

# The Increased Risk of Skin Cancer Is Persistent After Discontinuation of Psoralen + Ultraviolet A: A Cohort Study

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**Psoralen + ultraviolet A-treated psoriasis patients are at increased risk for nonmelanoma skin cancer. To assess the persistence of cancer risk among patients who have discontinued psoralen + ultraviolet A and the risk of a first tumor with the passage of time, we prospectively studied the incidence in a cohort of 1,380 psoriasis patients treated with psoralen + ultraviolet A.**

**We observed a total of 27,840 person-years of which 59.4% were considered years without psoralen + ultraviolet. No significant decrease in risk was noted during the first 15 years after psoralen + ultraviolet A was discontinued. Subsequently, the risk of squamous cell carcinoma was reduced (incidence rate ratio = 0.79; 95% CI = 0.62, 1.01 on treatment vs > 15 years off). After**

**25 years, about 7% of patients with  $\leq 200$  psoralen + ultraviolet A treatments and more than half of the patients with  $\geq 400$  treatments develop at least one squamous cell carcinoma. After 25 years, almost one third of the patients exposed to  $\geq 200$  treatments developed at least one basal cell carcinoma.**

**In conclusion, substantial exposure to psoralen + ultraviolet A dramatically increases the risk of nonmelanoma skin cancer and prior exposure to psoralen + ultraviolet A remains an important issue in the management of patients because the cancer risk associated with psoralen + ultraviolet A is persistent. *Key words: psoriasis/epidemiology/squamous cell carcinoma/basal cell carcinoma. J Invest Dermatol 121:252–258, 2003***

Since its introduction in 1974, psoralen + ultraviolet A treatment (PUVA) (Parrish *et al*, 1974) has been widely used to treat patients with psoriasis and other skin conditions. PUVA therapy is mutagenic and carcinogenic (Dunnick *et al*, 1991). The determinants of the risk of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) in PUVA-treated patients vary with the level of exposure to PUVA and other potentially carcinogenic therapies and patient attributes. The change in risk over long periods of time, however, are less well understood.

Both European and US studies have demonstrated that patients exposed to high doses of PUVA therapy have a substantially increased risk of SCC (Stern *et al*, 1979, 1984; 1998; Henseler *et al*, 1987; Stern and Lange, 1988; Forman *et al*, 1989; Lindelof *et al*, 1991; Chuang *et al*, 1992; Stern and Laird, 1994; Maier *et al*, 1996; Lindelof *et al*, 1999; Hannuksela-Svahn *et al*, 2000). Some data also indicate a small but significant increase of BCC risk (Stern and Lange, 1988; Forman *et al*, 1989; Bruynzeel *et al*, 1991; Stern and Laird, 1994; Stern *et al*, 1998; Lindelof *et al*, 1999). Most studies analyzed incidence in patients within the first decade after starting PUVA. Only two studies extended these observations into a second decade and prior study has included the third decade (Stern *et al*, 1998; Lindelof *et al*, 1999).

Since the enrollment of 1380 patients in our cohort study in 1975 to 1976, we have documented the occurrence of more than 4000 nonmelanoma skin cancers (NMSC), an average of three NMSC per patient. Almost 50% of these tumors have occurred since 1995. These additional data permitted us more fully to assess the relation of PUVA, other exposures, and attributes to tumor risk over time. In addition, we have more robustly quantified the persistence of risk after stopping PUVA and the likelihood over the long term of an individual developing a first skin tumor.

## MATERIALS AND METHODS

**Study population** The PUVA Follow-up Study has prospectively studied 1380 patients with psoriasis first treated with PUVA in 1975 to 1976 at 16 university centers in the USA. At time of enrollment all patients provided written informed consent. From 1975 to 2001, we have performed 19 cycles of follow-up interviews. Structured questions concerning health events, including skin cancers and their use of psoriasis treatments are included in each follow-up. The Beth Israel Deaconess Medical Center Committee on Clinical Investigation has approved the study.

**Tumor risk** We determined the incidence of SCC and BCC counting all tumors in the incidence calculation. The values for all variables were determined for each patient for each calendar year and hence were time dependent. In each year, we classified each patient according to PUVA exposure, treatment exposures, and their disease and demographic attributes, including age. For each type of tumor, the analysis included 27,840 observations (i.e., one for each year for each patient). Only biopsy confirmed SCC (not including SCC *in situ* or keratoacanthoma) or BCC were considered. We defined PUVA exposure according to total number of treatments received up to that year. As previously, high ultraviolet (UV)B and tar exposure were defined as 300 or more UVB treatments and/or 45 mo or more of tar use (Stern *et al*, 1979) and high methotrexate exposure was defined as 36 mo or more of therapy (Stern *et al*, 1984).

