# Oral Psoralen and Ultraviolet-A Light (PUVA) Treatment of Psoriasis and Persistent Risk of Nonmelanoma Skin Cancer

*Robert S. Stern, Elissa J. Liebman, Liisa Väkevä, and the PUVA Follow-up Study**

***Background/Methods:*** **The treatment of psoriasis with high-dose exposure to oral psoralen and ultraviolet-A light (i.e., PUVA) substantially increases the risk of cutaneous squamous cell cancer, but not of basal cell cancer, within a decade of beginning treatment. To assess the persistence of cancer risk among individuals treated with PUVA, including those who discontinued therapy long ago and those without substantial exposure to other carcinogens, we prospectively studied a cohort of 1380 patients with psoriasis who were first treated during the period from January 1, 1975, through October 1, 1976, and evaluated risk factors associated with the development of cutaneous squamous cell cancers and basal cell cancers after 1985.** ***Results:*** **From 1975 through 1996, 237 patients developed 1422 cutaneous squamous cell cancers. From 1986 through 1996, 135 (12.5%) of 1081 patients without a prior squamous cell cancer developed 593 such tumors. From 1975 through 1997, 247 patients developed 1042 basal cell cancers; these patients included 151 individuals with a first basal cell cancer after 1985. Among those without a squamous cell or a basal cell cancer in the first decade of the prospective study, a strong dose-related increase in the risk of squamous cell cancer was observed in the subsequent decade (adjusted relative risk [⩾337 treatments versus <100 treatments] = 8.6; 95% confidence interval = 4.9–15.2). Risk of basal cell cancer was substantially increased only in those patients exposed to very high levels of PUVA (⩾337 treatments).** ***Conclusions:*** **High-dose exposure to PUVA is associated with a persistent, dose-related increase in the risk of squamous cell cancer, even among patients lacking substantial exposure to other carcinogens and among patients without substantial recent exposure to PUVA. Exposure to PUVA has far less effect on the risk of basal cell cancer. The use of PUVA for psoriasis should be weighed against the increased cancer risk. [J Natl Cancer Inst 1998;90:1278–84]**

Since its development in 1974, oral methoxsalen photochemotherapy, i.e., psoralen and ultraviolet-A light (PUVA), has been widely used to treat patients with psoriasis *(1)*. PUVA treatment is mutagenic and carcinogenic *(2)*. Both European and U.S. studies *(3–6)* have demonstrated that patients exposed to high doses of PUVA therapy have a significantly increased risk of squamous cell carcinoma of the skin. These data largely reflect the experience of patients within the first decade after starting PUVA therapy. Some investigators *(7)* claim that PUVA acts largely as a promoter of squamous cell cancer. If this is true, this risk is likely to be greatest among patients with substantial previous exposure to other cutaneous carcinogens and would diminish if use of PUVA declines. A comparable increase in the risk of basal cell cancer has not been observed, but epidemiologic studies *(8,9)* suggest that the interval between exposure to a carcinogen and tumor development may be longer for basal cell cancer than for squamous cell cancer.

In the general U.S. population, most (about 65%) squamous cell cancers and basal cell cancers occur on the head and neck *(10–12)*. Most patients using PUVA shield their head and neck for at least some of each treatment. In addition to less exposure to PUVA than other sites, the head and neck are most often exposed to sunlight, the most important risk factor for nonmelanoma skin cancer in the general population *(13)*. Therefore, we expected that the excess and attributable risk of skin tumors due to PUVA might be less for the head and neck than for other body sites.

The persistence of an increased risk of squamous cell cancer after declining PUVA usage, the occurrence of excess tumors among patients who survived at least a decade without a tumor, and a higher risk of appearance of tumors on anatomic sites other than the head and neck would all suggest that PUVA is a complete carcinogen. If this is the case, PUVA should be considered carcinogenic for all patients with substantial lifetime exposure to this therapy. We have conducted a prospective study to assess the persistence of cancer risk among all treated patients, including those who discontinued treatment long ago or lack substantial exposure to other carcinogens.

