Review

UVB phototherapy and skin cancer risk: a review of the literature

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Abstract

Background UVB phototherapy is a common treatment modality for psoriasis and other skin diseases. Although UVB has been in use for many decades, many clinicians are hesitant to use this type of phototherapy because of concern over increasing the skin cancer risk. Over the past 20 years, numerous studies have been published examining this issue, but a consensus or analysis of the skin cancer risk is required for the dermatologist to make an educated risk–benefit analysis.

Objective To assess the risk of skin cancer associated with UVB phototherapy.

Methods All prospective or retrospective studies were identified in MEDLINE from 1966 to June 2002. Bibliographies were searched to identify any additional studies examining this issue. All studies that attempted to quantify or qualify any additional skin cancer risk from UVB phototherapy were included. Study selection was performed by two independent reviewers.

Results Eleven studies (10 of which concerned psoriasis patients), involving approximately 3400 participants, were included. Of note, three of the studies involved the same cohort: members of the 16-center US Psoralen plus UVA (PUVA) Follow-up Study. Other than the most recent Finnish study, all studies eventually showed no increased skin cancer risk with UVB phototherapy. One of the PUVA cohort studies examined genital skin cancers, and found an increased rate of genital tumors associated with UVB phototherapy, although this study has not been duplicated.

Conclusion The evidence suggests that UVB phototherapy remains a very safe treatment modality.

Introduction

For dermatologists who refer patients to or who practice UVB phototherapy, one question that is likely to be asked by patients is, "Will I get skin cancer from having UVB phototherapy?" Although UVB from sunlight is known to be a risk factor for skin cancer, the exact skin cancer risk from UVB phototherapy is still under debate. On reviewing the literature, we could not identify a comprehensive resource that could help clinicians to answer this question adequately. This clinical question provided the impetus for this report, which provides a critical review of the world literature for studies conducted to ascertain this risk, not just in the Caucasian population, but also in non-Caucasians. It also reviews available data on skin cancer risks with narrow-band UVB, retinoids–UVB, and retinoids–narrow-band UVB.

Objectives

The primary objective was to determine whether there is evidence of increased skin cancer risk in patients treated with UVB phototherapy vs. those who have not been exposed to this treatment modality.

The secondary objective was to review the data in the context of Caucasian as well as non-Caucasian populations, narrow-band UVB, retinoids–UVB, and retinoids–narrow-band UVB.

Methods

This review was performed by searching MEDLINE via the PubMed interface from 1966 to 2002 for any articles with the keywords UVB, phototherapy, and skin cancer risk. The references contained in these articles were also examined to identify any studies "prior to the computer age," or those that were missed with the MEDLINE search, that investigated the relationship between skin cancer risk and exposure to UVB phototherapy. In order for studies to be included in this review, a comparison of skin cancer rates needed to be performed between a group of subjects exposed to UVB vs. another group of similar subjects without exposure to UVB.

Description of Studies

The studies fell into one of two groups: seven studies in which UVB was the primary treatment modality of disease (e.g.

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Goeckerman therapy) and four studies in which patients were primarily treated with another modality [e.g. psoralen plus UVA (PUVA)] and in which investigations into the possible contribution of UVB exposure were "piggy-backed" onto the other study. In fact, the only other studies that examined the link between skin cancer risk and UVB were those of patients who had previously received PUVA. The results of these groups are considered separately. In total, 11 studies, involving approximately 3400 participants, were included. The details of these studies are summarized in Table 1.

Results

Skin cancer risk – studies in which UVB was the main treatment modality

Although UVB phototherapy is used to treat a variety of skin disorders, including cutaneous T-cell lymphoma,[1–4] vitiligo,[5] alopecia, atopic dermatitis, and pruritus, it is used most commonly for psoriasis patients. As a result, psoriasis patients are the most common source of information with regard to whether UVB phototherapy increases the risk of skin cancer.[6,7] Surprisingly, however, the first published study on the rate of skin cancer in patients primarily treated with UVB was performed on atopic dermatitis patients. Maughan *et al.*[8] followed 305 patients with atopic dermatitis treated with Goeckerman therapy from 1950 to 1954 for up to 25 years and found 11 patients with nonmelanoma skin cancer (NMSC). Compared with the expected rates of NMSCs if the patients had lived in each of the regions reported in the Third National Cancer Survey,[9] the incidence was less than that of Dallas-Fort Worth (expected number of NMSC, 18.8), but greater than that of San-Francisco-Oakland (9.4), Minneapolis-St. Paul (6.7), and Iowa (5.3). The authors stated that their patients were a varied group geographically, including many that lived in southern areas of the USA, but all patients were diagnosed with atopic dermatitis at the Mayo Clinic in Rochester, MN.