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Abbreviations: NMSC, non melanoma skin cancer; PUVA, psoralen and ultraviolet-A light; HR, hazard ratio; IRR, incidence rate ratio.

We considered calendar years with  $\geq 10$  PUVA treatments to be PUVA-exposed years. Those with 10 or fewer treatments to be non-exposed years. In calculating years since last PUVA therapy we excluded the first calendar year after 10 or more treatments as a year of no PUVA exposure. All analyses were done separately for BCC and SCC.

**Statistical methods** We used the Chi-square test to determine the statistical significance of difference in the distribution of categorical variables. Initially, we applied Poisson regression models to our data to relate risk factors to skin cancer incidence; however, when we tested for goodness-of-fit of the Poisson model to our data, the fit was poor. Therefore, we applied a negative binomial regression model to calculate the incidence rate ratios (IRR) and calculate 95% confidence intervals (CI) (Glynn and Buring, 1996). We included all factors significantly associated with incidence in the univariate analysis in a multivariate negative binomial regression model. This model also included calendar year. The multivariate negative binomial regression model estimated the IRR and 95% CI for each factor after adjusting for all other significant predictors of tumor incidence.

To quantify the risk of a first tumor with the passage of time since first exposure to PUVA, we utilized proportional hazards models to estimate the hazard ratios (HR) and 95% CI associated with risk of first tumor for levels of PUVA exposure, age, and gender. In the multivariate analysis, the HR and 95% CI for PUVA dose was adjusted for age and gender, both significant predictors of the risk of a first tumor in the univariate analysis. Kaplan-Meier and predicted survival functions were generated using standard techniques.

All these statistical models incorporated time-dependent variables. All statistical tests were two sided and all except Chi-square tests were performed with Stata 7.0 (Stata Corp., College Station, Texas). Crunch version 4 (Crunch Software Corp., California) was used to calculate the chi-square tests.

## RESULTS

We have prospectively followed the 1380 members since 1975/1976 with an average of more than 20 y per person. At enrollment 64% were male and the mean age was 46. The status of cohort patients at representative times during the study are presented in **Table I**. From first treatment to most recent follow-up this cohort has been observed for 27,840 person-years of which 19,138 (68.7%) person-years were years with less than 10 PUVA treatments reported (nonexposed years). For 16,318 (85.3%) of these 19,138 person-years, no use of PUVA was recorded. The median number of years of follow up after calendar year with PUVA exposure reported is 10. At time of enrollment, 127 patients of the inception cohort (9.2%) reported high-dose exposure to methotrexate and 250 patients high exposure to tar and/or UVB (18.1%). In **Table II**, we present the number of person-years of exposure to each level of each therapy. In addition, we present the distribution of patient's levels of exposure at their last follow up.

### Tumor risk

**SCC** Between 1975 and 2001, a total of 2147 invasive SCC were documented in 303 persons (21.9% of the inception cohort) with a median of 3.0 SCC per person with one or more SCC (25th

**Table I. Status of 1380 patients originally enrolled in the PUVA follow-up status by the end of the year**

	Year				
	1979	1984	1989	1995	2001
Interviewed	1293	1152	988	860	609
Dead	59	134	223	395	510
Not interviewed <sup>d</sup>	28	94	169	125	261

<sup>d</sup>Includes lost and resigned. Some lost patients are interviewed in subsequent years.