## Patients and Methods

At the time they enrolled in the PUVA study, all patients provided written informed consent. The PUVA Follow-up Study was approved by the institutional review boards at the participating centers. During the period from January 1, 1975, through October 1, 1976, a total of 1380 patients were enrolled in a 16-university center prospective study[1] that was designed to assess the long-term risks and benefits of PUVA therapy. The mean age of the patients at study entry was 44 years, and 65% of the cohort were male. Each patient's exposure to alternative carcinogens, such as ionizing radiation (grenz rays or x-rays for the treatment of psoriasis), ultraviolet-B (UVB) radiation, tar, and methotrexate, both before and after exposure to PUVA was documented. Patients were placed on a standard PUVA protocol. This protocol entails a patient receiving a dose of 0.4–0.6 mg/kg psoralen orally, followed 1.5–2.0 hours later by a UVA treatment administered with the patient standing in an ultraviolet irradiation unit. The most common unit used is an approximately 7 foot vertical enclosure with an interior

**Affiliation of authors:* Department of Dermatology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.

*Correspondence to:* Robert S. Stern, M.D., Department of Dermatology, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Ave., Boston, MA 02215 (e-mail: rstern@bidmc.harvard.edu).

*See* ''Notes'' following ''References.''

composed of fluorescent bulbs with emissions in the range of 320–400 nm. The patients are started on low doses of UVA, generally 1.5–5 J/cm$^2$ depending on their photosensitivity. During the clearing phase, the patients undergo two or three light treatments per week. The dose of UVA is gradually increased with each treatment according to the degree of erythema or pigmentation produced. The patients typically reach a maximum UVA dose of 8–15 J/cm$^2$. As their disease improves, the patients receive fewer light treatments per week and slowly taper off therapy. When the patients' disease flared, they were treated again with PUVA or other therapies for psoriasis as determined by their physician. These patients have been followed every year since enrollment, regardless of whether they continued to use PUVA *(3,4).* On average, every 15 months since enrollment, the study personnel interviewed cohort patients. Since 1989, we have used telephone interviews, completing the 18th cycle of interviews in 1997. In each cycle, about 90% of surviving enrollees are interviewed. They are asked about skin cancer development, general medical problems, and current psoriasis therapy. Each time a patient reports a skin cancer, the diagnosis is confirmed on the basis of histologic findings as read by a board-certified pathologist. During the period from 1977 through 1989, eight cycles of study-sponsored, structured follow-up physical examinations were conducted. Most study patients have severe psoriasis and are under regular dermatologic care.

Study interviews document exposure to PUVA therapy and other treatments for psoriasis including UVB radiation, topical tar, and methotrexate. Both patient interviews and the physical examinations focus on the detection of skin cancers and cancers at other body sites.

Overall and separately for the head and neck and other body sites, we assessed risk factors for the development of squamous cell cancer and basal cell cancer of the skin occurring more than 10 years after first treatment with PUVA. We separately considered the occurrence of squamous cell or basal cell tumors among the surviving patients who did not have skin cancer of that type detected during the first decade of study—from enrollment in the study (January 1, 1975, through October 1, 1976) to December 31, 1985—and those with a tumor detected in the first decade. In addition to assessing overall risk, we separately analyzed risk factors for tumors located on the head and neck and other body sites.

We classified PUVA exposure according to the number of treatments recorded at the follow-up interview closest to January 1, 1986, and by the number of PUVA treatments received subsequent to this interview or up to the development of a first skin cancer of that type (Table 1). The cohort was divided into the following four PUVA dose categories according to the number of PUVA treatments received prior to January 1, 1986: 1) fewer than 100 treatments, 2) 100–159 treatments, 3) 160–336 treatments, and 4) 337 treatments or more. We defined the highest dosage group as the number of treatments received by the top decile of cohort members who survived to 1986 without a squamous cell cancer (i.e., ⩾337 PUVA treatments).

As in prior analyses, we characterized exposure to other potential cutaneous carcinogens as high or not high (low) by use of the following definitions of high: topical tar other than shampoos (high dose, ⩾45 months), UVB therapy (high dose, ⩾300 treatments), methotrexate (high dose, ⩾208 weeks of use; methotrexate is generally given at a dose of 7.5–25 mg/week), all as of 1989, and documentation of any exposure to x-rays or grenz rays for treatment of psoriasis at entry into the study *(4).*

