Epidemiological evidence that UVA radiation is involved in the genesis of cutaneous melanoma
Philippe Autier\textsuperscript{a}, Jean-François Dore\textsuperscript{b}, Alexander M.M. Eggermont\textsuperscript{c} and Jan W. Coebergh\textsuperscript{d,e}

\textsuperscript{a}Department of Epidemiology and Biostatistics, International Prevention Research Institute (IPRI), \textsuperscript{b}INSERM U 590, Lyon, \textsuperscript{c}Cancer Institute Gustave Roussy, Villejuif, France, \textsuperscript{d}Department of Public Health, Erasmus University MC, Rotterdam and \textsuperscript{e}South Netherlands Cancer Registry, Comprehensive Cancer Centre South, Eindhoven, The Netherlands

Correspondence to Dr Philippe Autier, International Prevention Research Institute (IPRI), Cours Lafayette 95, F-69006 Lyon Cedex 08, France
E-mail: philippe.autier@i-pri.fr

Current Opinion in Oncology 2011, 23:000–000

Purpose of review
Epidemiological data have contributed to the classification in 2009 of the full ultraviolet (UV) radiation spectrum as carcinogenic to humans. We reviewed the epidemiological evidence that UVA could be involved in the genesis of cutaneous melanoma.

Recent findings
Use of artificial UV tanning devices (sunbeds) consists mainly of repeated exposure to high UVA doses. Epidemiological studies published over the last years confirmed the association between sunbed use and melanoma. Sunbed use is the most probable cause of an epidemic of melanoma that took place in Iceland from 1990 to 2006. The four-fold increase in melanoma incidence was not followed by an increase in melanoma mortality. Sunscreens were primarily devised for the prevention of sunburn, and UVB is the wavelength causing most sunburns. All observational studies and randomized trials show that sunscreen use may extend sun exposure intended for getting a tan, while it does not necessarily decrease sunburn occurrence. Sunscreen use for tan acquisition would thus lead to similar exposure to UVB and greater exposure to UVA, which could explain the slightly higher melanoma risk often found among sunscreen users.

Summary
UVA could be involved in the occurrence of non-life-threatening melanoma. The increasing use of sunbeds and of sunscreens may partly explain why melanoma incidence increases in most light-skinned populations without concomitant increase in mortality.

Keywords
indoor tanning, melanoma, sunscreens, ultraviolet radiation

Introduction
The burden of melanoma is still rising in most light-skinned populations. There is now a large body of scientific evidence that the ultraviolet (UV) wavelength is the main environmental cause of skin cancer, including melanoma. In 2009, the International Agency for research on cancer classified the full UV spectrum [including the UVA (>315–400 nm), UVB (>280 to 315 nm) and UVC (200–280 nm)], as well as artificial UV tanning devices (sunbeds) as carcinogenic to humans (group 1 carcinogens) \cite{1}. In support of this classification, the full sequencing of the genome of a malignant melanoma showed that the dominant mutational signature in melanoma cells reflects DNA damage due to UV light exposure \cite{2}. However, the UV-induced biological mechanisms critical for initiating the development of this potentially life-threatening cancer are still largely unknown.

The UV radiation reaching the Earth’s surface is composed of 2–10% UVB and of 90–98% UVA. By the end of the 1980s, the carcinogenic properties of UVB were already well documented and it was recognized as the main environmental factor involved in squamous cell carcinoma (SCC) \cite{3}. Basic research data have accumulated over the recent years on the capacity of UVA to induce DNA mutations and affect DNA repair, immune function, cell integrity, cell cycle regulation, and other critical biological functions (e.g., \cite{4–6,7}). These studies showed that the carcinogenic mechanisms of UVA and UVB differ but sometimes overlap.

Despite basic research findings, animal experiments failed to show that irradiation with UVA could trigger a tumour resembling a human nevus or melanoma (reviewed in \cite{8}). An experiment on Xiphophorus fish by Setlow et al \cite{9} showed that UVA was
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as effective as UVB in triggering nonmetastasizing melanomas in the fish. This unique experiment has fuelled the UVA/UVB controversy during nearly two decades. In 2009, the same experiment was repeated, using a much larger number of Xiphophorus fish in stringently controlled experimental conditions [10]. It showed no impact of UVA on melanoma development in the fish.

The overall concern regarding these experiments is to establish how their results apply to humans. The bare human skin is very different from rodent skin and laboratory experiments cannot reproduce the complex human sun behaviours.

Epidemiological data have contributed to the IARC classification of the full UV range and of artificial UV devices as carcinogenic to humans. In this paper, we review the evidence provided by epidemiological studies that UVA can be involved in the genesis of cutaneous melanoma. We also present a hypothesis as to the type of melanoma induced by UVA, and how this hypothesis may explain epidemiological features of this cancer.

