

# The New England Journal of Medicine

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VOLUME 336

APRIL 10, 1997

NUMBER 15



## MALIGNANT MELANOMA IN PATIENTS TREATED FOR PSORIASIS WITH METHOXSALEN (PSORALEN) AND ULTRAVIOLET A RADIATION (PUVA)

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FOR THE PUVA FOLLOW-UP STUDY\*

### ABSTRACT

**Background** Photochemotherapy with oral methoxsalen (psoralen) and ultraviolet A radiation (PUVA) is an effective treatment for psoriasis. However, PUVA is mutagenic, increases the risk of squamous-cell skin cancer, and can cause irregular, pigmented skin lesions. We studied the occurrence of melanoma among patients treated with PUVA.

**Methods** We prospectively identified cases of melanoma and documented the extent of exposure to PUVA among 1380 patients with psoriasis who were first treated with PUVA in 1975 or 1976. Using incidence data, we calculated the expected incidence of melanoma in this cohort and compared it with the observed incidence. Using regression models, we assessed the risks of melanoma associated with a long time ( $\geq 15$  years) since the first treatment and with a large number of PUVA treatments ( $\geq 250$ ).

**Results** From 1975 through 1990, we detected four malignant melanomas, about the number expected in the overall population (relative risk, 1.1). From 1991 through 1996, we detected seven malignant melanomas (relative risk, 5.4; 95 percent confidence interval, 2.2 to 11.1). The risk of melanoma was higher in the later period than in the earlier one (incidence-rate ratio, 3.8) and higher among patients who received at least 250 PUVA treatments than among those who received fewer treatments (incidence-rate ratio, 3.1).

**Conclusions** About 15 years after the first treatment with PUVA, the risk of malignant melanoma increases, especially among patients who receive 250 treatments or more. (N Engl J Med 1997;336:1041-5.)

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**P**HOTOCHEMOTHERAPY using oral methoxsalen (8-methoxypsoralen, or psoralen) and ultraviolet A radiation (PUVA) is a highly effective treatment for severe psoriasis.<sup>1</sup> However, long-term therapy increases the risk of squamous-cell carcinoma of the skin.<sup>2-4</sup> In many patients who receive PUVA therapy irregular, pigment-

ed macules develop and persist long after the therapy is stopped.<sup>5,6</sup> Histologically, these lesions are proliferations of large, cytologically atypical melanocytes.<sup>7,8</sup> PUVA has induced melanocytic tumors in a mouse, and it stimulates the growth of melanoma cells in vivo.<sup>9,10</sup> Although experiments in animals suggest that exposure to ultraviolet A radiation may contribute to the induction or progression of melanoma, the relation between cumulative exposure to sunlight in adults and the risk of melanoma is controversial.<sup>11-14</sup>

In 1975, we began a multicenter, prospective study of the long-term benefits and risks of PUVA, especially the risk of skin cancer.<sup>2</sup> Recently, we noted an increase in the incidence of malignant melanoma, especially among patients receiving high doses of PUVA.

### METHODS

The PUVA Follow-up Study prospectively evaluated 1380 patients who began PUVA treatment for psoriasis at 16 university centers in 1975 and 1976. Since enrollment, these patients have been followed regardless of whether they continued to receive PUVA treatment, or for how long. They are interviewed annually, and they received standardized dermatologic examinations periodically until 1989. The study methods have been described in detail elsewhere.<sup>2-4</sup> In most years, more than 90 percent of the patients have been interviewed.

We noted an apparent increase in the incidence of melanoma beginning in 1991 (approximately 15 years after the first treatment with PUVA). We therefore postulated that about 15 years must pass before the effect of PUVA on the risk of melanoma becomes clinically apparent. We also noted a clustering of cases in patients who had more than 280 PUVA treatments. Therefore, in this study we designated the receipt of at least 250 treatments as a high level of exposure. By 1991, 305 of the 1069 surviving members of the cohort (29 percent) had received at least 250 treatments.

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\*The centers and investigators participating in the PUVA Follow-up Study are listed in the Appendix.

### Statistical Analysis

Using published data on the incidence of melanoma in the United States,<sup>15</sup> we calculated the number of melanomas that would be expected in each of four groups of patients defined according to the calendar year of follow-up (a surrogate for the number of years since the first treatment) and the total number of PUVA treatments. We then studied data on each patient, collected in the follow-up interviews, to determine for each calendar year of the study (1975 to 1996) whether the patient had received a cumulative total of at least 250 PUVA treatments. We then categorized the patients according to whether in that year their cumulative exposure to PUVA was high ( $\geq 250$  treatments) or low ( $< 250$  treatments). To calculate the expected incidence of melanoma for each patient in each year, we used age- and sex-specific incidence rates for whites for 1975 through 1992, the years for which such data were available.<sup>15</sup> For 1993 through 1996, we applied the 1992 incidence rates. To calculate the number of melanomas expected in a given group of patients, we summed the numbers expected for each patient in the group.

