

Melanoma Epidemiology and Sun Exposure

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The worldwide incidence of melanoma has increased rapidly over the last 50 years. Melanoma is the most common cancer found in the young adult population, and its incidence is very high among geriatric populations. The incidence of melanoma varies by sex, and this factor is also associated with differences in the anatomical site melanoma. Adolescent and young adult women have a higher incidence than men. This may be, in part, due to the greater use of sunbeds, as well as intentional sun exposure among girls and, in general, risky behaviours in seeking to suntan, due to socially-determined aesthetic needs. Indeed, the World Health Organization declared that there is sufficient evidence to classify exposure to ultraviolet radiation (sunbed use and sun exposure) as carcinogenic to humans. Although pigmentation characteristics, such as skin colour, hair and eye colour, freckles and number of common and atypical naevi, do influence susceptibility to melanoma, recommendations regarding prevention should be directed to the entire population and should include avoiding sunbed, covering sun-exposed skin, wearing a hat and sunglasses. Sunscreen use should not be used to prolong intentional sun exposure. Primary prevention should be focused mainly on young adult women, while secondary prevention should be focused mainly on elderly men. In fact, after the age of 40 years, incidence rates reverse, and the incidence of melanoma among men is greater than among women. This is probably due to the fact that men are less likely than women to examine their own skin or present to a dermatologist for skin examination.

Key words: sunburn; sunbed; sunscreen; phenotype; melanoma; sun exposure.

Accepted Apr 27, 2020; Epub ahead of print Apr 28, 2020

Acta Derm Venereol 2020; 100: adv00136.

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Melanoma arises through malignant transformation of melanocytes, pigment-containing cells. Melanoma typically occurs in the skin, but may rarely occur in the mouth, intestines, or eye. Cutaneous melanoma (CM) is the most aggressive and lethal form of all skin cancers, which occurs when unrepaired DNA damage to skin cells (most often caused by ultraviolet radiation

SIGNIFICANCE

Young women present particularly high risky behaviours in terms of melanoma risk, such as tanning, related to social determined aesthetic needs. Indeed, the highest prevalence of sunbed use is found among female adolescents. Prevention recommendations include avoiding sunbed use, covering sun-exposed skin, wearing a hat and sunglasses. Sunscreen should not be used to prolong intentional sun exposure. Primary prevention should focus on young women, and secondary prevention in older men. In fact, at older ages, the incidence of melanoma among men is greater than among women, probably because men are less likely than women to examine their own skin or present to a dermatologist for skin examination.

(UVR)) triggers mutations or genetic defects that lead the skin cells to multiply rapidly and form malignant tumours. CM represents approximately 5% of all skin cancers, but it accounts for approximately three-quarters of all skin cancer deaths (1).

The worldwide incidence of melanoma has risen rapidly over the course of the last 50 years. According to GLOBOCAN 2018 (2), the expected world number of new cases of CM is 287,723 in 2018, with an age-standardized incidence rate of 3.1 per 100,000/year and a mortality rate of 0.63 per 100,000/year. In populations of European origin, incidence and mortality rates were, respectively, 11.2 and 1.7 per 100,000/year in Europe, 12.2 and 1.4 in the USA and 33.6 and 3.4 per 100,000/year in Australia and New Zealand. Worldwide, CM incidence rates vary 100-fold among different populations depending on ethnicity, with the highest rates observed in New Zealand and Australia, intermediate rates in Europe and USA, and the lowest rates in South-Central Asia. In Europe, the highest estimates of CM incidence rates were observed in Sweden and Denmark and the lowest rates in Greece. This variation is mainly attributed to exposure to UVR, and genetically determined phenotypic characteristics. Differences by ethnicity were also observed for CM subtypes and body location. Although the most common melanoma subtype among populations of European origin is superficial spreading melanoma (SSM), melanomas in the African-American population occur more often on non-sun-exposed skin, such as the palms and the soles, and acral lentiginous melanoma

(ALM) is the most common histopathological type (3). The age range with highest number of CM diagnoses is between 40 and 60 years. The median age at diagnosis and death are, respectively, 57 and 67 years. The incidence rates start to increase from 40 years of age; thus CM is generally considered a tumour affecting young and middle-aged people, almost a decade before most solid tumours (e.g. breast, colon, lung or prostate cancers). A study that examined incidence rates time trends of CM in 39 population-based cancer registries from 1953 to 2008 (4) found that incidence rates of melanoma increased in most European countries (primarily Southern and Eastern Europe). However, indications of a stabilization or decreasing trend were observed in Australia, New Zealand, the USA, Canada and Norway, mainly in the youngest age group (25–44 years). Possible explanations of these results include decreasing sun exposure in children following intensive preventive campaigns in these countries, and changes in the proportion of young individuals at low risk of melanoma due to immigration to these countries over recent decades.