Sunbed use is associated with melanoma occurrence

The majority of modern canopy-like UV-tanning units are equipped with low-pressure fluorescent lamps with a spectrum mainly emitting in the UVA range plus some UVB (which is necessary for inducing a deep long-lasting tan). High-pressure lamps producing large quantities of long-wave UVA (>335–400 nm) per unit of time are also marketed. Sunbeds deliver UVA dosages that are 5–15 times higher than what is delivered by the summer mid-day sun on a Mediterranean beach. Compared with the summer midday sunlight, these machines emit much higher fluxes of UVA and lower fluxes of UVB.

Observational studies

Observational studies from 1994 to 2005 have documented that exposure of sun-susceptible individuals to sunbed can trigger melanoma, mainly when this exposure started before 30 years of age [11**,12]. Epidemiological data published after the IARC report of 2006 [11**] further documented the links between artificial UV tanning and melanoma. They included three large case–control studies in the USA [13*,14,15], the prospective U.S. Nurse’s Health Study [16] and the confirmation of previous results of the Norwegian–Swedish cohort study [17**]. Even in Australia where sunshine is abundant, a case–control study organized within the Australian Melanoma Family Study found sunbed use to be associated with increased risk of early-onset melanoma [18].

The melanoma epidemic in Iceland

A few years ago, we predicted that melanomas associated with solarium use would be preferentially localized to anatomic sites that are usually only intermittently sun exposed such as the trunk [19]. This phenomenon should be mainly noticeable among women because sunbed use allows unrestricted UV exposure of the trunk. Iceland is a Nordic country situated at 64–66° north latitude where bright, sunny days are rare. In a collaborative work with the Iceland Cancer Registry and Icelandic dermatologists, we described an epidemic of melanoma starting in 1995 [20**]. Before 1995, the melanoma incidence in Iceland was lower than in Denmark and Sweden (Fig. 1) [21]. In the 1990s, it started to rise steeply and after 2000, it surpassed the incidence in other Nordic countries. This phenomenon was mainly noticeable among women. A particular feature of this epidemic was that it mainly concerned melanoma occurring on
the trunk of women under the age of 50. Around the year 2000, the incidence of trunk melanoma in women had surpassed the incidence of lower limb melanoma (Fig. 2). This latter aspect was in sharp contrast with the usual observations prior to 1995 whereby the greatest increase in melanoma incidence in women occurred on lower limbs [22].

Our investigation concluded that the only plausible explanation for this epidemic was the massive exposure of Icelandic youths to artificial tanning devices after 1985 [23]. The decrease in incidence after 2001 in women and 2004 in men (Fig. 1) is most probably due to campaigns initiated by the Icelandic health services at the end of the 1990s to discourage sunbed use.

**Sunbed use and recent changes in melanoma incidence in women**

The Icelandic data are not a unique story. In the UK and the USA, rebounds of increase of melanoma incidence from 1998 onwards have been reported for women 20–39 years old [24,25], possibly due to the spread of the indoor tanning fashion. In Northern Ireland and Scotland, the UK areas where sunbed use is most prevalent [26], the highest increase in incidence rates was observed on the female trunk [27,28]. In the USA, after 1996, trunk melanomas among younger women are increasing relative to all other anatomic body sites [29]. Sunbed use has been popular in Sweden since the beginning of the 1980s. Over the last 20 years, the incidence of trunk melanoma in Swedish women has caught up the incidence of lower limb melanoma [30].

**Sunscreen use during intentional sun exposure may increase the risk of melanoma**

Sunscreens have the ability to prevent sunburn occurrence, and the higher the sun protection factor (SPF) of a sunscreen, the greater the protection against sunburns. Modern sunscreens contain both organic filters and mineral oxides and may hence also filter a variable proportion of UVA, but SPF is a UVB-dependent characteristic since this wavelength is one thousand times more efficient than UVA for triggering sunburn. Because of the known association between sunburn and melanoma, it was believed that prevention of sunburns through sunscreen use would also prevent melanoma.

**The sunscreen-melanoma quagmire**

Retrospective and prospective population-based epidemiological studies often found that sunscreen use during intentional sun exposure (ISE, i.e., sunscreen use for sunbathing or for allowing longer stays in the sun) increased the risk of melanoma or of high nevus count [31–33]. Various explanations, including residual confounding or bias by indication were proposed for these unexpected results, as well as the possibility that sunscreens would allow individuals with poor tanning ability to spend more time in the sun than otherwise possible [34].