In 1981, Pittelkow *et al.*[10] published the first large-scale study on UVB phototherapy for psoriasis patients and skin cancer risk from an investigation of 260 psoriasis patients treated with UVB and tar also at the Mayo Clinic between 1950 and 1954. These patients were followed for up to 25 years, with a mean of 20.1 years. Nineteen patients in this cohort developed NMSC, showing no increase in skin cancer risk from UVB phototherapy. This group of patients was presumably older on average than the atopic dermatitis group; hence, the number of persons expected to develop skin cancer in this group was approximately 26.6.[9]

Halprin *et al.*,[11] in 1981, retrospectively studied 150 psoriasis patients admitted to their hospital between 1976 and 1980. Using patients with diabetes admitted to the hospital during the same time period as a control, the number of skin cancers in both groups was assessed with an average follow-up of 6.8 years. Ninety-five of the 150 patients were treated with coal tar and UVB and 13 (14%) had skin cancer. The non-UVB-exposed psoriasis patients showed a 13% rate of skin malignancy and the control group showed a 5% rate of skin cancer. This study raises the question of whether skin cancer is increased in psoriasis patients, but no additional increase was seen in patients treated with UVB.

Larko and Swanbeck,[12] in 1982, followed 85 Swedish psoriasis patients extensively treated with UVB alone for up to 25 years (average, 16.2 years). The prevalence of premalignant/malignant skin lesions in patients with psoriasis treated with UVB phototherapy (5.9%) was not significantly different from that of the population control group (10.1%). The control group (n = 338) was extracted from a city's (Gothenburg) official birth and address registry, matching the patients and controls for sex and age. Another study by Bhate *et al.*[13] in the UK followed 2247 psoriasis patients for 9–15 years and found a lower incidence of NMSC in patients treated with UVB (11/925 = 1.2%) vs. patients not treated with UVB (1.8%).

The risk of UV light has also been assessed in the general population. Bajdik *et al.*[14] performed a case–control study of the general population in which they investigated the risk of NMSC with exposure to non-solar UV radiation. They found that the odds ratio was 0.8–0.9 for exposure to UV lamp treatments (it was not stated whether the light was UVB or UVA) after correcting for age, skin, hair color, and occupational exposure to the sun.

The most recent investigation on this subject, a cohort study, examined psoriasis, its treatment, and cancer in 5687 Finnish patients.[15] Of these patients, 30 cases of squamous cell carcinoma (SCC) were placed in a case–control study with 137 controls. These controls had no SCC, were chosen from the original psoriasis cohort, and were matched for sex and year of birth. A history of UVB exposure was found in 21 (70%) cases and 63 (46%) controls, giving a relative risk of 1.6 (95% confidence interval, 0.4–6.4) for SCC with UVB treatment. A history of Goeckerman therapy was found in 12 (43%) cases and 33 (24%) controls, giving a relative risk of 1.5 (95% confidence interval, 0.3–7.3). Neither of these findings was statistically significant for an increased risk of SCC.

Skin cancer risk – studies in which patients received primary treatment with a modality other than UVB phototherapy

Most of the other available data on UVB phototherapy and skin cancer risk come from the 16-center US PUVA Follow-up Study. This inquiry followed 1380 patients from multiple centers across the USA who had been exposed to PUVA therapy to determine the long-term risks and benefits of PUVA photochemotherapy. All of the patients examined in this investigation thus have the additional confounding factor of having been exposed to PUVA therapy. PUVA therapy is

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Table 1 Summary of studies assessing UVB phototherapy and cancer risk

