Ultraviolet A and melanoma: A review

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The incidence and mortality rates of melanoma have risen for many decades in the United States. Increased exposure to ultraviolet (UV) radiation is generally considered to be responsible. Sunburns, a measure of excess sun exposure, have been identified as a risk factor for the development of melanoma. Because sunburns are primarily due to UVB (280-320 nm) radiation, UVB has been implicated as a potential contributing factor to the pathogenesis of melanoma. The adverse role of UVA (320-400 nm) in this regard is less well studied, and currently there is a great deal of controversy regarding the relationship between UVA exposure and the development of melanoma. This article reviews evidence in the English-language literature that surrounds the controversy concerning a possible role for UVA in the origin of melanoma. Our search found that UVA causes DNA damage via photosensitized reactions that result in the production of oxygen radical species. UVA can induce mutations in various cultured cell lines. Furthermore, in two animal models, the hybrid *Xiphophorus* fish and the opossum *(Mondelphis domestica)*, melanomas and melanoma precursors can be induced with UVA. UVA radiation has been reported to produce immunosuppression in laboratory animals and in humans. Some epidemiologic studies have reported an increase in melanomas in users of sunbeds and sunscreens and in patients exposed to psoralen and UVA (PUVA) therapy. There is basic scientific evidence of the harmful effects of UVA on DNA, cells and animals. Collectively, these data suggest a potential role for UVA in the pathogenesis of melanoma. To date evidence from epidemiologic studies and clinical observations are inconclusive but seem to be consistent with this hypothesis. Additional research on the possible role of UVA in the pathogenesis of melanoma is required. (J Am Acad Dermatol 2001;44:837-46.)

The incidence and mortality rates of melanoma have been rising during the past several decades in the United States.[1,2] Among the reasons for these trends, increased exposure to ultraviolet (UV) radiation, as a result of lifestyle changes, has been generally recognized as an important factor. Sunburns, a measure of excessive sun exposure, have been determined to be a risk factor for the development of melanoma. Because sunburns are primarily caused by UVB (280-320 nm) radiation and UVB is strongly absorbed by DNA, which results in chromosomal damage, it has been inferred that this portion of the solar UV spectrum could be a major causative factor for melanoma. However, the adverse role of UVA (320-400 nm) as a possible etiologic factor for melanoma has received less attention, even though excessive sun exposure

Abbreviations used:

IPD:	immediate pigment darkening
IPD-PF:	immediate pigment darkening protection factor
MED:	minimal erythemal dose
PPD:	persistent pigment darkening
PUVA:	psoralen (P) and ultraviolet A (UVA)
SPF:	sun protection factor
UV:	ultraviolet
UVA:	ultraviolet A
UVB:	ultraviolet B

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is also associated with excessive exposure to UVA (320-400 nm).

The UVA bandwidth (80 nm) is twice that of UVB (40 nm), and 90% to 95% of solar UV radiation energy (measured in watts per square meter) that reaches the surface of the earth is UVA[3]; only 5% to 10% of it is UVB. In addition to solar radiation, high-dose exposure to UVA can also come from devices such as sunbeds/sunlamps and PUVA therapy units. UVA has longer wavelengths than UVB and thus penetrates deeper into skin. It is estimated that about 19% to 50% of the solar UVA can reach the depth of melanocytes,[4-6] whereas only about 9% to 14% of solar UVB reaches the melanocytes.[4-6] This long-wavelength property of UVA also allows it to pass through most automobile, office, and household windows, whereas UVB is blocked by window glass. Recently, during a study on UV protection offered by cotton fabrics used in summer clothing,[7] a substantially greater percent transmission of UVA, as compared with UVB, occurred through these fabrics. This means that people wearing summer clothing may receive substantially more UVA than UVB even in clothed areas.

The two UV spectra also have different biologic effects. UVB is about 1000 times more effective than UVA in inducing sunburn.[8] UVA, on the other hand, is much more potent in inducing immediate pigment darkening (IPD)[9,10] and persistent pigment darkening (PPD).[11] Both types of pigment darkening are characterized by darkening of the skin immediately after UVA exposure. The observed pigment in IPD fades within minutes after exposure, whereas PPD is stable for at least 2 to 3 hours. The induction of IPD and PPD is readily observed in dark-skinned persons (Fitzpatrick type III and above) and more difficult to see in those with light skin (Fitzpatrick types I and II). Because UVA does not readily produce erythema or pigment darkening in light-skinned persons, the immediate effects after UVA exposure in light-skinned persons are virtually "silent." However, biologic damage occurs. UVA causes formation of singlet oxygen radicals that subsequently lead to DNA-strand breakage, nuclear base damage, and mutations.

