Incidence and Risk Factors Associated with a Second Squamous Cell Carcinoma or Basal Cell Carcinoma in Psoralen + Ultraviolet A Light-treated Psoriasis Patients

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Psoralen + ultraviolet A-treated psoriasis patients are at increased risk for squamous cell carcinomas and basal cell carcinomas; however, the incidence and risk factors associated with second squamous cell carcinomas and basal cell carcinomas in this population are not well qualified. Incidence and risk factors for second squamous cell carcinomas and basal cell carcinomas were studied in a cohort of 1380 psoralen + ultraviolet A-treated psoriasis patients prospectively followed for over 20 y; 264 had a squamous cell carcinoma and 258 a basal cell carcinoma after beginning psoralen + ultraviolet A therapy. After a first squamous cell carcinoma, the risk of a second squamous cell carcinoma was 26% at 1 y, 62% at 5 y, and 75% at 10 y. Risk increased with high psoralen + ultraviolet A exposure prior to the first squamous cell carcinoma (hazard ratio 3.32, 95% confidence interval 1.53, 7.18). Higher rates of post-first squamous cell carcinoma psoralen + ultraviolet A treatment also were associated with greater risk (hazard ratio 1.56 for every additional 10 treatments per year for patients with low pre-first squamous cell carcinoma psoralen + ultraviolet A exposure, 95% confidence interval 1.35, 1.81). Patients exposed to high levels of tar and/or ultraviolet B before a first squamous cell carcinoma were also at higher risk (hazard ratio 1.72, 95% confidence interval 1.14–2.60). Risk of a second basal cell carcinoma was 21% at 1 y, 49% at 5 y, and 61% at 10 y. There was some evidence that high exposure to psoralen + ultraviolet A before a first basal cell carcinoma was associated with increased risk of second basal cell carcinoma (hazard ratio 1.45, 95% confidence interval 0.97–2.17). Higher post-first tumor psoralen + ultraviolet A treatment rates also increased risk (hazard ratio 1.24 for every additional 10 treatments per year, 95% confidence interval 1.06–1.47). Psoralen + ultraviolet A-treated psoriasis patients appear to have a greatly increased incidence of second squamous cell carcinoma compared with the general population. Patients who develop a squamous cell carcinoma after starting psoralen + ultraviolet A therapy should be closely monitored for a subsequent squamous cell carcinoma. *J Invest Dermatol 118:1038–1043, 2002*

Since demonstrated in 1974 to be highly effective for psoriasis (Parrish *et al*, 1974), orally administered psoralens and long-wave ultraviolet radiation (UVA) (PUVA) have been widely used to treat psoriasis.

Non-melanoma skin cancers (NMSC) increasingly account for morbidity and health-care costs as well as mortality (Preston and Stern, 1992). An estimated 1.3 million NMSC [approximately 20% squamous cell carcinomas (SCC) and 80% basal cell carcinomas (BCC)] will be diagnosed in the United States in 2001, making them the most common cancers in that country (Miller and Weinstock, 1994; Alam and Ratner, 2001).

Psoriasis patients not exposed to carcinogenic therapies do not appear to be at substantially increased risk for SCC or BCC compared with the general population (Stern *et al*, 1982a; Alderson and Clarke, 1983; Hogan *et al*, 1989; Lindelof *et al*, 1990); however, compared with the general population, PUVA-treated psoriasis patients have an increased risk of cutaneous cancers, including NMSC, particularly SCC and, to a lesser extent, BCC (Stern *et al*, 1979, 1984, 1998; Henseler *et al*, 1987; Stern and Lange, 1988; Forman *et al*, 1989; Bruynzeel *et al*, 1991; Lindelof *et al*, 1991; Chuang *et al*, 1992; Stern and Laird, 1994).