**Table II. The number of person-years of exposure to each level for each variable and the distribution of patient's characteristics at final follow up in the PUVA Follow-Up Study**

	No. of person-years (%) (n = 27,840)	No. of persons at last follow-up (%) (n = 1380)
Age (y)		
< 45	8856 (31.8%)	129 (9.3%)
45-64	12,135 (43.6%)	565 (40.9%)
> 64	6849 (24.6%)	686 (49.7%)
Men <sup>a</sup>	17,602 (63.2%)	892 (64.6%)
Skin type <sup>a</sup>		
I-II	7983 (28.7%)	402 (29.1%)
III-VI	19,857 (71.3%)	978 (70.9%)
Region <sup>a</sup>		
North	15,846 (56.9%)	781 (56.6%)
Middle	4960 (17.8%)	233 (16.9%)
South	7034 (25.3%)	364 (26.4%)
Methotrexate exposure		
Low	23,020 (82.7%)	1039 (75.3%)
High <sup>b</sup>	4820 (17.3%)	341 (24.7%)
Tar and/or UVB exposure		
Low	19,969 (71.7%)	877 (63.6%)
High <sup>c</sup>	7871 (28.3%)	503 (36.5%)
X-ray therapy prior to entering study		
No	21,230 (75.3%)	1053 (76.3%)
Yes	6516 (23.4%)	327 (23.7%)
No. of PUVA treatments		
< 100	12,469 (44.8%)	497 (36.0%)
100-199	7753 (27.9%)	371 (26.9%)
200-299	3838 (13.8%)	218 (15.8%)
300-399	1831 (6.6%)	121 (8.8%)
400-499	918 (3.3%)	70 (5.1%)
$\geq 500$	1031 (3.7%)	103 (7.5%)
Years since stopping PUVA		
< 2	11,296 (40.6%)	85 (6.2%)
2-5	5818 (20.9%)	235 (17.0%)
6-10	4898 (17.6%)	324 (23.5%)
11-15	3256 (11.7%)	268 (19.4%)
> 15	2572 (9.2%)	468 (33.9%)

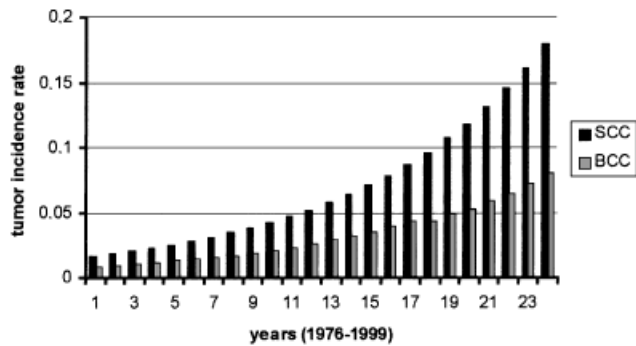
<sup>a</sup>No. of persons presents the distribution at time of enrollment.

<sup>b</sup>High methotrexate exposure is  $\geq 36$  mo of therapy.

<sup>c</sup>High tar is  $\geq 45$  mo of therapy and high UVB exposure is  $\geq 300$  treatments.

percentile = 1.0 and 75th percentile = 7.0). The average incidence of SCC is 7700 per 100,000 person-years. The incidence of SCC has increased dramatically over the 25 y of the study (**Fig 1**) and now is nearly 20,000 per 100,000 person-years.

In the univariate analysis, the incidence of SCC is 30 times higher in the highest PUVA dose group compared with patients with low-dose exposure (**Table III**). Other factors were much more modestly associated with SCC risk. The results of the multivariate analysis, which adjust each risk estimate for all significant predictors of SCC risk, are presented in **Table IV**. Level of PUVA exposure is the single most strongly factor associated with SCC risk (**Table IV, Fig 2**). Patients with high PUVA exposure ( $> 500$  treatments) were 19 times more likely to develop SCC compared with patients with low-dose exposure. Even 15 y after stopping PUVA, the risk of SCC was not lower than the risk observed while still utilizing PUVA (IRR = 0.93; 95% CI = 0.58-1.52). Early intense therapy with PUVA (defined as  $\geq 200$  PUVA treatments in the first 5 y of study) was not significantly related to SCC risk. For most other significant predictors of risk for SCC, including methotrexate, X-ray, UVB, and tar, the risk estimates from the multivariate analysis were somewhat lower than the univariate estimates (**Tables III and IV**).



**Figure 1.** The age-adjusted incidence rate of SCC and BCC by calendar year in the PUVA cohort adjusted for age based on a negative binominal regression model.

**BCC** Between 1975 and 2001, we documented 1363 BCC in 294 persons (21.3% of the inception cohort) with a median of 2.0 SCC per person with one or more BCC (25th percentile = 1.0 and 75th percentile = 5.0). The average BCC incidence is 4400

per 100,000 person-years, but has increased substantially over the last 10 y of this study and now is more than 12,500 per 100,000 person-years (**Fig 1**).