Adjusting for age, adolescent and young adult women have higher melanoma incidence rates than men (5). This may be, in part, due to the greater use of sunbeds by girls, which is associated with increased melanoma risk (6). In general, girls have greater tanning risky behaviours and socially determined aesthetic needs (7). However, after the age of 40 years, rates reverse, and the incidence of melanoma among men is greater than that of women. Men are less likely than women to examine their own skin or seek help from dermatologists for skin examination (8). Considerable sex differences in melanoma awareness and detection practices have been reported in population-based studies (9).

Looking at mortality rates, they were found to increase in the USA and in Europe since 1980s but at much slower rates than incidence. This may be due to overdiagnosis, with diagnosis and removal of very thin, not lethal, me-

lanomas. At all ages, mortality rates are higher in males than in females, with a cumulative mortality at 70 years of 0.37% in men and 0.17% in women in Australia. A pooled analysis of the European Organization for Research and Treatment of Cancer (EORTC) trials showed that, in both localized and advanced disease, women have a significant and independent advantage, across different clinical endpoints concerning disease progression and survival (10). This seems to depend on both biological sex trait and behavioural differences regarding primary (sun exposure, UVR protection) and secondary (skin screening) prevention (11).

We review the literature regarding UV exposure and phenotypical risk factors. A brief summary of risk estimates is presented in **Table I**.

EPIDEMIOLOGICAL RISK FACTORS

Ultraviolet radiation

According to WHO estimates, 65,161 people a year worldwide die from too much sun. Sun exposure is indeed the most significant environmental cause of skin cancer and UVR is the wavelength associated with the occurrence of this disease.

The International Agency for Research on Cancer (IARC) classified the entire spectrum of UVR as “carcinogenic to humans” (Group 1) based on substantial evidence from both basic and epidemiological research. Laboratory data and animal experiments (on DNA mutations and repair, immune function, cell integrity, cell cycle regulation, and other critical biological functions) have documented a role for both UVB and UVA radiation in skin carcinogenesis. Experiments in human volunteers have also shown that exposure to UVA and UVB can weaken the immune system through interacting and overlapping mechanisms, increasing vulnerability to cancer as well as other diseases. Furthermore, evidence

Table I. Summary of epidemiological risk factors for melanoma development

Category of risk factors	Risk factors	Effect estimates	Notes
UV radiation	Sun exposure	High intermittent/intentional vs. low: approximately 60% increased risk High continuous/occupational vs. low: no association	Intermittent: mainly increases risk of SSM Chronic: increases risk of LMM. Decrease risk on occasionally exposed sites
	Sunburns	History of sunburns vs. no history: double increased risk	Increases risk of SSM and LMM, not for NM
	Indoor tanning	Ever exposure vs. never: approximately 20% increased risk	Evidence of dose-response effect; mainly affects young women
	Sunscreen use	Some evidence that high SPF may decrease risk compared with no use	Sunscreen use may increase risk if used to prolong intentional sun exposure
Phenotype	Eye colour	Light colours vs. dark: approximately 50% increased risk	Increased risk of NM and SSM, not for LMM
	Hair colour	Red vs. dark: more than triple risk Blonde vs. dark: almost double risk Light-brown vs. dark: approximately 60% increased risk	
	Freckles	High-density vs. none: more than double risk	Dose-response trend of risk according to level of skin type
	Skin colour/type	Fair vs. dark: more than double risk Phototype I vs. IV: more than double risk Phototype II vs. IV: approximately 80% increased risk Phototype III vs. IV: approximately 70% increased risk	
	Common naevi	> 100 vs. < 15: almost 7-times higher risk	
Atypical naevi	≥ 5 vs. 0: more than 6-times higher risk		

LMM: lentigo maligna melanoma; NM: nodular melanoma; SPF: solar protection factor; SSM: superficial spreading melanoma.

from a large number of observational studies is generally consistent, showing a significant positive association with residing in areas with high ambient UVR through life, in early life, and even for short periods in early adult life (12). Lastly, several meta-analyses showed significant increases in melanoma risk and non-melanoma skin cancer (NMSC) with high sun exposure and indoor UV tanning (6, 13).