For all patients without a squamous cell cancer or basal cell cancer as of January 1, 1986, on the basis of age-, sex-, and geographic area-specific rates, we calculated the expected number of tumors of each type separately on the head or neck for the period 1986 through 1996 (and for basal cell cancer through 1997) for each stratum defined by levels of exposure to PUVA up to January 1, 1986, and PUVA therapy after 1985 as defined in Table 1, by levels of exposure to UVB radiation/tar therapy and methotrexate, and by whether ever exposed to x-rays/grenz rays for treatment of psoriasis. We first calculated the relative risk (RR) of each type of skin cancer compared with that expected on the basis of population incidence rates, counting as an incident event only one tumor in each calendar year (population rates) even if a patient developed multiple tumors that year *(13).* To calculate the site-specific expected number of tumors, we assumed, on the basis of previous studies *(10–12),* that in the general population about 65% of squamous cell cancers and basal cell cancers occurred on the head and neck and 35% developed on all other skin sites.

We next examined the relationship between various exposures (or levels of exposure) for both types of skin cancer and both body areas (head and neck and other areas); we counted each patient with a specific type of nonmelanoma cancer at either site (head/neck and other) only once. These analyses excluded patients with a tumor of that type at that site prior to 1986. In our multivariate analyses, to determine the association between exposure to PUVA and the risk of a first squamous cell cancer or basal cell cancer overall and on each of the two anatomic areas after 1985, we used Poisson regression models to adjust observed counts for other exposures that were significant predictors of risk in the univariate analyses. We also tested for interactions between significant predictors of risk *(14).* All statistical tests are two-sided.

**Table 1.** Number (and percent) of cohort patients followed after 1985 and number with a first squamous cell cancer (SCC) or basal cell cancer (BCC) by treatment duration and by level of exposure to PUVA*

| Exposure | No. (%) of patients with cancers developing after 1985 | | |
|---|---|---|---|
| | Total | SCC | BCC |
| PUVA treatments up to 1986† | | | |
| <100 | 435 (37) | 18 (13) | 29 (19) |
| 100–159 | 243 (21) | 15 (11) | 30 (20) |
| 160–336 | 373 (32) | 68 (50) | 58 (38) |
| ⩾337 | 132 (11) | 34 (25) | 34 (23) |
| Total‡ | 1183 | 135 | 151 |
| PUVA treatments after 1985 | | | |
| <50 | 877 (74)§ | 66 (49) | 99 (66) |
| ⩾50 | 306 (26) | 69 (51) | 52 (34) |
| Total‡ | 1183 | 135 | 151 |

*PUVA = oral psoralen and ultraviolet-A light.

†Based on data from interview nearest to and including January 1, 1986.

‡Excludes 197 patients who died before 1986 or who lack follow-up data after December 31, 1985.

§Includes 669 patients who had no PUVA treatments after 1985.

## Results

From enrollment (January 1, 1975, through October 1, 1976) to October 2, 1996, a total of 1422 cutaneous squamous cell carcinomas were detected in 237 (17.2%) of 1380 patients. Of these 237 patients, 102 (43%) had a first tumor detected before January 1, 1986 *(15),* and developed a total of 829 squamous cell cancers. As of 1986, there were 1081 surviving patients without a squamous cell cancer. From 1986 through 1996, 135 (12.5%) of these 1081 patients developed a first squamous cell cancer after the last interview in 1985. These 135 patients had a total of 593 squamous cell carcinomas detected during that period.

From enrollment (January 1, 1975, through October 1, 1976) to September 1, 1997, a total of 1042 basal cell cancers were detected in 247 (17.9%) of 1380 patients. Ninety-six (39%) of these 247 patients developed their first basal cell cancer before 1985 *(15),* and 151 (61%) did so after 1985. On average, about three times as many tumors of both types were detected each year after 1985 compared with the average number detected each year between 1975 and 1985. Therefore, the incidence was more than three times higher after 1986 than before 1986 (Table 2), increasing from three cancers to 10 cancers per 100 person-years for squamous cell cancer and from two cancers to seven cancers per 100 person-years for basal cell cancer.