**Randomized trials on sunscreen use and sun exposure duration**

In 1997 and 1998, two randomized controlled trials we conducted within the frame of the EORTC Melanoma Group showed that sunscreen use by young populations during their holidays in sunny resorts increased the
duration of sun exposure [35,36] (Table 1), a phenomenon likely to explain the association found between sunscreen use and melanoma risk. These trials contributed to the conclusion of the International Agency for Research on Cancer that ‘in intentional sun exposure situations, sunscreen use may conduct to increasing the risk of melanoma’ [32,33].

In addition to extended sun exposure duration, a plethora of other changes in sun exposure behaviours was observed in the two trials, further documenting that sunscreen use may allow sun exposure behaviours that would not be possible otherwise [37,38]. For example, the two randomized trials consistently showed that as a holiday progressed, populations using high SPF sunscreen tended to start sunbathing earlier in the day, while populations using a low SPF sunscreen tended to start sunbathing later in the afternoon (Fig. 3) [35,36]. During the day, UVA and UVB fluxes peak around solar noon but the solar spectrum in the morning and in the late afternoon is poor in UVB [3]. Sunbathing typically entails brisk exposure of the trunk to sunlight and trial results suggested that in the absence of sunscreen use, this usually sun protected site would not stand long exposure to UVB-rich sunlight.

Sunscreen use increases sun exposure duration and UVA

Table 1 summarizes the main results of the randomized trials on sunscreen use by suntan worshippers. The number of sunburns reported was similar for populations using low or high SPF sunscreens, while sun exposure duration was greater among high SPF sunscreen users. In support of results of these two trials, all observational studies and randomized trials studies that examined sun exposure duration in relation to sunscreen use found increased ISE and no change in sunburn occurrence [33,37].

The apparent paradox of sunscreen use not associated with decreasing sunburn occurrence suggests that during ISE, amounts of UVB reaching the skin are similar when a sunscreen is used or not. The only difference is that with sunscreen use, more time is needed to accrue the amount of UVB necessary to tan or to burn (to tan or to burn first depends on the skin phototype of sunscreen user). During that extra time of ISE, more unfiltered UV wavelength can pass through the sunscreen layer. These additional amounts of UV presumably mainly consist in UVA. Would presence of UVA filters in the sunscreen avoid the greater

<table>
<thead>
<tr>
<th>Trial outcome</th>
<th>Use of SPF 30 vs. SPF 10 sunscreen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantity of sunscreen used</td>
<td>Similar</td>
</tr>
<tr>
<td>Time spent in the sun during each day with sun exposure</td>
<td>Increased</td>
</tr>
<tr>
<td>Time in the day for sun exposure</td>
<td>More often around solar noon, when sunlight is richer in UVB</td>
</tr>
<tr>
<td>For women, sunbathing with naked breasts</td>
<td>Increased</td>
</tr>
<tr>
<td>Number of sunburns</td>
<td>Similar</td>
</tr>
<tr>
<td>Numbers of skin reddening episodes</td>
<td>Similar</td>
</tr>
</tbody>
</table>

SPF, sun protection factor. Data from [35,36].

Figure 3 Hour of start of sunbathing activities

Mean hour of start of sunbathing activities in days with sunbathing. Days without sunbathing were skipped. The time in the figure is the so-called ‘summer hour’ in Continental Europe, equivalent to the solar hour plus 2 h. Adapted with permission from [36].
UVA exposure? Probably not if the goal of sunscreen use is to acquire a tan or to stay long in the sun, as tan acquisition is the signature that UV-induced DNA damage occurred [39].

Figure 4 illustrates the relationships between sunscreen use, UVB, sun exposure duration, sunburns and UVA in sun-sensitive populations. Figure 4 assumes that the sunscreen has no ability to block the UVA, and that sun exposure is (definitely or temporally) discontinued after sunburn occurrence. When no sunscreen is used, populations engaging in ISE (e.g., in sunbathing) will reach their specific sunburn threshold after \((x)\) minutes, \((x)\) depending on their inherited sun sensitivity. The UVB dose will thus be equivalent to sunburn threshold and the UVA dose to \((a)\). When a sunscreen is used, more time \([y = (a)]\) is needed for reaching sunburn threshold. During that extra time, an extra dose of UVA \([b/C0(a)\]

UVA has a greater ability than UVB to penetrate deep into the dermis and induce DNA damage in inner skin layers [40], which would explain the increased risk of higher nevus count and of melanoma associated with sunscreen use.

In conclusion, sunscreen use enables populations to withstand high UVB fluxes, which in turn probably leads to greater exposure to high UVA fluxes. This situation would be mainly true for the trunk, the body site typically intermittently exposed.

There are indications that sunbed-induced melanomas are less life threatening

The sunbed-induced melanoma epidemic we described in Iceland developed without concomitant increase in melanoma mortality. The steepest increases in melanoma incidence were observed in young subjects and for trunk melanoma. Trunk melanoma is known to be more dangerous than limb melanoma. However, Fig. 5 shows no appreciable change over time of melanoma mortality in Icelandic men and women, with rare cases of death before age 50.