In addition to PUVA, factors reported to increase risk of NMSC among PUVA-treated psoriasis patients include lighter skin type (Forman *et al*, 1989; Stern and Laird, 1994), tar, and ultraviolet (UV) B treatments (Henseler *et al*, 1987; Maier *et al*, 1996), X-ray therapy (Henseler *et al*, 1987), and arsenic therapy (Honigsmann *et al*, 1980; Stern *et al*, 1984; Maier *et al*, 1996). Methotrexate use was demonstrated to increase risk of NMSC in one report (Henseler *et al*, 1987) but not in an earlier study of the cohort analyzed in this paper (Stern *et al*, 1982b, 1984). Ionizing radiation therapy increased risk of NMSC in the cohort analyzed in this study in an early (Stern *et al*, 1979) but not a later analysis (Stern and Laird, 1994). Finally, a recent report found cyclosporine use to be associated with an increased NMSC incidence in this cohort (Marcil and Stern, 2001).

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Abbreviations: BCC, basal cell carcinoma; HR, hazard ratio; NMSC, nonmelanoma skin cancer; SCC, squamous cell carcinoma.

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Incidence of second NMSC in the general population has been studied (Epstein, 1973; Bergstresser and Halprin, 1975; Robinson, 1987; Schreiber *et al*, 1990; Frankel *et al*, 1992; Marghoob *et al*, 1993) and recently reviewed and subject to a meta-analysis (Marcil and Stern, 2000). Second NMSC among PUVA-treated psoriasis patients, however, have not been systematically assessed. Utilizing data from a cohort prospectively studied for more than two decades, this analysis quantifies the incidence and risk factors of second SCC and BCC among PUVA-treated psoriasis patients.

MATERIALS AND METHODS

Study population and follow-up The PUVA Follow-up Study enrolled 1380 psoriasis patients at 16 centers in the United States in 1975 and 1976. Data for this analysis were collected through July 1, 1999. During each of 18 follow-up cycles since enrollment, patients were telephoned and asked about number of PUVA treatments received as well as about health events, including skin cancer diagnoses. Dates, types, body locations, and numbers of reported skin tumors were confirmed by pathology reports. Patients were asked about: (i) past X-ray and arsenic therapy at the time of enrollment; (ii) tar, UVB, and methotrexate therapy at entry and during each follow-up cycle; and (iii) cyclosporine use during each follow-up cycle. This analysis includes all patients who had at least 6 mo of follow-up after a first postenrollment BCC or SCC.

Definitions of variables and outcomes Separate analyses were done for SCC and BCC. Only prospectively ascertained SCC (not including SCC *in situ* or keratoacanthomas) or BCC occurring after first treatment with PUVA were considered in the analysis. Tumors diagnosed during a 180 d ''wash-out'' period after a first tumor, including multiple tumors diagnosed on the same day as the index tumor, were not considered second tumors in this analysis. For incidence as well as hazard ratio calculations, time at risk was defined as beginning 6 mo after diagnosis of a first SCC or BCC (i.e., after the ''wash-out'' period) and ending with the diagnosis of a second SCC or BCC, respectively, or with loss to follow-up. Tumor dates and locations on the body were taken from pathology reports. Only tumors thought to be new primaries, rather than suspected recurrences, were counted as second tumors.

Age was the age at development of the first tumor. Skin types were categorized in two groups, I–II or III–VI. Regions of the United States where patients initially received treatment were categorized as northern, middle, or southern, as in prior analyses (Stern *et al*, 1979). Body locations of first tumors were categorized as more (head or neck) or less (rest of body) sun exposed.

The number of PUVA treatments received through the interview cycle during which the first tumor was diagnosed was categorized as low (0–159), medium (160–259), or high (260+). Exposure to X-ray therapy or arsenic therapy reflected patient self-reporting. Cyclosporine exposure was considered positive if a patient had used cyclosporine for at least three consecutive months. High tar and/or UVB exposure corresponded to 45 or more months of tar treatments and/or 300 or more UVB treatments by 1989, provided the first SCC or BCC was diagnosed by 1989. Similarly, high methotrexate exposure reflected more than 3 y of therapy, again provided a first SCC or BCC diagnosis by 1989.

