

## Increased UVA exposures and decreased cutaneous Vitamin D<sub>3</sub> levels may be responsible for the increasing incidence of melanoma <sup>☆</sup>

Dianne E. Godar <sup>a,\*</sup>, Robert J. Landry <sup>a</sup>, Anne D. Lucas <sup>a</sup>

<sup>a</sup> US Food and Drug Administration, Center for Devices and Radiological Health, 10903 New Hampshire Avenue (HFZ-120), Silver Spring, MD 20993-0002, USA

### ARTICLE INFO

#### Article history:

Received 6 June 2008

Accepted 12 September 2008

### SUMMARY

Cutaneous malignant melanoma (CMM) has been increasing at a steady exponential rate in fair-skinned, indoor workers since before 1940. A paradox exists between indoor and outdoor workers because indoor workers get three to nine times less solar UV (290–400 nm) exposure than outdoor workers get, yet only indoor workers have an increasing incidence of CMM. Thus, another “factor(s)” is/are involved that increases the CMM risk for indoor workers. We hypothesize that one factor involves indoor exposures to UVA (321–400 nm) passing through windows, which can cause mutations and can break down vitamin D<sub>3</sub> formed after outdoor UVB (290–320 nm) exposure, and the other factor involves low levels of cutaneous vitamin D<sub>3</sub>. After vitamin D<sub>3</sub> forms, melanoma cells can convert it to the hormone, 1,25-dihydroxyvitamin D<sub>3</sub>, or calcitriol, which causes growth inhibition and apoptotic cell death *in vitro* and *in vivo*. We measured the outdoor and indoor solar irradiances and found indoor solar UVA irradiances represent about 25% (or 5–10 W/m<sup>2</sup>) of the outdoor irradiances and are about 60 times greater than fluorescent light irradiances. We calculated the outdoor and indoor UV contributions toward different biological endpoints by weighting the emission spectra by the action spectra: erythema, squamous cell carcinoma, melanoma (fish), and previtamin D<sub>3</sub>. Furthermore, we found production of previtamin D<sub>3</sub> only occurs outside where there is enough UVB. We agree that intense, intermittent outdoor UV overexposures and sunburns initiate CMM; we now propose that increased UVA exposures and inadequately maintained cutaneous levels of vitamin D<sub>3</sub> promotes CMM.

Published by Elsevier Ltd.

### Introduction

Outdoor solar UV radiation (UVR; 290–400 nm) and indoor UVR exposures contribute toward skin cancer.

Outdoor workers can get three to nine times as much erythemally weighted solar UVR exposure as indoor workers [1–3]. In the United States around 39°N, the average adult indoor worker and child gets about 25 kJ/m<sup>2</sup> of erythemally weighted outdoor UVR each work or school year, or about 33 kJ/m<sup>2</sup> including a conservative vacation [4–6]. In Europe at 52.5°N, the average indoor worker gets about 12.5 kJ/m<sup>2</sup> of erythemally weighted outdoor

**Abbreviations:** ASTM, American Society for Testing and Materials; BCC, basal cell carcinoma; CIE, Commission Internationale de l'Eclairage; CMM, cutaneous malignant melanoma; RR, relative risk; SCUP-h, skin cancer Utrecht Philadelphia-human; SCC, squamous cell carcinoma; UVR, ultraviolet radiation; UVA1, 341–400 nm; UVA2, 321–340 nm, UVA, 321–400 nm; UVB, 290–320 nm; UVC, 200–290 nm; UVR, 290–400 nm; VDR, vitamin D<sub>3</sub> receptor; WHO, World Health Organization; XP, xeroderma pigmentosum.

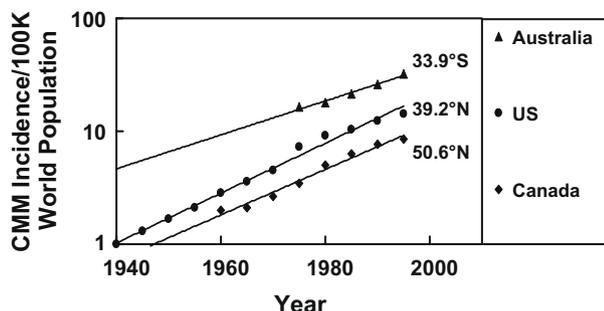
<sup>☆</sup> The opinions or assertions identified by brand name or otherwise are the private views of the authors and are not to be construed as conveying either an official endorsement or criticism by the United States Department of Health and Human Services or the Food and Drug Administration.

\* Corresponding author. Tel.: +1 301 796 0299; fax: +1 301 796 9826.

E-mail address: [DEG@CDRH.FDA.GOV](mailto:DEG@CDRH.FDA.GOV) (D.E. Godar).

UVR each work year, or about 13.8 kJ/m<sup>2</sup> including a vacation [3]. Paradoxically, although outdoor workers get much higher outdoor solar UV doses than indoor workers get, only the indoor workers' incidence of cutaneous malignant melanoma (CMM) has been increasing at a steady exponential rate since before 1940 (Fig. 1, World Health Organization, WHO, and Connecticut cancer registry). Likewise, the calculated lifetime risk for getting CMM follows the same pattern [7,8]. In fact, outdoor workers have a lower incidence of CMM compared to indoor workers [9–11]. Thus, unlike squamous cell carcinoma (SCC), some factor(s) other than cumulative UVR exposures plays a role in CMM.

Outdoor exposures include UVB (290–320 nm) radiation, so that previtamin D<sub>3</sub> and thermal conversion to vitamin D<sub>3</sub> can occur in the skin [12,13]. Vitamin D<sub>3</sub> can then be converted to its most hormonally active form, 1,25-dihydroxyvitamin D<sub>3</sub> or calcitriol, which kills melanoma cells and SCC *in vitro* [14,15] and reduces tumor growth *in vivo* [16,17]. Calcitriol is not only formed by enzymes in the kidneys and liver but also by enzymes in melanoma cells [18] and keratinocytes [19]. Calcitriol can control or eliminate melanoma cells by binding to the vitamin D<sub>3</sub> receptor (VDR) on the nuclear membrane signaling for either growth inhibition or cell death via apoptosis [15,20–22], while it protects normal melanocytes from apoptosis [23]. Calcitriol can exhibit these effects on a



**Fig. 1.** The temporal incidence of CMM in fair-skinned countries around the world at different latitudes. Note that the slope at each latitude is the same throughout the decades, indicating a constant exponential increase in the incidence of CMM over time, which increases toward the equator where there is more UVB. Data is from the World Health Organization.

variety of cancer cells possessing a functional VDR: melanoma, leukemia, breast, prostate, colon, and other cancers as well [24–26]. Calcitriol regulates an estimated 60 nuclear genes [24]. It causes down-modulation of proto-oncogenes, such as *c-myc*, *c-fos*, and *c-jun* [26], cell cycle arrest in G1 [27], DNA repair [28], and selective inhibition of DNA polymerase alpha [29]. In addition, calcitriol affects the immune system [30,31]. For example, high concentrations of calcitriol suppress immunoglobulin production and thymic proliferation *in vivo* [32], while low concentrations of calcitriol suppress cell-mediated immunity *in vivo* [33]. Moreover, UVB makes the precursor of vitamin D<sub>3</sub>, previtamin D<sub>3</sub>, while UVA (321–400 nm) can only break down vitamin D<sub>3</sub> and can do so in human serum while bound to the vitamin D binding protein [34]. Because 35–50% of the incident UVA radiation can penetrate to the dermal layer of the skin [35], UVA cannot only possibly break down the vitamin D<sub>3</sub> in the skin but also the vitamin D circulating through the capillaries. Thus, indoor workers may be at a higher risk for getting melanoma because they make little vitamin D<sub>3</sub> locally in the skin during their workweek and UVA window exposures can break down any vitamin D<sub>3</sub> just formed in the skin or circulating through the capillaries.

Besides breaking down vitamin D, indoor solar UVA window exposures can cause detrimental biological effects. For example, UVA1 (341–400 nm) radiation can cause oxidative stress [36–39], damage to organelles, red blood cell lysis [37,40], humoral immune suppression [41] and photoaging [42]. Moreover, UVA radiation causes DNA damage [43] and mutations [44,45], which can lead to initiating SCC in mice [46,47] or premelanocytic lesions in marsupials [48]. In addition, UVA can promote SCC tumor formation in mice after initiation by UVR [49] and, recent findings in a mouse melanoma model show that UVA can increase the number of melanomas after initiation by UVB [F. Noonan, 34th Meeting of the American Society for Photobiology in Burlingame, CA, June 20–25, 2008].

We agree that intense (including sunburns), intermittent (weekends and vacations) outdoor UV overexposures can initiate melanoma [50], while we now propose that increased UVA exposures along with inadequately maintained vitamin D<sub>3</sub> levels in the skin can promote melanoma. In support of this hypothesis are the reports that calcitriol decreases stage II (promotional phase) carcinogenesis *in vivo*, while it does not significantly affect stage I carcinogenesis (initiation phase; [16]). Calcitriol decreases the incidence, number, and size of skin tumors as well as melanoma xenographs *in vivo* [16,17,51]. It also inhibits the *in vitro* invasiveness and *in vivo* pulmonary metastasis of mouse melanoma [52]. In addition, UVB-absorbing sunscreens statistically enhanced the growth of syngeneic melanoma cells implanted in mice

[53], suggesting a possible role for UVA-induced mutations and/or diminution of cutaneous vitamin D<sub>3</sub> levels in promoting melanoma.