Table 3 presents the RR compared with that expected on the basis of population incidence rates for each type of cancer at any site after 1985 among the surviving cohort members without a skin cancer of that type detected by January 1, 1986. The risk of squamous cell cancer was elevated more than that of basal cell cancer, both overall and at every dose level (Table 3). When tumors occurring after 1985 for all cohort patients were included

**Table 2.** Total number of nonmelanoma skin cancers by type of tumor, date of detection, and anatomic site, detected since enrollment among cohort patients receiving PUVA* treatments

| Tumor type and anatomic site | Date of detection | | |
|---|---|---|---|
| | Before 1986† | Beginning in 1986 | Total‡ |
| Squamous cell cancer§ | | | |
| Head and neck | 43 | 118 | 161 |
| Other sites | 328 | 920 | 1248 |
| Unknown site | 4 | 9 | 13 |
| Total‡ | 375 | 1047 | 1422 |
| Basal cell cancer‖ | | | |
| Head and neck | 139 | 441 | 580 |
| Other sites | 82 | 380 | 462 |
| Total‡ | 221 | 821 | 1042 |

*PUVA = oral psoralen and ultraviolet-A light.

†Tumor detection since enrollment (1975–1976) to December 31, 1985.

‡Anatomic site could not be determined for 13 squamous cell cancers (four in the before 1986 count and nine in the beginning in 1986 count).

§Detected as of September 1996.

‖Detected as of September 1997.

(i.e., including those who had tumors in both the first and second decades after the treatment), among patients with exposure to at least 337 treatments, and only one squamous cell cancer per year was counted, the risk of squamous cell cancer after 1985 was increased more than 100-fold compared with that expected on the basis of population incidence data (RR = 104; 95% confidence interval [CI] = 88.3–121.9). Except for patients exposed to at least 337 PUVA treatments, the risk of basal cell cancer was elevated only moderately compared with that expected on the basis of general population rates for the United States (Table 3).

After 1985, a total of 54 patients developed a first squamous cell cancer of the head and neck and 119 developed a first tumor of this type on other anatomic sites. After 1985, there were 106 patients with a first head and neck basal cell cancer and 95 with a first skin tumor of this type on other body sites. When we counted only a first tumor at each site in patients who had tumors in the first and/or second decade, after 1985 the risk of squamous cell cancer was increased fivefold (RR = 5.2; 95% CI = 3.9–6.7) on the head and neck and 21-fold (RR = 21.2; 95% CI = 17.6–25.8) on other body sites compared with that expected on the basis of population rates. For basal cell cancer, the corresponding RRs were 2.5 (95% CI = 2.1–3.1) and 4.2 (95% CI = 3.4–5.2).

**Table 3.** Relative risk (RR) and 95% confidence interval (CI) of any first squamous cell cancer (SCC) or first basal cell cancer (BCC) after 1985, following PUVA* therapy among cohort patients without a skin cancer of that type detected before 1986 compared with the number expected in the general population†

| Total PUVA treatments through 1986 | Type of tumor | | | |
|---|---|---|---|---|
| | SCC | | BCC | |
| | RR | 95% CI | RR | 95% CI |
| <100 | 5.1 | 3.5–7.2 | 1.7 | 1.2–2.3 |
| 100–159 | 8.4 | 5.6–12.1 | 3.9 | 3.0–5.0 |
| 160–336 | 26.5 | 22.2–31.4 | 4.5 | 3.5–5.7 |
| ⩾337 | 68.5 | 54.9–84.5 | 11.7 | 9.3–14.5 |
| All dosages | 17.6 | 15.6–19.8 | 4.1 | 3.7–4.6 |

*PUVA = oral psoralen and ultraviolet-A light.

†Adjusted for age, sex, and area of residence; only one tumor of a given type is counted each year.

Table 4 presents the results of the univariate analysis relating level of exposure to potentially carcinogenic treatments of psoriasis to the risk of squamous cell carcinoma for each site. These analyses are all adjusted for age, sex, and area of residence. The risk of a first squamous cell cancer after 1985 was substantially increased even among patients with as few as 160 PUVA treatments by 1986 compared with patients with exposure to fewer than 100 PUVA treatments (not head and neck, RR = 4.5 [95% CI = 2.5–8.0]; head and neck, RR = 7.1 [95% CI = 2.7–18.3]). The pattern of increasing risk with increasing exposure to PUVA was similar for tumors occurring on the head and neck and those occurring on other sites. Except for exposure to PUVA, higher levels of exposure to other potential carcinogens did not have a substantial impact on risk of squamous cell cancer (Table 4). Higher levels of exposure to PUVA in both the first and second decades were associated with substantially increased risks of squamous cell cancer. After adjustment for all significant risk factors including exposure to PUVA and considering all patients who had cancer in the first and/or the second decade, the risk of squamous cell cancer was four times higher for body sites other than the head and neck than on the head and neck, which are often shielded during PUVA treatments (odds ratio [OR] = 4.0; 95% CI = 2.9–5.6).