Logistic regression models were initially fitted using the raw number of post-first tumor PUVA treatments. Preliminary results that showed, counterintuitively, a protective effect of increasing PUVA treatments were hypothesized to reflect the fact that patients who did not develop second tumors had more time to receive more PUVA treatments. To correct for this, the number of post-first tumor PUVA treatments was divided by the number of years of follow-up, yielding a post-first tumor PUVA treatment rate that was used in all subsequent analyses. The rate was modeled using two variables, allowing simultaneous estimation of effects of a rate of zero, or an increasing rate of, PUVA treatments after the first tumor. The reference group for this variable throughout the analyses is patients with a rate of nearly (but not) zero PUVA treatments per year.

Statistical analysis For univariate analyses, all variables were individually entered linearly into Cox proportional hazards models (Cox, 1972; Armitage and Berry, 1994; Collett, 1994). In each analysis, only variables trending toward significance in univariate analyses ($p < 0.15$) were entered into a multivariate model. Backward-stepwise procedures (Altman, 1991) were used to identify variables significantly related to second tumor risk in multivariate analyses. Interactions between all variables in final models were tested for significance using likelihood ratio tests. Proportional hazards assumptions for each model were tested using score residuals (Collett, 1994; Stern Reference Manual, 1999). Kaplan–Meier and predicted survival functions were generated using standard techniques. All statistical analyses were performed with Stata 6.0 (Stata, College Station, TX).

RESULTS

Baseline and follow-up characteristics Of 1380 PUVA Follow-up Study patients, 276 had a postenrollment SCC and 265 a postenrollment BCC before July 1, 1999. Of these, 264 with an SCC and 258 with a BCC had at least 6 mo of follow-up and were included in this analysis. Characteristics of these cohorts are shown in **Table I**. For the SCC cohort, median overall follow-up time was 2.5 y (minimum 0.5, maximum 22.5, 1080.2 total person-years of follow-up). For BCC, it was 3.3 y (minimum 0.5, maximum 21.5, 1326.6 total person-years of follow-up).

Based on Kaplan–Meier estimates (**Fig 1**), the percentages with a second SCC at 1, 3, 5, 10, and 15 y were 26.2%, 49.7%, 62.1%, 75.1%, and 90.8%, respectively. For a second BCC the corresponding percentages were 21.1%, 40.8%, 49.2%, 61.4%, and 69.9%, respectively.

Univariate analyses of risk factors associated with second tumors In univariate analyses for both cohorts (**Table II**), PUVA exposure prior to a first tumor was significantly related to risk of a second tumor of the same type. The rate of post-first tumor PUVA exposure was also associated with second tumor risk for both cohorts. Among patients who received a minimal (but nonzero) rate of post-first tumor PUVA treatments, risk of a second SCC or BCC increased linearly with the rate; however, for both tumor types, risk was, counterintuitively, higher among patients who received no post-first tumor PUVA treatments than those who received low rates. High tar and/or UVB exposure prior to the first SCC was significantly related to risk of developing a second SCC, and there was some evidence of a similar relationship for BCC. Treatment with methotrexate prior to developing a first tumor was a significant risk factor for a second SCC.

Multivariate analyses of risk factors associated with second tumors In multivariate analysis (**Table III**), high pre-first tumor PUVA exposure remained a significant risk factor in both cohorts. Patients with high pre-first SCC PUVA exposure had a hazard ratio of 3.32 (95% CI 1.53, 7.18) compared with those with low pre-first SCC PUVA exposure, assuming that both had very low (but nonzero) post-first SCC PUVA treatment rates.

For BCC (**Table IV**), evidence for an association between pre-first tumor PUVA exposure and risk of a second BCC was of borderline statistical significance ($p = 0.07$). Nevertheless, because this finding was biologically plausible, it was kept in the multivariate model. For second BCC, patients with high pre-first SCC PUVA exposure had a hazard ratio of 1.45 (95% CI 0.97, 2.17) compared with patients with low pre-first BCC PUVA exposure, regardless of the post-first BCC PUVA treatment rate for either patient.