A study conducted in Canada estimated the current attributable and future avoidable burden of melanoma related to exposure to UVR and modifiable UVR risk behaviours. They estimated that 62.3% of melanomas in Canada were attributable to exposure to UVR and that 29.7% were attributable to the combination of sunburn (7.4%), sunbathing (17.8%), and indoor tanning (7.0%). They also concluded that a 50% reduction in modifiable UVR behaviour could avoid an estimated 11,980 melanoma cases by 2042 (14).

Recognizing the importance of establishing skin cancer prevention as a national priority, The Surgeon General's Call to Action to Prevent Skin Cancer in 2014 described prevention strategies and called on the community sectors to play a role in protecting Americans from UVR from the sun and artificial sources (15). Strategies that support goals related to lifestyle modifications to reduce the burden of melanoma included reducing the harms from indoor tanning, youth education approaches, and community-wide interventions focused on modifying healthy behaviours, including decreasing UVR exposure (16).

Sun exposure and sunburn

Measurements of individual sun exposure vary between studies, but are commonly classified as "intermittent" (short, intense sun exposure through activities such as sunbathing, outdoor recreation and holidays in sunny locations), "chronic" (continuous exposure, such as occupational sun exposure) and "total" (the sum of intermittent and chronic exposures).

The first systematic review and meta-analysis, summarizing 57 studies on sun exposure and melanoma, found a 60% significant increased risk of melanoma due to recreational sun exposure (summary relative risk (SRR) of CM for intermittent sun exposure of 1.61; 95% confidence intervals (95% CI) 1.31–1.99), while no association was suggested for chronic sun exposure (SRR: 0.95; 95% CI 0.87–1.04).

Sunburn is a biological response to intermittent exposure to the sun in poorly adapted skin and in multiple analyses a stronger predictor than intermittent exposure itself (13). The SRR for sunburns, which is the main indicator of sun exposure, was 2.03 (95% CI 1.73–2.37).

Despite the clear role of sunburn in increasing CM risk, a survey conducted in USA in 2013 (Youth Risk Behavior Survey (17)) highlighted that preventive practices are not

regularly followed: most respondents (57%) reported having experienced 1 or more sunburns in the prior year.

Holman et al. (18) first proposed 2 distinct biological pathways by which CM might develop. One by way of intermittent sun exposure, acting primarily as a promoter of melanoma arising on pigmented naevi and mainly of the SSM type, and the other by way of a more continuous pattern of sun exposure, leading principally to lentigo maligna melanoma (LMM). In 1992, Green (19) proposed a theory of site-dependent susceptibility of melanocytes to malignant transformation. According to this hypothesis, people with a low propensity for melanocyte proliferation (small number of common naevi) need a continuous exposure to sunlight in order to drive the clonal expansion of initiated melanocytes. The melanomas arising from this pathway are more likely to be located on chronically sun-exposed body sites, to be of LMM subtype, and to occur in older patients with a history of solar damage and NMSC. On the other hand, people with a high propensity to melanocyte proliferation are more likely to develop melanomas on intermittently sun-exposed body sites, to be of SSM or nodular (NM) histological subtypes and to occur in patients with no history of sun damage or NMSC. Thus, both pathways include early initiation by sun exposure, but later proliferation is driven, in one pathway, by accumulation of sun exposure in non-naevus-prone people and, in the other pathway, by host factors in naevus-prone people (20). In the same study by Green (19), it was found that sun exposure and phenotypic characteristics were positively associated with all the main histological subtypes of melanoma. However, NM was not found to be associated with sunburns, in contrast to LMM and SSM. LMM was not found to be associated with freckling, light eye colour and hair colour, in contrast to NM and SSM, which were significantly associated with all 3.

This 2-pathway hypothesis for melanoma was confirmed and refined by many authors who observed an inverse correlation between number of naevi and clinical signs of sun damage (20–22), and identified a few genes differentially mutated in LMM vs. SSM and NM. Briefly, melanomas characterized by mutations in *BRAF*, *NRAS* and *TERT*, and approximately 80% of melanomas carry UVR signature mutations (C-T or CC-TT), along with other genes coding for downstream components of the tyrosine kinase RAS-BRAF signal transduction pathway (e.g. *CDKN2A* and *CDK4*), were suggested to be more frequent on intermittently exposed skin (23–25). Most of these are considered "passenger" mutations and not "driver" mutations; however, this high prevalence is clearly indicative of a role for UVR in melanomogenesis as is noted also by presence of somatic mutations in normal skin. BRAF mutations, which are present in approximately 40% of CM in people of European origin, are associated with characteristics of the naevus-associated pathway: younger age at diagnosis, occurrence on the

trunk, SSM type and absence of chronic sun damage in the skin (26). *TERT* promoter mutations (associated with UVR exposure) are present in approximately 43% of CM, occur more frequently at sun-exposed sites, and tend to co-occur with *BRAF* alterations (27).