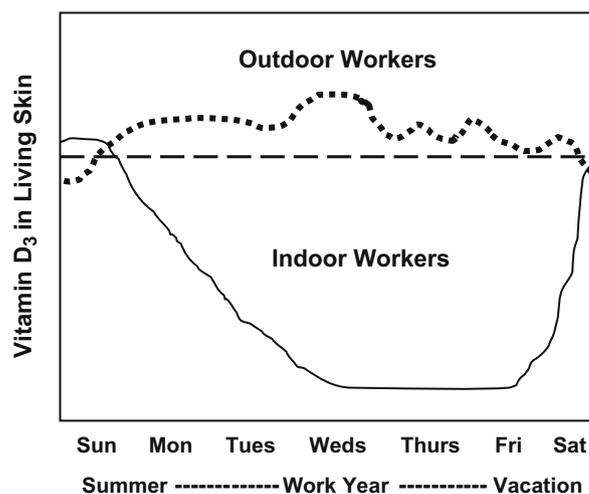
To begin investigating our hypothesis, we looked at indoor UV exposures using a standard solar emission spectrum in the Northern Hemisphere and actual window transmission data as well as actual spectral measurements in June. To estimate the contributions in effective W/m<sup>2</sup>, or their effective irradiance, toward different biological endpoints, we weighted the emission spectra by the different action spectra: erythema [54], SCC (Skin Cancer Utrecht Philadelphia-human, SCUP-h; [55,56]), melanoma in a fish model [57], and previtamin D<sub>3</sub> formation in human skin [58]. We compare the contributions in W/m<sup>2</sup> from outdoor solar UV, indoor solar UV, and indoor fluorescent light emissions toward these biological endpoints and we investigated if indoor lighting can make any previtamin D<sub>3</sub>. We also discuss how our hypothesis explains the epidemiological data collected for melanoma.

### Hypothesis

We agree that intense, intermittent overexposure to solar UVR and sunburns initiate melanoma [50]. Here we now propose that indoor solar UVA exposures, which cause mutations [45] and depletes vitamin D<sub>3</sub> in the skin [34], and inadequately maintained amounts of cutaneous vitamin D<sub>3</sub> can promote CMM.

In the early 20th century, people went against evolution by going indoors during the day to work, which drastically decreased their daily amount of cutaneous vitamin D<sub>3</sub> and, along with it, their blood levels. With the addition of larger buildings and sky scrapers, people created an unnatural UV barrier when windows were developed and used in abundance. The UV barrier created by window glass divided UVB from UVA, so that the vitamin D making UVB was excluded from our indoor working environment; only the vitamin D-breaking and DNA-mutating UVA was included. Because this unnatural UV environment existed for decades in buildings and cars, CMM began to steadily increase about 20–30 years later in the mid-1930s (Fig. 1).

Our basic hypothesis involves increases in UVA exposures and a fluctuating cutaneous vitamin D<sub>3</sub> profile, or “vitamin D roller coaster,” for indoor workers compared to a consistent cutaneous vitamin D<sub>3</sub> profile for outdoor workers (see Fig. 2; the dotted line



**Fig. 2.** The cutaneous vitamin D<sub>3</sub> “roller coaster” that indoor workers experience during the workweek and work year compared to outdoor workers. The curve for indoor workers (solid) rises on some weekends and during most vacations, while outdoor workers (dotted) cutaneous vitamin D<sub>3</sub> remains fairly constant and above the theoretical line for ‘sufficient’ cutaneous vitamin D<sub>3</sub>.

represents the hypothetical protective level of vitamin D<sub>3</sub> in the skin). Indoor workers go to and from work five days a week, usually before 9 a.m. and after 4 p.m., respectively, when the solar UVB is negligible, so that indoor workers hardly make any vitamin D<sub>3</sub> commuting during the workweek and work year. Meanwhile, people can be exposed to UVA passing through the windows of their cars [59], which can break down vitamin D<sub>3</sub> [34]. While at work, many indoor workers are exposed to some UVA through their office windows and to minor amounts of UVA and UVB from fluorescent lights, but they usually get little or no short-term (5–15 min) moderate UVB exposure during the peak hours (11 a.m.–3 p.m.) of their workdays and, most people do not go outside at all. In the northern regions of the world (above 37°N), a vitamin D<sub>3</sub> “winter” occurs from at least November–February, when the dose-rate of UVB is too low to make any previtamin D<sub>3</sub> even if an office worker goes outside during peak hours [60]. Meanwhile, the UVA entering through their windows can cause DNA damage [43] and mutations [44,45] that accumulate during the week. On the weekend, indoor workers can go outside and make vitamin D<sub>3</sub> (although not in the winter above 37°N), weather permitting, but they either do not or cannot go out every weekend during ‘peak UVB hours. Worse yet, indoor UVA exposures can break down vitamin D<sub>3</sub> formed in the skin from outdoor UVB exposures. In fact, after only 3 h of winter sunlight exposure near 42°N (primarily UVA) only 26% of the initial amount of vitamin D remained in human serum, neither the vitamin D binding protein nor other serum components can prevent its photodegradation [34]. On the other hand, outdoor workers get little UVA alone exposures from windows, but do get some UVB exposure during the ‘peak’ vitamin D making hours of their work day (11 a.m.–3 p.m.).

### Supporting evidence

The following published findings offer some supporting evidence for this melanoma hypothesis. First, UVB exposure alone cannot explain the increasing incidence of CMM because outdoor workers get much more UVB than indoor workers, yet indoor workers have a higher incidence of CMM [9–11]. Second, the blood levels of vitamin D in outdoor workers (gardeners), who get about five times the solar dose (218 J/m<sup>2</sup>) that indoor workers get (37 J/m<sup>2</sup>), are about twice as high as indoor workers [61]. Third, the prediagnostic levels of vitamin D (i.e., D<sub>2</sub> and D<sub>3</sub> are actually measured as 25-hydroxyvitamin D) serum levels in melanoma patients were significantly lower (at the 94% level of confidence) than controls [62]. Forth, UVB-absorbing sunscreens are associated with a significant increased risk of melanoma in humans [63]; they promote the growth of melanoma in mice [53], while they suppress cutaneous vitamin D<sub>3</sub> formation [64]. Fifth, an all-year-tan is protective against melanoma [65], and outdoor workers, who get three to nine times the erythemally effective UV dose that indoor workers get [1–3] have a significantly lower incidence of melanoma [9–11]. Sixth, outdoor activities in childhood decrease the incidence of melanoma (excluding sunburns; [11,66]) and there is no “critical period,” such as childhood, where intense exposures contribute more towards the induction of melanoma [67,68]. In fact, some studies found that sunburns throughout life are an important risk factor for melanoma [11,67], while low level solar UV exposures are protective [25]. Seventh, melanoma patients who receive regular sun exposures live longer than those who do not [69], while those with polymorphisms in their VDR receptors have a poor prognosis [70]. Eight, UVA not only promotes skin tumor growth in mice after initiation by artificial sunlight, but also causes twice as many tumors to form [49]. Ninth, UVA increases melanomas in a mouse model after initiation by UVB [F. Noonan, 34th ASP Meeting, Burlingame, CA, June 20–25, 2008]. Finally, further sup-

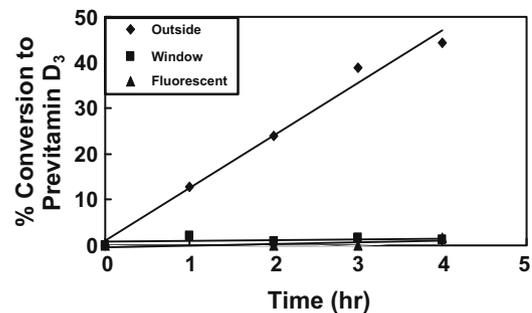


Fig. 3. Provitamin D<sub>3</sub> conversion to Previtamin D<sub>3</sub>; Outside (solar UVB) versus inside (window glass or fluorescent light) exposures.

port for this hypothesis is the report that calcitriol decreases stage II (promotional phase) carcinogenesis *in vivo*, while it does not significantly affect stage I carcinogenesis (initiation phase; [16]). Thus, lack of cutaneous calcitriol/vitamin D<sub>3</sub> as well as increased UVA exposures may promote CMM in humans.

### Supporting data

Unlike outdoor solar UVR exposures that make previtamin D<sub>3</sub> in a dose-dependent manner because UVB is present, indoor exposures, either from window UVA or from fluorescent light UVR cause no previtamin D<sub>3</sub> formation for up to 4 h (11 a.m.–3 p.m., see Fig. 3). Outdoor UVA can be about four times higher than indoor UVA (see below), but even four hours of indoor UVA window exposure (11 a.m.–3 p.m.) did not convert any provitamin D<sub>3</sub> to previtamin D<sub>3</sub>, whereas, one hour of outdoor UVA (and UVB) exposure converted about 10% of provitamin D<sub>3</sub> to previtamin D<sub>3</sub>. To determine the amount of previtamin D<sub>3</sub> made from provitamin D<sub>3</sub> (Sigma Chem. Co., St. Louis, MO and the gift of M.F. Holick), we used a published method with slight modifications [58]. Briefly, we exposed 1 ml samples of provitamin D<sub>3</sub> (26 nM) in 100% hexane under different conditions using 1 cm path-length quartz cuvettes (5 ml volume) with Teflon covered caps. To determine the amount of previtamin D<sub>3</sub> made from provitamin D<sub>3</sub>, we used a Waters high-pressure liquid chromatographic (HPLC) system, equipped with 515 pumps, a 717 autoinjector, and a 996 photodiode array detector (set at 354 nm, the peak absorption of provitamin D<sub>3</sub>) using Waters Empower chromatographic software (Milford, MA). Separation is performed isocratically with a 5 μm Supelco Supelco-sil LC ABZ column, 15 cm × 4.6 mm; the mobile phase was 10/90% ethyl acetate/hexane at a flow rate of 1.5 ml/min. The data is calculated as the percent remaining provitamin D<sub>3</sub> and is plotted as the percent converted to previtamin D<sub>3</sub>.

