Occupational Knowledge International

9836 '00 JUN -6 P2:05

Ms. Jennie Butler
Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

June 1, 2000

Re: Petition 00P-1210/ item code ZP1 to Restrict Sale of Coal Tar-Containing Products

Dear Ms. Butler,

I have conducted some additional research after our initial submittal to FDA for the above mentioned petition and discovered several significant omissions from our package. The following epidemiological articles and other materials are attached for distribution for FDA to consider in the review:

1) Maier, H., et al. (1996) "Skin Tumors in Photochemotherapy for Psoriasis: A Single-Center Follow-Up of 496 Patients":

This study finds that coal tar treatments for Psoriasis patients result in a Relative Risk of 9.92 for squamous cell carcinoma.

2) Stern, Robert, S., et al. (1998) "Oral Psoralen and Ultraviolet-A Light (PUVA) Treatment of Psoriasis and Persistent Risk of Nonmelanoma Skin Cancer":

This cohort study of 1,380 psoriasis patients provides follow-up to previously published data by the same authors. With the additional years of follow-up, the study demonstrates that coal tar in combination with ultraviolet-B (UVB) treatments for Psoriasis patients results in a statistically significant Odds Ratio of 1.4 for squamous cell carcinoma. The authors conclude that their study may "underestimate the carcinogenic effects of these exposures".

3) Letzel, S., et al. (1998) "Occupationally related tumors in tar refinery workers":

This study of 606 workers from a coal tar refinery in Germany demonstrates a 25% incidence rate of squamous cell carcinoma (151 of 606 workers). In addition, the authors note that 380 squamous cell carcinomas observed reverse the rate of basal cell to squamous cell carcinomas from an expected ratio of 10:1 to 1:1.7. The study also demonstrates that UV light may not be a significant cofactor for this cohort.

00P-1210

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4) Halprin, Kenneth M., et al. (1982) "Cancer in Patients with Psoriasis":
This study of 150 non-PUVA treated patients demonstrates a three fold increase in skin cancer incidence for psoriasis patients over a control group of diabetes patients. In addition, the observed ratio of basal cell to squamous cell carcinoma of 6:14 was much greater than expected.

I have also enclosed examples of two current Dermatology textbooks that address coal tar shampoo application. I believe that these may prove useful in considering the exposure estimate as they demonstrate the following:

a) That coal tar shampoos are used for infants with cradle cap (seborrheic dermatitis) who are known to have thinner skin and much greater skin absorption than adults;
b) That the shampoos are intended to be kept on the hair for five minutes and not just rinsed off after application;
c) and that at least one textbook currently in print suggest using coal tar shampoo frequently on infants with cradle cap to prolong remission.

Please contact me if you have any questions at (415) 441-5199.

Sincerely,

Perry Gottesfeld

Perry Gottesfeld, M.P.H.
Executive Director

Clinical and Laboratory Investigations

Dermatology

Dermatology 1996;193:185–191

8837 '00 JUN -6 22:05

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Skin Tumors in Photochemotherapy for Psoriasis: A Single-Center Follow-Up of 496 Patients

Key Words
Photochemotherapy
Psoralen
Nonmelanoma skin cancer

Abstract
Background: The significance of oral psoralen photochemotherapy (PUVA) for the development of nonmelanoma skin cancers (NMSC) is still controversial. **Objective:** We evaluated 496 psoriatics, who received PUVA treatment according to the European PUVA protocol in order to reassess the influence of the cumulative UVA dose on the development of NMSC and to answer the question if there is a UVA threshold dose above which the carcinogenic risk is increased. **Methods:** The study was conducted as a retrospective investigation. All patients were seen personally. Age, sex, skin type, cumulative UVA dose and carcinogenic risk factors (arsenic, X-rays, tar, UVB, methotrexate) were recorded and investigated by marginal (MA) and partial effects analyses (PA) according to the Cox regression model. **Results:** In 14 patients (2.8%), one or multiple histologically confirmed NMSC were diagnosed. Nine patients (1.8%) had squamous cell carcinoma (SCC), 5 patients (1.0%) had basal cell carcinoma (BCC). No patient had both types of NMSC. None of the SCC had metastasized. By taking the appearance of BCC and SCC as the endpoint, arsenic [MA: relative risk (RR) = 7.62; PA: RR = 5.36], tar (MA: RR = 4.51; PA: RR = 3.83) and methotrexate (MTX; MA: RR = 4.97; PA: RR = 4.07) appear to produce strong and significant effects ($p < 0.05$), both in MA and PA. Using the endpoint SCC only, the effect of the natural logarithm of UVA (ln UVA; RR = 2.47), arsenic (RR = 11.2), tar (RR = 9.92) and MTX (RR = 7.1) is significant ($p < 0.05$) in MA. In PA, only the effect of arsenic (RR = 5.19) is strong and significant ($p < 0.05$) while the effects of tar (RR = 7.85), MTX (RR = 3.22) and ln UVA (RR = 2.77) are strong but of borderline significance ($p = 0.05–0.11$). Nonlinear effects of ln UVA on the risk of SCC were far from significant ($p > 0.2$). **Conclusion:** PUVA with the European treatment protocol appears to be only a weak carcinogen by itself for SCC with a linear increase in tumor risk but not for BCC development.

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Photochemotherapy with oral psoralens and UVA radiation (PUVA) has been introduced in 1974 as a new treatment for psoriasis [1]. Today it represents one of the first-line treatment modalities for severe disease and is well accepted by the patients. Although the molecular mechanisms which lead to the antipsoriatic effect are still subject to debate, the interactions of psoralens with DNA seem to play an important role [2, 3]. Upon UVA irradiation bifunctional furocoumarins undergo photochemical reactions with DNA bases resulting in monofunctional adducts and interstrand cross-links. The covalent binding to DNA, however, has raised considerable concern about the mutagenic and carcinogenic risk of such a treatment.

Mutagenicity and carcinogenicity are well established effects of exposure to PUVA in vitro and in animal models [4–7]. In 1979, an increased incidence of nonmelanoma skin cancers (NMSC) in psoriatics treated with long-term PUVA was reported [8]. The majority of tumor patients among the study population had a history of previous treatment with ionizing radiation or had suffered from NMSC before PUVA. Surprisingly only whole-body irradiation therapy but not local therapeutic irradiation was reported as a risk factor. This publication marked the beginning of an ongoing controversy about the role and relevance of psoralen photochemotherapy in human photocarcinogenesis.

Numerous clinical trials have been conducted since in order to evaluate the risk of the development of NMSC in long-term PUVA patients [9–24]. Most authors appear to agree that PUVA patients with a cumulative UVA dose of more than 1,500–3,000 J/cm² have an increased risk of NMSC. There is a high proportion of patients among these study populations who have received treatments of known or suspected carcinogenic potential such as arsenic, tar, X-rays, UVB, methotrexate (MTX) and other cytotoxic drugs. Obviously, these patients are at a higher risk to develop NMSC [8–11, 13, 15–18, 21–23]. Only a small fraction of psoriatics who are long-term PUVA patients (because of the severity of their disease) have never received any other carcinogenic treatment regimens [24].

Six years after our last follow-up [23], 496 psoriatics were evaluated in order to reassess the influence of the cumulative UVA dose on the development of NMSC in our PUVA patients and to answer the question if there is a UVA threshold above which the carcinogenic risk is increased.

Table 1. Characteristics of the study population

Characteristic	All patients	
Number	496	
Sex		
Male	273	(55%)
Female	223	(45%)
Skin type		
I	67	(13%)
II	178	(36%)
III	224	(45.3%)
IV	25	(5.1%)
n.d.	2	(1%)
Age, years		
Median	50	
Min./max.	12/87	
Q1/Q3	39/63	
ln UVA dose, J/cm²		
Median	6.17	(476)
Min./max.	3.0/9.1	(20/8,604)
Q1/Q3	5.23/7.0	(186/1,085)
Duration of follow-up, months		
Median	82	
Min./max.	3/206	
Q1/Q3	57/127.5	
Risk factors		
Arsenic	58	(11.7%)
X-rays	103	(20.8%)
Tar	193	(39%)
UVB	111	(22.4%)
MTX	44	(8.9%)
Retinoids	237	(47.8%)

n.d. = Not determined; Q1 = first quartile; Q3 = third quartile.

Methods

Patients

This investigation was conducted as a retrospective study. We invited 1,149 patients in whom PUVA treatment had been initiated before 1987 and who had received more than five exposures to PUVA. Only 496 patients accepted, and therefore we investigated the causes of noncompliance: 107 patients had moved to other places, 39 had died and 69 informed us that they were not interested in a follow-up. No information about the reason of noncompliance could be obtained in 438 cases although we contacted them twice. One patient died from stroke and another from heart attack. In all other cases it was impossible to obtain information about the cause of death.

Most patients who did not appear at the follow-up had suffered only from mild psoriasis and had received only one or few PUVA courses. A large number of patients who did appear for the follow-up suffered from moderate or severe disease with many relapses and high cumulative UVA doses. 238 patients had cumulative UVA doses of more than 500 J/cm². 54 patients had cumulative UVA doses of more than 2,000 J/cm². 312 (62.9%) patients had a positive history of one or more risk factors with known or suspected carcinogenic potential. In

Table 2. Tumor patients

Patient	Sex	Age years	Skin type	Risk factors					Retinoids	NMSC	UVA J/cm²	Time months
				AS	X-ray	tar	UVB	MTX				
M.B.	F	59	II	1	0	1	0	0	1	SCC	641	41
H.B.[a]	M	58	II	1	0	0	0	0	0	SCC	2,982	70
E.B.	M	54	I	1	1	1	0	1	0	SCC	886	68
D.F.	F	40	III	0	0	1	0	0	1	SCC	2,510	65
A.H.	M	66	III	1	0	1	0	1	1	SCC	1,951	47
F.K.	M	51	II	1	0	1	0	1	0	SCC	2,594	68
E.S.	M	54	I	1	0	1	0	0	1	SCC	685	63
F.ST.	M	62	III	0	0	1	0	1	0	SCC	5,820	182
M.F.	F	81	II	0	1	1	1	0	1	SCC	1,390	183
H.P.[b]	M	45	III	1	1	1	0	0	0	BCC	185	57
M.E.	F	33	II	0	0	1	0	0	0	BCC	509	97
H.K.	M	64	III	0	0	0	0	0	0	BCC	82	101
A.M.	F	53	II	1	1	0	1	1	0	BCC	964	71
O.SCH.	M	48	I	0	0	1	0	0	1	BCC	142	47

AS = Arsenic; 1 = positive history of retinoids and risk factors; 0 = negative history of retinoids and risk factors; time = time from onset of PUVA treatment to tumor event.

[a] Patient with noninvasive genital cancer.

[b] Patient with multiple BCC at follow-up.

many ways, our patient group represented a high-risk population for the development of NMSC.