For basal cell cancer, only exposure to at least 337 PUVA

**Table 4.** Odds ratio (OR) and 95% confidence interval (CI) for a first squamous cell cancer following PUVA* therapy on head and neck and other body sites after 1985 by exposure (univariate analysis)†

| Exposure | Body site | | | |
|---|---|---|---|---|
| | Not head and neck | | Head and neck | |
| | OR | 95% CI | OR | 95% CI |
| PUVA treatments through 1985 | | | | |
| <100 | 1‡ | | 1‡ | |
| 100–159 | 1.8 | 0.9–3.7 | 1.5 | 0.4–5.6 |
| 160–336 | 4.5 | 2.5–8.0 | 7.1 | 2.7–18.3 |
| ⩾337 | 10.0 | 5.4–18.6 | 15.0 | 5.4–41.2 |
| All ⩾100 | 4.2 | 2.5–7.1 | 5.1 | 2.2–12.0 |
| PUVA treatments after 1985 | | | | |
| <50 | 1‡ | | 1‡ | |
| ⩾50 | 3.3 | 2.3–4.8 | 1.6 | 0.9–2.8 |
| UVB/tar§ | | | | |
| Low | 1‡ | | 1‡ | |
| High | 1.7 | 1.1–2.5 | 1.5 | 0.8–2.7 |
| Methotrexate‖ | | | | |
| Low | 1‡ | | 1‡ | |
| High | 1.4 | 0.9–2.3 | 2.0 | 1.0–3.7 |
| Grenz rays/x-rays¶ | | | | |
| Not exposed | 1‡ | | 1‡ | |
| Exposed | 1.0 | 0.7–1.6 | 1.6 | 0.9–2.8 |

*PUVA = oral psoralen and ultraviolet-A light.

†All analyses were adjusted for age, sex, and area of residence.

‡Referent stratum.

§Ultraviolet-B radiation (UVB)/tar high dose = 300 or more treatments of UVB and 45 months or more of topical tar application.

‖Methotrexate high dose = 208 weeks or more of use.

¶Exposure or no exposure of patients to grenz rays and/or x-rays for therapeutic purposes.

treatments was associated with a substantial (more than threefold) increase in risk compared with that for members of the cohort exposed to low doses (fewer than 100 treatments) (Table 5). Recent utilization of PUVA was not significantly associated with increased risk of basal cell cancer at either site (Table 5). After adjustment for all significantly associated risk factors (UVB radiation, tar, x-rays, and grenz rays), the risk of a basal cell cancer was only very modestly higher on sites other than the head and neck compared with the head and neck (OR = 1.6; 95% CI = 1.2–2.2).

Table 6 presents the results of the multivariate analysis that includes all exposures associated with a significantly increased risk for that type of tumor on either anatomic area. The results of the multivariate analyses demonstrate that, among patients who did not have a tumor detected during the first 10 years after starting PUVA treatment, the level of exposure to PUVA was the most important risk factor for squamous cell cancer in the subsequent decade. Only very high exposure to PUVA by 1985 (⩾337 PUVA treatments) was associated with a substantially increased incidence of a first basal cell cancer in the subsequent decade. The extent of recent PUVA treatment was weakly but significantly associated with the risk of squamous cell cancer but not of basal cell cancer.

## Discussion

Except for an earlier report by our study group *(4)* that included 13 years of follow-up, reports of the risk of nonmelanoma cancer among those treated with PUVA are generally confined to a decade or less of observation *(3,4,7,15–22)*. Among studies with substantial power and reasonably complete follow-up *(4,15–17,23)*, patients with high levels of exposure to PUVA had an increased risk of squamous cell carcinoma. Not only are these studies of limited duration but also a large proportion of patients studied were on active treatment with PUVA. Therefore, these reports provide only limited information about the long-term effects of PUVA or the persistence of these effects after use of PUVA treatment diminishes. Our cohort's melanoma experience and the long latency between exposure to many carcinogens and the development of cancer further argue that data from shorter studies probably do not sufficiently define the full carcinogenic risk of PUVA therapy *(24)*. Additional reasons for concern that early and late carcinogenic effects of PUVA might differ are the multiple effects of PUVA on the skin. PUVA is immunosuppressive in the skin *(25)*. As a result, during active treatment, it may increase the risk of skin cancer in a pattern similar to that observed with persons undergoing immunosuppressive therapy *(26)*. In this circumstance, one expects the highest risk to be observed in those with previous exposure to other carcinogens and to diminish if treatment is stopped. PUVA, however, is not only immunosuppressive but also mutagenic; moreover, it is a potent photocarcinogen in animals *(2,27)*. With the passage of time and because the utilization of PUVA has decreased markedly among members of our cohort, it is now possible to evaluate the persistence of the carcinogenic effect of PUVA and to determine whether the increased risks of tumors are largely confined to persons with substantial exposure to other carcinogens.