Given the short-term poor prognosis of advanced melanoma and in view of the formidable increase in incidence that took place between 1990 and 2006, it is unclear why mortality remained stable at younger ages. Nonetheless, the contrast between incidence and mortality trends suggests that the rapid increase in incidence in the 1990s was confined to melanoma of limited capacity to disseminate in distant organs.

The first epidemic of melanoma was described in the Hunter District (New South Wales, Australia) in 1987–1992 [41]. The cause of this sudden rise in melanoma incidence remains unknown. Similarly to Iceland, the sharp rise in incidence did not affect melanoma mortality, and it was concluded that the epidemic mainly consisted of a nonmetastasizing form of melanoma [42].

Formulation of the ‘UVA-shift’ hypothesis

We view the results on sunbed and sunscreen studies as providing indirect evidence that UV wavelengths in the
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Figure 5 Annual age-adjusted (World Standard population) melanoma mortality rates in Iceland 1960–2006, by age group

Icelandic men

Icelandic women

From Nordcan database [21].

UVA range might be involved in the genesis of melanoma. Also, time between ‘UVA exposure’ and melanoma occurrence would be a few years. One possible hypothesis underlying a short lag time would be the stimulation, by repeated high UVA doses, of melanocytes in preexisting nevi that developed earlier during life.

The main limitation is that UV wavelength was rarely measured during epidemiological studies on sunbeds and sunscreens. Exposure data collected by epidemiological studies are thus by no means reflecting exposure to pure sources of UVA or UVB. However, these results can inform on the type of wavelength possibly involved in melanoma occurrence.

Melanoma incidence is still on the rise in most light-skinned populations, in particular in young women. In contrast, melanoma mortality stabilized in the 1980s and 1990s and even started to decrease slightly, mainly among younger female populations in the Nordic countries, Australia, UK and USA [27,43*,44–47]. The incidence rise was essentially due to thin melanoma less than 2 mm thickness. In contrast, the incidence of thick melanoma (i.e., 2 mm and more) has remained quite stable [27,43*,44,48*]. The epidemics in the Hunter district and in Iceland would represent extreme examples of the discrepancy between incidence and mortality.

We hypothesize that sunbed and sunscreen use would lead to a ‘UVA-shift’ in UV exposure that would contribute to increasing the number of thin invasive melanoma having little potential for distant dissemination. Sunbed use and sunscreen use are more common in younger age groups, predominantly in women. This hypothesis could partly explain why in most light-skinned populations less than 60 years of age, and in women in particular, melanoma incidence is still rising without a concomitant rise in mortality.

Conclusion

If the UVA hypothesis is grounded, the main question to be solved is the nature of deadly melanoma: do they have same risk factors as the thin, non-life-threatening melanoma? Which wavelength is involved in their occurrence? One clue may come from earlier studies on migrants. Melanoma mortality is greater for populations born in sunny areas than for those who migrated at later age [49]. Hence, probably deadly melanoma that occurs mainly in older ages would develop from melanocytes initiated during early life, whereas the major part of the rising incidence would be due to melanocytes exposed to high UVA doses during adolescence and adulthood that would take less time to develop into thin melanomas.

In conclusion, growing epidemiological evidence suggests that at least two different forms of melanoma exist, that would have different clinical course. ‘UVA-induced’ melanoma would be caused by intermittent exposure to high UVA doses. These melanomas would develop rapidly but usually, they would not be aggressive. The environmental causes of more aggressive melanoma, most of which occur in older ages, remain to be defined.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).


Genesis of cutaneous melanoma Auiter et al. 7


This IARC report is a comprehensive review of skin cancer issues associated with artificial UV tanning. The meta-analysis of epidemiological studies found a 75% (95% CI 35 – 126) increase in melanoma risk when sunbed use started before 30 years of age, as well as a higher risk for first exposure during a time, that is 10 – 20 years before the diagnosis of melanoma.


This large population-based case–control study included 1167 melanoma cases and 1101 controls 25 – 59 years of age. It could avoid major biases seen in more ancient studies using a case–control design.


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43 Linos E, Swetter SM, Cockburn MG, et al. Increasing burden of melanoma in the United States. J Invest Dermatol 2009; 129:1666–1674. This study is an in depth analysis of over 70,000 new cases of malignant melanoma registered in the U.S. SEER cancer registries, the largest such assessment to date. It suggests a continued rise in new cases of malignant melanoma in the United States that is not only due to greater skin screening. The increase in incidence is mainly due to melanoma less than 1 mm thickness and is found in all age groups. Melanoma mortality mainly concerns older populations while it tends to decrease in younger populations.