All patients were seen personally by the authors at the follow-up. For patients with NMSC, the endpoint of follow-up was considered to be the date of the diagnosis of the first tumor. All suspicious lesions were biopsied or excised, processed for routine histopathology and evaluated independently by two experienced dermatopathologists. Age, sex, skin type, total cumulative UVA dose, accompanying treatment with retinoids and exposure to carcinogenic risk factors (arsenic, X-rays, tar, UVB, MTX) were recorded.

Statistical Methods

The distribution of the factors of interest is described by frequencies in the dichotomous case and by medians in the continuous or ordinal case. Because of its skewness, the variable UVA dose was transformed into the natural logarithm (ln UVA). The prognostic importance of the factors considered was analyzed by a univariate and multivariate analysis, more precisely by simple and multiple Cox proportional hazards regression models [25]. While the marginal results from univariate analysis refer to the effect of a prognostic factor ignoring other factors, the partial results from multivariate analysis refer only to those effects which cannot be explained by the other factors considered. Factors considered are: sex, age, skin type, cumulative UVA dose, exposure to arsenic, X-rays, tar, UVB, MTX and retinoids. The prognostic strength of these factors is described by the relative risk (RR) of NMSC when the value of a prognostic factor is increased by 1. The RR is directly related to the parameter b in a Cox regression: RR = exp(b). The results were obtained using program 2L of BMDP [26]. All p values refer to two-sided tests. Further analyses deal with the evaluation of the relative importance of the possible risk factors according to Schemper [27]. These methods can provide answers of whether the RR associated with prognostic factors are significantly different.

Results

Study Population

496 patients (273 males, 223 females) who had received PUVA treatment according to the European PUVA protocol [28] participated in this study (table 1). The estimated median follow-up period was 82 (3–206) months. In 84 patients (16.9%), the follow-up period was 15 years or more. The median age was 50 (12–87) years, the median ln UVA 6.17 (3.0–9.1). 45% of the study population were of skin type III, 36% of skin type II, 13% of skin type I and 5% were of skin type IV. The skin type was not determined in 1% of the study population. 171 patients (34.5%) had a history of one carcinogenic risk factor, 94 patients (19%) of two, 38 patients (7.7%) of three and 9 patients (1.8%) had a history of four risk factors. 184 patients (37.1%) had no history of risk factors. 58 patients (11.7%) had been treated previously with arsenic, 103 patients (20.8%) with therapeutic X-rays, 193 patients (39%) with tar, 111 (22.4%) with UVB radiation and 44 (8.9%) had been treated with MTX. 237 (47.8%) PUVA patients had received accompanying retinoid treatment.

Tumor Patients

In 14 patients, one or multiple invasive and noninvasive NMSC were diagnosed (table 2). This was equivalent to a tumor frequency of 2.8%. Nine patients (1.8%) had squa-

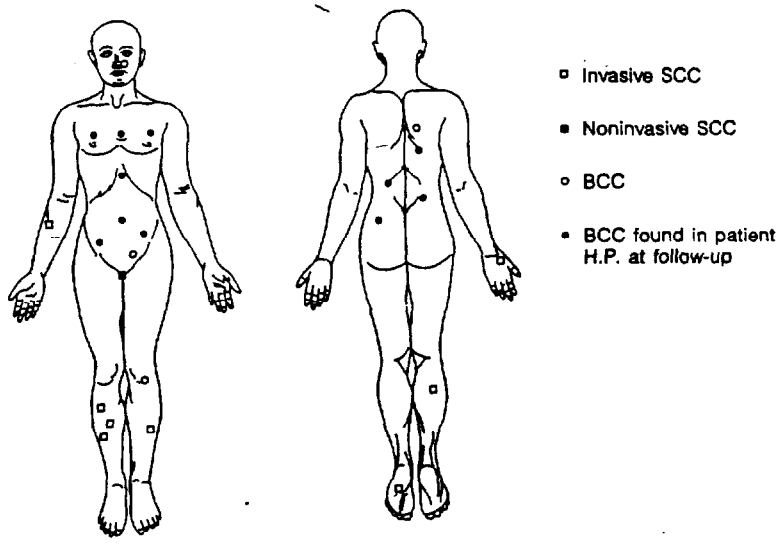

Fig. 1. Tumor location.

Table 3. Results from Cox analysis (BCC and SCC as endpoint)

Factors	Marginal analysis		Partial analysis	
	RR	p	RR	p
Sex	0.73	0.57	1.00	0.99
Age	1.01	0.47	0.99	0.72
Skin type	0.72	0.31	0.69	0.29
ln UVA	1.39	0.15	1.17	0.61
Arsenic	7.62	0.0002	5.36	0.0059
X-rays	1.60	0.43	0.94	0.92
Tar	4.51	0.021	3.83	0.04
UVB	0.41	0.25	0.36	0.20
MTX	4.97	0.0042	4.07	0.028
Retinoid	0.58	0.31	0.45	0.18

Table 4. Results from Cox analysis (only SCC as endpoint)

Factors	Marginal analysis		Partial analysis	
	RR	p	RR	p
Sex	0.67	0.58	2.00	0.44
Age	1.03	0.21	1.02	0.56
Skin type	0.66	0.31	0.46	0.11
ln UVA	2.47	0.009	2.77	0.056
Arsenic	11.2	0.0007	5.19	0.033
X-rays	1.14	0.87	0.77	0.77
Tar	9.92	0.031	7.85	0.061
UVB	0.32	0.28	0.19	0.18
MTX	7.10	0.0036	3.22	0.11
Retinoid	0.95	0.94	0.51	0.38

mous cell carcinoma (SCC), 5 patients (1.0%) had basal cell carcinoma (BCC). No patient had both types of NMSC [29]. The median age of patients with NMSC was 60 (33–81) years, the median ln UVA was 6.83 (4.41–8.67). None of the SCC had metastasized to the lymph nodes at the follow-up or developed metastases later on [30].

Tumor Location

The location of the individual tumors is demonstrated in figure 1. One SCC was located on the forearm, 1 on the back of the hand, 5 on the lower leg and 1 on the sole of the foot. Patient H.B., who had been exposed to arsenic and ln UVA of 8.0 (2,982 J/cm²), presented with a genital SCC in situ.

All but 2 BCC were found on the trunk. One of these 2 BCC was located on the nasolabial fold, the other on the knee. Patient H.P., with a history of arsenic, tar, X-rays and an ln UVA of 5.22 (185 J/cm²), presented with 11 BCC on the trunk at the follow-up (fig. 1).

Carcinogenic Risk Factors and Tumor Frequency

Among 184 PUVA patients, who had no history of carcinogenic treatment regimens, only 1 BCC patient with an ln UVA of 4.41 (82 J/cm², H.K; table 2) was found (0.5%). All other 13 tumor patients (4.2%) belonged to the subgroup of 312 patients with carcinogenic risk factors. Eight of 58 patients (13.8%) with a history of arsenic suffered from NMSC. NMSC developed in 4 of 103 patients (3.9%)

treated with X-rays, in 11 of 193 (5.7%) with tar, in 2 of 111 patients (1.8%) with UVB radiation and in 5 of 44 patients (11.4%) with MTX.

Using the appearance of BCC and SCC as the endpoint, the factors arsenic, tar and MTX appear to produce strong and significant effects, both in the marginal and partial analysis (table 3). Using the endpoint SCC only, the effect of ln UVA, arsenic, tar and MTX is definitely significant in marginal analysis. In partial analysis, only the effect of arsenic is significant and strong while the effects of tar, MTX and ln UVA are strong but with p values only in the range of 0.05–0.11 (table 4). As a general judgment using both marginal and partial results, the effects of ln UVA, arsenic, tar and MTX could be declared unfavorable. The results for the effect of ln UVA on the risk of SCC in tables 3 and 4 refer to a possible linear increase in risk with increasing ln UVA. Nonlinear effects (quadric, cubic) were checked in the modeling stage but in any case were far from significant ($p > 0.2$).

Analyses of possible differences in the importance of the factors considered could only confirm that the risk produced by arsenic is higher ($p < 0.05$) than that produced by possibly unfavorable levels of skin type, UVB, X-rays and sex and, similarly, that the risk associated with ln UVA exceeds the risk by X-rays. These results apply only to the marginal effects analyses in table 4.

A measure of explained variability according to Schemper [27] made it possible to grade dichotomous (arsenic, X-rays, tar, MTX) and continuous (cumulative UVA dose) variables with regard to their carcinogenic potential as follows: (1) arsenic (2.6%), (2) ln UVA, tar, MTX (1.7% each), (3) UVB (0.7%).

Discussion

Oral psoralen photochemotherapy has been used for 20 years for the treatment of severe psoriasis. The actual PUVA regimens differ considerably between Europe and the USA [31]. The European approach maximizes and maintains doses at near phototoxic levels and gives more rapid clearing with lower cumulative UVA doses [32]. Additionally, considerable variability exists in the practice of PUVA in the different institutions. These differences are a possible source of the discordance of early reports on PUVA carcinogenesis. Another source of discordance is the definition of the NMSC patient: this means whether a patient with multiple tumors is counted multiple times or is considered as one single case. Some studies counted each occurrence of NMSC as a new case no matter whether it appeared in the same patient or in a different one [13, 22]. In the past 15 years, several clinical reports about PUVA-induced NMSC have appeared in the literature [8–24]. Although the treatment regimens are variable and different approaches to assess the incidence of PUVA-induced NMSC were used, it seems clear that high cumulative doses (more than 1,500–3,000 J/cm^2) represent a carcinogenic risk in PUVA patients. We had to conduct the study as a retrospective investigation with all the problems connected with a retrospective study design: different periods of follow-up, different distributions of risk factors and lack of an ideal control population. The ideal control population should consist of psoriatics with the same history of risk factors but without PUVA treatment. Such a control group does not exist for obvious reasons since in our patient population those with the severest psoriasis have been treated with PUVA during the past 20 years. Apart from that, information about the doses of other antipsoriatic treatment modalities was missing in most cases.

NMSC developed in 2.8% of our study population, out of these 1.8% were SCC. This is rather low considering that the majority had a history of carcinogenic risk factors. In the patient group without risk factors only 1 tumor patient with an extremely low cumulative UVA exposure was found.

By using two different endpoints of our analysis (BCC + SCC, and SCC only), it turned out that previous treatment with arsenic, tar and MTX increases the risk of the development of both types of NMSC whereas in contrast to other studies [8, 16, 19, 33] a positive history of treatment with X-rays seems to have no carcinogenic potential. Previous UVB treatment turned out to have no influence on NMSC development. This is in agreement with the results of other studies [8, 16, 19, 33]. An increase in cancer risk by earlier UVB treatment was found by Lindelöf et al. [20]. Our finding that arsenic seems to have the strongest carcinogenic potential is in agreement with most studies on PUVA carcinogenesis [13, 15, 16, 18, 19, 20, 22, 23]. Whereas Stern et al. [8, 33] did not comment on the carcinogenicity of arsenic, the finding of the PUVA-48 cooperative study that arsenic does not increase the NMSC risk [10] was revised in their follow-up study 8 years later [18]. In the studies by Stern et al. [8] and Henseler et al. [16] tar did not increase the tumor risk. The statements in some of the studies mentioned above [8, 16, 19, 23] concerning the carcinogenic potential of MTX and other immunosuppressive drugs are contradictory.