To our knowledge, our cohort was the first large group to

**Table 5.** Odds ratio (OR) and 95% confidence interval (CI) for a first basal cell cancer following PUVA* therapy on head and neck and other body sites after 1985 by exposure (univariate analysis)†

| | Body site | | | |
|---|---|---|---|---|
| | Not head and neck | | Head and neck | |
| Exposure | OR | 95% CI | OR | 95% CI |
| PUVA treatments through 1985 | | | | |
| <100 | 1‡ | | 1‡ | |
| 100–159 | 2.8 | 1.4–5.3 | 1.6 | 0.9–2.9 |
| 160–336 | 2.6 | 1.4–4.8 | 1.9 | 1.1–3.2 |
| ⩾337 | 5.9 | 3.1–11.5 | 4.4 | 2.5–7.8 |
| All (⩾100) | 3.01 | 1.79–5.23 | 1.68 | 0.92–3.07 |
| PUVA treatments after 1985 | | | | |
| <50 | 1‡ | | 1‡ | |
| ⩾50 | 1.4 | 0.9–2.2 | 1.4 | 0.9–2.1 |
| UVB/tar§ | | | | |
| Low | 1‡ | | 1‡ | |
| High | 2.0 | 1.3–3.1 | 1.4 | 0.9–2.1 |
| Methotrexate‖ | | | | |
| Low | 1‡ | | 1‡ | |
| High | 1.8 | 1.1–2.9 | 1.0 | 0.6–1.7 |
| Grenz rays/x-rays¶ | | | | |
| Not exposed | 1‡ | | 1‡ | |
| Exposed | 1.9 | 1.2–2.9 | 1.4 | 0.9–2.1 |

*PUVA = oral psoralen plus ultraviolet-A light.

†All analyses were adjusted for age, sex, and area of residence.

‡Referent stratum.

§Ultraviolet-B radiation (UVB)/tar high dose = 300 or more treatments of UVB and 45 or more months or more of topical tar application.

‖Methotrexate high dose = 208 weeks or more of use.

¶Exposure or no exposure of patients to grenz rays and/or x-rays for therapeutic purposes.

**Table 6.** Multivariate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for a first squamous cell cancer and first basal cell cancer of the skin after 1985 after exposure to PUVA* and other therapies†

| | Squamous cell cancer | | Basal cell cancer | |
|---|---|---|---|---|
| Exposure | OR | 95% CI | OR | 95% CI |
| PUVA treatments through 1985 | | | | |
| <100 | 1 | | 1 | |
| 100–159 | 1.6 | 0.9–3.1 | 2.0 | 1.3–3.1 |
| 160–336 | 4.5 | 2.7–7.4 | 2.1 | 1.4–3.1 |
| ⩾337 | 8.6 | 4.9–15.2 | 4.7 | 3.1–7.3 |
| PUVA treatments after 1985, ⩾50 versus <50 | 1.4 | 1.0–2.0 | ‡ | |
| UVB/tar,§ high versus low | 1.4 | 1.0–2.0 | 1.5 | 1.1–2.0 |
| Methotrexate,‖ high versus low | 1.3 | 0.9–1.9 | 1.1 | 0.7–1.5 |
| Grenz rays/x-rays,¶ exposed versus not exposed | ‡ | | 1.5 | 1.1–2.0 |

*PUVA = oral psoralen plus ultraviolet-A light.

†Each estimate was simultaneously adjusted for all other significant risk factors as well as for age, sex, geographic area of residence, and anatomic site (head and neck or other). PUVA treatments of <100 exposures was the referent stratum.

‡Not a significant risk factor for this type of tumor in univariate analysis.

§Ultraviolet-B radiation (UVB)/tar high dose = 300 or more treatments of UVB and 45 or more months of topical tar application.