People can get considerable UVA exposure from windows. For example, the ASTM standard outdoor solar spectrum (atmosphere 1.5, 37 tilt; 71) gives a value of about 30 W/m<sup>2</sup> of outdoor solar UVR (see Table 1a; about 26 W/m<sup>2</sup> is UVA1, 4.29 is UVA2 from 321 to 340 nm, and about 0.9 is UVB); whereas, inside a building, about 20% of the outside UVR or 6.27 W/m<sup>2</sup> of only UVA passes through a storm window and, almost all of it is UVA1 (see Fig. 4a and Table 1a). According to this calculated value, if a person sits 3 m or less from a double-pane window on the sunlit east or west side of a building for about 4 h, they can get about 90 kJ/m<sup>2</sup> of UVA in one day. An entire work year (5 days/wk for 48 wk) of this exposure could give a UVA dose around 21,700 kJ/m<sup>2</sup>. Note that these numbers do not apply for other types of windows or thicknesses of glass because UV transmission can vary tremendously, from <1% to as high as 86% [72]. For example, a single-pane window (4.76 mm thick) can allow about 30% of the outdoor UVA or about 9 W/m<sup>2</sup> to enter a room.

**Table 1a**

ASTM standard outdoor solar UV emission spectrum (atmosphere 1.5, 37° tilted surface; 71): total outdoor solar UVR (290–400 nm), UVB (290–320 nm), UVA (321–400 nm), UVA1 (341–400 nm), and UVA2 (321–340 nm) irradiances in W/m<sup>2</sup> compared to the indoor solar UVA, UVA1, and UVA2 irradiances passing through two different window types; a double-pane storm window (2 × 6 mm glass with a 13.2 mm air space in between) and a single-pane window (4.76 mm thick).

Parameter	ASTM outside (W/m <sup>2</sup> )	ASTM inside (W/m <sup>2</sup> ) double pane	ASTM inside (W/m <sup>2</sup> ) single pane
290–400 nm (Total UVR)	30.94	6.27 (20.9%)	8.98 (29.9%)
290–320 nm (UVB)	0.8892	6.63 × 10 <sup>-8</sup>	8.95 × 10 <sup>-6</sup>
321–400 nm (UVA)	30.05	6.27	8.98
341–400 nm (UVA1)	25.76	6.24	8.96
321–340 nm (UVA2)	4.29	0.0334	0.0106

Ironically, lower daily doses of UVA have a higher effectiveness toward the induction of SCC than higher daily doses [73]. For example, daily doses of 75 kJ/m<sup>2</sup> of UVA contribute, per dose unit, about twice as much toward SCC as daily doses of 240 kJ/m<sup>2</sup>. We concluded this based on calculations of accumulated doses to *t*<sub>50</sub>, the time needed for 50% of the mice to develop tumors (personal communication with J.C. van der Leun).

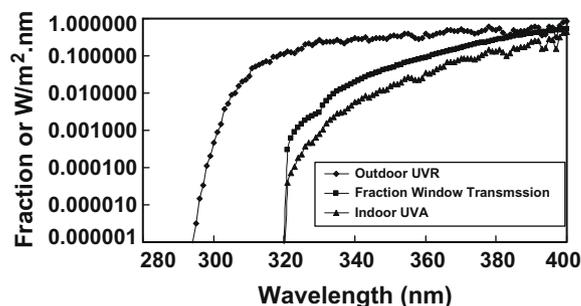
We also took real measurements at 10 a.m. on June 29 and 30, 2004, in Silver Spring, MD (about 39°N) of the outdoor solar UV and the UV transmission through both the single and double windowpanes and found them to yield results that are close to the calculated ASTM-derived values (see Fig. 4b and Table 1b). The ASTM standard Sun gives 30.94 and our averaged measurements give 36.6 W/m<sup>2</sup> of total UVR. Concerning indoor UVA, the ASTM standard Sun gives 6.27 and 8.98 W/m<sup>2</sup> and our measurements give 4.05 and 9.82 W/m<sup>2</sup> for double and single windowpanes, respectively. Our actual measurements at a 45° tilted surface are in good agreement with the ASTM standard Sun values at a 37° tilted surface. However, unlike the ASTM standard Sun value, which applies for an entire year, the actual measurements will vary with the zenith angle of the Sun (time of year and day). For example, at noon on June 29th around 39°N, the total outdoor solar UVR was 48.8 W/m<sup>2</sup>, while the indoor UVA was 7.63 W/m<sup>2</sup> and 2.38 W/m<sup>2</sup> for a single and double windowpane, respectively. For comparison, fluorescent lighting is about two orders of magnitude lower than UVA or UVA1 through windows and outdoor UVB, while the UVA2 is comparable to the UVA2 passing through windows. Fig. 4c compares both the calculated and measured indoor UVA through a storm window to an average fluorescent light emission. Notice that the indoor UVA through this type of window is about 60 times greater than that from fluorescent lights. Other types of glass and windows can give values that are even higher than what we show here. The UVA transmission is about average for the various kinds of windows that are usually used.

We used the CIE erythema [54], SCC (SCUP-h; [55]), fish melanoma [57], and previtamin D<sub>3</sub> [58] action spectra to weight the outdoor solar UV, the indoor solar UVA, and the fluorescent light

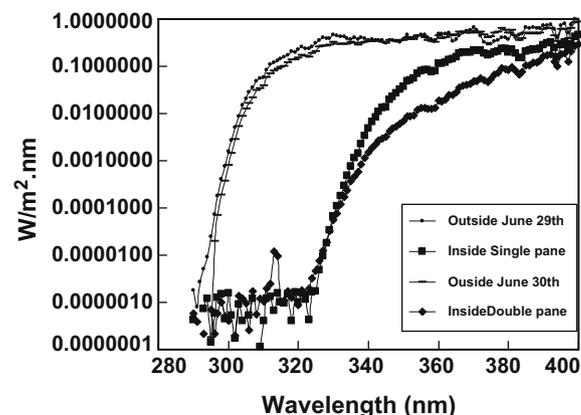
**Table 1b**

Actual measurements on June 29th and 30th, 2004, at 10 a.m. (45° tilted surface) of the total outdoor solar UV (290–400 nm), UVB (290–320 nm), UVA (321–400 nm), UVA1 (341–400 nm), and UVA2 (321–340 nm) irradiances (W/m<sup>2</sup>) compared to the indoor solar UVA, UVA1, and UVA2 irradiances passing through two different windows; a double-pane storm window (2 × 6 mm glass with a 13.2 mm air space in between) and a single-pane window (4.76 mm thick). Fluorescent light measurements are also shown for comparison.

Parameter	Measured outside (W/m <sup>2</sup> )	Measured inside (W/m <sup>2</sup> ) double pane	Measured inside (W/m <sup>2</sup> ) single pane	Measured inside (W/m <sup>2</sup> ) fluorescent lights
290–400 nm (Total UV)	36.6	4.05 (11.1%)	9.82 (26.8%)	5.37 × 10 <sup>-2</sup>
290–320 nm (UVB)	1.52	4.65 × 10 <sup>-5</sup>	2.34 × 10 <sup>-5</sup>	1.11 × 10 <sup>-2</sup>
321–400 nm (UVA)	35.08	4.05	9.82	4.26 × 10 <sup>-2</sup>
341–400 nm (UVA1)	28.81	4.05	9.80	3.36 × 10 <sup>-2</sup>
321–340 nm (UVA2)	6.27	5.61 × 10 <sup>-3</sup>	1.49 × 10 <sup>-2</sup>	8.95 × 10 <sup>-3</sup>

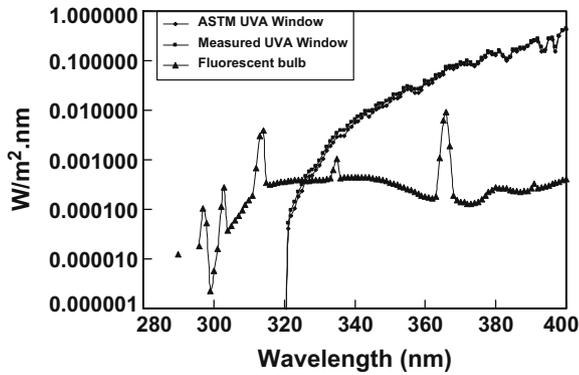


**Fig. 4a.** Solar ASTM UV emission spectrum, fraction of UV transmission through a double-pane (storm) window, and UVA entering through a double-pane window glass (2 × 6 mm thick with a 13.2 mm air space between panes). We obtained the percent transmission of UV through a double-pane storm window (Solarscreen 2000 low-E insulating glass, VE-2 M, 2.52 cm thick: 6 mm glass, +13.2 mm air, +6 mm glass) from the company (Viracon, Owatonna, MN). We used every nm of the American Society for Testing and Materials (ASTM) annually averaged standard solar spectrum for 1.5 atmospheres and a 37° tilted surface [71] to calculate the average transmission through this glass.



**Fig. 4b.** Actual measurements on June 29 and 30, 2004, in Silver Spring, MD (about 39°N) at 10 a.m. of the solar emission spectra and the UVA entering through a single (4.76 nm) or double-pane (6 mm glass, 13.2 mm air, 6 mm glass) glass window. Note that the small peak around 313 nm for the double-pane window is from indoor fluorescent lighting. We measured every nm of the outdoor solar irradiance and actual spectral transmission through this double-pane storm window and a single-pane window (4.76 mm thick) at 10 a.m. on June 29 and 30, 2004, in Silver Spring, MD (about 39°N) using a double-grating portable spectroradiometer (Optronics Model OL 754; Optronics Laboratories, Inc., Orlando, FL). We calibrate our spectroradiometer using a 1000 W standard lamp that is traceable to the National Institute of Standards and Technology.