Higher rates of post-first tumor PUVA treatments were also significant risk factors for both cohorts. For the SCC cohort only, risk associated with post-first tumor rates depended on pre-first tumor PUVA exposure ($p < 0.01$ for the interaction). The additional risk associated with every 10 treatment rate increase was highest among patients who had low pre-first tumor PUVA exposure (HR 1.56, 95% CI, 1.35, 1.81) and lowest among patients with high pre-first tumor PUVA exposure (HR 1.12, 95% CI 1.06, 1.18). As in univariate analyses, patients in either cohort who received no PUVA treatments after a first tumor were at higher risk than those who received low rates of post-first tumor PUVA treatment. For second SCC, the magnitude of this risk also depended on the level of pre-first tumor PUVA exposure, with risks highest among patients with low exposure (HR 3.64, 95% CI 1.75, 7.56) and lowest among patients with medium exposure (HR 2.45, 95% CI 1.28, 4.69).

In the BCC cohort, risk associated with post-first tumor PUVA treatment rates was independent of pre-first tumor PUVA expos-

Table I. Characteristics of psoriasis patients in the PUVA Follow-up Study who developed a SCC or a BCC and had at least 6 mo of follow-up

	Patients with a first SCC (n = 264)	Patients with a first BCC (n = 258)
Mean age at first tumor (SD)	60.7 11.9	61.1 (12.5)
Men (%)	198 (75.0)	184 (71.3)
Skin type (%)		
1–2	80 (30.3)	82 (31.8)
3–6	157 (59.5)	155 (60.1)
Missing	27 (10.2)	21 (8.1)
Region of residence at time of initial survey (%)		
North	139 (52.7)	144 (55.8)
Middle	43 (16.3)	47 (18.2)
South	81 (31.1)	67 (26.0)
First tumor located on head or neck (%)	44 (16.7)	67 (26.0)
Number of PUVA treatments before first tumor (%)		
Low (0–159)	91 (34.5)	117 (45.4)
Medium (160–259)	74 (28.0)	61 (23.6)
High (260+)	99 (37.5)	80 (31.0)
Number of PUVA treatments after first tumor		
Patients with 0 treatments (%)	145 (54.9)	164 (63.6)
If > 0, median number of treatments (minimum, maximum)	75 (1, 464)	65.5 (1, 485)
History of X-ray therapy for psoriasis at time of entry into study	80 (30.3)	75 (29.1)
History of arsenic therapy for psoriasis at time of entry into study	10 (3.8)	10 (3.9)
History of tar treatment (45+ months) and/or UVB treatments (300+) as of January 1, 1989	84 (31.8)	85 (33.0)
History of methotrexate therapy (3+ years) as of January 1, 1989	81 (30.7)	75 (29.1)
History of cyclosporine therapy (3 or more consecutive months) during follow-up	8 (3.0)	9 (3.5)
Percentage of with a second tumor of same type (95% confidence interval) at:		
1 y	26.2 (21.3, 32.0)	21.1 (16.6, 26.7)
3 y	49.7 (43.5, 56.2)	40.8 (34.8, 47.3)
5 y	62.1 (55.7, 68.7)	49.2 (43.8, 55.9)
10 y	75.1 (68.4, 81.2)	61.4 (54.5, 68.4)
15 y	90.8 (81.2, 96.7)	69.9 (61.0, 78.3)