‖Methotrexate high dose = 208 weeks or more of use.

¶Exposure or no exposure of patients to grenz rays and/or x-rays for therapeutic purposes.

utilize PUVA treatments in the United States. Of the 1380 patients originally enrolled in the PUVA study, 984 were still alive in early 1996. During two decades of prospective study, these patients have developed more than 2900 squamous cell carcinomas, squamous cell carcinoma *in situ*, and basal cell cancers, an average of more than two nonmelanoma skin cancers per enrollee.

We separately studied risk factors for squamous and basal cell cancers for a 10-year period beginning 10 years after first exposure to PUVA. Within our cohort, there was a significant and substantial absolute and dose-dependent increase in the risk of squamous cell carcinoma. Overall from 1986 to 1996, cohort patients with at least 337 PUVA treatments by 1986 had a more than 100-fold increase in the risk of squamous cell cancer compared with that expected from population incidence rates. In analyses that excluded cohort members with a squamous cell cancer detected in the first decade of the prospective study (from enrollment to 1986), surviving patients exposed to fewer than 100 treatments in the first decade had only a fivefold increase in the risk of squamous cell carcinoma. However, comparable patients who had received at least 337 PUVA treatments by 1986 had a nearly 70-fold increase in this risk in the subsequent decade. Risks for basal cell cancer were much less dramatic.

We believe that the incidence rates we used to calculate the expected numbers of tumors of each type are the most appropriate available to adjust for age, sex, and area of residence *(13)*. RR estimates that compare our cohort's experience with that of the general population are subject to a number of potential biases. The exclusion of patients with both basal and squamous cell cancers from the calculations of the basal cell cancer incidence provides an upward bias in RR estimates of about 7% for basal cell cancer RR. Less complete ascertainment in the federal survey or a temporal increase in skin cancer incidence in the general population would also upwardly bias these estimates. In our primary analyses, we excluded the patients at highest risk (i.e., those with a tumor in the prior decade). This substantially lowered our RR estimate. Since many patients treated with PUVA develop multiple tumors in a year, our counting only one tumor per year per patient probably underestimated the true RR of these tumors in our cohort compared with the general population.

The incidence of both squamous cell carcinoma and basal cell carcinoma has tripled in the second decade compared with the first decade of prospective study. At the same time, the proportion of cohort patients utilizing PUVA and the intensity of treatment among those who continue to rely on PUVA have diminished greatly. By 1996, we documented more than 274 000 PUVA treatments in our cohort. About 80% of these treatments were provided from 1975 to 1985, and only 40% of the original cohort had any recorded exposure to PUVA after 1985. In spite of the substantial reduction in the use of PUVA and even after exclusion of those at highest risk for skin cancer (i.e., members of the cohort who had developed a tumor of a specific type in the first decade), skin cancer incidence was still higher in the second than in the first decade of prospective study.

A substantially increased risk in the second decade of both squamous and basal cell cancers among persons who survived the first decade without a skin cancer of that type supports the hypothesis that the carcinogenic risks of PUVA are not confined to those with substantial prior exposure to other carcinogens. This finding indicates that the carcinogenic effects of PUVA are unlikely to solely reflect the immunosuppressive effects of PUVA in the skin, which diminish after curtailment of treatment *(28)*.

The primary risk factor for squamous cell cancer after 1985 was the level of exposure to PUVA by 1986. After adjustment for PUVA exposure, sites other than the head and neck that are most exposed to PUVA were at four times higher risk than the head and neck. Treatments after 1985 also added to the risk of squamous cell cancer on sites other than the head and neck (which are often shielded for at least some of each treatment). The higher risk associated with continued PUVA treatment after 1985 for sites other than the head and neck may reflect the increased use of shielding of the face and neck as the carcinogenic risk of PUVA became known *(3,4,15)*. The very limited additional risk associated with continued treatment after 1985 is further evidence that PUVA was not now acting primarily as a promoter.

The risks associated with high levels of exposure to other carcinogenic treatments for psoriasis among patients who had survived for at least a decade without a squamous cell cancer were all small; none exceeded a twofold increase. Except for therapeutic ionizing radiation for which we compared any exposure with no exposure, our analysis of other risk factors included low-dose-exposed patients in the referent stratum. Therefore, our estimates of the risk attributable to exposure to high doses of tar, UVB, or methotrexate might underestimate the carcinogenic effects of these exposures, particularly if risk is not dose dependent. Our multivariate analysis confirmed these relationships. After adjustment for age, sex, area of residence, and other exposures, the risk of squamous cell carcinoma was significantly increased among patients with 160 or more exposures in the first decade and was increased more than eightfold among those individuals with more than 336 exposures compared with patients exposed to fewer than 100 PUVA treatments.