The possibility that UVA can cause melanoma in humans has been hypothesized by Garland, Garland, and Gorham.[12] They suggested that the rising incidence of melanoma might in part be related to the widespread use of sunscreens providing only UVB protection, thereby allowing more prolonged exposure to UVA radiation. In addition, Setlow et al[13] demonstrated that UVA is capable of producing melanoma in *Xiphophorus* hybrid fish.

Currently, the role of UVA in the pathogenesis of melanoma is controversial. In this study, we review evidence from the basic sciences, epidemiology, and clinical observations concerning this controversy. The role of UVB in causing melanoma is not discussed in this review.

BASIC SCIENCE EVIDENCE

Cancer may be viewed as a disease that progresses through multiple stages that involve initiation, promotion, progression, and metastasis. Each stage is accompanied by further changes in DNA. UVB is known to cause mutations in oncogenes and tumor suppressor genes that eventually initiate the cascade of events resulting in skin cancers.[14-16] To substantiate that UVA has the potential to induce melanoma, it is necessary to demonstrate that UVA is capable of producing biologic damage. It has been shown that UVA is capable of producing DNA damage via photosensitized reactions that result in oxygen radical species (eg, hydrogen peroxide, singlet oxygen, superoxide anion).[17] These reactive species can cause single-strand breaks,[18] mutations, sister chromatid exchanges, and chromosomal aberrations that can result in cytotoxicity and carcinogenesis.[19] Furthermore, the singlet oxygen and superoxide anions generated by UVA1 (340-400 nm) can damage mitochondria and induce apoptosis in cell culture.[20]

UVA damage to DNA in cell-culture models

UVA radiation has been shown to cause mutations in mammalian cells. Studies in murine cell lines have demonstrated that broadband UVA can induce mutations.[21,22] In addition, monochromatic UVA at 365 and 334 nm are mutagenic to a human epithelial P3 cell line[23] and to a Chinese hamster ovary cell line,[24] respectively. Enninga et al[25] have demonstrated that radiation at 365 nm is potentially mutagenic to cultured human fibroblasts. Wenczel et al[26] measured DNA single-strand breaks in cultured human melanocytes after UVA exposure. They showed that pheomelanin or melanin intermediates (or both) were the most likely chromophores that react with the UVA radiation, leading to the DNA single-strand breaks.

Using monochromatic radiation, Kvam and Tyrrell[27] demonstrated that the wavelengths causing almost all of the oxidative DNA base damage (eg, 7,8-dihydro-8-oxoguanine) in a human skin fibroblast cell line are in the UVA and visible light range. In addition, they estimated that the total amount of such guanine base damage induced by sunlight in fibroblasts of the skin equals or exceeds the amount of the major type of direct DNA damage, cyclobutane pyrimidine dimers induced mainly by UVB. Drobetsky, Turcotte, and Chateauneuf[28] have characterized a specific mutation at the ade-

nine phosphoribosyltransferase locus in Chinese hamster ovary cells irradiated with UVA. They demonstrated a high frequency (≤ 50%) of T → G transversion, a rare class of mutations ("fingerprint" mutation), in UVA-irradiated cells, compared with 9% in UVB-irradiated cells. A moderately high frequency (25%) of T → G transversion was seen with cells irradiated with simulated sunlight, leading to their conclusion that most of the T → G transversion mutations in cells irradiated with simulated sunlight can be attributed to the UVA portion of sunlight, with little, if any, contribution from UVB.

In addition to the aforementioned studies with different mammalian cell lines, the potential carcinogenic effect of UVA has also been demonstrated in cultured human melanocytes. Marrot et al[29] induced DNA breaks in the nucleus of Caucasian human melanocytes with broad-spectrum UVA (320-400 nm) irradiation. DNA breakage in cells was assessed via the comet assay, a technique used extensively for analyzing genotoxic effects by environmental chemicals[30] or by UV components of the solar spectrum.[31,32] The investigators suggested that the endogenous pigments and/or melanin-related molecules seem to enhance DNA breakage after UVA irradiation. This is evidenced by higher DNA breakage in melanocytes than in fibroblasts, in cells with higher melanin content, and in cells stimulated for melanogenesis by culturing in tyrosine-rich medium. In addition, Marrot et al[29] demonstrated that there is an increased level of p53 expression in the irradiated melanocytes, indicating DNA damage.