The melanocortin-1 receptor (MC1R), a pigmentation gene associated with melanoma risk (28–30), is involved in the same signalling pathway and has been found to interact positively with *BRAF* and *CDKN2A* in the aetiology of melanoma occurring on usually unexposed skin (31, 32). On the other hand, p53-positive melanomas were usually associated with features of chronic sun exposure (33), supporting the hypothesis that different molecular pathways can lead to melanoma development (34, 35).

Looking at the distribution by body site of different histological types of CM, SSM is the more frequent type on the trunk in men and legs in women, while LMM is more frequent on the face and neck (36). It is likely that melanocytes on different body sites have different characteristic in terms of differentiation: atypical naevi are more commonly found on the trunk, whilst they are very rare on the face. Similarly, intradermal naevi, which are mature melanocytic lesions, are commonly found on the face, but are much rarer on limbs. It is possible that during embryogenesis, melanocytes have different properties according to head and neck, trunk and limb locations, because of migration to different body sites, and this is likely to be influenced by key developmental genes.

The complex interplay between sun exposure, pigmentation characteristics and melanocytic naevi was investigated in a meta-analysis including 24 studies for a total of 16,180 cases of melanoma (37). Considering each measure of sun exposure (intermittent, chronic, sunburns and actinic damage) SRRs for CM risk were 1.31 (95% CI 0.94–1.81) and 1.77 (95% CI 1.30–2.41) respectively for occasionally vs. usually sun-exposed body sites. Chronic sun exposure was weakly, but significantly, negatively associated with CM on occasionally sun-exposed sites. Overall, these results suggest that sun exposure is associated with CM on all body sites (except for mucosal), but in particular with CM on head and neck in older individuals.

The apparently protective effect of chronic sun exposure on CM on occasionally exposed sites and, at most, weakly causal effect on usually exposed sites is puzzling. Enhanced melanin production and melanosome delivery to keratinocytes (38) and increased thickness of the top layers of the epidermis due to continuing sun exposure may be a possible explanation; however, they would not be expected to reduce incidence to a level below that present in the absence of sun exposure. Other possible explanations are the lower melanin content, sunburn, and lower DNA repair capacity of intermittently exposed skin compared with habitually exposed skin. Sunburn

can lead to cell proliferation in replacing apoptotic cells, and habitually exposed skin may have somewhat thicker stratum corneum, and thus models protection from tanning, and some upregulation of DNA repair pathways exemplified by fewer thymine dimers after repeated low exposure (39–41). However, it is important to note that the reference category for calculating RRs in epidemiological studies of melanoma and sun exposure is “low sun exposure”, not “no sun exposure”.

Migrant studies provide convincing evidence that childhood and adolescence are critical periods for the development of melanoma in adulthood. Indeed, it was found that adults were at increased risk of melanoma if they spent their childhood in sunny locations or if they received above average intermittent sun exposure during vacations and/or recreation. In an Australian case-control study published in 1984 (42), earlier age at arrival of immigrants to Australia was a melanoma risk predictor with little residual effect of duration of residence. Specifically, children who migrate from a less sunny country before the age of 10 years had similar incidence rates of native-born Australians, while the estimated incidence in those arriving after age 15 years was approximately a quarter of the native-born rates. Similarly, in a European case-control study (43), age <10 years old at arrival in a sunny location of residence (i.e. the Mediterranean, subtropics, or tropics) conferred a 4-fold increased risk of developing melanoma.

Studies investigating the role of residence in childhood provide further evidence that sun exposure in childhood and adolescence is more closely associated with melanoma risk than adult sun exposure. A case-control study nested in the Nurses' Health Study cohort (44) showed an increased melanoma risk in women whose residence during the ages 15–20 years was more equatorial in latitude, whereas latitude of residence after 30 years of age was not significantly related to melanoma risk. Finally, in another study of 474 cases and 926 controls, those who lived near the coast before the age of 15 years had an increased risk of melanoma compared with those who never lived far away from the coast (odds ratio (OR)=1.6; 95% CI 1.0–2.6) (45).