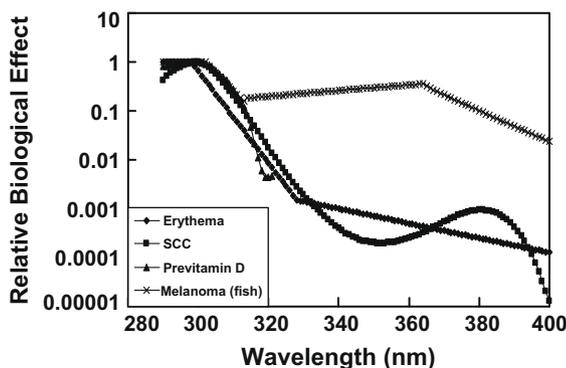
irradiances to get their contributions in W/m<sup>2</sup>, or their effective irradiance, toward each of these endpoints. The effective irradiance is the sum of the products of the spectral irradiance and the spectral weighting factor, wavelength (nm) for wavelength (nm), from 290 to 400 nm. Note the order of validity for these action spectra:



**Fig. 4c.** Indoor solar UVA passing through a double-pane window using the ASTM Sun and Real Measurements on June 30, 2004, at 10 a.m. in Silver Spring, MD (39°N) compared to a typical fluorescent light emission spectrum. We measured an average, unshielded fluorescent light emission from a bank of three, four-foot bulbs housed in a reflector unit using the same double-grating portable spectroradiometer at a distance of 1.65 m: the distance to the office workers' sitting position, approximately 1 m from the floor.

erythema > SCC > melanoma ~ previtamin D<sub>3</sub>. Also, note that reproduction of the last two action spectra by other laboratories has not yet occurred.

To get the contribution in W/m<sup>2</sup> or the effective irradiance toward each biological endpoint, we weighted the outside and inside spectral irradiances with the different action spectra (see Fig. 5): erythema, SCC (SCUP-h), melanoma (fish), and previtamin D<sub>3</sub>. Integrating the area under the resulting curves shown in Figs. 6a and 6b gives the total contribution toward each biological endpoint in W/m<sup>2</sup>. The outdoor contribution of UVB toward SCC is only three to four times more than UVA after weighting by the ASTM standard solar spectrum. Indoor UVA exposures have about 20–30% of the outdoor UVA irradiance, depending on the thickness and type of window glass as well as the solar zenith angle. The outdoor solar UV ratios (Table 2a) and the indoor solar UVA ratios (Tables 2b and 2c) of the different biological endpoints compared to erythema are all within the same order of magnitude, except melanoma (fish) and previtamin D<sub>3</sub> production. According to the (fish) melanoma action spectrum, the outdoor contribution toward melanoma is about 100 times higher than erythema, while the indoor contribution toward melanoma is about 400–500 times higher than erythema. In contrast, the indoor solar UVA contribution toward previtamin D<sub>3</sub> production is about four orders of magnitude lower than all the other endpoints. In addition, an average fluorescent bulb emission hardly contributes at all toward the different biological endpoints (Table 2d): erythema, SCC (SCUP-h), mela-



**Fig. 5.** Action spectra; erythema (CIE), SCC (SCUP-h), previtamin D<sub>3</sub>, and melanoma (fish).

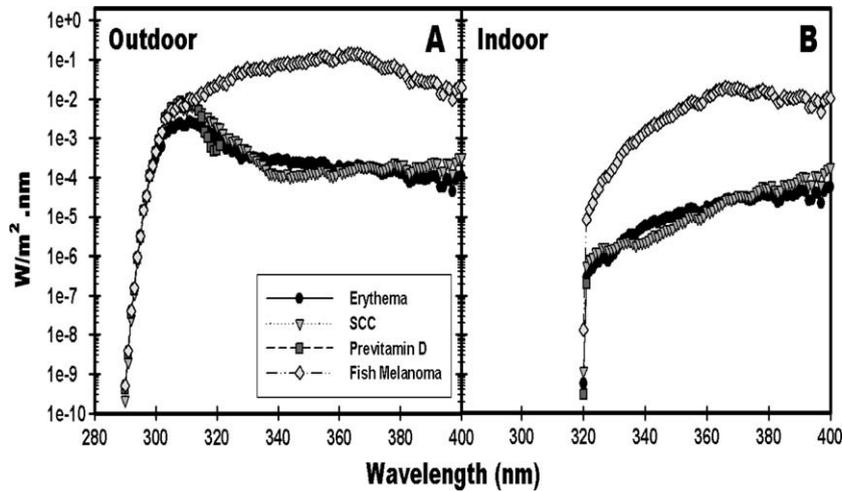
nomia (fish) and previtamin D<sub>3</sub>. Notice that the effective UVA irradiance for melanoma from the fluorescent lighting (~17 W/m<sup>2</sup>) is about 25 times lower than the indoor solar UVA passing through windows (400–500 W/m<sup>2</sup>) and about six times lower than the contribution from outdoor exposures (107 W/m<sup>2</sup>). Only UVB radiation can make previtamin D<sub>3</sub>: UVA radiation makes virtually no previtamin D<sub>3</sub> [58], while it can break down vitamin D<sub>3</sub> [34]. There is only one point in the action spectrum in the UVA region, at 321 nm that can contribute toward previtamin D<sub>3</sub> production, while wavelengths ranging from 315 to 335 nm can break down vitamin D<sub>3</sub>. Note that the variation of solar zenith angle throughout the day and year will alter the relative ratios of the different biological endpoints to erythema resulting in somewhat lower or higher indoor values from reflection off the surface of the glass. That is, the higher the Sun is in the sky (summer), the lower the indoor values will be; the lower the Sun is in the sky (winter), the higher the indoor values will be.

The contribution toward melanoma may be higher than what the SCC (SCUP-h) action spectrum predicts; but it is probably lower for humans than what the melanoma action spectrum in a fish model predicts. It is difficult to estimate the risk for getting melanoma from indoor solar UVA exposure because an action spectrum for the initiation of mammalian melanoma is currently nonexistent. Other action spectra for promoting mammalian melanoma, once initiated by UVB [74] in the presence or absence of vitamin D<sub>3</sub> are also unavailable. Moreover, even if an action spectrum for human melanoma were available, it would not be useful because CMM is not dependent on cumulative UV exposure, as shown by the lower incidence in outdoor workers [9–11]. However, we can still make a hypothetical case from our findings and other known facts.

## Discussion

Any hypothesis concerning the increasing incidence of melanoma must explain the documented observations such as intense intermittent exposures and sunburns (weekend and vacation), incidence over time, and distribution over body surface. It must also explain the following epidemiologic observations: sun (or other) exposure; latitude; prevalence in upper pay scale and white-collar occupations and higher incidence in indoor workers (especially office workers) compared to outdoor workers. Our hypothesis appears to explain all the observations to date. Overexposures and especially sunburns from UVB exposures initiate melanoma, while UVA exposures and inadequate levels of vitamin D<sub>3</sub> in the skin may promote it.

The lifetime risk for getting CMM [7,8] and the increase in the incidence of CMM began its exponential increase back in 1936 [Connecticut cancer registry] and, although many cultural changes occurred since then, the slope of the lines have not changed to this day (Fig. 1). In fact, nothing culturally important that occurred after the first noted increase in the incidence of CMM should have been blamed for its increase because anything that could have been responsible had to occur about 10–30 years before, rather than after, the first documented increase. The major thrust of the industrial revolution began about 30 years before the increase in CMM, when both windows, along with high-rise, steel-reinforced office buildings, cars, and gasoline containing volatile lead (tetraethyl lead), which is a co-carcinogen with UVC (200–290 nm; [75]), became abundant. However, if volatile lead were responsible, then outdoor workers would have a higher incidence of melanoma than indoor workers of the same socio-economic status because they would have been exposed to it all day; but the opposite is true [9]. Sunlamps, sunscreens, cultural changes (clothes and outdoor activities), as well as fluorescent light exposures [76] have all been



**Fig. 6.** (A) Outdoor ASTM solar contribution of UV (290–400 nm) toward erythema, SCC (SCUP-h), fish melanoma, and previtamin D<sub>3</sub> production. (B) Indoor ASTM solar contribution of UVA (321–400 nm) through a storm window (2 × 6 mm with a 13.2 mm air space) toward erythema, SCC (SCUP-h), fish melanoma, and previtamin D<sub>3</sub> production.

blamed for the increasing incidence of melanoma, but they all occurred after 1936 when the first increase in CMM in the US was

documented in Connecticut. However, the new high-pressure, UVA-emitting sunlamps may now be contributing toward increas-

**Table 2a**

Outdoor contribution of ASTM solar UV (total UV, UVB, UVA, UVA1&2) in W/m<sup>2</sup> toward erythema, SCC (SCUP-h), fish melanoma, and previtamin D<sub>3</sub> production; and their 290–400 nm ratios compared to erythema.