The cumulative UVA dose does not appear to strongly affect the risk of BCC development. The risk of the development of SCC increases continuously with the cumulative

UVA dose. In other words, there is no dose-dependent threshold. This is in sharp contrast to other investigations on PUVA carcinogenesis which found a clear increase in the tumor risk in patients with cumulative UVA doses of more than 1,500–3,000 J/cm² [16–19, 23, 24].

The evaluated risk factors can be graded with regard to their carcinogenic potential as follows: (1) arsenic, (2) ln UVA, tar, MTX and (3) UVB. Apart from that, our data indicate that a cancer-protective effect of retinoids is rather unlikely.

Considering the attitude to sun exposure of psoriatics we should not underestimate the contribution of solar irradiation to carcinogenesis. All but 1 SCC were located in areas which are exposed to natural sunlight during sunbathing, especially the lower extremities as was pointed out by two recent studies [24, 33]. In contrast to one of these investigations [33], only 1 BCC was found on the head and neck. Although the genital region of all patients was not shielded during PUVA treatment, we did not find an extraordinary increase in NMSC in the male genital region as reported by one study [34]. This is in agreement with all other studies dealing with PUVA carcinogenesis.

In conclusion, our data indicate that PUVA with the European treatment protocol may be only a weak carcinogen by itself for SCC but not for BCC development.

No increased risk of NMSC has been demonstrated so far for PUVA-treated vitiligo patients although they usually receive high cumulative UVA doses over the years [35, 36]. Severe psoriatics are quite commonly treated with many different treatment modalities some of which have carcinogenic potential. Obviously these patients are the ones who have also received the heaviest burden of PUVA. However, it is of great importance to reduce the cumulative UVA dose wherever possible.

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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

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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 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 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. 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	5.4–41.1
All ≥100	4.2	2.5–7.1	5.1	2.2–12.1
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 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.

ıtilize PUVA treatments in the United States. Of the 1380 pa-
ients originally enrolled in the PUVA study, 984 were still alive
n early 1996. During two decades of prospective study, these
ıatients have developed more than 2900 squamous cell carcino-
nas, squamous cell carcinoma *in situ*, and basal cell cancers, an
ıverage of more than two nonmelanoma skin cancers per en-
ollee.

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

We believe that the incidence rates we used to calculate the
xpected numbers of tumors of each type are the most appro-
riate available to adjust for age, sex, and area of residence *(13)*.
R estimates that compare our cohort's experience with that of
ıe general population are subject to a number of potential bi-
ses. The exclusion of patients with both basal and squamous
ell cancers from the calculations of the basal cell cancer inci-
ence provides an upward bias in RR estimates of about 7% for
asal cell cancer RR. Less complete ascertainment in the federal
ırvey or a temporal increase in skin cancer incidence in the
eneral population would also upwardly bias these estimates. In
ır primary analyses, we excluded the patients at highest risk
.e., those with a tumor in the prior decade). This substantially
wered our RR estimate. Since many patients treated with
JVA develop multiple tumors in a year, our counting only one
mor per year per patient probably underestimated the true RR
these tumors in our cohort compared with the general popu-
tion.

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

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

The primary risk factor for squamous cell cancer after 198
was the level of exposure to PUVA by 1986. After adjustme
for PUVA exposure, sites other than the head and neck that a
most exposed to PUVA were at four times higher risk than th
head and neck. Treatments after 1985 also added to the risk
squamous cell cancer on sites other than the head and nec
(which are often shielded for at least some of each treatmen
The higher risk associated with continued PUVA treatment aft
1985 for sites other than the head and neck may reflect th
increased use of shielding of the face and neck as the carcino-
genic risk of PUVA became known *(3,4,15)*. The very limite
additional risk associated with continued treatment after 1985
further evidence that PUVA was not now acting primarily as
promoter.

The risks associated with high levels of exposure to othe
carcinogenic treatments for psoriasis among patients who ha
survived for at least a decade without a squamous cell cance
were all small; none exceeded a twofold increase. Except fo
therapeutic ionizing radiation for which we compared any ex-
posure with no exposure, our analysis of other risk factors in-
cluded low-dose-exposed patients in the referent stratum. There-
fore, our estimates of the risk attributable to exposure to hig
doses of tar, UVB, or methotrexate might underestimate th
carcinogenic effects of these exposures, particularly if risk is no
dose dependent. Our multivariate analysis confirmed these rela-
tionships. After adjustment for age, sex, area of residence, an
other exposures, the risk of squamous cell carcinoma was sig-
nificantly increased among patients with 160 or more exposure
in the first decade and was increased more than eightfold among
those individuals with more than 336 exposures compared wit
patients exposed to fewer than 100 PUVA treatments.

The relationships between the risk of basal cell cancer an
exposure to PUVA among individuals who had survived for
decade without a basal cell cancer were very different from thos
observed for squamous cell cancer. Overall, the incidence o
basal cell cancer was elevated only modestly. Among patient
with fewer than 100 exposures, the risk of a first basal cel
cancer on the head and neck was not significantly elevated com-
pared with that expected from population incidence data, and th
risk of a first basal cell cancer on other anatomic sites was a
most modestly increased among patients with little exposure t
PUVA. Only among patients with very high levels of exposur
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 an
substantial increase in the risk of squamous cell carcinoma i
patients following high-dose exposure to PUVA. This risk per-
tains to all patients with substantial exposure to PUVA, ever
those without substantial exposure to other carcinogens and wit
little exposure to PUVA in recent years. Patients developing
first squamous cell cancer in the second decade after startin
PUVA were younger and had fewer other risk factors for skin
cancer than those who developed these tumors in the first de-

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In our cohort,
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nude. 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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inct Altered Patterns of p27^{KIP1} Gene Expression enign Prostatic Hyperplasia and Prostatic cinoma

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ound: The p27^{KIP1} gene, whose protein product is a e regulator of the cell cycle, is a potential tumor sup- r gene; however, no tumor-specific mutations of this ave been found in humans. This study was undertaken tify and to assess potential alterations of p27^{KIP1} gene sion in patients with benign prostatic hyperplasia and patients with prostate cancer. *Methods:* We ana- 30 prostate carcinomas from primary and metastatic s well as prostate samples from normal subjects and atients with BPH. Immunohistochemistry and *in situ* ization were used to determine the levels of expression e microanatomical localization of p27 protein and ger RNA (mRNA), respectively. Immunoblotting and odepletion assays were performed on a subset of the e tumors. Associations between alterations in p27^{KIP1} sion and clinicopathologic variables were evaluated nonparametric test. The Kaplan–Meier method and rank test were used to compare disease-relapse-free l. Prostate tissues of p27^{Kip1} null (i.e., knock-out) and pe mice were also evaluated. *Results:* Normal human e tissue exhibited abundant amounts of p27 protein gh levels of p27^{KIP1} mRNA in both epithelial cells and l cells. However, p27 protein and p27^{KIP1} mRNA were undetectable in epithelial cells and stromal cells of sions. Furthermore, p27^{Kip1} null mice developed en- (hyperplastic) prostate glands. In contrast to BPH, te carcinomas were found to contain abundant ^{1} mRNA but either high or low to undetectable levels protein. Primary prostate carcinomas expressing evels of p27 protein appeared to be biologically more sive (two-sided P = .019 [Cox regression analysis]). *sions/Implications:* On the basis of these results, we hat loss of p27^{Kip1} expression in the human prostate e causally linked to BPH and that BPH is not a pre- cursor to prostate cancer. [J Natl Cancer Inst 1998;90:1284- 91]

Inactivation of the tumor suppressor genes p53 (also know as TP53) and RB (retinoblastoma) has been implicated in t development and progression of a number of different cance *(1,2)*. It has also been hypothesized that the loss of function a new family of negative cell cycle regulators that act as cycli dependent kinase (CDK) inhibitors (termed CKIs) might al lead to tumor development *(3)*. CKIs fall into two families, KI and INK, on the basis of sequence homology *(4)*. KIP fami members include p21 (also known as WAF1, Cip1, or Sdi *(5–7)*, p27^{KIP1} *(8–10)*, and p57^{KIP2} *(11,12)*. The INK group i cludes four members: p16$^{INK4A/MTS1/CDKN2}$ *(13)*, p15$^{INK4B/MT}$ *(14)*, p18^{INK4C} *(15)*, and p19^{INK4D} *(16)*. p27 is a negative reg lator implicated in G_1-phase arrest by transforming growth fa tor-β, cell–cell contact, agents that elevate adenosine 3′,5 cyclic phosphate, and the growth-inhibitory drug rapamyc *(17–21)*. p27 associates with multiple G_1-phase CDKs in no proliferating cells, nullifying their activity *(4,8–10)*.

To assess its role as a potential tumor suppressor, we a others mapped the p27^{KIP1} gene to 12p12–p13.1 and observe no tumor-specific genomic mutations in a large group of prima

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See "Notes" following "References."

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uman cancers *(22–24)*. roteasome-mediated de cycle and that this degra nd colon carcinomas of his study to identify a p27^{KIP1} expression in pa (BPH) and in a well-cha nary and metastatic pro

Materials and Metl

Patient Characteristics

A cohort of 130 patients wit ncluded 98 patients with prima mine with metastases to lym primary tumors (n = 98) repre ent radical prostatectomy fo hrough 1991 at the Memorial nd were followed up at the ce n the basis of the availabilit obtained from the Department Center. Samples were formalin al prostatic tissues (n = 4) ddition, BPH lesions were o ases analyzed; these were also normal and tumor prostate tiss ive analyses of results from i munodepletion assays (*see be* ections were examined to ev esions to be analyzed, includi crodissection techniques.

