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CANCER PREVENTION (J CUZICK, SECTION EDITOR)

# Sun Exposure, Sunbeds and Sunscreens and Melanoma. What Are the Controversies?

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**Abstract** The association between various measures of sun exposure and melanoma risk is quite complex to dissect as many case–control studies of melanoma included different subtypes of melanomas which are likely to be biologically different, so interpretation of the data is difficult. Screening bias in countries with high levels of sun exposure is also an issue. Now that progress is being made in the genetic subclassification of melanoma tumours, it is apparent that melanomas have different somatic changes according to body sites/histological subtypes and that UV exposure may be relevant for some but not all types of melanomas. Melanoma behaviour also points to non-sun-related risk factors, and complex gene–environment interactions are likely. As UV exposure is the only environmental factor ever linked to melanoma, it is still prudent to avoid excessive sun exposure and sunburn especially in poor tanners. However, the impact of strict sun avoidance, which should not be recommended, may take years to be apparent as vitamin D deficiency is a now a common health issue in Caucasian populations, with a significant impact on health in general.

**Keywords** Melanoma · Sun exposure · Sunbeds · DNA repair ·

## Sun Exposure

The link between sun exposure and melanoma has been studied for more than 50 years in epidemiological, migration and laboratory studies. The fact that fair-skinned individuals with poor tanning ability are more at risk of melanoma supports the role of UV exposure in the pathogenesis of melanoma. Skin types I and II have a twofold increased risk of melanoma compared with darker skin types III and IV [1, 19, 32]. Melanoma is also very rare in non-Caucasians and affects mainly the palms and soles when found in non-Caucasians, so melanocyte behaviour is greatly affected by ethnicity. Sun exposure measured as the number of weeks of holidays in sunny climates is also a risk factor, with relative risks on the order of 1.5–2 [1–3, 19, 32]. However, this association often disappears when adjustments are made for skin type, suggesting that host responses are important for melanoma rather than just the dose of UV radiation [2, 3]. In many studies, chronic sun exposure in outdoor workers appears to be protective for melanoma, so the relationship between melanoma and UV exposure is very complex [1–3, 19, 32]. Regarding sun-sensitive individuals, there are also possible non-UV-related risk factors which may explain why fair-skinned individuals are especially prone to melanoma. Melanoma like many other cancers is linked to body mass index (BMI), and there is evidence that pigmentation may explain some of the link between higher BMI and melanoma [4•, 5]. The *FTO* gene has also recently been linked to melanoma risk, and this may be mediated by a difference in pigmentation and BMI [6]. The agouti gene determining coat colour in mice (also important in human pigmentation) has long been linked to higher BMI in the mouse model, and recent results from genome-wide association studies have shown that many genes involved in pigmentation are also relevant for BMI [7]. The melanocortin pathways (from melanocortin 1 receptor to melanocortin 4 receptor) are also involved in immune responses and neuroendocrine functions, so one cannot assume that the link between fair skin and melanoma risk is explained by poor tanning ability alone; research is ongoing in this field [8, 9] .

Migration studies in the 1980s showed that the age of migration to Australia is crucial in determining melanoma risk in adulthood, and the critical age at migration appears to be 20 years, above which the risk of melanoma remains the same as