Endpoint/wavelength	Erythema CIE	SCC	Melanoma (fish)	previtamin D <sub>3</sub>
290–400 nm (UVA + B)	5.18 × 10 <sup>-2</sup>	1.08 × 10 <sup>-1</sup>	5.55	9.22 × 10 <sup>-2</sup>
290–320 nm (UVB)	3.45 × 10 <sup>-2</sup>	8.62 × 10 <sup>-2</sup>	1.95 × 10 <sup>-1</sup>	9.15 × 10 <sup>-2</sup>
321–400 nm (UVA)	1.73 × 10 <sup>-2</sup>	2.22 × 10 <sup>-2</sup>	5.35	6.36 × 10 <sup>-4</sup>
341–400 nm (UVA1)	9.40 × 10 <sup>-3</sup>	1.09 × 10 <sup>-2</sup>	4.35	0
321–340 nm (UVA2)	7.92 × 10 <sup>-3</sup>	1.13 × 10 <sup>-2</sup>	1.00	6.36 × 10 <sup>-4</sup>
Ratio (290–400 nm)/erythema	1.0	2.08	107	1.78

**Table 2b**

Indoor contribution of ASTM UVA (1&2) through a double-pane storm window in W/m<sup>2</sup> toward erythema, SCC (SCUP-h), fish melanoma, and previtamin D<sub>3</sub> production; and their UVA ratios compared to outdoor exposure (321–400 nm) and to erythema.

Endpoint/wavelength	Erythema CIE	SCC	Melanoma (fish)	Previtamin D <sub>3</sub>
321–400 nm (UVA)	1.51 × 10 <sup>-3</sup>	2.59 × 10 <sup>-3</sup>	6.12 × 10 <sup>-1</sup>	1.91 × 10 <sup>-7</sup>
341–400 nm (UVA1)	1.47 × 10 <sup>-3</sup>	2.56 × 10 <sup>-3</sup>	6.04 × 10 <sup>-1</sup>	0
321–340 nm (UVA2)	4.07 × 10 <sup>-5</sup>	3.28 × 10 <sup>-5</sup>	8.26 × 10 <sup>-3</sup>	1.91 × 10 <sup>-7</sup>
Ratio (321–400 nm)/erythema	1.0	1.72	405	1.26 × 10 <sup>-4</sup>

**Table 2c**

Indoor contribution of ASTM UVA (1&2) through single-pane window in W/m<sup>2</sup> toward erythema, SCC (SCUP-h), fish melanoma, and previtamin D<sub>3</sub> production; and their UVA ratios compared to outdoor UVA exposure (321–400 nm) and to erythema.

Endpoint/wavelength	Erythema CIE	SCC	Melanoma (fish)	previtamin D <sub>3</sub>
321–400 nm (UVA)	2.56 × 10 <sup>-3</sup>	4.38 × 10 <sup>-3</sup>	1.24	3.99 × 10 <sup>-9</sup>
341–400 nm (UVA1)	2.54 × 10 <sup>-3</sup>	4.38 × 10 <sup>-3</sup>	1.23	0
321–340 nm (UVA2)	1.13 × 10 <sup>-5</sup>	5.72 × 10 <sup>-6</sup>	2.72 × 10 <sup>-3</sup>	3.99 × 10 <sup>-9</sup>
Ratio (321–400 nm)/erythema	1.0	1.71	484	1.56 × 10 <sup>-6</sup>

**Table 2d**

Contribution of an average fluorescent light in W/m<sup>2</sup> toward erythema, SCC (SCUP-h), fish melanoma, and previtamin D<sub>3</sub> production, and their UV (290–400 nm) ratios compared to outdoor UV (290–400 nm) and erythema.

Endpoint/fluorescent light source	Erythema CIE	SCC	Melanoma (fish)	Vitamin D <sub>3</sub>
Average fluorescent bulb UV (290–400 nm)	7.68 × 10 <sup>-4</sup>	1.55 × 10 <sup>-3</sup>	1.30 × 10 <sup>-2</sup>	1.67 × 10 <sup>-3</sup>
Average fluorescent bulb UVA (321–400 nm)	3.27 × 10 <sup>-5</sup>	3.96 × 10 <sup>-5</sup>	1.04 × 10 <sup>-2</sup>	1.76 × 10 <sup>-6</sup>
Ratio UV(290–400 nm)/erythema	1.0	2.02	16.93	2.17

ing the incidence of melanoma in the population of indoor tanners who use them [77] and UVB-absorbing sunscreens may have increased the incidence among beach goers. The industrial revolution caused two critical events to occur that possibly pertain to the increasing incidence of melanoma: most people began working indoors and, as a result, made less vitamin D<sub>3</sub> in their skin and more windows became available to expose people to the mutagenic and vitamin D-depleting effects of UVA radiation.

Windows were around for hundreds of years prior to the industrial revolution; however, they were smaller in size, contained smaller panes of glass, and few people could afford them. The industrial revolution and some technical advances made large windowpanes easy to mass-produce and readily distribute, so that everyone could afford to have them in abundance [78]. In addition, high-rise office buildings, needing many large windowpanes, became increasingly popular around the mid 1910s [79], about 20 years prior to the first observed increase in the incidence of CMM. The time-line for the industrial revolution fits the CMM observations, unlike the introduction of fluorescent lights in the mid-1940s [80] or any other events that occurred after the mid-1930s. Thus, the industrial revolution caused many workers to stay indoors during the day reducing their cutaneous vitamin D<sub>3</sub> levels and, the UVA entering their offices caused photodegradation of vitamin D<sub>3</sub> and mutations to the DNA of their skin cells.

Beral and co-workers made an interesting epidemiologic observation back in the early 1980s, when they thought they found a significant dose–response increase in the incidence of CMM from fluorescent light exposures [81,82]. Their epidemiology study, unbeknownst to them at that time, also included UVA exposures from windows. Unlike all the other fluorescent light epidemiology studies that followed, they used homemakers as their control group. Thus, they not only controlled for indoor fluorescent light exposure, but inadvertently also controlled for indoor UVA window exposures and for cutaneous vitamin D<sub>3</sub> production. Because homemakers do errands during the day, they can get some midday exposure to solar UVB and, consequently maintain adequate cutaneous levels of vitamin D<sub>3</sub>. Note that fair-skinned people only need 15–30 min of sunlight every other day during the midday hours from spring to fall to produce adequate amounts of vitamin D<sub>3</sub> [83]. Evidently, the homemakers made enough vitamin D<sub>3</sub> in their skin to get protection from getting CMM, unlike their female office/indoor-working counterparts, because their incidence of CMM was similar to that noted in the overall population [82]. Female office workers appeared to have a dose response increase in their relative risk (RR) for getting melanoma from fluorescent light exposure at the 95% confidence level: 1–9 year, RR is 2.4; 10–19 year, RR is 2.8; ≥20 year, RR is 4.3. Other female indoor workers had lower RRs than office workers: 1–9 year, RR is 1.6; 10–19 year, RR is 2.3; >20 year, RR is 2.0.

We can also explain the broader CMM distribution over body surface area [84] and the resemblance to the CMM distribution in Xeroderma pigmentosum (XP) patients [85]. UVB initiates CMM when normal people are overexposed and this usually happens when they have minimal clothing on, exposing most of their body to intense sunlight. They wear clothes at work covering these body sites, so that when and if, they do go outside they cannot make vitamin D<sub>3</sub> locally in the covered skin that was previously exposed. In addition, due to its longer wavelengths, UVA penetrates clothing much better than UVB [86] and clothing prevents the formation of previtamin D<sub>3</sub> [87]. People tend to remove their suit jackets at work in their offices allowing UVA to penetrate through their shirts, decreasing vitamin D<sub>3</sub> and increasing mutations in the trunk skin, thus increasing the occurrence of CMM on their trunks, especially in men. Furthermore, unlike men, women can wear skirts and dresses to work allowing their legs to get more UVA exposure, even through stockings, thus increasing the occurrence

of CMM on their legs. XP patients have windows as well, but are more concerned with UVB than with UVA exposures. Doctors advise them to minimize their exposure to both UVB and UVA and to shield their windows, but they do not, or cannot, always comply. Furthermore, this patient cohort used so-called protective clothing and UVB-absorbing sunscreens, which allowed them to be exposed to UVA radiation because broad-spectrum sunscreens were not available during that study period (1989–1995). Although XP patients blood levels of vitamin D are low, but within the so-called normal range [88], they have more melanomas on their face, head, and neck (males 48%, females 27%) than normal people have (males 24%, females 17%; 85). This may be because XP patients do not make vitamin D<sub>3</sub> in that skin because they are not exposed to UVB, while normal people are exposed to UVB and consequently make vitamin D<sub>3</sub> in that regularly exposed skin.

In opposition to SCC, the occurrence of CMM decreases on chronically exposed body sites [84]. For example, SCC is more prevalent on the face and hands compared to melanomas. We can explain why this occurs. When people go outside, their hands and face can get exposed to UVB and make vitamin D<sub>3</sub> locally in that skin. If a melanoma cell forms on the hands or face, the vitamin D<sub>3</sub> produced from outdoor UVB exposure can cause it to be growth inhibited or to die via apoptosis. The melanoma cells in those skin areas can take up the newly formed vitamin D<sub>3</sub> and convert it to calcitriol [14] before the person has a chance to go back inside and possibly destroy it from UVA window exposure. In contrast, if a person goes outdoors during workdays, they will not make vitamin D<sub>3</sub> on body sites covered by clothing: so, any melanoma cells formed by sunburns from previous exposures in those areas can survive and multiply. Vitamin D or 25-hydroxyvitamin D is present in the blood and circulates throughout the body, so that it can enter skin that was not exposed to UVB. However, the circulating concentration may not provide enough vitamin D<sub>3</sub> or calcitriol to cause growth arrest or cell death of the melanoma cells.

It is important to understand that UVB must first initiate the formation of a melanoma cell before vitamin D<sub>3</sub> (converted to calcitriol inside melanoma cells) can have an effect on it. The presence of vitamin D<sub>3</sub> in the skin will not prevent the initiation of a melanoma cell; it can only affect it after the melanoma cell has formed. Vitamin D<sub>3</sub> only reduces the promotion of melanoma, not its initiation [16].