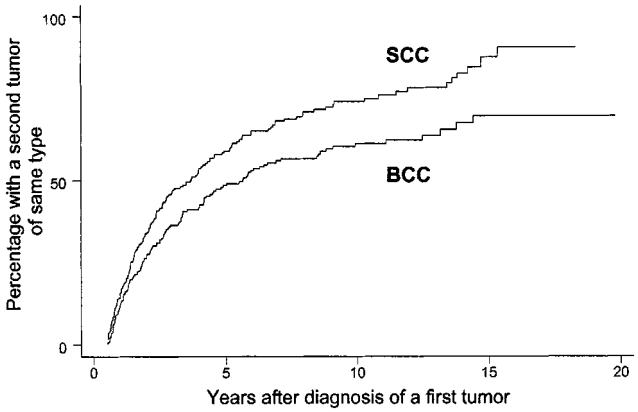

Figure 1. Kaplan–Meier survival curves for PUVA-treated psoriasis patients in the PUVA Follow-up Study. The curves show the percentage of patients who developed either a second SCC after a first postenrollment SCC or a second BCC after a first postenrollment BCC. After a 6 mo "wash-out" period, the 1 y, 3 y, 5 y, 10 y, and 15 y incidences of a second SCC were 26%, 50%, 62%, 75%, and 91%. Corresponding incidences for a second BCC were 21%, 41%, 49%, 61%, and 70%.

ure. The hazard ratio for every additional 10 treatments per year after a first BCC was 1.24 (95% CI 1.06, 1.47). Patients with no post-first BCC PUVA treatments had a hazard ratio of 4.18 (95% CI, 2.54, 6.88) compared with patients with low (but nonzero) rates of treatment.

A high level of exposure to tar and/or UVB prior to a first tumor was a risk factor only for second SCC and did not depend on pre-first SCC PUVA exposure (HR 1.72, 95% CI 1.14, 2.60). Methotrexate was not a significant risk factors for second SCC or BCC in the multivariate analyses.

Based on the multivariate models, predicted percentages of patients with various combinations of risk factors developing a second SCC or BCC over time are shown in **Figs 2 and 3**. Among patients with a first SCC, 50% of highest-risk patients (group H in **Fig 2**) would be expected to have a second SCC in 0.9 y after the "wash-out" period. By comparison, the model predicts that it would take 14.8 y after the "wash-out" period for half of patients with the lowest-risk profile (group A in **Fig 2**) to have a second SCC. For patients with a first BCC, the median predicted time to a second BCC is 2.8 y for highest-risk patients (group F in **Fig 3**), whereas even after 20 y of follow-up less than half of the lowest-risk patients (group A in **Fig 3**) would be expected to have had a second BCC.

DISCUSSION

PUVA-treated psoriasis patients appear to have a higher incidence of second SCC than other populations studied. In this study's cohort, 26% had a second SCC in the first year of follow-up after the 6 mo "wash-out" period, compared with 9% of patients enrolled in a clinical trial of β-carotene to prevent skin cancer (Karagas *et al*, 1992) and 17% of patients living in south-east Arizona, a high-risk area (Schreiber *et al*, 1990). Within 3 y, 47% of our cohort had had a second SCC, compared with an estimate of only 18% of patients in a meta-analysis (Marcil and Stern, 2000). The 5 y incidence of a second SCC in our cohort (62%) was markedly higher than both the clinical trial (31%) (Karagas *et al*, 1992) and the Arizona study (≈ 20%) (Schreiber *et al*, 1990). Owing to limited follow-up, no other study has reported a 10 y incidence of second SCC (75% in our cohort) or a 15 y incidence (91%). Additionally, as this analysis did not count as positive for second

Table II. Univariate analysis of potential risk factors associated with development of a second SCC or a second BCC in patients in the PUVA Follow-up Study