That different UVA wavelengths induce mutations in different cell lines can be explained by the different types and amounts of photosensitizers or chromophores in these cells. Unlike UVB, UVA must first react with endogenous photosensitizers (eg, flavins, porphorins, melanins) that in turn generate reactive oxygen species that cause single-strand breaks or photoadducts. The different sensitivities and mechanisms for DNA damage induced by UVA and by UVB are important to elucidate to improve the formulation of sunscreens with broad-spectrum coverage. Because the most effective wavelength in causing photoproduct formation in human skin is around 300 nm in the UVB spectrum,[33] efforts could be focused on developing UVB-protective sunscreens with maximal protection at or around this wavelength. However, the various photosensitizers in skin have different absorption spectra. These photosensitizers absorb different spectral bands of UVA and then generate oxygen radicals. Thus for UVA-protective sunscreens to be maximally effective, they should have broad coverage across the entire UVA spectrum.

Animal models

Two animal models have demonstrated the possible role of UVA in inducing melanoma and melanoma precursor lesions. Setlow et al[13] showed that the pigmented backcross hybrids of the genus *Xiphophorus* (platyfish and swordtail) are very sensitive to melanoma induction after a single exposure to any of several UV monochromatic radiations (302, 313, 365, 405, and 436 nm). The wavelength that yielded the highest induction rate per incident photon was 302 nm. However, after factoring in the intensity of various wavelengths in sunlight, it was found that the 365-nm wavelength in sunlight would be the most effective wavelength for melanoma induction in these fish. These authors also suggested that if the action spectrum for human melanoma was similar to that of the fish, then approximately 90% of the melanoma-inducing effects of sunlight might result from UVA and visible radiation.

Ley[34] demonstrated that melanoma precursors could be induced in opossums (*Monodelphis domestica*) after prolonged exposure to broad-spectrum UVA. The animals were exposed to 2.5×10^4 J/m^2 of UVA 3 times per week. After a period of 81 weeks, 22% of the animals developed melanocytic hyperplasia, a precursor of melanoma.

UVA-induced DNA damage in human skin

In an effort to directly assess the potential for UVA to induce DNA damage in human skin, Burren et al[35] irradiated the buttocks of healthy volunteers with either UVA1 (340-400 nm) alone, UVA1 plus UVA2 (320-340 nm), or solar-simulating radiation, which contains UVB in addition to UVA. They assayed for both p53 protein expression and the presence of pyrimidine dimers. Pyrimidine dimers are formed in DNA as the result of UV-induced damage; increased p53 levels are part of an effort by cells to repair such damage. Irradiation with UVA1 plus UVA2 induced p53 in epidermal keratinocytes. The levels were about half that observed with equivalent doses of solar-simulated UV. Low doses of UVA alone induced p53 expression in basal keratinocytes, whereas higher doses affected all layers of the epidermis. An erythemal dose of solar-simulated UV also induced p53 in all epidermal layers. All 3 types of radiation resulted in similar amounts of pyrimidine dimer formation. These studies provide in vivo evidence that DNA damage in human skin may be caused not only by UVB, but also by UVA.

Role of UVA in inducing immunosuppression

UV radiation, especially UVB, has been implicated in causing immunosuppression.[36,37] Mainly from work with UVB radiation, it is known that the num-

ber of antigen-presenting Langerhans cells and their functions are adversely affected by UV. Furthermore, UV radiation induces keratinocytes to release various cytokines that influence immune balance in skin. Three cytokines, interleukin 10 (IL-10), IL-12, and interferon gamma (IFN-γ), have been widely studied. IL-10 appears to have an immunosuppressive function, inhibiting antigen-presentation ability of the Langerhans cells[38] and suppressing the contact hypersensitivity response.[39] On the other hand, IL-12 and IFN-γ have immunopotentiating effects that promote and enhance T helper cell 1 activity. In addition, IFN-γ appears to block the production of IL-10 by macrophages,[40] possibly mitigating potential IL-10–induced immunosuppression.