We now have to explain total accumulated sun exposure. Scientists examined the relationship between total accumulated sun exposure and the incidence of melanoma from 1969 to 1990. Only two out of 14 scientific studies found a significant positive association between outdoor solar UVR exposure and the incidence of melanoma [89,90]. Seven of 14 (50%) case-controlled studies found no association at all [50,81,91–95] and, quite remarkably, five studies found a negative correlation [95–100]. Furthermore, outdoor workers get more solar exposure than indoor workers get, but have a lower incidence of CMM [10,11]. Thus, intense overexposure to solar radiation can initiate CMM, but unlike SCC, CMM is not dependent on cumulative UV exposure. In fact, continuous, rather than intermittent, exposure may reduce the risk for getting CMM, as demonstrated by the lower incidence in outdoor workers [9–11].

We can best understand latitude variation in CMM as opposing gradients of initiation decreasing and promotion increasing toward the Earth's poles. The incidence of melanoma has a much flatter latitudinal gradient than SCC or Basal cell carcinoma (BCC; [101]). For example, from latitudes <29°S to >37°S in Australia, SCC, which is dependent on cumulative UVR exposures, increases 9-fold and BCC increases 4.2-fold, while melanoma only increases 2-fold [102,103]. UVB changes much more dramatically than UVA with latitude, altitude, and solar zenith angle, i.e., season

and time of day. For example, the northernmost latitudes (>55°N < 80°N) have little UVB for more than half the year, while UVA is prevalent all year. Curiously, in the northern latitudinal countries of Europe, the incidence of CMM is higher than in the Mediterranean latitudinal countries [104]. In fact, the latitudinal gradient reverses at higher latitudes in Europe, with Scandinavian countries having a higher incidence than even mid-latitude countries [105; we confirm these findings, unpublished results]. These findings support a role for UVA promoting CMM because many Scandinavian people in upper pay-scale occupations go to the Mediterranean for vacations, where they can get intense, intermittent UVB exposure and sunburns that initiate melanoma, and then return to their country to reduce their cutaneous levels of vitamin D<sub>3</sub> and get UVA mutations that promote melanoma. The lack of UVB, and consequently lower levels of vitamin D<sub>3</sub> in populations that live at higher latitudes, supports our vitamin D<sub>3</sub> “roller coaster” hypothesis as well. For if solar UVB overexposures were completely responsible for the increases in CMM, then the reverse latitudinal situation would be true; evidently, it is not, and this fact suggests that at extreme northern latitudes the effect of UVA exposures and insufficient cutaneous vitamin D levels predominates.

The prevalence of CMM in higher socio-economic and white-collar occupations [106] may be because they can afford extended vacations at lower latitudes, increasing their probability of intermittent overexposures and sunburns. They also tend to have offices with windows rather than cubicles and they have corner offices with twice as many windows as other employees.

Finally, several studies found seasonal variation in CMM [107,108]. The diagnostic incidence peaks in the summer months around July and troughs in the winter months around February. The investigations ruled out increased visibility during the spring and summer months due to less clothing and more visible skin and, instead, concluded the seasonal variation was due in part to relatively recent Sunlight exposures. This data also fits our hypothesis because sunburns and overexposures during the summer months that initiate CMM can then be promoted by increased UVA window exposures and decreased cutaneous vitamin D<sub>3</sub> levels during the winter months, allowing CMM to multiply and reach a visible size for diagnosis in the spring and especially during the summer months only a year after being initiated.

Thus, when humankind went against evolution by working indoors during the day and created an artificial barrier (window glass) dividing UVB from UVA in their outdoor and indoor environments, respectively, they inadvertently increased their incidence of CMM.

### Implications and further testing of hypothesis

Ironically, some exposure to UVB may be important for protection against the promotion of CMM because vitamin D<sub>3</sub> is produced in the skin and converted by melanoma cells to 1,25-dihydroxyvitamin D<sub>3</sub> or calcitriol. Calcitriol then binds the VDR signaling for growth inhibition or cell death. Although dietary supplements of vitamin D (primarily vitamin D<sub>2</sub> or ergosterol from plants) reduce the occurrence of rickets, there is no current evidence showing that it can help with all human vitamin D requirements. The seemingly paradoxical fact that outdoor workers get fewer melanomas than indoor workers get, in the absence of any other data, suggests that insufficiently maintained levels of vitamin D<sub>3</sub> in the skin and indoor solar UVA exposures play a role in promoting CMM. Therefore, if vitamin D<sub>3</sub> is present in high enough concentrations in the skin and the VDR receptor is fully functional in melanoma cells, growth arrest, cell cycle arrest, and repair of DNA damage or apoptotic cell death can occur reducing the incidence of CMM. Thus, we propose that along with decreased levels of cutaneous vitamin D<sub>3</sub>, UVA exposures, which can promote tumor formation and inci-

dence, cause DNA mutations, and break down vitamin D<sub>3</sub>, can together significantly promote melanoma.

A melanoma mouse model could be used with topical vitamin D<sub>3</sub> compared to oral vitamin D<sub>3</sub> and only UVA and only UVB and UVB and UVA exposures and in combination with vitamin D<sub>3</sub> or calcitriol to determine how much vitamin D<sub>3</sub> or UVA and both together contribute toward CMM. Another approach could be epidemiological in nature where population exposures to UVB alone (UVB detector) and UVA alone (UVA detector) and together (UVR) to determine the amount of indoor UVA exposure compared to Sun exposure along with monitoring cutaneous and blood levels of vitamin D<sub>3</sub> in populations of indoor and outdoor workers over time with follow up of CMM incidence. Another approach in combination with UV window filters, would be the topical and/or oral application of calcitriol and/or vitamin D<sub>3</sub> on different groups of XP patients to compare their incidence through life with previous patient cohorts that were not given topical or oral calcitriol or vitamin D<sub>3</sub> to see if either form or either route of administration can significantly decrease their incidence of melanoma. Another approach would be to use UV filters on all windows in buildings and cars to see if the incidence of CMM levels off or begins to decrease after 20–30 years in the overall fair-skinned population. However, if the latency period for CMM is shorter than suspected, as suggested by the seasonal diagnostic observations, the leveling off and decrease in the incidence may occur in less than 10 years.

### Acknowledgments

The authors would like to thank Professor J.C. van der Leun for calculating the UVA t<sub>50</sub> values in mice, Sergio G. Coelho for taking the spectroradiometer readings, and Drs. Michael F. Holick and Kenneth Kraemer for critically reviewing this manuscript prior to submission.

### References

- [1] Godar DE. UV doses worldwide. *Photochem Photobiol* 2005;81:736–49.
- [2] Thieden E, Philipsen PA, Heydenreich J, Wulf HC. UV radiation exposure related to age, sex, occupation, and sun behavior based on time-stamped personal dosimeter readings. *Arch Dermatol* 2004;140:197–203.
- [3] Slaper H. Skin cancer and UV exposure: investigations on the estimation of risks. PhD dissertation, University of Utrecht; 1987. p. 24–48 [chapter 2].
- [4] Godar DE, Wengraitis SP, Shreffler J, Sliney DH. UV doses of Americans. *Photochem Photobiol* 2001;73:621–9.
- [5] Godar DE. UV doses of American children and adolescents. *Photochem Photobiol* 2001;74:787–93.
- [6] Godar DE, Urbach F, Gasparro FP, van der Leun JC. UV doses of young adults. *Photochem Photobiol* 2003;77:453–7.
- [7] Rigel DS, Friedman RJ, Kopf AW. The incidence of malignant melanoma in the United States: issues as we approach the 21st century. *J Am Acad Dermatol* 1996;34:839–47.
- [8] Rigel DS, Carucci JA. Malignant melanoma: prevention, early detection, and treatment in the 21st century. *CA-Cancer J Clin* 2000;50:215–36.
- [9] Lee JAH. Melanoma and exposure to sunlight. *Epidemiol Rev* 1982;4:110–36.
- [10] Vagero D, Ringback G, Kiveranta H. Melanoma and other tumors of the skin among office, other indoor, and outdoor workers in Sweden 1961–1979. *Brit J Cancer* 1986;53:507–12.
- [11] Kennedy C, Bajdik CD, Willemze R, De Gruij FR, Bouwes Bavinck JN. The influence of painful sunburns and lifetime sun exposure on the risk of actinic keratoses, seborrheic warts, melanocytic nevi, atypical nevi, and skin cancer. *J Invest Dermatol* 2003;120:1087–93.
- [12] Holick MF, MacLaughlin JA, Clark MB, Holick SA, Potts Jr JT, Anderson RR, et al. Photosynthesis of pre-vitamin D<sub>3</sub> in human skin and the physiological consequences. *Science* 1980;210:203–5.
- [13] Holick MF. Skin: site of the synthesis of vitamin D and a target tissue for the active form, 1,25-dihydroxyvitamin D<sub>3</sub>. *Ann NY Acad Sci* 1988;548:14–26.
- [14] Seifert M, Diesel B, Meese E, Tilgen W, Reichrath J. Expression of 25-hydroxyvitamin D-1alpha-hydroxylase in malignant melanoma: implications for growth control via local synthesis of 1,25(OH)D and detection of multiple splice variants. *Exp Dermatol* 2005;14:153–4.
- [15] Lehman B, Pietzsch J, Kampf A, Meurer M. Human keratinocyte line HaCaT metabolizes 1α-hydroxyvitamin D<sub>3</sub> and vitamin D<sub>3</sub> to 1α,25-dihydroxyvitamin D<sub>3</sub> (calcitriol). *J Dermatol Sci* 1998;18:118–27.
- [16] McGuire TF, Trump DL, Johnson CS. Vitamin D<sub>3</sub>-induced apoptosis of murine squamous cell carcinoma cells. *J Biol Chem* 2001;276:26365–73.