Sunbeds and indoor tanning

Sunbeds and sunlamps used for tanning purposes represent the major source of deliberate exposure to UVR. Indoor UVR tanning has been widely practiced in Northern Europe and the USA since the 1980s and this trend has gained popularity in sunnier countries, such as Australia. Modern indoor UVR tanning equipment emits mainly in the UVA range, but a fraction (<5%) of this spectrum is in the UVB range, which is needed to induce a deep, long-lasting tan. Both UVA and UVB radiation cause DNA damage and immunosuppression (6, 46–48). Moreover, powerful UVR tanning units may be 10–15 times

stronger than the midday sun in the Mediterranean Sea area, and repeated exposure to large amounts of UVA, delivered to the skin in relatively short periods (typically 10–20 min) constitutes a new experience for human beings. There are several types and denominations of tanning devices (sunbeds, tanning beds/booths/canopies, and solarium): the term “sunbeds” is commonly used to generally define them all.

In 2012, an updated meta-analysis (6) summarized 27 epidemiological studies that quantified risk of CM associated with artificial UVR tanning. The SRR estimate for “ever” vs. “never use” of indoor tanning was 1.20 (95% CI 1.08–1.34) and the risk was independent of skin sensitivity or population and a dose-response effect was evident. When the analysis was restricted to 18 studies with a population-based sampling of cases and controls, the SRR increased to 1.25 (95% CI 1.09–1.43). The analysis restricted to exposure at a young age in 13 studies showed consistent results. For those starting first exposure to sunbeds before the age of 35 years, and increased risk of 1.59 (95% CI 1.36–1.85) was estimated with no significant between-study heterogeneity and no indication of publication bias. Studies on exposure to indoor tanning and NMSC showed a significantly increased risk of basal cell carcinoma (SRR=1.29; 95% CI 1.08–1.53) and of squamous cell carcinoma (SCC) (SRR=1.67; 95% CI 1.29–2.17). Based on the results of a meta-analysis published in 2009, it could be estimated that of 63,942 new CM cases diagnosed each year in Western Europe, 3,438 (5.4%) could be caused by sunbed use. Women represented the majority of this burden, with 2,341 estimated cases (6.9% of all melanoma cases in women) induced by sunbed use; while the figure for men was 1,096 cases annually (3.7% of all cases in men). Taking a melanoma incidence to mortality ratio of 3.7 for European men and 4.7 for European women in EU15 countries, approximately 498 women and 296 men would die each year from a melanoma caused by artificial UVR tanning.

In 2009, Hirst et al. (46) estimated the numbers of potential skin cancers that could be prevented through regulation of solarium and the associated cost-savings to the Federal Government in Australia (for each 100,000 people: 18–31 melanomas, 200–251 SCCs and \$AU 256,054 associated costs).

In a paper published the following year, Hery et al. (49) noted a sharp increase in melanoma incidence among young women in Iceland, which began after 1990 with a peak in 2000. At the same time, the prevalence of sunbeds in Iceland rapidly increased, from 1979 to 1988, suggesting a possible link between the 2 observed trends. However, another possible explanation could be the increase in melanoma screening, which occurred all over Europe in the 1990s. Authors also observed a decline in melanoma rates among women after 2001, following a reduction in prevalence of sunbeds. However, it should

be taken into account that the lag time between exposure and melanoma onset is quite long and the decline in melanoma incidence is unlikely to be due to the reduced use of sunbeds in the early 2000s.

Some authors hypothesized that indoor tanning could act as a protective factor for melanoma risk, by preventing sunburns. Recently 2 publications expressed scepticism about the carcinogenicity of indoor tanning (50, 51). Some authors have used the lack of randomized clinical trials (which would be unethical) to imply that the relationship between sunbed use and melanoma is not causal. Suppa & Gandini (52) recently showed, however, that the large amount of data coming from observational studies in fact provides enough information to infer that sunbed use does cause melanoma: they were able to demonstrate the applicability of all epidemiological criteria for causality to the relationship between sunbed use and melanoma. They found that recent studies have reinforced previous knowledge about the detrimental effects of first sunbed exposure at young age, especially in women (53, 54). In fact, new insights on sunbed use have emerged, such as its relevance for the development of additional primary melanomas (55), its association with melanoma of the lower limbs (most common in women) (56) and its correlation with other melanoma risk factors, including high naevus count, atypical naevi and sun damage (57).