Assuming a Poisson distribution of the observed events and using the method of Rothman and Boice, we calculated 95 percent confidence intervals for the relative risks comparing the observed and expected numbers of melanomas, both in each group and overall.<sup>16</sup> To determine whether the level of exposure to PUVA and the time since the first treatment were linked to the risk of melanoma, we used Poisson regression models.<sup>2,17</sup> By applying the observed and expected numbers of melanomas in each group to these models, we could calculate the excess risks among patients in the high-exposure group as compared with those in the low-exposure group and among those with 15 years or more of follow-up (patients studied as of 1991 or later) as compared with those with less than 15 years of follow-up (patients studied in the early period of surveillance, 1975 to 1990).

Since the expected number of tumors in each of the four groups was calculated from incidence rates specific to each patient and each calendar year (that is, rates that incorporated each patient's sex, the patient's age in that year, and the incidence of melanoma in that year among white persons of that age and sex in the United States), we could use Poisson regression techniques to calculate maximum-likelihood estimates of the incidence-rate ratios for persons with at least 250 PUVA treatments as compared with fewer treatments and for the passage of at least 15 years since the first treatment (follow-up ending between 1991 and 1996) as compared with less than 15 years (follow-up ending between 1975 and 1990).

### RESULTS

Of the 1380 patients enrolled in the study in 1975 or 1976, 984 remained alive on February 29, 1996, a number not substantially different from that expected for a cohort with similar characteristics. The median interval from the first treatment to the most recent follow-up interview was 19 years. This report includes 22,104 person-years of follow-up from the first treatment to the date of the most recent examination. There were 18,052 person-years of follow-up from enrollment through December 31, 1990, and 4052 person-years of follow-up from January 1, 1991, through February 29, 1996. At the time of enrollment, the average age of the patients was 44 years; 1337 (97 percent) were 18 years old or older, 892 (65 percent) were male, and 97 percent were white. Table 1 shows the clinical features of the nine patients in whom a total of 11 melanomas developed after enrollment in the study.

Table 2 shows the observed and expected num-

bers of melanomas and the relative risk of melanoma in each of the four groups defined according to the time since the first PUVA treatment and the total number of treatments. Overall, the risk of melanoma was significantly higher in the study patients than in white persons of similar age and sex in the U.S. population (relative risk, 2.3; 95 percent confidence interval, 1.1 to 4.1). From enrollment to the end of 1990, four malignant melanomas were detected in four patients, an incidence nearly identical to that expected on the basis of the incidence data of the Surveillance, Epidemiology, and End Results program of the National Cancer Institute (relative risk, 1.1; 95 percent confidence interval, 0.3 to 2.9). However, from the beginning of 1991 through February 29, 1996, a total of seven melanomas were detected in six patients (relative risk, 5.4; 95 percent confidence interval, 2.2 to 11.1). The patients who received 250 treatments or more had the greatest increase in the risk of melanoma (Table 2). All the melanomas occurred in white patients.

We used a Poisson regression model to factor age, sex, and the increase in the incidence of melanoma over time in the United States into our calculations of the number of melanomas expected in each group. Using the number of PUVA treatments as an independent predictor, we found a significant association between a high level of exposure to PUVA and the risk of melanoma (incidence-rate ratio, 4.1; 95 percent confidence interval, 1.3 to 13.4). Using the time from the first treatment as an independent predictor, we found a significant increase in the risk of melanoma beginning in 1991 as compared with the earlier period of surveillance, from 1975 to 1990 (incidence-rate ratio, 4.7; 95 percent confidence interval, 1.4 to 16.1). When we incorporated into the model both the level of exposure to PUVA and the time since the first treatment as independent predictors, the risk of melanoma remained increased (Table 3). This model was the one that best fit our data. Adding an interaction term that combined the level of exposure and the interval since the first treatment as an additional predictor variable did not improve the fit of the model.

The increase in risk associated with the passage of at least 15 years was especially notable. Our calculations took account of the aging of our cohort and the increase over time in the incidence of melanoma in the general population.<sup>15</sup> The expected incidence rate of melanoma in our cohort for 1991–1996 was 32 per 100,000 person-years, a 68 percent increase from the rate calculated for the first five years of the study (19 per 100,000 person-years).