The results of the univariate analysis are summarized in **Table III**. BCC risk is significantly associated with increasing PUVA use, the years since first PUVA treatment and age. In the multivariate analysis, which adjusted for all significant predictors in the univariate analysis, BCC risk increased greatly with very high levels of PUVA exposure ( $\geq 500$  PUVA treatments; IRR = 12.69, 95% CI = 6.34–25.40) (**Fig 2**). For most significant predictors of risk for BCC, including years since stopping PUVA, there was little difference in the estimates obtained in the univariate and multivariate analysis (**Tables III and IV**). The risk of BCC increases significantly with the passage of time since stopping PUVA and is about three times higher 10 y after stopping PUVA than during treatment (**Table IV**).

#### Risk of first tumor

**SCC** Total PUVA exposure was significantly associated with an individual's risk of a first SCC (**Tables V and VI**). Males had a modestly, but significantly higher risk of developing a first SCC.

**Table III.** Univariate analysis of potential risk factors associated with development of SCC and BCC in patients in the PUVA Follow-up Study (n = 1380)

	SCC		BCC	
	IRR	95% CI	IRR	95% CI
Age (y)				
< 45	1 <sup>a</sup>		1 <sup>a</sup>	
45–64	3.76	3.02–4.70	3.82	2.91–5.02
> 64	6.64	5.22–8.44	12.26	9.27–16.21
Men, compared with women	1.53	1.27–1.83	2.54	2.07–3.12
Skin type, compared with:				
III–VI	1 <sup>a</sup>		1 <sup>a</sup>	
I–II	1.67	1.40–2.01	1.17	0.96–1.44
Region				
North	1 <sup>a</sup>		1 <sup>a</sup>	
Middle	0.59	0.47–0.76	0.97	0.75–1.25
South	1.15	0.94–1.41	1.33	1.07–1.65
Years since stopping Puva				
< 2 y	1 <sup>A</sup>		1 <sup>A</sup>	
2–5 y	1.73	1.38–2.17	2.63	2.03–3.39
6–10 y	1.54	1.21–1.96	3.41	2.62–4.43
11–15 y	1.46	1.11–1.94	3.44	2.55–4.64
> 15 y	1.06	0.77–1.46	3.79	2.75–5.23
High methotrexate exposure (36 + mo) compared with low	3.26	2.66, 3.99	2.03	1.61–2.56
High tar (45 + mo) and/or UVB exposure (300 + treatments) compared with low	1.94	1.62–2.33	2.31	1.90–2.81
X-ray therapy prior to entering study compared with none	2.37	1.96–2.87	2.33	1.90–2.86
No. of PUVA treatments				
< 100	1 <sup>a</sup>		1 <sup>a</sup>	
100–199	3.99	3.21–4.98	2.39	1.90–3.00
200–299	7.67	6.00–9.80	3.52	2.69–4.62
300–399	12.09	8.98–16.29	4.96	3.52–6.98
400–499	19.24	13.22–28.00	5.69	3.63–8.90
$\geq 500$	29.83	20.99–42.40	9.59	6.36–14.47
No. of PUVA treatments during first 5 y of study				
< 100	1 <sup>a</sup>		1 <sup>a</sup>	
100–199	2.70	2.24–3.25	1.77	1.44–2.17
$\geq 200$	5.47	4.31–6.93	2.25	1.72–2.94
Period				
1975–80	1 <sup>a</sup>		1 <sup>a</sup>	
1981–85	2.17	1.64–2.88	2.51	1.89–3.34
1986–90	4.01	3.05–5.28	4.48	3.42–5.86
1991–95	7.51	5.70–9.90	10.30	7.99–13.28
1996–2000	11.09	8.34–14.73	11.93	9.24–15.41

<sup>a</sup>Base stratum.

