB dose was not registered. All patients had received different topical treatments, and about 10% of the patients had been given systemic retinoids or methotrexate. The concentration of trioxsalen in the bath varied from 0.08 to 0.3 mg/L depending on the light sensitivity of the patient. UV A light was given with three UV A sources: PUVA 22 (Airam, Helsinki, Finland) and Waldmann UV 8001 K (Herbert Waldmann GmbH & Co.) emitting an average of 11.0 mW/cm² of UV A at the treatment distance were used for inpatients throughout the study period and for outpatients from 1990 onwards. Metec Helarium (Metec-Medizin-Technische Gmbh, Munich, Germany) with irradiance from 0.012–0.04 J/cm² up to 1.0 J/cm² UVC from 1975 to 1982. From 1983 onward, a Waldmann PUVA 3001 (Waldmann Werk fur Lichttechnik, Villingen-Schwenningen, Germany) equipped with 14 Sylvania PUVA fluorescent tubes and emitting 12 mW/cm² of UV A and 0.4 mW/cm² of UVB at the treatment distance was used. The average treatment period lasted for 4–8 weeks with 3 weekly treatments. The UV A dose was slowly increased from the initial 0.012–0.04 J/cm² up to 1.0 J/cm². The minimal phototoxic dose was not tested for the initial dose. No maintenance therapy was given.

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of 11·2 mW/cm² UV A and 0·4 mW/cm² UVB at the treatment distance was used in the outpatient department in 1986–90. The inpatients were treated daily and the outpatients three times a week up to about 15 times with UV A doses ranging from the initial 0·06±0·2 J/cm² up to 0·33±2·6 J/cm². The minimal phototoxic dose was not tested for the initial dose. Maintenance therapy was given to about half of the patients at 1–3 weeks intervals in 1977–85.

**Results**

There were altogether 944 patients (581 men and 363 women) in the combined cohort. The mean follow-up time was 14·7 years for squamous cell skin carcinoma and cutaneous malignant melanoma. No excess of squamous cell skin carcinoma was found (SIR 1·1, 95% CI 0·2±3·2) (Table 1). Three patients had one squamous cell skin carcinoma each and they had received 43, 125 and 160 trioxsalen bath PUVA exposures, respectively, by the time of data collection. Two cases of cutaneous malignant melanoma were observed in the cohort, while the expected number was 2·2 (Table 1). The incidence of basal cell skin carcinoma was not studied.

The mean follow-up time for non-cutaneous cancers in the combined cohort was 10·7 years. The incidence of all non-cutaneous cancers was similar to that in the general population. SIRs for kidney cancer and non-Hodgkin’s lymphoma were significantly increased (Table 2).

**Discussion**

A joint analysis of the Finnish and Swedish bath PUVA studies was meaningful due to the notable similarities between the cohorts. The main characteristics of the patients were similar. The patients were Caucasians of the same skin types. The treatment regimen with trioxsalen bath PUVA was almost the same in Finland as in Sweden. There were some differences in the spectrum of the UV A light sources. Different topical treatments were used during the PUVA treatment period in Finland, but not in Sweden. This study combined the results of the two largest follow-up studies on patients with psoriasis treated with trioxsalen bath PUVA. The study design was a historical cohort study, which is usually less accurate than a prospective study with regard to documentation of treatment data.

Previous studies have stated that trioxsalen bath PUVA is mutagenic in bacteria, but not carcinogenic in mice. The present study found no increase in the squamous cell skin carcinoma risk in patients with psoriasis treated with trioxsalen bath PUVA. A 3±2-fold or higher excess risk could be excluded with 97·5% probability. The risk estimate for squamous cell skin carcinoma (SIR 1·1) was markedly lower than the

### Table 1. Observed (O) and expected (E) numbers, standardized incidence ratios (SIR) with 95% confidence intervals (95% CI) for squamous cell skin carcinoma (SCC) and cutaneous malignant melanoma (CMM) in a joint analysis of 944 Finnish (cancer incidence 1977–1995) and Swedish (cancer incidence 1975–1994) patients with psoriasis treated with trioxsalen bath PUVA

<table>
<thead>
<tr>
<th>Gender</th>
<th>Males</th>
<th></th>
<th>Females</th>
<th></th>
<th>Both</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O</td>
<td>SIR</td>
<td>95% CI</td>
<td>O</td>
<td>SIR</td>
<td>95% CI</td>
</tr>
<tr>
<td>SCC</td>
<td>2</td>
<td>0.9</td>
<td>0.1–3·4</td>
<td>1</td>
<td>1.6</td>
<td>0.0–8·8</td>
</tr>
<tr>
<td>CMM</td>
<td>1</td>
<td>0.7</td>
<td>0.0–3·8</td>
<td>1</td>
<td>1.3</td>
<td>0.0–7·2</td>
</tr>
<tr>
<td>SCC+CMM</td>
<td>3</td>
<td>0.8</td>
<td>0.2–2·4</td>
<td>2</td>
<td>1.4</td>
<td>0.2–5·2</td>
</tr>
</tbody>
</table>

### Table 2. Observed (O) and expected (E) numbers of non-cutaneous cancers by site and standardized incidence ratios (SIR) with 95% confidence intervals (95% CI) in a joint analysis of 944 Finnish (cancer incidence 1977–1995) and Swedish (cancer incidence 1975–1987) patients with psoriasis treated with trioxsalen bath PUVA