The relationships between the risk of basal cell cancer and exposure to PUVA among individuals who had survived for a decade without a basal cell cancer were very different from those observed for squamous cell cancer. Overall, the incidence of basal cell cancer was elevated only modestly. Among patients with fewer than 100 exposures, the risk of a first basal cell cancer on the head and neck was not significantly elevated compared with that expected from population incidence data, and the risk of a first basal cell cancer on other anatomic sites was at most modestly increased among patients with little exposure to PUVA. Only among patients with very high levels of exposure to PUVA in the first decade was a substantial increase in the risk of basal cell cancer observed.

Our data that now span 20 years document a persistent and substantial increase in the risk of squamous cell carcinoma in patients following high-dose exposure to PUVA. This risk pertains to all patients with substantial exposure to PUVA, even those without substantial exposure to other carcinogens and with little exposure to PUVA in recent years. Patients developing a first squamous cell cancer in the second decade after starting PUVA were younger and had fewer other risk factors for skin cancer than those who developed these tumors in the first de-

cade. Only patients exposed to very high levels of PUVA had a substantially increased risk of basal cell cancer, and the magnitude of this increase in risk was still far lower than that seen for squamous cell cancer. Recent use of PUVA did not substantially affect the risk of basal cell cancer. These findings are consistent with epidemiologic studies relating sunlight exposure and basal cell cancer *(8,9)*. These studies suggest that the latency between carcinogenic exposure and the development of these tumors is long or that younger persons are more susceptible to these effects than are older persons. Our cohort includes only a few persons who were less than 18 years old at enrollment, but one of these patients did develop multiple basal cell cancers by age 21 *(29)*.

In our cohort, squamous cell carcinoma has resulted in substantial morbidity and even death. Metastases and genital tumors are particularly important *(30)*. Nine (3.8%) of 237 patients with squamous cell carcinoma, including four younger than age 50, developed metastases. Twenty-two (2.5%) of 876 male patients developed invasive or *in situ* squamous cell carcinoma of the penis or scrotum. In addition, some patients developed multiple tumors, necessitating repeated and sometimes disabling or disfiguring surgery. In general, the morbidity associated with basal cell cancer is less. No metastases from basal cell cancer have been detected in our cohort.

Although PUVA remains an exceptionally effective treatment for psoriasis, the recently described increased risk of melanoma and the persistent increased risk of squamous cell carcinoma quantified in this study indicate that PUVA should be utilized only in those patients who would benefit sufficiently to justify its use *(24,30)*. Persons exposed to high doses of PUVA need to be monitored carefully for the development of skin cancers, even after treatment is stopped. Continued surveillance of our cohort can better help quantify and document the ultimate carcinogenic risk of PUVA therapy and determine whether these risks will increase over time, especially among individuals exposed to lower doses of PUVA.

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## Notes

[1]*Cooperating centers (investigators):* Stanford University School of Medicine, CA (E. Bauer); University of California Medical School, San Francisco (J. H. Epstein); Baylor College of Medicine, Houston, TX (J. Wolf); Washington Hospital Center, Washington, DC (T. P. Nigra); University of Michigan Medical School, Ann Arbor (T. F. Anderson); Columbia University College of Physicians and Surgeons, New York, NY (J. Prystowsky); Mayo Graduate School of Medicine, Rochester, MN (M. McEvoy); University of Miami, FL (J. R. Taylor); Mt. Sinai Medical Center, Miami, FL (N. Zaias); Temple University School of Medicine, Philadelphia, PA (F. Urbach); Beth Israel Hospital, Boston, MA (K. A. Arndt); Dartmouth Medical School, Hanover, NH (R. D. Baughman); Yale University of Medicine, New Haven, CT (I. M. Braverman); Duke University Medical Center, Durham, NC (J. Murray); University of Pennsylvania Hospitals, Philadelphia (V. Werth); and Massachusetts General Hospital, Boston (T. B. Fitzpatrick, J. Parrish, and C. Taylor).

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