There is still a great deal of controversy concerning the effect of UVA in causing immunosuppression. An in vitro study by Iwai et al[41] demonstrated that UVA irradiation decreased the ability of murine epidermal keratinocytes to present antigens to T cells. This decrease was dose-dependent. In addition, they showed that UVA radiation also decreased the expression of costimulatory molecules (ie, intercellular adhesion molecule 1, B7-1, and B7-2) on Langerhans cells. Costimulation is a necessary component for immune action. The antioxidant glutathione was able to mitigate the UVA-induced suppression of antigen-presenting function in a dose-dependent fashion. They concluded that UVA radiation induces immune suppression, at least partially, via an oxidative pathway.

In an animal study using a contact hypersensitivity model, Bestak and Halliday[42] irradiated C3H/HeJ mice with low-dose UVA (average cumulative dose of 45.9 J/cm^2) over a 4-week period. They demonstrated that UVA caused a significant reduction in the number of epidermal Langerhans cells and local but not systemic immunosuppression in these animals. In contrast, Reeve et al[43] found that in hairless mice a single dose of UVA exposure (38.7 J/cm^2) not only was immunologically innocuous but also reversed the immunosuppressive effect of UVB radiation and *cis*-urocanic acid in a contact-hypersensitivity model.

Evidence for immunosuppression in humans also comes from contact hypersensitivity studies. Using subjects allergic to nickel, Damian, Barnetson, and Halliday[44] demonstrated that low-dose UVA exposure induced immunosuppression. The UVA-induced immunosuppressive effect was maximal in subjects receiving a 3-day course of UVA exposure, but subjects receiving 4- or 5-day courses of UVA exposure did not show significant immunosuppression. They suggested that acute UVA exposure may initially be immunosuppressive but subsequently be immunoprotective. Potential mechanisms that restore the immune functions were suggested; these include the formation of antioxidant ferritin in the dermis and the formation of photoadducts with inhibitory effects on *cis*-urocanic acid. LeVee et al[45] demonstrated that a single exposure to UVA2 (320-340 nm) at 4 minimal erythema doses (MEDs) reduces the number of Langerhans cells. In addition, they have shown that UVA2 leads to decreased local sensitization to dinitrochlorobenzene in human subjects. Furthermore, Fourtanier et al[46] demonstrated that sunscreens with enhanced UVA protection were more effective in reducing immunosuppression by solar-simulated radiation. However, Sjovall and Christensen[47] found that UVB, but not UVA, suppressed contact hypersensitivity to nickel antigen in nickel-sensitive persons. The subjects in this study received total body irradiation with a cumulative UVA dose of 205 J/cm^2 over a 3-week period, a UVA dose that is higher than the subjects received in the studies by Damian, Barnetson, and Halliday[44] and LeVee.[45]

These conflicting results on the effects of UVA on immunosuppression may be related to the different protocols in these studies, namely: (1) the presence of different amounts of UVB contamination, (2) low versus high UVA dose, and (3) single exposure versus repeated exposures. Further studies are needed to resolve these discrepancies. However, until then, the possibility of UVA-induced immunosuppression and the consequent immune changes that allow the development of melanoma should be considered, especially in view of the fact that melanoma is an immunogenic tumor that appears to respond to immune-based therapy[48-50] and the fact that immunosuppressed patients have a higher risk of developing melanoma. Children with immunodeficiency have a 3- to 6-fold increased risk of developing melanoma, and those with Hodgkin's disease have an 8-fold increased risk.[51] Adults with Hodgkin's disease,[52] and those having kidney or cardiothoracic transplantation,[53,54] have an increased risk for the development of melanoma.

EPIDEMIOLOGIC EVIDENCE

Epidemiologic observations often reveal associations that provide valuable clues and new channels for further investigations, but these observations are not a substitute for understanding the pathogeneses of diseases. The validity of epidemiologic studies can be undermined by recall bias and confounding factors.

Sunbeds and sunlamps

Every year, approximately 25 million Americans use sunbeds/sunlamps,[55,56] and this use is particularly prominent in teenagers and young adults. The popularity of tanning salons can be traced largely to

the pervasive belief that tanned skin is more attractive and fashionable than pale skin. In addition, the tanning industry has recommended developing a "safe and protective tan" before vacationing in sunny climates.