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that for the country of origin. A more recent study in Israel showed that 10 years was the critical age, after which subjects who migrated to Israel had a reduced risk of melanoma compared with Israeli-born subjects [10]. However, this was affected by the country of origin, with European ancestry conferring the highest risk of melanoma, so gene pools are obviously very important in determining melanoma risk [10]. This suggests that sun exposure in early life is especially detrimental for melanoma [11]. There are some potential biases in these studies. For migration studies when Australians and South Africans move to the UK for example, their acquired screening behaviour remains the same, with regular skin examinations compared with UK-born subjects, so this could inflate the incidence of early melanomas. These individuals are also likely to be more prone to photoageing with solar keratoses, basal cell carcinomas and squamous cell carcinomas, and therefore will often be under some form of dermatological follow-up with more removal of pigmented lesions. In contrast, migrants to Australia are more likely to adopt the screening behaviour of their fellow Australians the younger they are when they migrate. However, it is estimated that childhood sun exposure represents up to 40–50% of lifetime exposure and the skin may be particularly sensitive to the harmful effects of UV radiation in children, so the need to protect children remains important. The number of naevi is mainly determined by genetic factors as shown by studies of twins both in the UK and in Australia [12–14], but may also be induced by sun exposure in childhood as naevus counts are higher in both children and adults when Australia is compared with the UK using the same naevus count protocol [15, 16, 33]. However, when the types of naevi found in excess in countries with high UV exposure are examined, they appear to be small junctional naevi on sun-exposed sites, whereas atypical naevi usually found on the trunk are more genetically determined [15–17, 33]. The relative risks for melanoma associated with naevi are also consistent across all Caucasian populations and are of the same magnitude, so genetic factors are important drivers for the naevi–melanoma association [18, 19]. Melanoma incidence in children also appears to increase with decreasing latitude, but again the effect of screening and the inclusion of melanoma in situ in some of these studies may have overinflated the incidence data [20]. Puberty is associated with a sudden rise in melanoma incidence, with most melanomas found between the ages of 14 and 20 years in children, so it is possible that hormonal factors are at play as well [20].

It is tempting to attribute the rapid rise in melanoma incidence over the last 30 years to changes in sun exposure in Caucasian populations in the 1960s and 1970s, but this can also, partly, be explained by increased screening in many educated populations, with the removal of many borderline melanomas. In Australia, for example, the rise in melanoma incidence over the last 20 years has been most apparent for melanoma in situ, and the incidence of melanoma in Caucasians populations mirrors the number of dermatologists and the education of the population in the respective countries [21, 22]. Screening for any type of cancer will always lead to the removal of many early lesions which biologically are likely to be different from more invasive tumours, and it is likely that many melanomas in situ may never progress to invasive tumours if left alone [21, 23]. The increasing gap between incidence and mortality for melanoma supports the fact that despite increased screening for melanoma in many Caucasian populations, mortality figures have not changed significantly over the last 30 years, so many very early melanomas removed nowadays may not have impacted the mortality figures if they had been left alone (http://www.seer.cancer.gov, [24])

## Sun Exposure and Melanoma Body Sites

Melanoma is not often found on chronically sun exposed sites and is commoner on intermittently exposed sites such as the trunk in males and the legs in females, and so differs significantly from nomelanoma skin cancers such as basal cell and squamous cell carcinomas. It is not cumulative UV damage on most exposed sites which is important for melanoma. The distribution of melanomas on the body is also similar across all Caucasian populations in the world irrespective of sun exposure levels and latitude, which suggests that nonenvironmental factors are important in determining melanoma body sites [15, 25, 33]. The only exception is lentigo maligna melanoma, which is mostly found on the face in chronically sun damaged and older individuals. Furthermore, sun exposure does not explain the striking difference between males and females, females having more melanomas on the legs, whereas in males they are found more commonly on the trunk [26]. This again is consistent all over the world and is not affected by clothing habits and latitude. It is very likely that gender affects melanocyte migration and differentiation in embryogenesis, which continues to affect naevi and melanoma behaviour throughout the lifetime. The distribution of naevi in children shows that gender affects melanocytes early in childhood as the difference in the distribution of naevi is already different in boys and girls and mirrors the distribution of melanomas in adults: boys have more naevi on the trunk, whereas girls have more naevi on the limbs from an earlier age [16]. Another observation regarding the body site in relation to potential sun exposure is that melanoma arising from a preexisting naevus is more likely to develop from a junctional naevus than from a more mature intradermal naevus. Junctional and dysplastic naevi are considered more unstable lesions with a higher chance of transformation into melanoma as they have not undergone maturation with migration of the melanocytes in the dermis. The distribution of junctional naevi versus intradermal naevi shows