In five additional patients, not included in this analysis, other melanocytic tumors have developed. Four were melanomas in situ, and one was a melanoma of the ocular choroid. One melanoma in situ was detected in 1989, two in 1994, and one in 1996.

**TABLE 1.** CHARACTERISTICS OF PATIENTS WITH MALIGNANT MELANOMA AFTER EXPOSURE TO PUVA.

PATIENT No.	TUMOR No.	YEAR OF TUMOR	SKIN TYPE*	SEX	AGE AT ENROLLMENT (YR)	No. OF PUVA TREATMENTS	No. OF YEARS, FIRST TREATMENT TO TUMOR	TUMOR LOCATION
1	1	1977	3	F	65	55	2	Foot
2	1	1981	3	M	47	284	7	Upper left calf
	2	1991				284	17	Ankle
	3	1992				284	17	Under thumbnail
3	1	1985	2	M	41	46	10	Upper back
4	1	1989	3	M	68	285	13	Upper back
5	1	1991	3	M	60	138	16	Upper abdomen
6	1	1993	3	F	29	62	18	Shoulder
7	1	1994	3	M	51	470	20	Forehead
8	1	1995	2	M	54	52	20	Back
9	1	1996	2	M	40	490	20	Back

\*In response to sunlight, skin of type 2 burns easily and tans with difficulty; skin of type 3 burns minimally and tans gradually and uniformly.

**TABLE 2.** NUMBER OF MALIGNANT MELANOMAS IN THE STUDY PATIENTS ACCORDING TO STUDY PERIOD AND NUMBER OF PUVA TREATMENTS, AS COMPARED WITH THE NUMBER OF MELANOMAS EXPECTED AMONG WHITES IN THE UNITED STATES.

STUDY PERIOD*	No. OF MELANOMAS		RELATIVE RISK (95 PERCENT CONFIDENCE INTERVAL)	No. OF PERSON-YR OF FOLLOW-UP
	OBSERVED	EXPECTED†		
1975 to 1990				
<250 treatments	2	2.9	0.7 (0.1-2.5)	15,638
≥250 treatments	2	0.6	3.1 (0.4-11.3)	2,414
All patients	4	3.5	1.1 (0.3-2.9)	18,052
1991 to 1996				
<250 treatments	3	0.8	3.5 (0.7-10.3)	2,765
≥250 treatments	4	0.4	8.9 (2.4-22.8)	1,287
All patients	7	1.3	5.4 (2.2-11.1)	4,052
1975 to 1996				
<250 treatments	5	3.7	1.3 (0.4-3.1)	18,403
≥250 treatments	6	1.1	5.5 (2.0-12.0)	3,701
All patients	11	4.8	2.3 (1.1-4.1)	22,104

\*The study patients began PUVA treatment in 1975 and 1976.

†Expected numbers of melanomas were calculated on the basis of age, sex, and incidence rates specific to each calendar year, as described in the Methods section.

Three of the four patients with melanoma in situ received more than 200 PUVA treatments.

Two of the four patients with melanomas who had at least 250 PUVA treatments also had squamous-cell cancers of the skin, but only one of the five patients with melanoma who received fewer PUVA treatments also had squamous-cell cancers. Four of the nine patients with melanomas have died as of this writing — two from metastatic melanoma,

**TABLE 3.** ADJUSTED RATE RATIOS AND 95 PERCENT CONFIDENCE INTERVALS FOR THE INCIDENCE OF MALIGNANT MELANOMA.\*

VARIABLE†	INCIDENCE RATE RATIO (95 PERCENT CONFIDENCE INTERVAL)
No. of PUVA treatments (≥250 vs. <250)	3.1 (0.9-10.5)
Years since first treatment (≥15 vs. <15)	3.8 (1.1-13.3)

\*The estimated effect of each predictor variable (the number of treatments and the number of years to the detection of melanoma) has been adjusted by Poisson regression to account for the other variable, as described in the Methods section.

†For the patients who had 250 or more treatments and those who had fewer than 250 treatments, the study included 3701 and 18,403 person-years, respectively.

one from metastatic squamous-cell carcinoma, and one from complications of cardiovascular disease.

**DISCUSSION**

PUVA is a highly effective treatment for psoriasis and other skin diseases, but it increases the risk of squamous-cell skin cancer when it is given for a long period.<sup>2,4</sup> Because PUVA also induces abnormal, lentiginous melanocytic proliferations and abnormal pig-

mentation of the skin and nails and is carcinogenic, the goal of our study was to determine the risk of malignant melanoma among patients receiving the treatment.<sup>5-8,18</sup> A number of cases of invasive cutaneous melanoma have been reported in patients treated for psoriasis with PUVA,<sup>19-23</sup> but these case reports do not allow an estimate of the risk of melanoma.