Reference	Treatment assessed	Disease treated	Number of patients treated with UVB	Number of patients not exposed to UVB	Years of follow-up	Observed number of events (i.e. skin cancers) in "treated" group	Observed number of events (i.e. skin cancers) in "comparison" group	Geographic region	Type of study	Relative risk and 95% CI if given
9	G	Atopic dermatitis	305	NCS	Mean, 25	11	N/A	USA	A	1.09
11	G	Psoriasis	260	NCS	Mean, 20.1 Range, 2–28	32 in 19 patients	N/A	USA	A	0.71
13	U (> 100 treatments; average 249)	Psoriasis	85	338	Mean, 16.2 Range, 0–25	5	34	Europe	A	0.58
12	G	Psoriasis	95	55	Mean, 6.8	13	7	USA	B	1.08
14	U	Psoriasis	925	1322	Range, 9–15	11	24	Europe	B	0.67
15	U	No disease	406	406	Range, 0–20	N/A	N/A	Canada	B	0.8–0.9 (Assessed only men. Not stated whether light was UVB or UVA)
19	G	Psoriasis	983	SEER	Mean, 2.7	N/A	N/A	USA	C	4.7 (2.2–10.0) (Significant for those with "high exposure" UVB + tar treatment compared with those with "nonhigh exposure." PUVA-treated patients
21	U	Psoriasis	70	SEER, CTR	Mean, 12.3	N/A	N/A	USA	C	4.6 (1.4–15.1) Significant relative risk of genital tumors associated with high dose UVB therapy as compared with low doses
20	U and G	Psoriasis	PUVA follow-up study	SEER[21]	Mean, 13.2	N/A	N/A	USA	D	No increase in RR found. (Conclusions in contrast with the results of the previous Stern study[18])
25	U	Psoriasis	111	385	Mean, > 5 Median, 6.83 Range, 0.25–17.17	2	12	Europe	D	0.36

Treatment assessed: G, UVB + coal tar; U, UVB.
NCS, data from Third National Cancer Study;[9] SEER, data from Surveillance, Epidemiology, and End Results;[22] CTR, data from Connecticut Tumor Registry.[23]
Type of study: A, cohort study in which UVB phototherapy was the main or one of the main treatment modalities; B, case–control study in which UVB phototherapy was the main or one of the main treatment modalities; C, cohort study in which PUVA photochemotherapy was the main treatment modality; D, case–control study in which PUVA photochemotherapy was the main treatment modality.
CI, confidence interval; N/A, not applicable or not available; PUVA, psoralen plus UVA; RR, relative risk.

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associated with an increased risk of SCC[16] and, possibly, melanoma,[17] although this is still debated.

The first paper from this PUVA cohort to consider UVB phototherapy and skin cancer risk examined the cumulative incidence of NMSC and divided the PUVA patients into high-, moderate-, and low-exposure UVB groups.[18] High exposure to UVB was defined as more than 300 UVB treatments and/or 90 months of coal tar use; moderate exposure was defined as 100–299 UVB treatments and 30–90 months of coal tar use; low exposure was defined as < 100 UVB treatments and < 30 months of coal tar use. Of significance, only 22% of these 1380 patients received exposure to either tar or UVB and only 3% to both. An analysis of the moderate-exposure group compared with the low-exposure group showed insignificant increases in the risk of developing NMSC. When the moderate- and low-exposure groups were combined into a "not high" group and given a relative risk of 1.0, the estimated crude relative rate of NMSC for patients with high exposure to tar, ultraviolet radiation, or both was 2.4 (95% confidence interval, 1.4–4.2). After controlling for age, sex, skin type, address, and exposure to ionizing radiation and PUVA, an odds ratio of 4.7 (95% confidence interval, 2.2–10.0) was obtained for those patients in the PUVA cohort with high exposure to coal tar or UVB. In 1994, however, Stern and Laird[19] presented an updated analysis from the PUVA Follow-up Study with regard to the carcinogenic risk of UVB phototherapy in which they no longer found an association between UVB and NMSC risk. Although long-term exposure to PUVA and methotrexate significantly increased the risk of SCC in patients with psoriasis, this updated analysis showed no relationship between UVB phototherapy exposure and SCC after correction for all other potential confounders, and suggested a low risk–benefit ratio with UVB phototherapy.

A second 12.3-year prospective study by Stern *et al.*[20] followed 892 men who were part of the PUVA cohort and who were examined for genital tumor incidence. The expected number of genital tumors was calculated in several ways. For invasive SCCs in all exposed genital sites, age-specific incidence rates for white men from a federal study of NMSC in eight geographic areas were used.[21] Data for white men from the Surveillance, Epidemiology and End Results (SEER) study were used for SCC and SCC *in situ* of the penis,[22] whilst the incidence rate from the Connecticut Tumor Registry was used to calculate the expected number of scrotal SCCs.[23] After controlling for the level of exposure to PUVA, the relative risk of genital tumors with high vs. low doses of UVB phototherapy (criteria stated above) was 4.6 (95% confidence interval, 1.4–15.1).[20]

Maier *et al.*[24] described 496 patients with psoriasis treated with more than five exposures of PUVA therapy before 1987. In the 385 patients not exposed to UVB, 11 (2.9%) cases of skin cancer occurred. Two (1.8%) cases of skin cancer were found in the 111 patients treated with UVB. The relative risk of NMSC after UVB therapy was 0.36 compared with the psoriasis patients not treated with UVB. This difference, however, did not reach statistical significance ($P = 0.2$).