Potential risk factor	Patients with a first SCC (n = 276)			Patients with a first BCC (n = 265)		
	Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
Age at first tumor, for every additional 10 y	1.01	0.89, 1.15	0.86	1.13	0.99, 1.30	0.08
Men, compared with women	1.20	0.84, 1.72	0.31	1.22	0.83, 1.77	0.31
Skin types III–VI, compared with types I–II	0.98	0.70, 1.37	0.90	1.43	0.97, 2.10	0.07
Region of residence, compared with			0.70[a]			0.02[a]
north						
middle	1.19	0.79, 1.80		0.54	0.32, 0.92	
south	1.00	0.71, 1.40		1.12	0.77, 1.63	
First tumor not on head or neck	1.16	0.77, 1.74	0.48	1.38	0.91, 2.08	0.13
Pre-first tumor PUVA treatment category, compared with			< 0.01[b]			0.04[b]
low category (< 160 treatments)						
medium (160–259 treatments)	1.37	1.14, 1.65		1.23	1.02, 1.50	
high (260+ treatments)	1.88	1.30, 2.72		1.52	1.03, 2.25	
Post-first tumor PUVA treatment rate			< 0.01[c]			< 0.01[c]
0	2.11	1.52, 2.94		4.31	2.63, 7.10	
If > 0, for every additional 10 treatments per year	1.13	1.10, 1.17		1.28	1.09, 1.51	
X-ray therapy prior to entering study	1.21	0.87, 1.68	0.26	1.17	0.82, 1.67	0.40
Arsenic therapy prior to entering study	0.87	0.38, 1.96	0.74	0.66	0.27, 1.61	0.36
High tar and/or UVB exposure prior to developing first SCC/BCC	1.85	1.25, 2.74	< 0.01	1.54	0.98, 2.42	0.06
High methotrexate exposure prior to developing first SCC/BCC	1.56	1.04, 2.40	0.03	1.45	0.91, 2.32	0.12
Cyclosporine use prior to developing first SCC/BCC	1.84	0.68, 4.98	0.23	1.64	0.60, 4.44	0.33
Cyclosporine use after developing first SCC/BCC	2.40	0.88, 6.50	0.09	0.93	0.29, 2.91	0.90

[a]p-value for region covariate overall.
[b]p-value for model of pre-first tumor PUVA treatment categories, fitted linearly.
[c]p-value for model of post-first tumor PUVA treatment rate, fitted using two variables (as explained in text), tested jointly for statistical significance.

Table III. Risk factors associated with a second postenrollment SCC in patients in the PUVA Follow-up Study, from multivariate analysis

Risk factor	Hazard ratio	95% CI	p-value
Pre-first SCC PUVA exposure category, compared with low (< 160 treatments), for patients with a PUVA treatment rate of nearly (but not) zero after the first SCC			< 0.01[a]
Medium (160–259 treatments)	2.23	1.01, 4.92	
High (260+ treatments)	3.32	1.53, 7.18	
Post-first tumor PUVA treatment rate			
0			
for patients with low pre-first SCC PUVA exposure	3.64	1.75, 7.56	
for patients with medium pre-first SCC PUVA exposure	2.45	1.28, 4.69	
for patients with high pre-first SCC PUVA exposure	2.72	1.63, 4.55	
If > 0, for every additional 10 treatments per year			
for patients with low pre-first SCC PUVA exposure	1.56	1.35, 1.81	
for patients with medium pre-first SCC PUVA exposure	1.14	1.07, 1.22	
for patients with high pre-first SCC PUVA exposure	1.12	1.06, 1.18	
Tar/UVB use prior to developing first SCC	1.72	1.14, 2.60	0.01

[a]P-value for pre-first SCC PUVA treatment category, post-first SCC PUVA treatment rate category, and terms for interactions between those two variables, tested jointly.

SCC 17 patients whose only subsequent SCC was during the ''wash-out'' period, our estimates may be more conservative than those of other studies.

In contrast, second BCC incidence during the first year of follow-up after the ''wash-out'' period (21%) within the ranges of 1 y incidences reported in the clinical trial (17%) (Karagas *et al*, 1992), the Arizona study (33%) (Schreiber *et al*, 1990), and a report on a northern California cohort (20%) (Epstein, 1973). The 3 y incidence (41%) was close to that reported in the meta-analysis (44%) (Marcil and Stern, 2000). The 5 y incidence in this cohort (49%) was similar to the rate among patients in the clinical trial (41%) (Karagas *et al*, 1992) and the rate among the Arizona patients (≈ 50%) (Schreiber *et al*, 1990). As for SCC, there are no studies that compare with the 10 and 15 y second BCC incidences in our cohort—64% and 70% in our cohort. As with the SCC cohort, conservative estimates of second BCC incidence may have resulted from the fact that 21 patients whose only subsequent BCC was diagnosed during the ''wash-out'' period were not considered as positive for second BCC.