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>O</th>
<th>E</th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All non-cutaneous sites</td>
<td>55</td>
<td>51.6</td>
<td>1.1</td>
<td>0.8–1·4</td>
</tr>
<tr>
<td>Pharynx</td>
<td>–</td>
<td>0.3</td>
<td>–</td>
<td>0.0–12</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>2</td>
<td>0.6</td>
<td>3.2</td>
<td>0.4–12</td>
</tr>
<tr>
<td>Stomach</td>
<td>4</td>
<td>3.3</td>
<td>1.2</td>
<td>0.3–3·1</td>
</tr>
<tr>
<td>Colon</td>
<td>3</td>
<td>3.2</td>
<td>0.9</td>
<td>0.2–2·7</td>
</tr>
<tr>
<td>Rectum</td>
<td>3</td>
<td>2.3</td>
<td>1.3</td>
<td>0.3–3·8</td>
</tr>
<tr>
<td>Liver</td>
<td>1</td>
<td>0.6</td>
<td>1.8</td>
<td>0.0–10</td>
</tr>
<tr>
<td>Larynx</td>
<td>–</td>
<td>0.6</td>
<td>–</td>
<td>0.0–6·6</td>
</tr>
<tr>
<td>Lung, bronchus</td>
<td>8</td>
<td>8.0</td>
<td>1.0</td>
<td>0.4–2·0</td>
</tr>
<tr>
<td>Breast</td>
<td>3</td>
<td>4.6</td>
<td>0.7</td>
<td>0.3–1·9</td>
</tr>
<tr>
<td>Prostate</td>
<td>4</td>
<td>7.0</td>
<td>0.6</td>
<td>0.2–1·5</td>
</tr>
<tr>
<td>Kidney</td>
<td>6</td>
<td>2.1</td>
<td>2.9</td>
<td>1.1–6·3</td>
</tr>
<tr>
<td>Bladder</td>
<td>3</td>
<td>2.7</td>
<td>1.1</td>
<td>0.2–3·2</td>
</tr>
<tr>
<td>Nervous system</td>
<td>1</td>
<td>1.7</td>
<td>0.6</td>
<td>0.0–3·2</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>5</td>
<td>1.4</td>
<td>3.7</td>
<td>1.2–8·6</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td>–</td>
<td>0.3</td>
<td>–</td>
<td>0.0–12</td>
</tr>
</tbody>
</table>
estimate obtained in the Swedish follow-up study on systemic 8-methoxypsoralen PUVA, in which the incidence of squamous cell skin carcinoma was 6-2 times higher (95% CI 4.1-9.0) among 4799 patients than in the general population. The retrospective design of that study, use of nation-wide cancer registry, ethnic background and skin types of the patients, the environment and the general treatment strategies for psoriasis were similar to the present study. The ratio of the SIRs of the Swedish systemic 8-methoxypsoralen PUVA study and the present joint analysis of trioxsalen bath PUVA was (6-2/1-1) 5.8 with 95% CI 1.8-30 [calculated with confidence interval analysis (CIA)]. Compared with patients who had received fewer than 200 oral 8-methoxypsoralen PUVA treatments, the ratio was (4.2/1.1) 3.9 with 95% CI 1.1-21.

In follow-up studies on systemic 8-methoxypsoralen PUVA, the risk of squamous cell skin carcinoma has remained small in the low-dose groups and increased dramatically in the high-dose groups. In the Swedish study on systemic 8-methoxypsoralen PUVA, the group of patients with more than 200 treatments had a 28 times (95% CI 14-49) higher risk of squamous cell skin carcinoma than the general population. Our study cohort included 83 patients who had been treated with bath PUVA more than 200 times. None of these patients had developed squamous cell skin carcinoma. As most of the patients had been exposed only to low doses of trioxsalen bath PUVA, the likelihood of not seeing any association with cancer increases.

If trioxsalen bath PUVA proves to be less carcinogenic than 8-methoxypsoralen PUVA, possible explanations might be lower UVA doses used in the treatment or different cellular effects compared with oral 8-methoxypsoralen PUVA. Trioxsalen bath PUVA has been found to be markedly more toxic for the lymphocytes than 8-methoxypsoralen PUVA, and it seems to mediate its effects through reduction of the number of lymphocytes rather than the number of keratinocytes.

According to the American PUVA follow-up study, the risk of cutaneous malignant melanoma was increased in patients with psoriasis treated with systemic 8-methoxypsoralen PUVA. We found no excess of melanoma in the present study.

Probably because of the increasing awareness of the non-melanoma skin cancer risk associated with systemic PUVA, 8-methoxypsoralen bath PUVA has been introduced in many countries during the past few years. Bath PUVA with 8-methoxypsoralen did not increase the skin cancer risk in a Finnish study on 158 patients after a mean follow-up of 7-6 years. In a Japanese cohort of 214 patients with psoriasis treated with topical 8-methoxypsoralen cream PUVA one patient developed multiple basal cell carcinomas about 12 years after the first PUVA treatment. No other cases of cutaneous cancer were found.

The increased incidence rates for kidney cancer and non-Hodgkin’s lymphoma may be due to chance and need to be confirmed in other follow-up studies. The overall cancer risk was not increased.

In conclusion, the statistical power of this analysis was large enough to exclude a threefold excess risk of squamous cell skin carcinoma, which is a markedly lower risk than that seen earlier with oral 8-methoxypsoralen PUVA. A larger cohort of patients with high PUVA exposures is still needed though, before the carcinogenicity of tri-oxsalen bath PUVA can be determined with certainty.

Acknowledgments
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