- [17] Danielsson C, Fehsel K, Polly P, Carlberg C. Differential apoptotic response of human melanoma cells to  $1\alpha,25$ -dihydroxyvitamin D<sub>3</sub> and its analogues. *Cell Death Differ* 1998;5:946–51.
- [18] Chida K, Hashiba H, Fukushima M, Suda T, Kuroki T. Inhibition of tumor promotion in mouse skin by 1 alpha, 25-dihydroxyvitamin D<sub>3</sub>. *J Cancer Res* 1985;45:5426–30.
- [19] Eisman JA, Barkla DH, Tutton PJ. Suppression of in vivo growth of human cancer solid tumor xenografts by 1,25-dihydroxyvitamin D<sub>3</sub>. *Cancer Res* 1987;47:21–5.
- [20] Colston K, Colston MJ, Feldman D. 1, 25-dihydroxyvitamin D<sub>3</sub> and malignant melanoma: the presence of receptors and inhibition of cell growth in culture. *Endocrinology* 1981;108:1083–6.
- [21] Frampton RJ, Omond SA, Eisman JA. Inhibition of human cancer growth by 1, 25-dihydroxyvitamin D<sub>3</sub> metabolites. *Cancer Res* 1983;43:4443–7.
- [22] Evans SR, Houghton AM, Schumaker L, Brenner RV, Buras RR, Davoodi F, et al. Vitamin D receptor and growth inhibition by 1, 25-dihydroxyvitamin D<sub>3</sub> in human malignant melanoma cell lines. *J Surg Res* 1996;61:127–33.
- [23] Sauer B, Ruwisch L, Kleuser B. Antiapoptotic action of  $1\alpha, 25$ -dihydroxyvitamin D<sub>3</sub> in primary human melanocytes. *Melanoma Res* 2003;13:339–47.
- [24] Minghetti PP, Norman AW. 1, 25(OH)<sub>2</sub>-vitamin D<sub>3</sub> receptors: gene regulation and genetic circuitry. *FASEB J* 1988;2:3043–53.
- [25] Ainsleigh GH. Beneficial effects of Sun exposure on cancer mortality. *Prev Med* 1993;22:132–40.
- [26] Studzinski GP, Moore DC. Sunlight - Can it prevent as well as cause cancer? *Cancer Res* 1995;55:4014–22.
- [27] Wang QM, Jones JB, Studzinski GP. Cyclin-dependent kinase inhibitor p27 as a mediator of the G1-S phase block induced by 1, 25-dihydroxyvitamin D<sub>3</sub> in HL-60 cells. *Cancer Res* 1996;56:264–7.
- [28] Wong G, Gupta R, Dixon KM, Deo SS, Choong SM, Halliday GM, et al. 1, 25-dihydroxyvitamin D and three low-calcemic analogs decrease UV-induced DNA damage via the rapid response pathway. *J Steroid Biochem Mol Biol* 2004;89–90:567–70.
- [29] Mizushima Y, Xu X, Murakami C, Okano T, Takemura M, Yoshida H, et al. Selective inhibition of Mammalian DNA polymerase alpha by Vitamin D<sub>2</sub> and D<sub>3</sub>. *J Pharmacol Sci* 2003;92:283–90.
- [30] May E, Asadullah K, Zugel U. Immunoregulation through 1, 25-dihydroxyvitamin D<sub>3</sub> and its analogs. *Curr Drug Targets Inflamm Allergy* 2004;3:377–93.
- [31] Rigby WFC. The immunobiology of vitamin D. *Immunol Today* 1988;9:54–8.
- [32] Yang S, Smith C, DeLuca HF. 1  $\alpha, 25$ -dihydroxyvitamin D<sub>3</sub> and 19-nor-1  $\alpha, 25$ -dihydroxyvitamin D<sub>3</sub> suppress immunoglobulin production and thymic lymphocyte proliferation in vivo. *Biochem Biophys Acta* 1993;1158:279–86.
- [33] Yang S, Smith C, Prah J, Luo X, DeLuca HF. Vitamin D deficiency suppresses cell-mediated immunity in vivo. *Arch Biochem Biophys Acta* 1993;303:98–106.
- [34] Webb AR, B.R. deCosta, M.F. Holick. Sunlight regulates the cutaneous production of vitamin D<sub>3</sub> by causing its photodegradation. *J Clin Endocr Metab* 1989;68:882–7.
- [35] Parrish JA, Anderson RR, Urbach F, Pitts D. Optical properties of the skin and eye. In: Parrish JA, Anderson RR, Urbach F, Pitts D, editors. UV-A: biological effects of ultraviolet radiation with special emphasis on human responses to long-wave ultraviolet. New York: Plenum press; 1978. p. 59–83.
- [36] Tyrrell RM, Keyse SM. The interaction of UVA radiation with cultured cells. *J Photochem Photobiol* 1990;4B:349–61.
- [37] Godar DE, Thomas DP, Miller SA, Lee W. Long-wavelength UVA radiation induces oxidative stress, cytoskeletal damage and hemolysis. *Photochem Photobiol* 1993;57:1018–26.
- [38] Godar DE. Light and death: photons and apoptosis. *J Invest Dermatol Symp Proc* 1999;4:17–23.
- [39] Godar DE. Singlet oxygen-triggered immediate preprogrammed apoptosis. *Meths Enz* 2000;319:309–30.
- [40] Godar DE, Swicord ML. Studies on the mechanism of UVA1-induced hemolysis. In: Holick MF, Kligman AM, editors. Biologic effects of light. New York: Walter de Gruyter; 1992. p. 349–53.
- [41] Godar DE, Beer JZ. UVA1-induced nuclear damage in mammalian cells. In: Urbach F, editor. Biological responses to UV-A. Overland Park, Kansas: Valdenmar Publishing Co.; 1992. p. 65–73.
- [42] Godar DE, Swicord ML, Kligman LH. Photoaging. In: Schopka H-J, Steinmetz M, editors. Environmental UV radiation and health effects. Munich-Neuherberg: BfS-ISH-Berichte; 1995. p. 123–31.
- [43] Peak JG, Peak MJ. Comparison of initial yields of DNA-to-protein crosslinks and single-strand breaks induced in cultured human cells by far- and near-ultraviolet light, blue light and X-rays. *Mutat Res* 1991;246:187–91.
- [44] Jones CA, Huberman E, Cunningham ML, Peak MJ. Mutagenesis and cytotoxicity in human epithelial cells by far- and near-ultraviolet radiations: action spectrum. *Radiat Res* 1987;110:244–54.
- [45] Halliday GM, Agar NS, Barnetson RS, Ananthaswamy HN, Jones AM. UV-A fingerprint mutations in human skin cancer. *Photochem Photobiol* 2005;81:3–8.
- [46] Sterenborg HJ, van der Leun JC. Tumorigenesis by a long wavelength UV-A source. *Photochem Photobiol* 1990;51:325–30.
- [47] Kligman LH, Crosby MJ, Miller SA, Hitchens VM, Beer JZ. Carcinogenesis by long wavelength UV-A and failure of reciprocity. In: Urbach F, editor. Biological responses to UV-A. Overland Park, Kansas: Valdenmar Publishing Co.; 1992. p. 65–73.
- [48] Ley RD. Ultraviolet radiation A-induced precursors of cutaneous melanoma in *Monodelphis domestica*. *Cancer Res* 1997;57:3682–4.
- [49] Staberg B, Wulf HC, Poulson T, Klemp P, Brodhagen H. Carcinogenic effect of sequential artificial sunlight and UV-A irradiation in hairless mice. *Arch Dermatol* 1983;119:641–3.
- [50] Elwood JM, Gallagher RP, Hill GB, Pearson JCG. Cutaneous melanoma in relation to intermittent and constant sun exposure - The Western Canada melanoma study. *Br J Cancer* 1985;35:427–33.
- [51] Wood AW, Chang RL, Huang MT, Uskokovic M, Conney AH. 1 alpha, 25-dihydroxyvitamin D<sub>3</sub> inhibits phorbol ester-dependent chemical carcinogenesis in mouse skin. *Biochem Biophys Res Commun* 1983;116:605–11.
- [52] Yudoh K, Matsuno H, Kimura T. 1-alpha, 25-dihydroxyvitamin D<sub>3</sub> inhibits in vitro invasiveness through the extracellular matrix and in vivo pulmonary metastasis of B16 mouse melanoma. *J Lab Clin Med* 1999;133:120–8.
- [53] Wolf P, Donawho CK, Kripke ML. Effect of sunscreens on UV radiation-induced enhancement of melanoma growth in mice. *J Natl Cancer Inst* 1994;86:99–105.
- [54] CIE Research Note. A reference action spectrum for ultraviolet induced erythema in human skin. *CIE J* 1987;6:17–22.
- [55] de Grijijl FR, van der Leun JC. Estimate of the wavelength dependency of ultraviolet carcinogenesis in humans and its relevance to the risk assessment of stratospheric ozone depletion. *Health Phys* 1994;67:314–25.
- [56] de Grijijl FR, Sterenborg HJ, Forbes PD, Daivies RE, Cole C, Kelfkens G, et al. Wavelength dependence of skin cancer induction by ultraviolet irradiation of albino hairless mice. *Cancer Res* 1993;53:53–60.
- [57] Setlow RB, Grist E, Thompson K, Woodhead AD. Wavelengths effective in induction of malignant melanoma. *Proc Natl Acad Sci* 1993;90:6666–70.
- [58] MacLaughlin JA, Anderson RR, Holick MF. Spectral character of sunlight modulates photosynthesis of previtamin D<sub>3</sub> and its photoisomers in human skin. *Science* 1982;216:1001–3.
- [59] Moehrl M, Soballa M, Korn M. UV exposure in cars. *Photodermatol Photoimmunol Photomed* 2003;19:175–81.
- [60] Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D<sub>3</sub>: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D<sub>3</sub> synthesis in human skin. *J Clin Endocrinol Metab* 1988;67:373–8.
- [61] Davie MWJ, Lawson DEM, Emberson C, Barnes JLC, Roberts GE, Barnes ND. Vitamin D from skin: contribution to vitamin D status compared with oral vitamin D in normal and anticonvulsant-treated subjects. *Clinical Sci* 1982;63:461–72.
- [62] Cornwell ML, Comstock GW, Holick MF, Bush TL. Prediagnostic serum levels of 1, 25-dihydroxyvitamin D and malignant melanoma. *Photodermatol Photoimmunol Photomed* 1992;9:109–12.
- [63] Autier P, Dore JF, Schifflers E, Cesarini JP, Bollaerts A, Koelmel KF, et al. Melanoma and use of sunscreens: an EORTC case-control study in Germany, Belgium and France. The EORTC Melanoma Cooperative Group. *Int J Cancer* 1995;61:749–55.
- [64] Matsuoka LY, Wortsman J, Hanifan N, Holick MF. Chronic sunscreen use decreases circulating concentrations of 25-hydroxyvitamin D. A preliminary study. *Arch Dermatol* 1988;124:1802–4.
- [65] Holly EA, Aston DA, Cress RD, Ahn DK, Kristiansen JJ. Cutaneous melanoma in women I. Exposure to sunlight, ability to tan, and other risk factors related to ultraviolet light. *Am J Epidemiol* 1995;141:923–33.
- [66] Kaskel P, Sandler S, Kron M, Kind P, Peter RU, Krahn G. Outdoor activities in childhood: a protective factor for cutaneous melanoma? Results of a case-control study in 271 matched pairs. *Br J Dermatol* 2001;145:602–9.
- [67] Pfahlberg A, Kolmel K-P, Gefeler O. Timing of excessive ultraviolet radiation and melanoma: epidemiology does not support the existence of a critical period of high susceptibility to solar ultraviolet radiation-induced melanoma. *Br J Dermatol* 2001;144:471–5.
- [68] Whiteman DC, Whiteman CA, Green AC. Childhood sun exposure as a risk factor for melanoma: a systematic review of epidemiologic studies. *Cancer Causes Control* 2001;12:69–82.
- [69] Berwick M, Armstrong BK, Ben-Porat L, Fine J, Kricaker A, Eberle C, et al. Sun exposure and mortality from melanoma. *JNCI* 2005;97:195–9.
- [70] Hutchinson PE, Osborne JE, Lear JT, Smith AG, Bowers PW, Morris PN, et al. Vitamin D receptor polymorphisms are associated with altered prognosis in patients with malignant melanoma. *Clin Cancer Res* 2000;6:498–504.
- [71] ASTM Subcommittee G03.09. ASTM G173-03 Standard Tables for reference solar spectral irradiance direct normal and hemispherical on 37° tilted surface. Annual book of ASTM standards, vol. 14.04. ASTM International; 2003.
- [72] <<http://www.viracon.com>>
- [73] de Laat A, van der Leun JC, de Grijijl FR. Carcinogenesis induced by UVA (365–nm) radiation: the dose-time dependence of tumor formation in hairless mice. *Carcinogenesis* 1997;18:1013–20.
- [74] Ley RD, Applegate LA, Padilla RS, Stuart TD. Ultraviolet radiation-induced malignant melanoma in *Monodelphis domestica*. *Photochem Photobiol* 1989;50:1–5.
- [75] Roy NK, Rossman TG. Mutagenesis and co-mutagenesis by lead compounds. *Mutation Res* 1992;298:97–103.
- [76] <[http://inventors.about.com/library/inventors/bl\\_fluorescent.htm](http://inventors.about.com/library/inventors/bl_fluorescent.htm)>
- [77] Miller SA, Hamilton SL, Wester UG, Cyr WH. An analysis of UVA emissions from sunlamps and the potential importance for melanoma. *Photochem Photobiol* 1998;68:63–70.