To evaluate prostatic tissue x more than 12-month-old animals. Guidelines established for the proper and humane us were dissected, weighed, and paraffin embedding. Tissue se osin for histologic analysis. S index by the use of Ki-67 anti Ki-67 proliferative activity by oreaction products at ×200 m inar cells per sample was ev

Antibodies and Immun

The following well-characte dilutions were used in all sa Ab-2; Oncogene Science, Inc anti-p27 affinity-purified rabb Center; 1 : 500 dilution), and a tor Laboratories, Inc., Burling erum and a mouse monoclona controls at similar working dil H_2O_2 to block endogenous immersed in boiling 0.01% c minutes to enhance antigen re normal horse serum or 10% immunoreactivities. Primary a Biotinylated horse anti-mous Laboratories, Inc.; 1 : 500 dil Laboratories, Inc.; 1 : 800 dilu biotin–peroxidase complexes t ories, Inc.; 1 : 25 dilution). Di and hematoxylin was used as nes were classified on a cont ectable levels or 0% to homo nto two categories, defined a more of tumor cells with nucl

Occupationally related tumors in tar refinery workers

Stephan Letzel, MD,[a] and Hans Drexler, MD[b] *Erlangen and Aachen, Germany*

Background: The study comprised 606 workers with tar-induced dermatosis employed in a German tar refinery. During the period from 1946 to 1996 they were recognized as having an occupational disease.
Objective: The aim of this study was to characterize the histologic findings and the localization of the occupational dermatosis and to determine the latency period of the carcinomas from the beginning of exposure in the tar refinery to the first occurrence of malignant skin tumors. Furthermore, the study aimed to check whether other skin changes were frequently diagnosed in addition to known tar-induced tumors.
Methods: The data were collected retrospectively from the documents of the Employer's Liability Insurance Association.
Results: Surgical removal of 4754 skin tumors was documented up to the end of 1996 in the study. In 90% of cases the histologic diagnosis was confirmed. Among other conditions, this yielded 2490 precancerous stages, 380 squamous cell carcinomas, 218 basal cell carcinomas, and 182 keratoacanthomas. The skin tumors were found mainly in the facial area, as well as on the forearms and hands. Latency from the first exposure in the tar refinery until manifestation of tar-induced dermatosis covered a period of 57 years.
Conclusion: In comparison to the general population, the ratio of squamous cell to basal cell carcinomas was shifted toward the squamous cell carcinomas (1.7:1). Sunlight is known to be a cofactor in the pathogenesis of keratosis, squamous cell carcinomas, and basal cell carcinomas. However, the difference in location of these tumors shows that the role sunlight plays in the pathogenesis of precancerous lesions and squamous cell carcinomas may be overvalued. The latency period from the beginning of exposure to the manifestation of squamous cell carcinomas could not be evaluated because of an intervention bias as a result of preventive excisions of precancerous lesions. The frequent occurrence of keratoacanthomas (in 18.7% of the workers) and the early age at which this disease became manifest relative to the general population (median, 55 years) indicate that employment in a tar refinery can primarily or secondarily cause keratoacanthomas.
(J Am Acad Dermatol 1998;39:712-20.)

Substances such as tar, soot, crude paraffin, anthracene, pitch, and substances with similar toxicologic effects after usually long-term and intensive exposure can lead to skin cancer or skin changes that tend to develop into cancer.[1-10] Since 1925 in Germany this has led to the recognition of tar-induced malignant skin tumors (squamous cell carcinomas, basal cell carcinomas) and their preliminary stages as an occupational disease,* provided that the sociolegal requirements are fulfilled. In Germany a continuous decrease in occupationally related tar-induced skin diseases has been observed during recent decades.

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*According to the "Sozialgesetzbuch VII" in Germany [§ 9 (1) SGB VII] (Federal Insurance Code), occupational diseases are irregular conditions of the body and mind, which, according to medical science, are caused by particular influences to which certain groups of persons are subjected through their work to a much greater degree than the rest of the population. The only adverse effects on health that can be considered an occupational disease in Germany are those which the government has listed by statutory order in the

This decrease is certainly due to the change in workplace conditions and in personal hygiene; however, the reduction over the past decades in the number of workplaces with such a potential hazard must also be taken into consideration. There is, or was in earlier times, an occupational risk involved when handling the aforementioned substances in such workplaces as tar refineries or impregnating works during the production of briquettes and electrodes and in road construction. Studies have been published with regard to technical procedures and details on these substances.[3,4,6,12-17] Changes to the skin earlier observed in chimney sweeps, which fall under this occupational disease, are today only of historical importance in Germany.

The skin changes that are observed with differing latency periods after exposure to soot, crude paraffin, tar, anthracene, pitch, and similar substances can be classified as acne, acute photodermatitis, precancerous stages, and malignant tumors of the skin. Without any latency period, occasionally only after marginal contact, and an individual predisposition, tar acne (or pitch, soot, or oil acne) can develop.

The most common sites are, in contrast to acne vulgaris, the forearms, thighs, and trunk. Comedones, inflammatory papules, pustules, and abscesses occur.[5,10] The reasons for this are probably a substance-induced impairment in follicle cornification with impeded desquamation and a disturbance in microbial colonization.

Within hours after exposure acute photodermatitis similar to sunburn can occur on areas of the body exposed to sunlight because of the photosensitizing effect of these substances. After recurrent exposure diffuse hyperpigmentation, similar to that seen in melanodermatitis toxica, can be explained.[18] The characteristic changes to the skin occurring mainly on the face after years of exposure are similar in their clinical symptoms to Favre-Racouchot disease and are probably also induced by UV light.

On skin previously damaged in this way, but also without these changes, even after cessation of the exposure, precancerous stages, squamous cell carcinomas, and basal cell carcinomas are observed. After exposure that complies with criteria established by the regulations for occupational diseases in Germany, these diseases can be recognized as an occupational disease and financially compensated under No. 5102* of the occupational diseases list. In this context, present knowledge indicates that malignant melanoma is not caused by the aforementioned substances. Moreover, it has been observed that after occupational exposure to tar and toxicologically similar substances, keratoacanthomas frequently occur.[19-21]

Areas particularly at risk of tar- or pitch-induced skin tumors, which macroscopically have the appearance of warts, are exposed to light (eg, face, hands); the scrotum is also at particular risk.[5,22,23] In addition to sunlight, localization also appears to be dependent on the kind of exposure and the substances concerned.[3]

Tar or pitch keratosis seems to be an obligatory precancerous stage. The tumors may be clinically diagnosed as verrucae vulgares, verrucae planae juveniles, and, on the extremities, stucco keratoses or arsenic keratoses. The latter often cannot be differentiated histologically from tar or pitch keratosis.[24] In addition, young seborrheic warts and Hopf's acrokeratosis verruciformis may have similar histologic features.[25] Bowen's disease, like keratosis, can also be induced by tar and related substances. In addition to squamous cell carcinomas, which develop from untreated keratoses, single or, more rarely, multiple basal cell carcinomas can occur.[1,26] The latency period up to the development of malignant changes as a rule lasts several years to decades for these occupationally related skin diseases. Fabry[1] has stated a period, depending on the person's age, of approximately 10 to 15 years. Because of the relatively long latency periods in some cases between the first skin contact with tar, soot, crude paraffin, anthracene, pitch, or other toxic substances and the occurrence of skin conditions that need treating, an

appendix to the currently valid Berufkrankheitenverordnung. However, with the admission of a disease in the list, only the general character of an occupational disease is recognized. The duty to compensate presupposes that in each individual case the essential cause of the disease can be found in all probability in the occupational activity. According to the "Sozialgesetzbuch VII" [§ 9 (2) SGB VII], however, a disease not listed in the appendix also can be compensated like an occupational disease. The prerequisite is the proof of an abundance of similar health impairments and the long-term monitoring of such symptoms in order to be able to conclude with certainty that the cause of the disease lies in hazardous work." The current appendix to the Berufskrankheitenverordnung in Germany lists 67 diseases or groups of diseases as being worthy of compensation. Modified according to 11

*BK-Nr. 5102: "Hautkrebs oder zur Krebsbildung neigende Hautveränderungen durch Ruß, Rohparaffin, Teer, Anthrazen, Pech oder ähnliche Stoffe."

Table I. Frequency of histologic skin diagnosis in tar refinery workers

Diagnosis	No.	%
Keratosis	2456	57.4
Squamous cell carcinoma	380	8.9
Verruca seborrheica	309	7.2
Fibroma	243	5.7
Basal cell carcinoma	218	5.1
Keratoacanthoma	182	4.3
Cell nevus	105	2.5
Verruca vulgaris	107	2.5
Epidermal cyst	95	2.2
Bowen's disease	34	0.8
Malignant melanoma	5	0.1
Others	146	3.4
Total	4280	100

occupational relationship is not always apparent. Therefore the pathogenesis of all occupationally related precancerous stages and malignant tumors of the skin is not always correctly determined.

METHOD

A collective of exposed workers from a tar refinery in Germany who had tar dermatosis recognized as an occupational disease was investigated to clarify the question of the carcinogenic potency of coal tar and its components. One of the aims of the study was to clarify the following points, bearing in mind what is already known:

1. What kind of tar-induced skin tumors were diagnosed?
2. Which regions of the body were mainly affected by these tumors?
3. How long was the latency period from the beginning of exposure in the tar refinery to the occurrence of malignant changes to the skin?
4. In addition to the known tar-induced tumors (precancerous stages, squamous cell carcinomas, basal cell carcinomas), are there in the collective other frequent skin tumors that could indicate a tar-induced pathogenesis?

The collective consisted of all 606 workers (601 men [99.2%], 5 women [0.8%]) from a German tar refinery in which crude coal tar is broken down into its individual components. During the period from Jan 1, 1946 to Dec 31, 1996, these workers were recognized as having an occupational disease, either for the first time or recurrently, in accordance with No. 5102 currently valid in the German occupational diseases list. The retrospective collection of data was done with the use of a standardized questionnaire based on the individual's occupational disease records. This procedure included consulting regularly documented dermatologic reports, which, as a rule, have been drawn up since the mid-1950s by the same physician. Only those skin tumors classified as being kept under observation or in need of treatment were considered in the coding of the skin changes. In addition to the location of the tumor, the date of diagnosis, the therapy, and, when available, the histologic evaluation were taken into account. The histologic reports were assumed to be accurate; considering the long observation period (51 years), it was not possible to retrospectively check the accuracy of the reports. All known findings up until Dec 31, 1996 were included in the evaluation. In addition, the company's safety engineers, in collaboration with the works committee, determined the specific exposure times.

The results were represented descriptively. Bearing in mind the wide distribution of birth dates (see next paragraph) and the selection bias regarding health toward the persons included in the study, the inclusion of a control collective in the evaluation was not possible. The beginning of tar-induced skin disease was defined as the date of the first surgical removal of a tar-related skin tumor (precancerous lesion, squamous cell carcinoma, basal cell carcinoma).

Because of the relatively long observation period (51 years), there was a large variation in the dates of birth (from 1882 to 1960; median, 1922). On the date of evaluation (Dec 31, 1996) 323 patients (53.3%) had already died, 277 (45.7%) were still alive, and no information was available on the vital status of 6 persons (1.0%). The distribution of the age at death (median, 71 years; range, 41-93 years) showed no anomalies relative to the general population. The median age on the date of evaluation of persons still living was 66 years (range, 36-87 years). Approximately one third of the persons (n = 204, 33.7%) had already started working in the tar refinery before 1940. The earliest date for beginning employment was 1908, the latest, 1987. No exact information on the beginning or the end of employment at the tar refinery could be gained from 24 persons (4%) because of, among other things, the loss of documents during and after the war. More than 77% of the workers from the collective were employed in the tar refinery for more than 20 years (median, 32 years; range, 2-51.5 years).