Unfortunately, cosmetic indoor tanning has various adverse health effects.[56] One such effect is that persons using tanning salons receive a large quantity of unnecessary UVA exposure. Currently, most of the tanning lamps on the market emit nearly 100% UVA radiation.[3,57] In addition, Miller et al[3] calculated that a typical tanner (20 sessions at 2 MEDs per session) could receive an annual UVA dose from the sunlamps that is 0.3 to 1.2 times that of an average annual cumulative UVA dose from the sun, which is estimated to be 7700 kJ/m^2. For more avid tanners (100 sessions at 4 MEDs per session), the UVA dose from sunlamps is 1.2 to 4.7 times that of their annual UVA dose from the sun, which is estimated to be 19,250 kJ/m^2. The higher estimated annual UVA dose from the sun seen in more avid tanners results from their greater sun-seeking behavior.[58] The UVA dose is even higher (12 times that from the sun) for the persons in the avid tanner group who use the high-pressure UVA sunlamps.[3] If UVA in fact plays a role in the development of melanoma, then the use of sunbeds with primary UVA emission could potentially be a contributor to the development of melanoma.

In 1998, Swerdlow and Weinstock[55] reviewed 19 case-control studies on the association of the use of tanning lamps and melanoma and reported that 6 of these 19 studies revealed a positive association between the use of tanning lamps and the development of melanoma. In some studies, this association was noted to have a dose-response relationship. However, problems were noted in many of these studies, such as the lack of detailed information on the spectral output of the sunlamps, recall bias, and potential confounding factors. These methodologic issues led the authors to conclude: "Although several investigators have found a positive relation between tanning lamp use and melanoma, in some instances, including dose-response or duration-response effects, the methodologic limitations preclude any firm conclusion regarding a causative relation." Swerdlow and Weinstock urged additional studies to elucidate the relationship between the use of these sunlamps and the development of melanoma.

In 1998, Chen et al,[59] who studied a population in Connecticut, demonstrated no significant difference overall between persons who ever used a sunlamp and those who never used a sunlamp. However, in persons who first used sunlamps at an age younger than 25 years, they found a borderline significant increase in the risk for the development of melanoma. The odds ratio for this group was 1.4 (95% confidence interval [CI], 0.9-2.1). One unequivocal finding from this study was that persons who used more than one type of sunlamp were more likely to develop melanoma. The odds ratio was 3.5 (95% CI, 1.3-9.1).

In 1999, Walter, King, and Marrett[60] reanalyzed their 1985 data to investigate the effects of intermittent and long-term sun exposure in a Canadian population. After adjustment for skin type, age, and sex, the odds ratio for the development of melanoma for those who have used sunbeds and sunlamps, one of the indicators for intermittent exposure, is approximately 1.5 (95% CI, 1.16-2.05). This increased risk is similar to other indicators of intermittent exposure to UV radiation, but higher than for long-term UV exposure. Unfortunately, the precise wavelengths of the sunlamps used by the subjects of this study are not known.

In 2000, through a population-based, matched, case-control study involving 571 patients with melanoma and 914 healthy controls, Westerdahl et al[61] evaluated the association between sunbed/sunlamp use and the development of melanoma in Sweden. After adjusting for hair color, skin type, and number of sunburns, they reported a significantly increased odds ratio for the development of melanoma after regular exposure to sunbeds (odds ratio, 1.8; 95% CI, 1.2-2.7). In addition, they reported a dose relationship between the total number of sunbed uses and melanoma risk. They also reported an odds ratio of 2.3 (95% CI, 1.2-4.2) in regular sunbed users who first used sunbeds before 36 years of age. The majority of the surveyed subjects in the study started to use tanning beds after 1980. Diffey and Farr[62] have demonstrated that tanning beds from the early 1980s produced mainly UVA plus a small fraction of UVB (<0.1%-2.1%). Hence Westerdahl et al[61] believed that the subjects in their study were mostly exposed to tanning beds that emit mainly UVA. Based on the results of this epidemiologic study and evidences from other studies,[3,13,63] Westerdahl et al[61] were tempted to suggest that UVA may play a role in the development of melanoma.

The current epidemiologic data raise the issue of a possible relationship between sunlamp use and increased risk for melanoma, but are not conclusive. Additional studies focusing on the relationship between the development of melanoma and the use of sunlamps that emit primarily UVA are needed.