that chronically sun exposed sites are less likely to have junctional naevi and atypical naevi. On the chronically sun exposed face, where intradermal naevi are commoner than junctional naevi, melanomas are quite rare (apart from the lentigo maligna type). These observations illustrate that melanoma behaviour at different body sites is more likely to be driven by different populations of melanocytes moving from the neural crest during embryogenesis to different body sites [27, 28•]. Indeed, body sites also affect the kind of somatic genetic signatures found in both naevi and melanoma, so supporting this hypothesis [29].

In nonmelanoma skin cancers, photoageing with solar elastosis, solar keratoses and solar lentigines is often a good marker of increased risk, whereas for melanoma, the presence of significant photoageing is not commonly seen (apart from lentigo maligna melanomas). In fact, the reverse is often seen, as subjects with melanoma on the trunk and limbs are not commonly very photoaged, which suggests that chronic sun damage is not relevant for these types of melanomas. This relative protection against photoageing is more likely to be seen in patients with multiple naevi. An excess of naevi is associated with longer telomeres, which in turn increase melanoma risk [30•, 31]. It is therefore postulated that longer telomeres are associated with delayed ageing of the skin, hence resulting in the reduced photoageing in melanoma patients with many naevi. The presence of solar keratoses is, however, a risk factor for melanoma on the head and neck, with odds ratios on the order of 2–4 [15, 32, 33]. But melanomas associated with significant photoageing are not associated with an excess of naevi, and several studies have shown that photoageing and an excess of naevi are mutually exclusive "at risk" phenotypes [15, 33, 34]. These observations led to the dual pathway hypothesis for melanoma with two distinct phenotypes conferring a risk for melanoma: photoageing or an excess of naevi [15, 33–35]. When solar elastosis is present histologically around a melanoma tumour, melanomas appear to have a better prognosis, so it is quite likely that these are biologically different [35]. Recent data on somatic mutations in different types of melanomas support the need to look at melanoma as a very heterogeneous disease, and it will be important to look at risk factors for melanomas in relation to specific subtypes of melanomas in the future, whether they are categorized histologically, genetically or by body sites [29, 36]. This will be invaluable to dissect the relative contribution of UV radiation in the induction of different types of melanomas.

## Laboratory Studies and Recent Genomic Data in Relation to UV Damage

UVB and UVA wavelengths are both damaging to cells, causing specific DNA lesions: pyrimidine dimers with C–T mutations for UVB and to a lesser extent C–T mutations for UVA as UVA causes the production of reactive oxygen species, which in turn damage DNA. However, there is recent evidence that most UVA damage is likely to be generated by pyrimidine dimers [37]. Skin has excellent DNA repair mechanisms, but these fail slowly with age, with the accumulation of DNA lesions which eventually affect the function of key cell cycle genes. The mouse model has been helpful to look at various genetic pathways involved in melanoma with the added effects of UV radiation on transgenic models as knockout transgenic animals for various key genes show that UV radiation can increase the number of melanoma tumours or their metastatic potential on a background of gene losses [38]. *BRAF* V600E mutations found in over 50% of melanomas can, in the mouse *BRAF* V600E transgenic model, lead to melanoma tumours, and the loss of ARF leads to inhibition of nucleotide excision repair, so this points to complex gene–environment interactions between key genes involved in melanocyte differentiation and DNA excision repair [39]. There are, however, quite a few differences in the location and behaviour of melanocytes in the mouse model compared with humans, so this model is not entirely applicable to human melanomas.