RESULTS

In the collective a total of 4754 skin tumors were surgically removed. Histologic diagnosis was available in 90% of cases (n = 4280). In 10% of cases (n = 474) no histologic investigation was carried out on the removed tissue or the findings

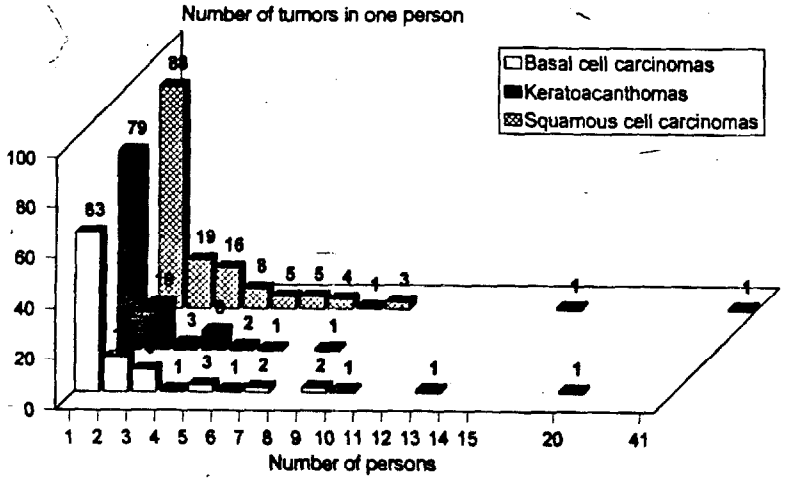

Fig 1. Distribution of histologically determined carcinomas, basal cell carcinomas, and keratoacanthomas.

were no longer available. The findings are listed in Table I. The skin changes (keratosis, Bowen's disease, squamous cell carcinomas, basal cell carcinomas) known to be related to tar exposure were of particular interest. Furthermore, during the collection of data, keratoacanthomas were shown to be more frequently diagnosed than was expected (for further details see below).

Keratosis and Bowen's disease are classified under precancerous stages in our study. Including the keratoacanthomas, a total of 3270 skin tumors could be attributed to occupational activity in this study population.

In total, 151 persons were affected by the 380 histologically determined squamous cell carcinomas and 98 persons by the 218 basal cell carcinomas. Bearing in mind the multiple occurrence of malignant tar-induced skin tumors in 1 patient, the 598 squamous cell carcinomas and basal cell carcinomas occurred in 207 persons (34.2%). The ratio of squamous cell to basal cell carcinomas was 1.7:1. The frequency distribution of histologically determined squamous cell carcinomas and basal cell carcinomas in the persons was skewed to the right (ie, the majority of patients only had 1 squamous cell carcinoma and/or 1 basal cell carcinoma) (Fig 1). A similar distribution pattern could also be seen for the keratoacanthomas. The maximum in 1 patient* was 41 squamous cell carcinomas of the skin and 6 keratoacanthomas. In addition, in this patient 14 histologically determined precancerous lesions were surgically removed.

The histologically determined precancerous lesions, keratoacanthomas, squamous cell carcinomas, and basal cell carcinomas in the study collective were present mainly in the head area, particularly on the face, as well as on the forearms, wrists, and hands (Table II). Although location of the basal cell carcinomas did not differ greatly from the preferred places known in the general population (eye region, temples, cheeks, side of the nose, bridge of the nose, nasolabial groove), some anomalies were seen in the precancerous stages, keratoacanthomas, and squamous cell carcinomas. The upper lip was more frequently affected than the lower lip (precancerous lesions, 44:18; keratoacanthomas, 6:1; squamous cell carcinomas, 13:11) and the forearms more frequently than the back of the hand (precancerous lesions, 297:244; keratoacanthomas, 13:10; squamous cell carcinomas, 41:32). Furthermore, skin tumors (72 precancerous lesions, 4 keratoacanthomas, 10 carcinomas) were found more frequently on the less sun-exposed parts of the nose (eg, around the nostrils) than on the more light-exposed bridge of the nose (22 precancerous lesions, 3 keratoacanthomas, 7 carcinomas).

The temporal course of tar-induced skin disease is shown in Table III. The diagnosis of occupationally related tar-induced skin tumors was first made in 1934.* Although squamous cell carcino-

*This patient (born 1905, died 1977) died of metastatic carcinoma of the large intestine and had been employed in the tar refinery from 1928 to 1962; the first tar-induced skin tumor appeared in 1938.

*Some persons of the collective had their first tar-induced tumor before the observation period.

Table II. Localization of histologically determined precancerous stages, keratoacanthomas, squamous cell carcinomas, and basal cell carcinomas

Localization	Precancerous stages	Keratoacanthomas	Squamous cell carcinomas	Basal cell carcinomas
Head				
Hair region	18	1	1	0
Forehead	53	4	10	19
Periorbital area	217	22	35	32
Nose				
Root	9	5	4	1
Bridge	22	3	7	10
Side	53	5	16	12
Tip	16	2	7	5
Nasal septum	5	0	2	0
Columella	3	1	1	0
Nostril	72	4	10	1
Nasal cavity	3	0	0	0
Nasolabial grove	9	0	0	5
Nose in general	13	4	4	4
Mouth				
Upper lip	44	6	13	2
Lower lip	18	1	11	1
Corner of the mouth	14	0	2	0
Oral cavity	2	0	0	0
Tongue	1	0	0	0
Mouth in general	0	0	0	0
Lower jaw	61	11	9	3
External ear	115	9	45	19
Behind the ear	22	7	10	10
Cheek	119	15	38	21
Temples	63	8	6	33
Face in general	2	1	2	1
Neck	131	11	3	4
Back of the neck	52	1	5	1
Trunk, shoulder, buttock	155	14	5	8
Axilla	43	0	0	0
Upper arm	36	0	1	0
Elbow	42	0	0	0
Forearm	297	13	41	14
Wrist	75	8	7	0
Hand				
Dorsum	244	10	32	10
Finger	193	7	12	0
Palm	13	0	0	0
Lateral aspect	2	0	0	0
Hand in general	29	2	4	0
Genitals/Anal region				
Perianal area	0	0	0	0
Perineum	1	0	0	0
Inguinal area	18	0	4	0
Scrotum	20	0	20	0
Penis	5	0	0	0
No details	2	0	0	0
Upper leg	53	2	2	0
Knee	24	2	2	0
Lower leg	41	2	2	0
Foot, ankle	48	1	4	2
No details	12	0	3	0
Total	2490	182	380	218

Table III. Temporal course of tar-induced skin diseases: Squamous cell carcinomas, basal cell carcinomas, and keratoacanthomas

Variable	No. of persons	Mean	Minimum	First quartile	Median	Third quartile	Maximum
Diagnosis of tar-induced skin disease							
Year	589	1967	1934	1959	1968	1974	1996
Age (y)	589	47.0	16.0	38	47	55	82
Latency period from first employment in the tar refinery to occurrence of disease (y)	579	20.2	< 1	10	19	28	57
First diagnosis of a squamous cell carcinoma							
Year	148	1964	1938	1953	1964	1971	1996
Age (y)	148	55.2	25	47	55	64	79
Latency period from first employment in the tar refinery to first diagnosis of a skin carcinoma (y)	142	29.4	2	19.8	28	39.5	61
First diagnosis of a basal cell carcinoma							
Year	98	1977	1954	1968	1976	1987	1996
Age (y)	98	60.7	35	55.8	61.5	66	84
Latency period from first employment in the tar refinery to first diagnosis of a basal cell epithelioma (y)	95	34	< 1	24	35	44	69
First diagnosis of a keratoacanthoma							
Year	113	1974	1961	1970	1973	1978	1996
Age (y)	113	55.7	21	47	55	64	80
Latency period from first employment in the tar refinery to first diagnosis of a keratoacanthoma (y)	110	29.7	3	19	29	40	63

mas of the skin were diagnosed for almost all of the observation period, a keratoacanthoma was first diagnosed in 1961.

The range of ages at which a tar-induced skin disease was diagnosed was 16 to 82 years. A 16-year-old male adolescent had a tar-induced tumor diagnosed in 1965 after a latency period of approximately 3 years after he began working in the tar refinery. In the following years (1965 to 1972) 7 precancerous lesions found on the face (n = 3), forearm (n = 3), and upper leg (n = 1) were surgically removed.

Anomalies were seen in the age distribution of the first manifestation of a keratoacanthoma. Keratoacanthomas occurred before 60 years of age in more than half of the affected persons (n = 67). The latency period from first exposure in the tar refinery to first manifestation of a tar-induced skin disease could be exactly determined in 579 persons (in 27 persons data were missing on the beginning of exposure or the first manifestation of a skin tumor, or both). The median latency period for tar-induced skin disease was 19 years, for squamous cell carcinoma 28 years, basal cell carcinoma 35 years, and keratoacanthoma 29 years. In 46 persons the tar-induced skin disease did not occur until 1 to 41 years (median, 6 years) after giving up the hazardous activity in the tar refinery.

DISCUSSION

The collective comprised persons whose skin was strictly monitored and evaluated for decades. As a rule, conspicuous skin changes were given surgical therapy very early and in the majority of cases (approximately 90%) a histologic investigation of the excised tumors was carried out. This certainly caused both selection and intervention bias. Quantification of these effects is not possible for methodical reasons. Furthermore, no suitable control collective was available because of the age distribution of the study collective (range [year of birth], 1882 to 1960) and the strict dermatologic monitoring; therefore exact quantification of the skin diseases caused by tar and related substances is also not possible.

Moreover, exact classification of the precancerous lesions in some cases caused methodologic problems because histologic findings from many decades were drawn up by various pathologists. Correspondingly varied was the nomenclature, which retrospectively did not always allow a clear diagnosis (eg, "benign tar wart," "pitch wart," "keratosis already with certain precancerous changes"). Furthermore, during the collection of the data, the impression arose that in those patients in whom tar-induced skin disease had already been acknowledged, the histologic diagnosis of a tar wart was given more generously.

We believe that the diagnostic certainty is greater with regard to the malignant tumors (squamous cell and basal cell carcinomas) and keratoacanthomas. For this reason we concentrated on these lesions. The 380 squamous cell carcinomas were observed in 151 persons. In comparison, the 218 basal cell carcinomas in 98 persons exposed to tar were rarer. Bearing in mind the known ratio of basal cell to squamous cell carcinomas in Germany (about 10:1),[22,27,28] the reversal of the relationship to 1:1.7 is particularly noteworthy, which makes the induction of basal cell carcinomas by tar seem less important. The locations of these occupationally caused basal cell carcinomas do not differ from the common sites known for this tumor.[22]

UV light is accorded high importance as a cofactor in the carcinogenesis of tar cancer.[1,5,18,22,26] However, there is some question about the particular importance of UV light. The initial histologic changes in tar warts can typically be detected in the follicle ostium. Therefore in an early stage differentiation of interfollicular solar keratosis is frequently possible.[23] In addition, according to an extensive study, photosensitive, sandy-haired, light-skinned men are not affected by tar warts any more often than their dark-skinned colleagues.[2] Finally, there is a total lack of any exposure to light in the frequently described incidence of tar warts on the distal lower legs and feet.[25] Likewise, the distribution of precancerous lesions and carcinomas we found compared with the basal cell carcinomas does not indicate that UV light is the predominant inducer of these lesions. The localization of the carcinomas on the upper lip, which is otherwise rare,[22,29] seems to be particularly worth mentioning; this could not be explained by holding tar-coated items in the mouth. In the case of carcinomas on the upper lip, the possibility of exposure to tar should therefore always be examined. On the bridge of the nose, which is often exposed to sunlight, there were also markedly fewer precancerous lesions and carcinomas than in the area of the nostril, which is certainly less exposed to light but, via the inspired air, more exposed to tar. The back of the hand, an otherwise preferred region of the squamous cell carcinoma,[27] was affected less often than the certainly more seldom sun-exposed forearm. Here, just as on the feet and distal lower legs, a more intensive contact with the hazardous agent via soiled working clothes can be assumed.