Sunscreen data

Sunburns have been identified as a marker of increased risk of melanoma[64,65] because of the interaction of high levels of intense intermittent sun

exposure on unadapted, sensitive skin. Sunscreen use is effective in preventing sunburn, actinic keratoses,[66,67] and squamous cell carcinomas.[68] For these reasons, it is generally assumed that sunscreens also offer protection against melanoma. Thirteen studies have examined the relationship between sunscreen use and melanoma and found inconsistent results.[64,69-79] (Berwick et al, unpublished data) Whereas 6 studies demonstrated a statistically significant positive association between sunscreen use and increased risk for the development of melanoma, 3 showed statistically significant inverse association with sunscreen use. Furthermore, 4 studies showed no association between sunscreen use and risk for the development of melanoma. These conflicting findings may partially be explained by the intractable problem of confounding, that is (1) sunsensitive persons who are inherently predisposed to the development of melanoma are those most likely to use sunscreens, and (2) sunscreen use allows persons to extend their hours of sun exposure.[80] Measurement error is likely to be large as well because subjects' use of sunscreen is imprecise.

In relation to the scope of this review, the sunscreen data are consistent with a possible role for UVA in the development of melanoma, especially when one considers that earlier sunscreens were developed to protect users from sunburns. Because UVB is 1000 times more effective than UVA in causing sunburn, the original sunscreens were developed to protect against UVB, but not against UVA. Even after the introduction of UVA-absorbing chemicals for sunscreens in 1989, most of these products only provided partial rather than broad-spectrum coverage for UVA. Currently, in the United States, the values of sun protection factor (SPF) on sunscreen products indicate the degree of protection against sunburn. Because the contribution of UVA in causing sunburn is minimal, the protection measurement based on the current SPF standard does not adequately assess UVA protection. Kaidbey and Barnes[81] assessed the ability of several sunscreens with different SPF values to inhibit the IPD reaction, which they called the immediate pigment darkening protection factor (IPD-PF). IPD has been suggested as an end point for assessing protection against UVA because UVA is more potent than UVB in inducing IPD. These authors demonstrated that there is no correlation between SPF values and IPD-PF. In addition, they showed that high SPF sunscreens may have, at best, only a modest IPD-PF. Therefore use of these high SPF sunscreens with relatively low IPD-PF values protect persons against sunburn, allowing the sunscreen users to be exposed to higher doses of UVA by staying in the sun longer. If UVA radiation is eventually proven to play a role in the development of melanoma, it follows that the use of sunscreens without adequate UVA protection may have accounted for some of the current increase in melanoma incidence.[82,83]

Fluorescent light data

Although the initial report of Beral et al[84] suggested the possible association of exposure to fluorescent lighting (which emits UVA radiation) as a risk factor for melanoma, subsequent reports[85-88] have cast doubt on this concept. Further work needs to be done to elucidate the role of exposure to fluorescent lighting as a factor in the causation of melanoma.

CLINICAL EVIDENCE

There are few controlled clinical studies investigating the independent effects that UVA radiation exerts on human skin. However, there are several clinical situations in which UVA is used to treat cutaneous diseases (eg, psoriasis, atopic dermatitis, cutaneous T-cell lymphomas, granuloma annulare, scleroderma)[89] from which indirect conclusions can be drawn. Unlike therapeutic UVB radiation, therapeutic UVA plus psoralens is associated with the development of large, irregular, unevenly pigmented, dark lentigines called "PUVA lentigines."[90] These lentigines frequently develop on skin that is not normally exposed to sunlight, such as the genitals. They frequently have a stellate configuration.[90,91] PUVA lentigines begin appearing 6 to 15 months after the initiation of PUVA therapy.[91,92] Histologically, there is a proliferation of melanocytes, many of which are large, clustered, binucleate, and atypical.[91,93-95] The melanocytes of PUVA lentigines often have many long dendrites and show cellular pleomorphism, nuclear hyperchromatism, and angular nuclei.[96] Ultrastructurally, there is an increase in the number and size of the melanosomes and an increase in DOPA reactivity.[91,97] There also is an increase in the pigmentation of keratinocytes with supranuclear caps extending about 3 cell layers up from the basal layer.[96] The atypical melanocytes induced by PUVA can persist for 7 years or more after cessation of PUVA therapy.[98] Similar atypical lentiginous melanocytic proliferations have also been observed in persons who are not taking psoralens but receive UVA exposure in tanning beds.[99,100] Finally, PUVA lentigines are clinically and histologically similar to the lentigines found in patients with xeroderma pigmentosum.[101]