Greater exposure to PUVA before a first tumor was significantly and strongly related to risk of second SCC ($p < 0.01$) but only marginally associated with risk of a second BCC ($p = 0.07$). These

Table IV. Risk factors associated with a second postenrollment BCC in patients in the PUVA Follow-up Study, from multivariate analysis

Risk factor	Hazard ratio	95% CI	p-value
Pre-first tumor PUVA treatment category, compared with low category (< 160 treatments)			0.07[a]
medium (160–259 treatments)	1.20	0.98, 1.47	
high (260+ treatments)	1.45	0.97, 2.17	
Post-first tumor PUVA treatment rate			< 0.01[b]
0	4.18	2.54, 6.88	
If > 0, for every additional 10 treatments per year	1.24	1.06, 1.47	

[a]p-value for model of pre-first tumor PUVA treatment categories, fitted linearly.
[b]p-value for model of post-first tumor PUVA treatment rate, fitted using two variables (as explained in text), tested jointly for statistical significance.

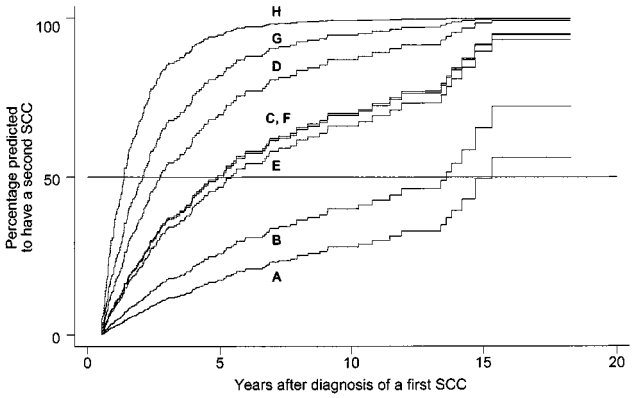

Figure 2. Percentages of PUVA-treated psoriasis patients predicted to develop a second postenrollment SCC over a 20 y follow-up period. According to PUVA treatment category prior to the first SCC, post-first SCC PUVA treatment rate, and history of tar/UVB therapy. Groups A–H are defined as follows:

Group	No. of PUVA treatments before first SCC	Average yearly PUVA treatment rate after first SCC	Prior tar/UVB
A	Low (<160)	Nearly zero	No
B	Low	10	No
C	Low	Zero	No
D	Low	Zero	Yes
E	High (260+)	Nearly zero	No
F	High	10	No
G	High	Zero	No
H	High	Zero	Yes

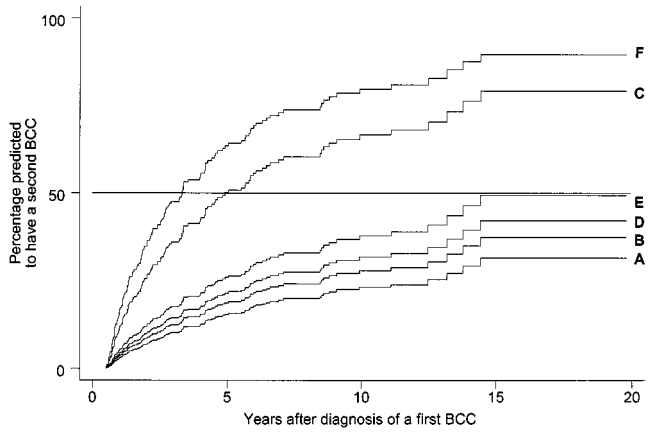

Figure 3. Percentages of PUVA-treated psoriasis patients predicted to develop a second postenrollment BCC over a 20 y follow-up period. According to PUVA treatment category prior to the first BCC, and post-first BCC PUVA treatment rate. Groups A–F are defined as follows:

Group	No. of PUVA treatments before first BCC	Average yearly PUVA treatment rate after first BCC
A	Low (<160)	Nearly zero
B	Low	10
C	Low	Zero
D	High (260+)	Nearly zero
E	High	10
F	High	Zero

findings accord with results from first tumor studies in our cohort and other PUVA-treated psoriasis cohorts, which have found that PUVA increases SCC risk more than it does BCC risk (Stern and Lange, 1988; Forman *et al*, 1989; Bruynzeel *et al*, 1991; Chuang *et al*, 1992; Stern and Laird, 1994; Stern and Lunder, 1998).