**Table IV. Multivariate estimates of IRR and 95% CI for SCC and BCC adjusted for all other significant risk factors and for study year in members of the PUVA Follow-up Study (n = 1380)**

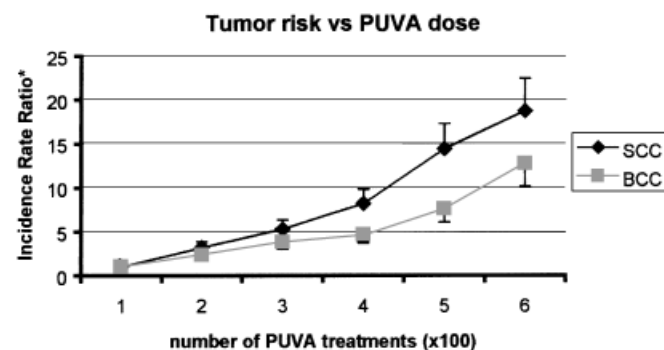
	SCC		BCC	
	IRR	95% CI	IRR	95% CI
Age (y)				
< 45	1 <sup>a</sup>		1 <sup>a</sup>	
45-64	2.08	1.63-2.65	2.19	1.64-2.92
> 64	3.40	2.63-4.40	5.13	3.82-6.89
Men, compared with women	1.38	1.15-1.66	1.91	1.55-2.35
Skin type				
III-VI	1 <sup>a</sup>		1 <sup>a</sup>	
I-II	2.90	2.43-3.47	1.41	1.15-1.72
Region				
North	1 <sup>a</sup>		1 <sup>a</sup>	
Middle	0.74	0.58-0.95	1.18	0.91-1.52
South	2.19	1.79-2.68	1.79	1.43-2.25
Years since stopping Puva				
< 2	1 <sup>A</sup>		1 <sup>A</sup>	
2-5	1.19	0.93-1.53	1.86	1.40-2.48
6-10	1.25	0.92-1.70	2.74	1.95-3.85
11-15	0.90	0.62-1.31	2.61	1.70-4.02
> 15	0.94	0.58-1.52	3.18	1.86-5.44
High methotrexate exposure (36 + mo) compared with low	2.18	1.79-2.66	1.46	1.17-1.81
High tar (45 + mo) and/or UVB exposure (300 + treatments) compared with low	1.02	0.85-1.22	1.61	1.33-1.95
X-ray therapy prior to entering study compared with none	2.87	2.40-3.44	2.13	1.75-2.60
No. of PUVA treatments				
< 100	1 <sup>a</sup>		1 <sup>a</sup>	
100-199	3.20	2.27-4.51	2.35	1.64-3.38
200-299	5.28	3.38-8.25	3.76	2.34-6.06
300-399	8.18	4.95-13.53	4.63	2.68-7.98
400-499	14.36	7.97-25.87	7.62	4.03-14.43
≥ 500	18.67	10.23-34.07	12.69	6.34-25.40
No. of PUVA treatments in first 5 y				
< 100	1 <sup>a</sup>		1 <sup>a</sup>	
100-199	1.10	0.83-1.46	0.86	0.63-1.17
≥ 200	1.39	0.95-2.03	0.75	0.49-1.14
Period <sup>b</sup>				
1975-80	1 <sup>a</sup>		1 <sup>a</sup>	
1981-85	0.99	0.71-1.39	0.84	0.57-1.25
1986-90	1.28	0.88-1.87	0.90	0.58-1.41
1991-95	2.18	1.43-3.30	1.32	0.80-2.18
1996-2000	2.76	1.71-4.48	1.12	0.64-1.97

<sup>a</sup>Base stratum used in the negative binomial regression model.

<sup>b</sup>Adjusted for all variables except study year.

Surprisingly, the risk of a first SCC and age were not significantly associated.

In 25 y, patients with fewer than 200 PUVA treatments have about 7% risk at least one SCC (Fig 3). After 25 y, more than



**Figure 2. The multivariate estimates (Table III) of SCC and BCC risk for PUVA dose with one-sided CI in PUVA follow-up Study.**

half of the patients with 400 or more treatments develop at least one SCC.

**BCC** More than 100 PUVA treatments was significantly associated with an individual's increased risk of a first BCC (Tables V and VI). Risk of developing at least one BCC was higher in males. Surprisingly, in the multivariate analysis the risk of a first BCC was lower among patients older than 44 than younger patients (Table VI). Risk of developing at least one BCC did not increase as sharply with increasing PUVA dose as did the risk of SCC. After 25 y, almost one-third of the patients with ≥ 200 treatments develop at least one BCC (Fig 4).

## DISCUSSION

From 1975 to 2001, our cohort has developed of 1380 PUVA-treated patients. The study continues. This experience enables us to determine the magnitude and persistence of carcinogenic effects of PUVA. Our cohort has developed more than 2100 invasive SCC, 1400 BCC as well as over 800 keratoacanthoma and SCC *in situ* (Bowen's disease).