DNA excision repair needed to repair UV-related lesions in DNA is relevant for melanoma as patients with deficient excision repair with xeroderma pigmentosum (XP) have increased risk [40]. However, the types of melanomas found in XP are mainly of the lentigo maligna melanoma type found on chronically sun exposed sites, so DNA repair may not be as relevant for other types of melanomas [41]. It is also important to note that XP patients are also more prone to solid tumours, so excision repair deficiency does not have an impact on UV-induced cancers alone. This illustrates the intricate links between several DNA repairs pathways and cancer risk for all types of cancers, and this is also seen in breast cancer, where various DNA repair pathways may be involved [42]. Furthermore, deficits in excision repair also have an impact on many other systems, including neurones, and not just the skin, so it is clear that these pathways are very complex [43].

The incidence of melanoma, like that of all cancers, increases with age, but reaches a peak in the mid 50s. It may be caused by deficiencies in DNA repair, accumulation of somatic mutations and changes in immune responses with age. The mean age of onset of melanoma is very similar in all Caucasian populations despite very different levels of UV exposure across the world. One would expect that UV exposure would reduce the mean age of onset in countries such as Australia or South Africa, but this is not the case. Recent exome sequencing of melanoma tumours has shown that C–T mutations (typical UV signatures) are common in melanoma tumours, again supporting the role of sunlight in the pathogenesis of melanoma [36, 44]. However, these C–T mutations are not exclusive to melanoma and are also found in other non-UV-related cancers such as pancreas cancer, so it has not been confirmed that these

dimers are specific to UV injury [45]. More data are needed to look at the relevance of these C–T mutations in the pathogenesis of melanoma, especially as they are also reported in acral melanomas, which are not thought to be related to UV damage [46]. Mucosal melanomas also have different genomic alterations, showing that the body site is again crucial when looking at the pathophysiology of melanoma [47].

## Sunbeds

The association between melanoma and sunbeds has long been controversial. Although many studies have reported an increased risk with sunbed use, many have not confirmed this association. A recent meta-analysis by Boniol et al. [48] including 28 case–control studies of melanoma published between 1981 and 2012 found a small increased risk with sunbed use. This large meta-analysis included more than 10,000 melanoma cases, but despite this very large sample size, the relative risks for different measures of sunbed use were often very close to 1 with borderline significance. Sunbed use before the age of 35 years was, however, more significantly associated with melanoma, with a relative risk of 1.59, which has been reported before [2, 3]. Sunbed use follows a north to south gradient in Europe, with decreasing use towards southern European countries, and this may be explained by a "light"-seeking behaviour in Nordic countries, where the days are very short in the winter. However, there have been very few studies on the psychological effects of sunbeds and they are not conclusive, but this is an area which warrants further research [49]. Sunbed use in Sweden is as high as 70%, compared with 20% in France, so there are very striking differences across Europe, which may be explained by decreasing levels of UV radiation from south to north and differences in skin pigmentation [3]. Frequent users of sunbeds tend to be those with a higher risk of melanoma, with red or blond hair and freckles, and with an inability to tan [3, 50, 51]. Females are also more frequent users than males all over Europe [3, 51]. Even if melanoma risk may not be significantly increased with sunbed use in adults, premature photoageing and an increased risk of basal cell and squamous cell carcinoma is still an issue. A large meta-analysis showed that nonmelanoma skin cancers were also associated with sunbed use [52]. Basal cell carcinoma was not as strongly associated with sunbed use, and the risk is more consistent for squamous cell carcinomas. As these types of skin cancers are much commoner, this can be a significant burden to health services. Many countries have now adopted bans on sunbed use by children and are implementing regulations for sunbed providers [51]. In psoriasis patients who receive UVA with orally administered psoralen for UV sensitization, the risk of squamous cell carcinoma is much higher, but psoralen plus UVA exposure is not comparable to exposure from sunbed use in terms of UV wavelength, and the added oral sensitizer potentiates the effects of UVA [53]. It is, however, interesting to note that basal cell carcinoma risk, again, is much smaller than that of squamous cell carcinomas in relation to psoralen plus UVA exposure as already observed for sunbed use [53].