Such intensive contact can probably be held responsible for the scrotal carcinomas already described by Pott[9] in 1775. However, because of changes in hygienic conditions, the scrotum no longer is affected to this extent. Nevertheless, 20 precancerous lesions and 20 squamous cell carcinomas of the scrotum were still found. Because the prognosis for these carcinomas, because of early metastasis, is much worse than for other areas of the body,[23] the genital area of exposed persons must be carefully examined during occupational-medical health checks.

The range of the latency period from the first day of employment in the tar refinery up to diagnosis of a tar-induced skin disease was approximately 57 years and increased continuously depending on age. We believe that the values on the latency period up to the first occurrence of a malignant tar-induced skin change are difficult to evaluate, at least for squamous cell carcinomas. Considerable intervention bias because of preventive excision of precancerous lesions probably plays an important role because tar-induced skin tumors that have not yet become malignant can no longer develop into squamous cell carcinomas after surgical removal. This is confirmed by the various latency periods from first exposure to the first excision among the patients with malignant and nonmalignant tar-induced skin tumors. The formation of squamous cell carcinomas therefore seems to be greatly dependent, in addition to individual factors, on timely operative intervention and the health consciousness of individual patients.

Anomalies were found with regard to keratoacanthomas, especially the year in which this tumor was first diagnosed, their frequency distribution, localization, the latency period from the first expo-

sure to the first manifestation of a keratoacanthoma, and the age at which this benign skin tumor was diagnosed.

A keratoacanthoma was diagnosed for the first time in 1961. If one considers the long observation period, this is surprising, particularly considering that more than one third (41.9%) of the cases of squamous cell carcinomas had already been diagnosed for the first time by 1961. This finding possibly occurred because, despite being described for the first time in 1888 by Hutchinson, the keratoacanthoma only drew scientific attention in the second half of this century in Germany[30] and thus medically only became generally known at this time. Therefore, in older German textbooks on dermatology, this tumor is not mentioned.[31] However, this means, perhaps, that in earlier times keratoacanthomas may not have been diagnosed but were subsumed in other diagnoses. The incidence of this skin tumor in the study collective would then be even higher than can be substantiated by the results.

In the international literature only limited data can be found on the incidence of keratoacanthomas. To date, only 1 prospective investigation specifically on the frequency of keratoacanthomas in the general population has been done.[32] An incidence of 104 cases of keratoacanthomas per 100,000 inhabitants a year was found for the white inhabitants of the island of Kauai, Hawaii. In the collective of persons with occupationally related tar-induced skin diseases described herein, at least 1 keratoacanthoma was seen during the observation period in 18.7% of subjects (n = 113). Because the total population from which this collective came cannot be determined retrospectively, no incidences can be calculated from the available data. Even taking into consideration possible selection effects (see above), it is nevertheless clear that in approximately every sixth person a keratoacanthoma developed. Because our collective consisted of persons whose skin was intensively exposed to coal tar and diverse constituents of coal tar, which must be regarded as proven by the occurrence of tar-induced skin diseases, occupational skin contact seems to represent an important factor in the development of a keratoacanthoma. This observation is supported by several reports.[19-21]

The latency period from the first exposure in the tar refinery to the first manifestation of a keratoacanthoma was almost identical to the latency period of the squamous cell carcinomas of the skin, as histologically determined. If one assumes this is not an artefact, it could indicate that similar pathogenic mechanisms are responsible for the formation of both skin tumors.

The age distribution for the first manifestation of a keratoacanthoma was particularly unusual. It is generally assumed that this tumor usually occurs in the later decades of life in the general population.[22,33] In systematic investigations a median age of 67.2 years for development of a keratoacanthoma was observed in the collective of Chuang et al[32]; Hundeiker* reported that keratoacanthoma developed at a median age of approximately 64 years. However, this benign skin tumor occurred in our collective at a median age of 55 years, on average 12.2 or 9 years earlier than in the 2 abovementioned studies. We believe that this unusual age distribution also indicates that occupational exposure is an important factor in the formation of keratoacanthoma.

The pathogenesis of keratoacanthoma is possibly multifactorial. If one considers the course of the disease to consist of a relatively fast growth phase, subsequent arrest of growth, followed by spontaneous remission, it would be pathogenically plausible (eg, considering a viral genesis[30]) that coal tar and some of its constituents, or chemically related substances similar to sunlight, can trigger the formation of this skin tumor.

The answers to the questions of the investigation as posed earlier in this article can be summarized as follows:

1. After histologic diagnosis keratotic and hyperkeratotic tar-induced skin changes were most numerous. Bowen's disease played only a minor role. Compared with the general population the ratio of squamous cell carcinomas to basal cell carcinomas was shifted toward the squamous cell carcinomas. In addition, we found frequent occurrence of keratoacanthomas.

2. The head, forearm, and hand (including the wrist) were primarily affected by tar-induced skin changes. On further differentiation of the localization, there was some question as to the importance of the influence of sunlight in the genesis of tar-induced precancerous lesions and carcinomas compared with direct skin contact.

*Hundeiker M. Keratoakanthoma. Presented at Sofia Dermatological Days, Sofia, Bulgaria, Nov 3-5, 1994.

3. An evaluation of the latency period from the first exposure to the first occurrence of malignant skin changes is not possible because of the intervention bias caused by preventive excision of precancerous stages.

4. The frequent occurrence of keratoacanthomas and the earlier age at which the tumor first occurred relative to the general population indicate that occupational activity in a tar refinery can contribute to development of keratoacanthoma, either primarily or secondarily.

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Cancer in patients with psoriasis

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In a study of 150 non–PUVA-treated patients with psoriasis matched against a control group of patients with diabetes, the incidence of skin cancer in the psoriasis group was 1.96/yr, which was three times that of the diabetes patients. This figure is statistically significant. The prevalence of internal cancer was only half that of the patients with diabetes. This figure, however, is not significant.
(J AM ACAD DERMATOL 7:633-638, 1982.)

PUVA has been accused of being a promoter[1,2] in studies in which patients receiving PUVA who had also been treated with x-ray[1] or arsenic[2] developed skin cancers at a rate (2%/yr) above that of the normal (0.5%/yr) population not treated with either of these substances. Control groups of psoriasis patients treated with just x-ray or just arsenic have not been reported. It is important to know how many of these patients treated with a carcinogen and PUVA would have developed skin cancers without PUVA.

We have previously reported[3,4] that approximately 10% (about 2%/yr) of patients with psoriasis who have not been treated with PUVA develop skin cancer. The twenty-nine patients reported who developed skin cancer did so especially during their fifties. Fourteen had skin cancers in non–sun-exposed areas of the skin. Thirteen of these fourteen patients had squamous cell lesions (including one keratoacanthoma and one Bowen's disease).

The previously reported patients were found by searching for them among our private practice and Veterans Administration patients, and it was impossible to draw accurate conclusions as to the true incidence of cancer in patients with psoriasis. We are now reporting a study of 150 non–PUVA-treated patients with psoriasis matched with a control group of diabetes patients. The incidence of skin cancer in the psoriasis group (1.96%/yr) was three times that of the diabetes group. However, the prevalence of internal malignancies in the psoriasis patients was half that of the patients in the diabetes group.

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METHODS

The medical records of 150 patients with psoriasis were examined. These patients had all been hospitalized at the Miami Veterans Administration Medical Center during the years 1976 through 1980 for treatment of psoriasis. This number (150) represents approximately one third of the psoriasis patients hospitalized during this time period, and they were randomly selected. No stringent definition of psoriasis was used. We included in this study patients who had psoriasis to such an extent that the disease required hospital treatment. Ordinarily this would mean that, at the least, 25% of the body surface was involved and that the patient could no longer manage his disease. Most of these patients had had repeated hospitalizations and had been treated with more than one treatment modality (Table I).

The following information was extracted from each record: year of birth, sex of patient, race, ethnicity (Jewish or Hispanic descent), treatment history, smoking history, and the date of the first and last visit to the hospital or hospital clinic. Smoking history was coded according to the State of Florida Cancer Data System.

Each record was then checked for a diagnosis of skin cancer made during the period of Jan. 1, 1971, to Dec. 30, 1980. Only diagnoses supported by a pathology

Table I. Treatment modalities used (1971-1980)

Treatment	No. treated (N = 150)	% treated
UV + coal tar	95	63
Methotrexate	57	32
Nitrogen mustard	44	23
Hydroxyurea	15	10
Topical steroids only	24	16

report were counted. For each skin cancer diagnosis the type of skin cancer, the date of diagnosis, and the location of the cancer were noted. The records were also checked for a diagnosis of internal malignancy. All diagnoses of internal cancers were recorded and were not limited to the 10-year span used for skin cancer recording. Date of diagnosis and location of the internal cancer were also noted.

For comparison purposes, a group of patients who had been diagnosed as having adult-onset diabetes mellitus without complications and hospitalized for control of diabetes was matched to the psoriasis patients. Each psoriasis patient was matched to a diabetes patient for year of birth, sex, and race. The hospital's Diagnostic Index, which lists all patients discharged from the hospital by diagnosis on a quarterly basis, was used to obtain the pool of diabetes patients. A stratified randomization procedure was used to select the individual patients to be included.

The date the patient was initially seen and the date he was last seen at the Medical Center were recorded to determine the number of years these patients had been followed. The average follow-up was 6.8 years. In addition, this allowed us to ensure that the matched psoriasis patient and the control diabetes patient were followed for the same length of time. Thus, if one or the other had a diagnosed cancer after the last visit of the patient with whom he was matched, that diagnosis was not tabulated.

Data were then entered into our Clinfo on-line computer system and analyzed.

RESULTS

Each group was composed of 147 male and three female patients. The preponderance of males reflects the fact that the patients were drawn from a Veterans Administration Hospital. The mean age was 62 with a range from 24 to 92.