We have demonstrated that the incidence of both SCC and BCC continues to increase dramatically over time. In contrast to the general population (Karagas *et al*, 1999; Harris *et al*, 2001) the SCC incidence is higher than the BCC incidence. Risk of both SCC and BCC are now extremely high for patients with very high levels of PUVA exposure. At least for 15 y, stopping PUVA in psoriasis patients does not reduce the risk of developing a SCC. Among patients with 200 or more PUVA treatments, about half will develop at least one SCC and almost a third at least one BCC in 25 y after achieving this dose level.

### Tumor risk

**SCC** SCC incidence has increased dramatically and is now about 20,000 SCC per 100,000 person-years. This rate is almost 25 times the SCC risk of a comparably aged population in Arizona (Harris *et al*, 2001). The SCC risk of patients with high-dose PUVA ( $\geq 400$  treatments), however, is 250-fold the risk of the comparably aged Arizona population. Patients with more than 200 treatments appear to be at higher risk of developing skin cancer than those exposed to other known carcinogenic treatments such as systemic immunosuppression in organ transplant recipients and therapeutic radiation therapy (Bouwes-Bavinck *et al*, 1991; London *et al*, 1995; Karagas *et al*, 1996; Caforio *et al*, 2000; Shore *et al*, 2002).

Our earlier data demonstrated a persistence of risk over shorter periods after stopping PUVA (Stern *et al*, 1998) and that discontinuation of PUVA treatment after a first SCC was not significantly related to the risk of a first tumor (Katz *et al*, 2002). This analysis demonstrates that even after 15 y after stopping therapy the risk of SCC is not significantly decreased compared with the years when PUVA was utilized. We detected no association between the intensity of PUVA treatment in the first 5 y of treatment and tumor risk. Although many factors not considered in this analysis could explain the differences between European and American results, this finding argues against the hypothesis that the difference in tumor incidence between European and American studies was due to different PUVA regimens (Henseler *et al*, 1987). The stabilization of SCC incidence after about 20 y of follow-up may reflect the death and/or loss of follow-up of highly susceptible patients or, at last, a stabilization of the SCC risk associated with PUVA therapy with the additional passage of time.

**BCC** In the last decade BCC incidence has increased substantially in our cohort (Fig 1). Compared with the risk in Arizona the BCC risk in our population is about a 4-fold higher during the last 5 y (Harris *et al*, 2001). Patients with  $\geq 500$  treatments, however, have almost a 50-fold increase of BCC risk compared with Arizonans of comparable age. Low-dose groups risks of BCC are only modestly elevated compared with Arizonans. Previously, we, and others, have reported a modest elevation of BCC risk in PUVA-treated patients (Stern and Lange, 1988; Forman *et al*, 1989; Bruynzeel *et al*, 1991; Stern and Laird, 1994; Stern *et al*, 1998; Lindelof *et al*, 1999). We now observe an increase in BCC risk with increasing PUVA exposure that we had previously only observed for SCC suggests the effect of high-dose PUVA on BCC risk is manifest only after a long latency period. Incidences of both tumor types increased significantly with the passage of time. In the multivariate analysis, however, BCC risk increased significantly after stopping PUVA. We do not have an explanation for this finding.

### Risk of first tumor

**SCC** The morbidity of each tumor whether a first or subsequent one is probably comparable. Therefore, our past analyses have emphasized absolute risk. The odds of a PUVA exposed patient remaining tumor free over time, however, is also of clinical interest. The risk of ever developing a first SCC is much higher among patients who have used at least 200 treatments (Fig 3).

Grodstein *et al* (1995) estimated that 0.2% of middle-aged white females develop a first SCC over 8 y. In a comparable period, we estimated about 50 times more of our patients with  $\geq 200$  PUVA treatments will develop a first SCC over this time. The risks of cutaneous SCC for patients immunosuppressed for 20 y for solid organ transplantation (London *et al*, 1995) and PUVA patients with at least 200 treatments appear to be roughly comparable.

**BCC** Patients with  $\geq 100$  PUVA treatments have a significantly increased risk of developing at least one BCC (Fig 4). About 13% of male caucasian US health professionals of 40 y to 75 y self-reported a first BCC during 8 y of follow-up (Van Dam *et al*, 1999). In a comparable period, our patients were about as likely to develop a first BCC after adjusting for age and gender. In up to 50 y of follow-up after ionizing radiation therapy almost every patient with radiodermatitis of the face developed a BCC (Davis *et al*, 1988) and about 40% of those treated on the scalp (Shore *et al*, 2002). When adjusted for length of follow-up the risks of ionizing radiation and those of substantial PUVA exposure appear to be highly comparable.