The data on our cohort during the first 10 years of follow-up showed no increased risk of melanoma.<sup>23</sup> Until at least 1989, and probably 1991, this pattern seemed unchanged. Two other studies of large cohorts of PUVA-treated patients, with an average follow-up of seven and eight years after PUVA therapy began, also failed to detect an increased risk of melanoma.<sup>24,25</sup>

In contrast to the four melanomas detected in the 14 years from 1976 through 1990, seven were detected from 1991 through early 1996. Our data suggest that high levels of exposure to PUVA, a period of at least 15 years from the time of the first exposure, or both are required before the risk of melanoma increases substantially. Among the patients in whom melanoma developed after 1990, none had received PUVA for at least five years, suggesting that the risk persists after treatment is stopped.

Ascertainment bias is unlikely to explain the increase in risk we observed beginning in 1991. The intensity of surveillance of our cohort has actually decreased over time, and the most recent series of study-sponsored, structured dermatologic examinations was completed in 1989. Since 1991, melanomas have been ascertained on the basis of interviews with patients and medical records.

Even among experts, agreement on the diagnosis of histologic subtypes of melanoma is only moderately good.<sup>26-28</sup> In our study there was frequent disagreement regarding the histologic subtypes. Therefore, we cannot conclude that exposure to PUVA increases the risk of a particular subtype of melanoma.

One patient in our cohort who received more than 250 treatments had three primary melanomas over an 11-year period. In the general population, multiple primary melanomas account for about 13 percent of all melanomas, a frequency not significantly different from that in our study ( $P = 0.16$  by Fisher's exact test).<sup>29</sup>

The conditions under which PUVA is administered and the treatment protocol have not changed substantially over the two decades since this cohort was first treated. However, the use of PUVA has decreased greatly. For 1991-1996, the average number of treatments per person-year for members of the cohort had declined by more than 75 percent from the rate in the first five years of the study.

As the use of PUVA in the cohort has decreased, the application of other treatments, especially ultraviolet B and perhaps exposure to sunlight, has increased. However, high levels of exposure to ultraviolet

B were no more frequent in our patients with melanoma than in the cohort overall, and cumulative exposure to sunlight (and probably ultraviolet B) in adults is not a strong risk factor for melanoma.<sup>30</sup>

Our data do not permit us to determine the number of PUVA treatments at which the risk of melanoma begins to increase substantially, or the relation between an increasing level of exposure and risk. Nevertheless, the increased risk of malignant melanoma that begins 15 years after the first PUVA treatment and is associated with a high level of exposure is a reason for caution in the long-term use of this therapy, especially in young people and those in early middle age. Patients receiving substantial numbers of PUVA treatments should be followed carefully for the development of both melanoma and nonmelanoma skin cancer.

*Note added in proof:* Since the acceptance of this manuscript, we have identified two additional cohort members who had melanoma. The first was a 59-year-old man who had received more than 450 PUVA treatments, with the last treatment occurring more than 10 years before the diagnosis of melanoma. The second was an 82-year-old man with malignant melanoma in situ with microinvasion who had received only 63 PUVA treatments.

Supported in part under a contract (NO1-AR-4-2214) with the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

## APPENDIX

The following centers and investigators participated in the PUVA Follow-up Study. Stanford University School of Medicine, Stanford, Calif.: E. Bauer; University of California Medical School, San Francisco: J. Koo and J.H. Epstein; Baylor College of Medicine, Houston: J. Wolf; Washington Hospital Center, Washington, D.C.: T.P. Nigra; University of Michigan Medical School, Ann Arbor: T.F. Anderson; Columbia University College of Physicians and Surgeons, New York: J. Prystowsky; Mayo Graduate School of Medicine, Rochester, Minn.: M. McEvoy; University of Miami, Miami: J.R. Taylor; Mt. Sinai Medical Center, Miami: N. Zaias; Temple University School of Medicine, Philadelphia: F. Urbach; Beth Israel Deaconess Medical Center, Boston: K.A. Arndt; Dartmouth Medical School, Hanover, N.H.: R.D. Baughman; Yale University School of Medicine, New Haven, Conn.: I.M. Braverman; Duke University Medical Center, Durham, N.C.: J. Murray; University of Pennsylvania Hospitals, Philadelphia: V. Werth; and Massachusetts General Hospital, Boston: T.B. Fitzpatrick, J. Parrish, and A. Sober.

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