The psoriasis patients had histories of psoriasis ranging from over 40 years to 1 year. The treatment modalities used between 1970 and 1980 are shown in Table I. Only 24 or 16% of the patients had been treated with topical steroids alone. Seventy or 46% had been treated with two or more treatment modalities, other than topical steroids, during the 10-year period. Thirty-eight (25%) of our patients also had psoriatic arthritis.

There were seven blacks in each group. There was no statistically significant difference between the psoriasis group and the diabetes group in the number of patients of Jewish and Hispanic descent, which are the largest ethnic groups in Miami. Neither was there a significant difference in the smoking habits of the two groups.

Skin cancers

Only skin cancers for which there was pathologic evidence and which were diagnosed between January, 1971, and December, 1980, were counted. Twenty of the psoriasis patients had a diagnosed, biopsy-proved skin cancer compared to seven of the diabetes patients. This was a significant difference ($p = 0.009$, $\chi^2 = 6.88$).

The psoriasis patients and the diabetes patients having skin cancers were approximately the same age at the time of diagnosis: 60 was the mean age for psoriasis patients and 62 for the diabetes patients. Fig. 1 shows the cumulative frequency of skin cancers at the age of diagnosis of both groups. In both groups the largest proportion of cancers were diagnosed between the ages of 50 and 60.

Using the first diagnosed skin cancer for analysis, squamous cell carcinomas outnumbered basal cell carcinomas 14 to 6 in the group of psoriasis patients. Eight of the squamous cell carcinomas were in non–sun-exposed areas of the body, as was 1 of the basal cell carcinomas. In the diabetes group there were 3 squamous cell carcinomas and 4 basal cell carcinomas. All of the skin cancers in the diabetes patients occurred in sun-exposed parts of the body except for one squamous cell carcinoma on the shoulder (Table II).

Of the 20 psoriasis patients with skin cancer, 9 had multiple skin cancers; 4 of the diabetes patients had multiple cancers. Two of the psoriasis patients had, by history, in excess of 20 cancers

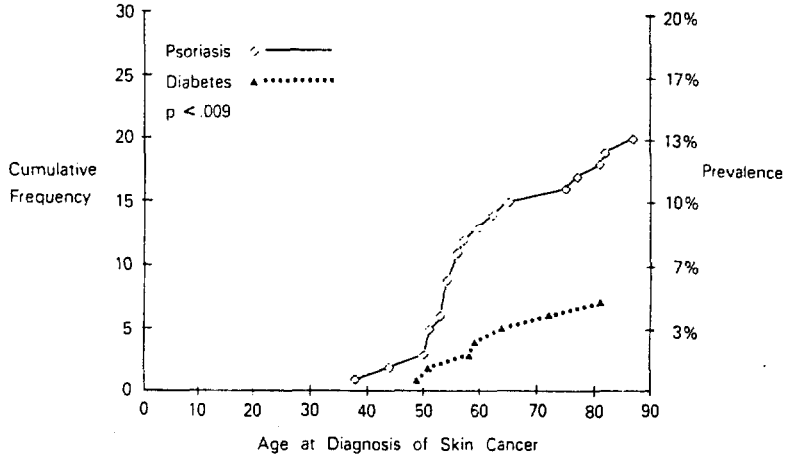

Fig. 1. Cumulative frequency at age of diagnosis of skin cancer for psoriasis patients and diabetes patients.

each: the total number of skin cancers in the psoriasis group was in excess of 56. The greatest number of skin cancers on one patient in the diabetes group was 16; the total number of cancers was 27. However, since all of these multiple cancers could not be documented by pathology reports, it was not possible to consider them in our analysis. Rather, we used the first documented skin cancer between 1971 and 1980 for our analysis.

The treatment history of the psoriasis patients with skin cancer is shown in Table III. In the group of patients with skin cancers in non–sun exposed areas, all but one had received previous treatment with a known carcinogen. The treatment most frequently noted was ultraviolet light and tar (Goeckerman therapy). Two patients had been treated with PUVA, but in each case the cancer was diagnosed very soon after starting PUVA therapy—3 weeks in one case and 3 months in the other. It is interesting to note that one patient had a squamous cell carcinoma on the thumb and this patient had received x-ray therapy to his hands in the past.

Internal cancers

The psoriasis group had half the number of internal cancers as did the diabetes group; however, this [illegible] not a significant difference. There were nine psoriasis patients with a diagnosed internal malignancy and eighteen diabetes patients. The mean age at the time of diagnosis was 65 for psoriasis patients and 52 for diabetes patients. Fig. 2 shows the cumulative frequency of the internal cancers in the two groups.

Table IV shows the location of the internal malignancies. Five or 55% of the psoriasis patients with internal cancers had cancer of the gastrointestinal tract. One patient had a long-standing diagnosis of leukemia. There were no lung cancers in the psoriasis group. Two psoriasis patients and one diabetes patient had both skin and internal cancers.

Table II

Parameter	Psoriasis	Diabetes
Average age at diagnosis	60	62
Patients with skin cancer	20	7
Squamous:basal	14:6	3:4
Exposed areas	11	6
Squamous:basal	5:5	2:4
Nonexposed areas	9	1
Squamous:basal	8:1	1:0
Multiple cancers	9	4
Incidence (%/yr)*	1.96	0.69
Squamous cell	1.3	0.3
Basal cell	0.6	0.4

*Incidence (%/yr) of skin cancers = prevalence ÷ average follow-up (yr).

DISCUSSION

Recent reports[1–5] have demonstrated that contrary to previous thought[6,7] patients with psoriasis

Table III. Treatment history

Sun exposed/ non–sun exposed	Location	Treatment history
Sun-exposed		
Basal cell carcinoma		
1	Nose	UV + tar, HN_2
2	Arm	Steroids
3	Nose	UV + tar, MTX, hydroxyurea
4	Ear	MTX, HN_2
5	Nose	Steroids
Squamous cell carcinoma		
1	Face	Steroids
2	Thumb	X-ray to hands, HN_2, arsenic
3	Lip	UV + tar, MTX, HN_2, hydroxyurea
4	Face	Steroids
5	Face	UV + tar
6	Neck	UV + tar, MTX
Non–sun-exposed		
Basal cell carcinoma		
1	Trunk	UV + tar
Squamous cell carcinoma		
1	Perianal	X-ray, MTX, UV + tar
2	Back	HN_2, MTX, UV + tar
3	Scrotum	HN_2, MTX, UV + tar, grenz ray, arsenic
4	Penis	MTX
5	Shin	UV + tar, HN_2
6	Calf	UV, HN_2
7	Perianal	MTX, HN_2, UV + tar, hydroxyurea, PUVA*
8	Leg	HN_2, UV + tar, PUVA†

*Only 3 weeks of PUVA before diagnosis of skin carcinoma.

†Only 3 months of PUVA before diagnosis of skin carcinoma.

do get skin cancers. Our study indicates that psoriasis patients are getting significantly more skin cancers than at least one segment of the population—people with diabetes.

We chose diabetes patients for our matched control because the two diseases have common characteristics. The tendency to have the disease is genetic. Neither disease is curable but each can be controlled with appropriate therapy. Management of the disease can require intermittent hospitalization and does require continuing outpatient medical attention. Each group of patients was part of the same Veterans Administration Hospital population during the same 4-year period and thus the climatic, environmental, and socioeconomic factors for both the psoriasis patients and the diabetes patients should be similar.

We seriously considered alternative groups for use as the control. We felt that the general hospital population would be inappropriate since this would include emergency and short-term procedures as well as patients with a primary diagnosis of cancer. It seemed to us, for the reasons mentioned above, that the diabetes patients would be an appropriate control.

We also considered the problem of underascertainment of skin cancers in the diabetes group. While it is true that dermatologists would be more likely than internists to diagnose skin cancers, all skin problems at the Miami Veterans Administration Medical Center are referred to the Dermatology Service for consultation. Also, we did not rely on the patient's memory or on reported but undocumented skin cancers. All skin cancers tabulated were supported by biopsy reports. We chose a group of diabetic patients who had no complica-

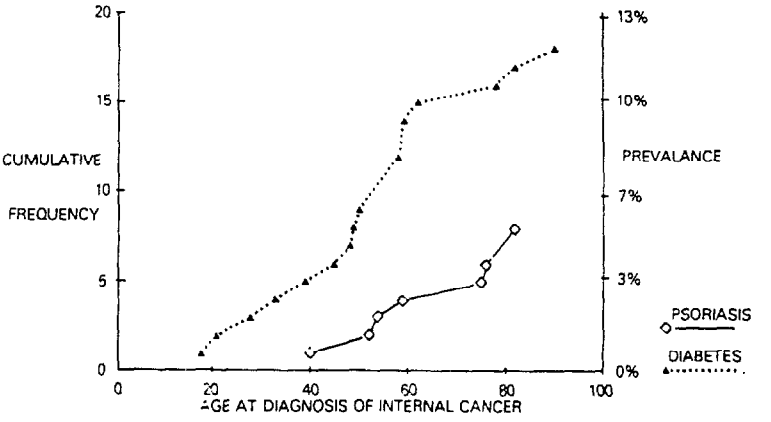

Fig. 2. Cumulative frequency at age of diagnosis of internal cancers for psoriasis patients and diabetes patients.

tions such as acidosis, nervous system complications, eye complications, ulcer complications, or gangrene. It was felt that in this group, because of the lack of extenuating complications, physicians would not hesitate to biopsy suspicious lesions. Furthermore, all inpatients are given a thorough physical examination upon admission, and it seems unlikely that a significant number of skin cancers which are progressively enlarging would remain undetected in this chronically followed population of diabetic patients.

A further question which must be considered is the degree to which our non–PUVA-treated patients are representative of psoriasis patients in general, particularly of those patients with severe psoriasis who are being treated with PUVA. Our patients do have severe psoriasis and have required hospitalization for treatment, usually with Goeckerman therapy or methotrexate therapy. At the present time we have no facilities for PUVA therapy and therefore cannot offer this treatment to our patients. Many of these patients, however, would be candidates for PUVA if it were available. Furthermore, if our patients have less severe psoriasis than PUVA patients in general, this should result in our skin cancer incidence being lower than the incidence reported in PUVA studies if, in fact, psoriasis therapies are carcinogenic.

One-third as many diabetes patients (4.7% or 0.69%/yr) as psoriasis patients (13.3% or 1.96%/yr) had skin cancers. Over half of the diabetes patients with skin cancer had a basal cell carcinoma: only one diabetes patient had a skin cancer in a non–sun-exposed area. This indicates that diabetes patients are getting their skin cancers the way most people do—through exposure to sunlight.[8,9]

Table IV. Internal cancers

Location	Psoriasis patients	Diabetes patients
Gastrointestinal tract	5	6
Genitourinary tract	2	6
Lung	0	4
Oropharyngeal	1	0
Leukemia	1	0
Lymphoma	0	1
Central nervous system	0	1
Total	9	18

As would be expected, the psoriasis patients also developed skin cancers in sun-exposed areas of the body. However, this group developed almost twice as many skin cancers in sun-exposed areas as did the diabetes group. The psoriasis patients did probably spend more time in the sun, as this is known to be helpful for their psoriasis. They were also exposed to known carcinogens in addition to the sunlight. All but four of the psoriasis patients with skin cancers in sun-exposed areas had previously been exposed to a carcinogen for the treatment of psoriasis.