**Translation to basic research** The carcinogenic effects of PUVA increase over time, are independent of the intensity of the initial therapeutic regimen and persist for many years after stopping treatment. This suggests that PUVA mutagenic effects are likely to be important in skin carcinogenesis (Nataraj *et al*, 1997; Kreimer-Erlacher *et al*, 2001; Seidl *et al*, 2001); however, the PUVA-induced mutation spectrum suggests that factor other than DNA photoadduct formation may be responsible of inducing skin cancer (Peritz and Gasparro, 1999). The persistent tumor risk after stopping PUVA and an increasing absolute risk over time suggest that accurate documentation of carcinogenic effects of photosensitizers both in human and experimental systems require substantial postexposure observation. The carcinogenic risks of ionizing radiation, UVB therapy, tar, and methotrexate in our cohort are modest and remarkably consistent over time (Stern and Lange, 1988; Stern and Laird, 1994; Stern *et al*, 1998).

Our findings are most consistent with additive effects of various carcinogenic exposures and argue strongly against PUVA acting primarily to enhance tumor progression by other epigenetic effects (Granstein *et al*, 1992; Gasparro *et al*, 1998; Lindelof *et al*, 1999). Many immunosuppressive agents, except methotrexate, substantially increase tumor risk in UV-exposed mice (Daynes *et al*, 1979; Kelly *et al*, 1987; Servilla *et al*, 1987). This finding in mice and our findings are consistent (Stern and Lange, 1988; Stern *et al*, 1998; Lindelof *et al*, 1999; Marcil and Stern, 2001). Methotrexate appears to be at most a modest risk factor for developing NMSC in contrast to the substantial enhancing effects of cyclosporine on tumor risk (Marcil and Stern, 2001) in PUVA-treated patients. Different immunosuppressive regimens in solid organ transplant recipients also have a different magnitude of carcinogenic effect (Jensen *et al*, 1999; Caforio *et al*, 2000). The mechanism and magnitude of interaction between ionizing radiation and UV is not well understood (Mohankumar *et al*, 2000; Shore *et al*, 2002). The carcinogenic effect of UVB has been well established, but it does not increase tumor risk in mice when simultaneously administered with PUVA compared with PUVA alone (Granstein *et al*, 1992). High levels of UVB exposure is a modest, but significant, risk factor for SCC and BCC among PUVA-treated patients.

**Methodologic aspects** Among the strengths of this study are its prospective nature, duration, completeness of follow-up, and pathologic confirmation of endpoints. The large number of tumors documented and the length of the follow-up increases our statistical power and precision. Our analyses used multivariate models to estimate the risks of developing a tumor or a first tumor which adjust for other significantly associated risk factors in the univariate analysis; however, not all risk

**Table V. Univariate estimates of HR and 95% CI for a first SCC (n = 303) and a first BCC (n = 294) in members of the PUVA Follow-up Study**

	SCC		BCC	
	HR	95% CI	HR	95% CI
Age (y)				
< 45	1 <sup>a</sup>		1 <sup>a</sup>	
45-64	2.00	1.44, 2.78	0.33	0.23, 0.46
> 64	2.31	1.63, 3.27	0.73	0.56, 0.94
Men, compared with women	1.98	1.53, 2.58	1.67	1.29, 2.16
No. of PUVA treatments				
< 100	1 <sup>a</sup>		1 <sup>a</sup>	
100-199	2.53	1.67, 3.76	1.64	1.17, 2.29
200-399	6.61	4.50, 9.71	2.64	1.89, 3.68
≥ 400	11.88	7.76, 18.19	3.75	2.53, 5.56

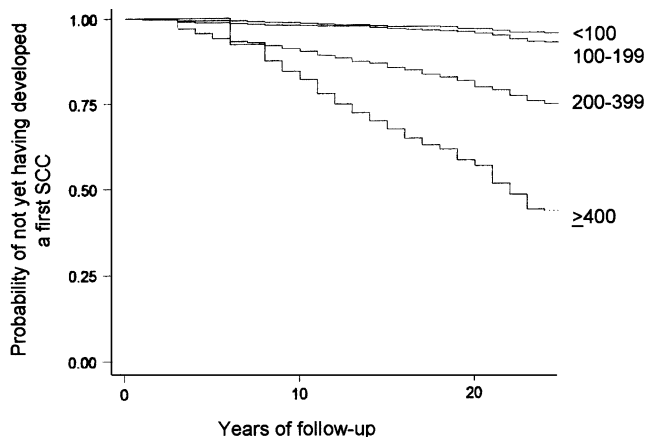
<sup>a</sup>Base stratum used in the negative binominal regression model.