Melanoma risk

The previously mentioned studies focused mostly on NMSC risk. Only a few of the above studies mentioned any melanoma cases and none gave a relative risk for melanoma with UVB phototherapy. Only three cases of melanoma were identified amongst approximately 1000 patients treated with UVB phototherapy. The results are summarized in Table 2. In one study by Elwood *et al.*,[25] the therapeutic use of "UV lamps" (type of UV rays not specified) for acne or psoriasis was not associated with an increased risk of melanoma, but the number of subjects using UV phototherapy was small (< 2%).

Discussion

Although UVB from sunlight is a known carcinogen, the worldwide data accumulated over recent decades suggest that the risk of skin cancer (melanoma or nonmelanoma) is not significantly increased with UVB phototherapy. Beginning with the large study by Maughan *et al.*,[8] reports since then have confirmed the result that UVB phototherapy generally does not increase the skin cancer risk. There is evidence that UVB phototherapy causes an increase in genital tumors in men from the PUVA cohort, but the results of this study have not been replicated.

A search was also performed to identify studies examining the risk of UVB phototherapy in patients with darker pigmentation, as the data to date apply predominantly to fair-skinned Caucasians. No such studies were identified, although it could reasonably be assumed that the risk to these populations is no greater. There is also the practice of using retinoids in combination with UVB phototherapy; this is clinically appealing because retinoids can reduce the doses of

Table 2 Published literature on melanoma incidence in patients treated with UVB phototherapy

Reference	Country	Number of subjects	Follow-up period (years)	Mean follow-up period (years)	Melanoma cases
9	USA	426	25	*	2
11	USA	260	2–28	20.1	1
12	USA	95	*	6.8	0
13	Sweden	85	0–25	16.2	0
21	USA	70	0–14	12.3	0
25	Austria	111	> 5	*	0

*Not stated in the text.

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UVB required to treat psoriasis.[26] In addition to lower UVB doses, retinoid–UVB treatment has the potential benefit of a long-term reduction in skin cancer. It is believed that retinoids prevent skin carcinomas through their ability to stimulate epithelial differentiation and restore normal growth.[27] McKenna and Murphy[28] described 16 renal transplant patients who received 0.3 mg/kg daily of acitretin over a 5-year period. There was a significant reduction in the number of new tumors excised in 12 of 16 patients during treatment compared with the same pretreatment interval. Taking the group as a whole, there were 21 [18 SCC, three basal cell carcinomas (BCC)] excised during acitretin therapy vs. 77 (64 SCC, 13 BCC) removed in the immediate equivalent pretreatment period. Although the studies examining the skin cancer risk with UVB phototherapy have all been negative, if a clinician is still worried about this risk, there is the potential to manage this with retinoid–UVB to reduce exposure and to obtain a possible anti-skin cancer effect by increasing the maturation of skin cells.

An inevitable question that will be asked is how this applies to narrow-band UVB. Although this treatment modality is widely used in Europe, the USA is only now beginning to become acquainted with narrow-band UVB. With regard to the relative carcinogenicity, there are conflicting data from murine studies.[29–33] This is an issue that requires further study. It is noteworthy that we could not identify any human data on the risk of NMSC with narrow-band UVB to determine the clinical relevance of this information.

In summary, our findings lead us to the following conclusions.

1 None of the published studies showed an increase in skin cancer risk with UVB phototherapy, except for one PUVA cohort analysis on genital cancer. Therefore, based on currently available data, even for fair-skinned Caucasians, no precise limit with regard to the number of allowable UVB treatments can be defined. It is recommended, however, that the current practice of genital shielding during UVB phototherapy should be continued.

2 This concern should be even less for darker skinned, non-Caucasians who have skin that is less prone to damage from UV rays.

3 The relative carcinogenicity of narrow-band UVB vs. broad-band UVB phototherapy remains to be determined.

4 There is a need for more controlled studies to evaluate the efficacy and safety of narrow-band UVB ± retinoids.

Conclusion

The world literature was systematically researched to update information on the skin cancer risk with UVB phototherapy. Most of the published studies on this topic were negative for an increase in nongenital skin cancer risk. In view of this, UVB phototherapy appears to have a high benefit–risk ratio for the treatment of moderate to severe psoriasis.

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