For both types of tumors, risk of a second tumor increased with the yearly rate of post-first tumor PUVA treatments. The finding in the SCC cohort that this risk was inversely related to pre-first SCC PUVA exposure suggests that PUVA-associated SCC risk may begin to plateau once a certain level of total PUVA exposure has been achieved.

For both SCC and BCC, patients receiving no post-first tumor PUVA treatments at all had a higher risk of second tumors than those who received a low rate of post-tumor PUVA. This counterintuitive finding is most likely consistent with selection bias, which may have resulted if PUVA had been discontinued altogether at the time of the first tumor for patients who were thought to be (and indeed were) at high risk for subsequent tumors, based on first tumor size or appearance or the clinical appearance of the patient's skin. These same concerns about second tumor risk might also have led to more frequent clinical follow-up for these patients, increasing the chance of earlier detection (but not development) of second tumors compared with other patients.

The finding that high tar and/or UVB exposure before a first SCC increased risk of a second SCC supports a prior observation of this association in first NMSC's among PUVA-treated psoriasis patients (Henseler *et al*, 1987). A similar effect was seen when cumulative high exposure to tar and/or UVB as of 1989 (regardless of date of first tumor) was entered into logistic regression models. It is important to note that this analysis cannot distinguish the effects of topical tar, which is no longer widely used in treating psoriasis, from those of UVB, which is still widely used. Nevertheless, a history of extensive treatment with tar and/or UVB prior to a first SCC should be considered in estimating the risk of further PUVA and/or UVB treatments.

Lack of an association between cyclosporine and second tumors in multivariate analysis was somewhat surprising, given that cyclosporine has been shown to increase NMSC incidence in this cohort over the long term (Marcil and Stern, 2001) and in transplant recipients, particularly with regard to SCC (London *et al*, 1995). The most likely explanation is a lack of power to detect an effect in this more focused analysis, limited to second tumors occurring at least 6 mo after a first tumor rather than all tumors occurring during the entire follow-up experience of patients in the cohort.

After adjustment for other factors, no significant effect of methotrexate was seen on risk of second tumors of either type, a finding consistent with prior investigations of this cohort (Stern *et al*, 1982b, 1984).

In contrast to some other studies of patients in the general population, our multivariate analyses found no association between risk of a second NMSC and age (Karagas *et al*, 1992), male sex (Epstein, 1973; Karagas *et al*, 1992), skin type (Robinson, 1987; Karagas *et al*, 1992), region of the country where a participant received treatment (Karagas *et al*, 1992), and the first tumor's location on a sun-exposed area of the body (Frankel *et al*, 1992). Differences in our findings from those in general populations studied may reflect intrinsic biologic differences in NMSC related to PUVA and those with other etiologies. Alternatively, differences could be due to limited power in this study.

This study should allow both treating physicians and psoriasis patients exposed to various PUVA treatments to estimate better risks of developing a second tumor. Given the demonstrated high risk of developing second tumors, PUVA-treated psoriasis patients who have developed an NMSC would appear to merit at least a yearly examination for new NMSC. Patients at particularly high-risk might warrant more frequent examinations. Finally, as second tumor risk increases with an increasing rate of post-first tumor PUVA treatments, continuation of PUVA treatment after a first NMSC among patients who have had only modest exposure to PUVA will require that physicians and patients balance risks of PUVA, including second tumors (and especially SCC), with the benefits it affords for the management of severe psoriasis.

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