**Table VI. Multivariate estimates of HR and 95% CI for a first SCC (n = 303) and a first BCC (n = 294) in members of the PUVA Follow-up Study<sup>a</sup>**

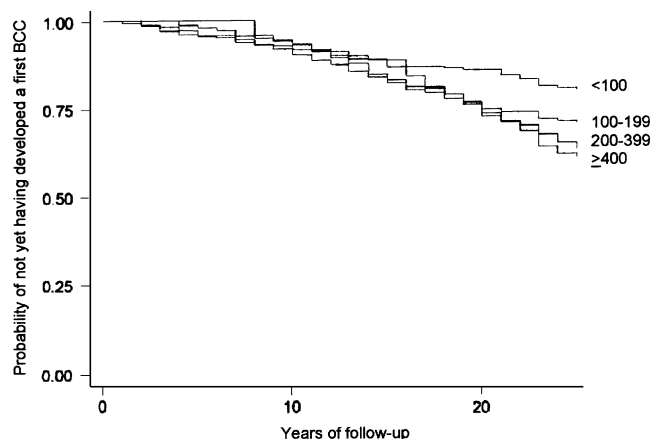
	SCC		BCC	
	HR	95% CI	HR	95% CI
Age (y)				
< 45	1 <sup>b</sup>		1 <sup>b</sup>	
45-64	1.37	0.98, 1.91	0.40	0.28, 0.57
> 64	1.50	1.06, 2.14	0.74	0.57, 0.95
Men, compared with women	1.75	1.35, 2.28	1.45	1.12, 1.88
No. of PUVA treatments				
< 100	1 <sup>b</sup>		1 <sup>b</sup>	
100-199	2.38	1.60, 3.54	1.52	1.09, 2.12
200-399	6.03	4.09, 8.88	2.26	1.62, 3.17
≥ 400	10.75	6.99, 16.54	3.17	2.13, 4.72

<sup>a</sup>Each variable adjusted for the other two variables.

<sup>b</sup>Base stratum.



**Figure 3. The risk of a first SCC over time according to PUVA dose.**



**Figure 4. The risk of a first BCC over time according to PUVA dose.**

factors such as exposure to sunlight were accounted for in this model.

Both observational and selection bias may have affected the findings of our tumor risk analysis because patients with high doses of PUVA and those with a prior tumor were more likely to be closely followed and/or to discontinue PUVA treatment. Moreover, only 54 of the 303 patients who reported at least one SCC developed a first SCC within 2 y prior to stopping PUVA (data not shown). In the risk-of-first-tumor analysis we adjusted

for age and gender. To correct for possible misclassification, we only considered years with 10 or more treatments and the first year after PUVA exposure as years of exposure. We may therefore have underestimated the tumor incidence in the period immediately after stopping PUVA. Moreover, the results from a preliminary analysis that considered years with one to 10 treatments to be years with PUVA exposure did not differ substantially from the results reported here (data not shown).

## CONCLUSIONS

After more than 20 y, substantial exposure to PUVA dramatically increases the risk of NMSC. Although alternative treatments such as narrow-band UVB are now available prior exposure to PUVA remains an important issue in the management of patients. The risk of SCC associated with PUVA appears to persist for more than 15 y after stopping treatment and the risk of BCC continues to increase after stopping PUVA. Past use of PUVA may effect the risk of subsequent therapies, particularly newer immunosuppressive and immunomodulatory agents that could potentially unmask and/or induce skin carcinogenesis in these high-risk patients (Marcil and Stern, 2001). We recommend that PUVA-treated patients be rigorously followed on a long-term basis.

Physicians and patients should carefully balance the risks of PUVA with the benefits it affords for the management of severe psoriasis and other skin diseases, and consider past use of PUVA in determining the safety of alternative therapies for an individual patient.

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