In contrast to the one skin cancer found in a non–sun-exposed area in the diabetes group, the psoriasis group had nine such cancers. Stern et al[1]

also found a high incidence of skin cancer in non-sun-exposed parts of the body in a PUVA-treated group of psoriasis patients; an increased number of squamous cell carcinomas was also found in this group. We, too, found a higher incidence of squamous cell to basal cell carcinoma (14:6) than would be expected,[8,10] especially in the non-sun-exposed areas (8:1). Stern et al suggested that this increase in skin carcinomas in psoriatics was due to PUVA treatment; i.e., PUVA was acting as a promoter. Our findings suggest that severe psoriasis patients who have not received PUVA therapy but have been exposed to carcinogenic agents (ultraviolet light B,[9] tar,[11] ionizing radiation,[12] arsenic,[13] and nitrogen mustard[14]) are developing skin cancers at a rate (1.96/yr) which may be similar to those who have had PUVA (2%/yr).

While it was not statistically significant ($p = 0.066$), the psoriasis patients had half the number of internal malignancies as did the diabetes group. Five of the nine internal cancers in the psoriasis group were cancers of the gastrointestinal tract: there were no lung cancers and only two genitourinary malignancies. This lower number of internal malignancies in the psoriasis group was somewhat surprising since diabetics are thought to have a lower mortality rate from cancer[15] and a lower incidence rate of cancer[16] than the general population. However, Bailin et al[17] reported that psoriasis patients receiving methotrexate therapy had a normal incidence of internal cancer. Also a follow-up of low-risk patients in the 16 Center Trial showed a normal death rate from various malignancies (including lung) as compared with the national expected average.[18] A recent study from the Mayo Clinic also found a normal amount of internal malignancies in psoriasis patients.[5]

In summary, our patients with psoriasis are not developing either significantly fewer or significantly more internal malignancies than patients without psoriasis. Our patients with severe psoriasis are, however, developing two to three times more skin cancers than our control group despite the absence of PUVA.

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CLINICAL DERMATOLOGY

A Color Guide to Diagnosis and Therapy

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THIRD EDITION

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Seborrheic Dermatitis

Seborrheic dermatitis is a common, chronic, inflammatory disease with a characteristic pattern for different age groups. The yeast *Pityrosporum ovale* probably is a causative factor, but both genetic and environmental factors seem to influence the onset and course of the disease. Many adult patients have an oily complexion, the so-called seborrheic diathesis. In adults, seborrheic dermatitis tends to persist, but it does undergo periods of remission and exacerbation. The extent of involvement among patients varies widely. Most cases can be adequately controlled.

INFANTS (CRADLE CAP)

Infants commonly develop a greasy adherent scale on the vertex of the scalp. Minor amounts of scale are easily removed by frequent shampooing with products containing sulfur and salicylic acid (e.g., Sebulex shampoo). Scale may accumulate and become thick and adherent over much of the scalp and may be accompanied by inflammation (Figure 8-26). Secondary infection can occur.

Treatment. Patients with serum and crust are treated with oral antistaphylococcal antibiotics. Once infection is controlled, erythema and scaling can be suppressed with group VI or VII topical steroid creams or lotions. Dense, thick adherent scale is removed by applying warm mineral or olive oil to the scalp and washing several hours later with detergents such as Dawn dishwashing liquid. Remission possibly can be prolonged with frequent use of salicylic acid or tar shampoos (see the Formulary, p. 852).

Figure 8-26
Seborrheic dermatitis (cradle cap). Diffuse inflammation with secondary infection. Much of the scale from this child's scalp was removed with shampoos.

THIRD EDITION

Dermatology

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biopsy will show a sparse lymphocytic infiltrate of the epidermis with necrotic keratinocytes closely approximating single infiltrating lymphocytes ("satellite cell necrosis"). For a definitive diagnosis, lymphoid chimerism or an increased number of activated T cells should be sought.

Allergic and Irritant Contact Dermatitis • The nature of these eruptions can often be ascertained by their distribution and a history of contact.

Pityriasis Rosea • Usually this disorder can be clearly distinguished by its sudden onset and short course and its well-delineated plaques with fine peripheral scale that are scattered over the trunk in a fir-tree distribution.

Psoriasis • Although psoriasis is an uncommon disorder in infants, it may mimic seborrheic dermatitis. Nevertheless, psoriasis can usually be distinguished by sharply defined plaques of erythema of the gluteal cleft, localization to sites of trauma with isomorphic Koebner's phenomena, nail involvement, family history, or a poor response to mild topical therapies, or a combination of these. In adults, psoriasis is usually easily distinguished from seborrheic dermatitis because psoriasis is not an eczematous condition and presents with marked epidermal hyperproliferation. If an adult patient has evidence of both psoriasis and seborrheic dermatitis the term *seborrhiasis* is often used.

Autoeczematization • Autoeczematization is a symmetric, often generalized, eczematous dermatitis that occurs in response to a local dermatitis. One can differentiate seborrheic dermatitis from this entity on the basis of evolution and resolution. Autoeczematization resolves within a few weeks when the local dermatitis is appropriately treated with either topical steroids or antifungals.

Darier's Disease • This familial dyskeratotic condition may initially assume the appearance of seborrheic dermatitis; however, biopsy examination will easily differentiate the two diseases.

Pityriasis Rubra Pilaris • Pityriasis rubra pilaris is an uncommon, chronic, noneczematous, hyperproliferative epidermal disorder; however, its clinical presentation when limited to the scalp may appear similar to seborrheic dermatitis. As the disease progresses to involve glabrous areas, it becomes easily distinguished from seborrheic dermatitis by its marked hyperkeratosis, acanthosis, and characteristic plugged patulous follicles.

Erythrasma • Seborrheic dermatitis of the groin must be differentiated from erythrasma, which is also often present between the fourth and the fifth toes. Bacterial cultures will yield *Corynebacterium minutissimum*, and Wood's light examination will reveal a characteristic coral-red fluorescence typical for the porphyrin made by this bacterium.

Dermatophyte Infection • Extensive dermatophyte infection, especially in AIDS patients, may mimic seborrheic dermatitis (Pernaciaro and Peters, 1986).

Benign Familial Chronic Pemphigus • Intertriginous seborrheic dermatitis must be distinguished from benign pemphigus, which is transmitted as an autosomal dominant trait. Histopathology is unique, revealing prominent intraepidermal vesicles and bullae, acantholysis with the formation of clefts above the basal cell layer onto which the acantholytic cells "tumble," a basal cell layer that remains attached to the dermis, and occasional prematurely keratinized cells.

Pemphigus Erythematosus • Scaling, crusted eczematous-appearing plaques of the midback and chest with a history of lupus is suggestive of pemphigus erythematosus. Histopathologic findings of pemphigus foliaceus and immunofluorescence showing IgG and complement in the intercellular and basement membrane sites are diagnostic.

TREATMENT

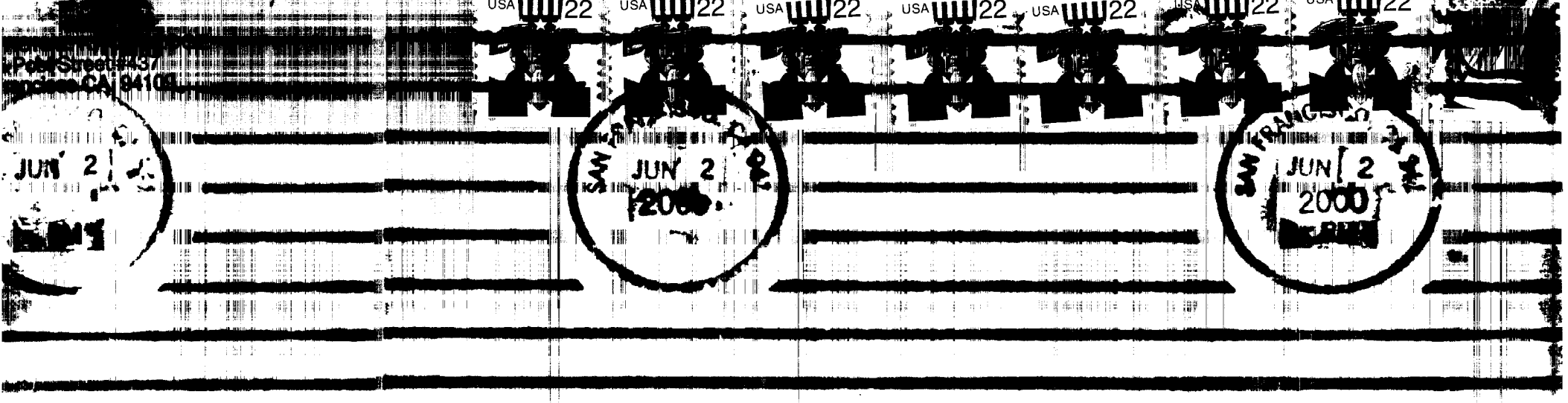
Conservative • Because the disease can have a wide spectrum of appearances, different treatment modalities are utilized. Initial scaling may only require scalp cleansing with a mild baby shampoo and skin hydration with emollients and creams. Daily baths are required, but irritating soaps should be avoided. More advanced disease may require the use of daily to two-times-weekly use of antidandruff shampoos. Those containing zinc pyrithione (Sebulon, Danex, Head & Shoulders), 1% selenium sulfide (Selsun Blue), tar derivatives, and salicylic acid and sulfur (Sebulex) may be used. These modalities when used should remain on the scalp for approximately 5 minutes. Because the scalp is being treated, not the hair, the residua of malodorous medicated shampoos can be removed by a more cosmetically pleasing shampoo.

Intensive • If conservative regimens fail to resolve the condition, either ketoconazole cream or mild topical steroids (1–2% hydrocortisone cream) up to three times a day may be necessary to treat glabrous lesions. Refractory cases for the most part can be handled effectively with overnight tar preparations such as 5, 10, 20% liquori carbonis detergens in Nivea oil or Aquaphor and covered by a stockinette. Although these preparations are malodorous, patients with severe disease will usually comply with therapeutic suggestions. Combination treatments can be used as alternate-day therapies or variations that the patient finds most pleasing. In infants the use of agents such as salicylates and stronger topical steroids should be avoided because increased absorption rates can lead to systemic side effects.

Special consideration is given to the treatment of blepharitis. The use of hot compresses with gentle débridement with a cotton-tipped applicator and baby shampoo one or more times daily is advocated. All other treatment modalities are best avoided secondary to both the irritating effects and the proximity to the eye.

COURSE/PROGNOSIS

Seborrheic dermatitis itself is self-limited and responds well to conventional topical therapies. How-



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