- [78] <<http://www.glasslinks.com/newsinfo/histppg.htm>>
- [79] <<http://www.inventors.about.com/library/inventors/blskyscapers.htm>>
- [80] Elwood JM, Williamson C, Stapleton PJ. Malignant melanoma in relation to moles, pigmentation, and exposure to fluorescent and other lighting sources. *Br J Cancer* 1986;53:65–74.
- [81] Beral V, Robinson N. The relationship of malignant melanoma, basal and squamous skin cancers to indoor and outdoor work. *Br J Cancer* 1981;44:886–91.
- [82] Beral V, Evans S, Milton G. Malignant melanoma and exposure to fluorescent lighting at work. *Lancet* 1982;2(8293):290–3.
- [83] Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr* 2004;80:1678S–88S.
- [84] Elwood JM, Gallagher RP. Body site distribution of cutaneous malignant melanoma in relationship to patterns of sun exposure. *Int J Cancer* 1998;78:276–80.
- [85] Kraemer KH, Lee M-M, Andrews AD, Lambert WC. The role of sunlight and DNA repair in melanoma and nonmelanoma skin cancer. *Arch Dermatol* 1994;130:1018–21.
- [86] Salih FM. Effect of clothing varieties on solar photosynthesis of vitamin D<sub>3</sub>: an in vitro study. *Photodermatol Photoimmunol Photomed* 2004;20:53–8.
- [87] Matsuoka LY, Wortsman J, Dannenberg MJ, Hollis BW, Lu Z, Holick MF. Clothing prevents ultraviolet-B radiation-dependent photosynthesis of vitamin D<sub>3</sub>. *J Clin Endocrinol Metab* 1992;75:1099–103.
- [88] Sollitto RB, Kraemer KH, DiGiovanna JJ. Normal vitamin D levels can be maintained despite rigorous photoprotection: six years' experience with xeroderma pigmentosum. *J Am Acad Dermatol* 1997;37:942–7.
- [89] Gellin GA, Kopf AW, Garfinkel L. Malignant melanoma. A case controlled study of possibly associated factors. *Arch Dermatol* 1969;99:43–8.
- [90] Grob JJ, Gouvernet J, Aymar D, Mostaque A, Romana MH, Collet AM, et al. Count of benign melanocytic nevi as a major indicator of risk of nonfamilial nodular and superficial spreading melanoma. *Cancer* 1990;66:386–95.
- [91] Klepp O, Magnus K. Some environmental and bodily characteristics of melanoma patients. A case-control study. *Int J Cancer* 1979;23:482–6.
- [92] Green A. Sun exposure and the risk of melanoma. *Australian J Dermatol* 1984;25:99–102.
- [93] Green A, Bain C, McLennan R, Siskind V. Recent results in Cancer Research. *Cancer Res* 1986;102:76–97.
- [94] Cristofolini M, Franceschi S, Tasin L, Zumiani G, Piscoli F, Talamini R, et al. Risk factors for cutaneous malignant melanoma in a northern Italian population. *Int J Cancer* 1987;39:150–4.
- [95] Holly EA, Kelly JW, Shpall SN, Shu-Hui Chiu MS. Number of melanocytic nevi as a major risk factor for malignant melanoma. *J Am Acad Dermatol* 1987;17:459–68.
- [96] Mackie RM, Aitchison T. Severe sunburn and subsequent risk of primary cutaneous malignant melanoma in Scotland. *Br J Cancer* 1982;46:955–60.
- [97] Graham S, Marshall J, Haughey B, Stoll H, Zielieny M, Brasure J, et al. An inquiry into the epidemiology of melanoma. *Am J Epidemiol* 1985;122:606–19.
- [98] Holman CDJ, Armstrong BK, Heenan PJ. Relationship of cutaneous malignant melanoma to individual sunlight exposure habits. *J Int Cancer Inst* 1986;76:403–13.
- [99] Osterlind A, Tucker MA, Stone BJ, Jensen OM. The Danish case-control study of cutaneous malignant melanoma: II. The importance of UV-light exposure. *Int J Cancer* 1988;42:319–24.
- [100] Beitiner H, Norel SE, Ringborg U, Wennersten G, Mattson B. Malignant melanoma: aetiological importance of individual pigmentation and sun exposure. *Br J Dermatol* 1990;122:43–51.
- [101] Moan J, Dahlback A, Setlow RB. Epidemiological support for an hypothesis for melanoma induction indicating a role for UVA radiation. *Photochem Photobiol* 1999;70:243–7.
- [102] Marks R, Staples M, Giles GG. Trends in non-melanocytic skin cancer treated in Australia: the second national survey. *Int J Cancer* 1993;53:585–90.
- [103] Barton IJ, Partridge GW. The Australian climatology biologically effective ultraviolet radiation. *Australian J Dermatol* 1979;20:68–74.
- [104] Diffey BL. Solar ultraviolet radiation effects on biological systems. *Phys Med Biol* 1991;36:299–328.
- [105] Crombie IK. Variation of melanoma incidence with latitude in North America and Europe. *Br J Cancer* 1979;40:774–81.
- [106] Pion IA, Rigel DS, Garfinkel L, Silverman MK, Kopf AW. Occupation and the risk of malignant melanoma. *Cancer* 1995;75:637–44.
- [107] Schwartz SM, Armstrong BK, Weiss NS. Seasonal variation in the incidence of cutaneous malignant melanoma: an analysis by body site and histologic type. *Am J Epidemiol* 1987;126:104–11.
- [108] Braun MM, Tucker MA, Devesa SS, Hoover RN. Seasonal variation in frequency of diagnosis of cutaneous malignant melanoma. *Melanoma Res* 1994;4:235–41.