## Sunscreens

Sunscreens have been proven to protect against the deleterious effects of sunlight, including erythema, photoageing, formation of pyrimidine dimer, p53 induction and immunosuppression [54]. For squamous cell carcinomas and solar keratoses, sunscreens have been shown to provide some protection in Australia, where intervention groups compared with controls showed reduced incidences [55, 56]. Green et al. [57] showed more recently that melanoma may be reduced by intervention studies in Queensland, Australia. The results are difficult to interpret as the number of melanomas in the intervention group compared with the control group included the number of melanomas in situ, which raises issues of screening bias. For a total of 1,621 subjects, the number of melanomas at follow-up was high at 33 for the two groups combined, and this supports screening bias. There were also issues of compliance in the intervention group as well as the fact that the control group was a sunscreen-user group. There are therefore no conclusive data on the protective or harmful effects of sunscreens on melanoma and basal cell carcinoma, and this was the conclusion of two meta-analyses including large numbers of cases and controls [58, 59]. Lazovich et al. [60] found that sunscreen use was not associated with a reduced risk of melanoma (unless the sunscreens were routinely used for all types of sun exposure), but other protective measures such as clothing or use of shade reduced melanoma risk. There are also concerns that sunscreens may increase intentional sun exposure as they provide a false sense of security by suppressing sunburn: one study reported that using sunscreens actually increases the risk of melanoma, but this is confounded by prolonged exposure with sunscreens and the inadequate application of sunscreens compared with what manufacturers recommend [61]. On average, the amount of sunscreen used is around a third of that recommended, especially as it is estimated that it may take 30 g to cover an adult body [62]. The costs of sunscreens, which can be substantial for an average family, and the inability to carry large quantities when travelling lead to significant underuse [62]. The use of sunscreens in daily moisturizers used all year round in temperate climates should be discouraged because of the low levels of UV outside the summer months. This will increase the risk of vitamin D deficiency as well as the risk of sensitization, with the added concern of the release of chemicals into the environment if sunscreens are used extensively in many skin care products [63, 64].

## Vitamin D

Vitamin D deficiency has been an increasing issue in many populations and has been underdiagnosed [65, 66]. Across all ethnic back grounds, vitamin D serum levels are lower in non-Caucasians than in Caucasians, but the optimal levels for different ethnic groups has not been determined especially as non Caucasians, despite their lower vitamin D serum levels, appear to have greater bone mass [68]. In Caucasians, vitamin D levels are actually lower in the fairest skin types and this, in part, may be explained by lower sun exposure in the most sun-sensitive individuals, but other factors linking pigmentation and vitamin D metabolism are likely to also be at play [65]. This area of research is becoming more topical in melanoma, as low vitamin D levels have been associated with increased susceptibility to melanoma as well as reduced survival [67]. Low vitamin D serum levels are also associated with increased susceptibility to many solid tumours and also overall mortality [69]. The associations between melanoma risk and polymorphisms in genes within the vitamin D pathway have been controversial, but a recent study reported an increased risk in a large case–control study with two polymorphisms in the vitamin D transporter gene (*GC*) but not in the vitamin D receptor gene (*VDR*) [70]. The *GC* polymorphism has already been proven to be associated with vitamin D serum levels in a large genome-wide association study, so this polymorphism associated with melanoma risk is likely to be relevant [71]. Vitamin D serum levels are also associated with BMI, and higher BMI is also a risk factor for melanoma. Lighter skin pigmentation with increasing latitude has been an adaptive process in evolution to maximize vitamin D production with migration to more temperate climates, and this highlights the risk of altering this adaptive response too rapidly [72]. There is an urgent need to assess the long-term impacts of recommending strict sun avoidance and widespread use of sunscreens in Caucasian populations.

#### Compliance with Ethics Guidelines

**Conflict of Interest** Veronique Bataille declares she has no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by the author.

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