Given the evidence that UVA radiation can stimulate melanocyte proliferation, cause DNA aberrations, and modify gene expression, it seems reasonable to hypothesize that UVA radiation could theoretically increase the risk for the development of

melanoma. Indeed, Stern, Nichols, and Vakeva[63] published a study in support of this hypothesis in which they showed that patients treated with PUVA therapy had more than a 5-fold increased relative risk for the development of melanoma. They observed a cohort of 1380 PUVA-treated patients with psoriasis from 1975 to 1997. In 6 of these patients, invasive melanomas developed within the first 15 years after their first PUVA treatment, in 7 patients invasive melanomas developed more than 15 years after their initial PUVA treatment, and in an additional 4 patients in situ melanomas developed. Many of these melanomas appear to have had a latency of as long as 10 to 15 years before becoming clinically apparent. However, Swedish PUVA follow-up studies on bath-PUVA (944 patients)[102] and systemic PUVA (4799 patients)[103] failed to show an increased risk for the development of melanoma during an average follow-up of between 15 and 16 years. Thus there are clinical data suggesting an association between PUVA therapy and development of melanoma, but the evidence is not conclusive. Furthermore, it has been argued that psoralens are DNA adducts and that the carcinogenic effects of PUVA may result from the mutagenic effects of psoralens after UVA radiation, not a direct effect of UVA.

DISCUSSION

In this review, we have examined evidence from various disciplines that surround the controversy concerning UVA as a causative factor in the development of human melanoma. Although no studies have shown this conclusively, we believe that the evidence currently available to us does not allow this relationship to be ruled out.

The clinical implications of a role for UVA in causing human melanoma are important. People who frequently use sunbeds and sunlamps have exposed themselves to large quantities of unnecessary UVA radiation. Furthermore, a person with a tan can stay in the sun longer before a sunburn develops, thereby receiving even more UVA exposure. As for sunscreen use, it is accepted that sunscreens not only offer protection against sunburn but also against actinic keratoses and squamous cell carcinomas.[66-68,104,105] However, most early sunscreens provided predominantly UVB but little or no protection against UVA-induced skin damage. Wearing those early sunscreens allows persons to prevent sunburn, to stay out in the sun longer, and inadvertently, to receive larger doses of UVA radiation. Furthermore, the change in UVA intensity with latitude is much smaller than that for UVB, and the change in melanoma incidence with latitude is much smaller than that for squamous cell carcinoma.[106] These data may support the idea that UVA is important in the induction of melanoma.

Hence, if the hypothesis that UVA plays a role in the pathogenesis of melanoma is valid, the public should be instructed to avoid the use of sunbeds and sunlamps, and when using sunscreens, to use products that provide adequate UVB and broad-spectrum UVA protection. Furthermore, they should also be encouraged to wear clothing for UV protection. Finally, people should be reminded that avoidance of excessive sun exposure is still the best strategy for preventing both UVB- and UVA-induced skin damage. Aside from public education, further research by the sunscreen, fabric, and chemical industries to develop new generations of products that offer better UVB and UVA protection would be helpful.

Effort is also needed to identify an appropriate specific end point for measuring protection against UVA. Currently, there are 3 in vivo end points (ie, erythema, IPD, and PPD) for assessing UVA protection being considered. However, the lack of consensus on which end point to use can hamper the development and assessment of UVA protective products. In selecting the appropriate end point for UVA protection, it is important to keep in mind that the ultimate objective of UVA protection is not to inhibit that end point (eg, PPD). Rather, the ideal end point should serve as the closest surrogate for assessing UVA protection against UVA-induced melanocarcinogenesis and immunosuppression. Finally, effort is needed to determine the electromagnetic action spectra for melanoma in humans.

In summary, we have reviewed evidence from various disciplines regarding the controversy concerning the role of UVA in the development of melanoma. It is evident that UVA is capable of inducing DNA damage in cell culture and in humans in vivo. UVA also appears to be capable of producing melanoma in backcross hybrids of *Xiphophorus* fish. However, evidence from epidemiologic studies and clinical observations is inconclusive. Further studies are needed to elucidate the scope of the relationship between UVA exposure and development of melanoma. Until a firm conclusion is reached, it is recommended that the public be instructed to minimize their exposure to both UVA and UVB radiation.

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