The large body of evidence prompted both the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) of the European Commission (58) and the WHO (59) to state that there is no safe limit for exposure to UV radiation from sunbeds.

Interestingly, an Italian survey on 4,703 subjects after the ban on sunbed use before 18 years of age estimated the overall prevalence of sunbed use to be as high as 20%, with higher proportion of female, young and highly-educated users (60). Moreover, participants at high risk of melanoma were those who used sunbeds more frequently: subjects with freckles and with red hair had the higher odds of using sunbeds than subjects without freckles and with dark hair (OR were, respectively, 1.89; 95% CI 1.27–2.80 and 3.92; 95% CI 1.91–8.06). Another Italian survey on 3,089 students highlighted the important role of parents on indoor tanning practices of children (61). Indeed, students who attended a targeted educational intervention were more aware that sunbed use cannot prevent sunburns ($p=0.03$) than those who did not attend; however, sunbed use by parents influenced the desire to use a sunbed more than participation in the educational intervention ($p<0.0001$).

OTHER EPIDEMIOLOGICAL RISK FACTORS RELATED TO ULTRAVIOLET RADIATION

The association of sun exposure with melanoma risk is influenced by other factors such as phenotype.

Phenotypic characteristics

Pigmentation characteristics, such as skin colour, hair and eye colour, and freckles are well-established host risk factors for melanoma.

A previous meta-analysis found SRR for blue, green and hazel eye colour compared with dark eye colour of 1.47 (95% CI 1.28–1.69), 1.61 (95% CI 1.06–2.45) and 1.52 (95% CI 1.26–1.83), respectively (62). According to hair colour, the highest association with melanoma was found for red-haired individuals, who have a more than tripled risk of melanoma compared with dark-haired subjects (SRR; 95% CI 3.64; 2.56–5.37). Blond-haired and light brown-haired subjects are, as well as increased melanoma risk, compared with dark-haired subjects (SRR; 1.96; 95% CI 1.41–2.74 and 1.62; 95% CI 1.11–2.34, respectively). Looking at skin colour, light-pigmented subjects had a doubled risk of melanoma compared with darker pigmented subjects (SRR 2.06; 95% CI 1.68–2.52). This result was in agreement with the analysis of skin phototype (defined according to the Fitzpatrick classification as indicator of skin sensitivity to sun): indeed, all 3 lighter skin phototypes I, II and III increased melanoma risk compared with skin phototype IV, with a trend in the calculated SRR, that were, respectively, 2.09 (95% CI 1.67–2.58), 1.84 (95% CI 1.43–2.36) and 1.77 (95% CI 1.23–2.56). Finally, high density of freckles was associated with a significantly doubled risk of melanoma: SRR 2.10 (95% CI 1.80–2.45).

In a recently published population-based prospective study including 38,854 subjects, melanoma risk was assessed in association with pigmentation characteristics and other phenotypes, and additive interactions were explored. During a mean follow-up of 3.5 years, 642 (1.5%) participants developed melanoma. Inability to tan was a recognized risk factor (no tan vs. deep tan hazard ratio (HR) 3.11 (95% CI 1.50–6.43)), while propensity to sunburn was not associated with melanoma after tanning inability was adjusted for (63). The highest population attributable fractions (PAFs), helpful in estimating the burden of disease occurring within sub-groups of a population, were observed for skin phototypes I/II (0.27, 95% CI 0.21–0.31), presence of freckles (0.23, 95% CI 0.19–0.26) and blonde hair (0.23, 95% CI 0.20–0.26). For eye colour, the PAF for blue/blue-grey eye colour was higher than for green/grey/hazel eye colour (0.18 vs. 0.13), while the PAF associated with red hair colour was 0.10 (95% CI 0.09–0.11) compared with 0.23 for blonde and 0.15 for light brown hair colour.

Common and atypical naevi

High number of common naevi and the presence of atypical naevi are major risk factors for CM. According to a previous meta-analysis including 10,499 cases and 14,256 controls (64), the presence of more than 100 common naevi was associated with almost 7-times higher

risk of melanoma compared with less than 15 common naevi: the SRR was 6.89 (95% CI 4.63–10.25). In the same meta-analysis, the SRR for the presence of at least 5 atypical naevi vs. no atypical naevi was 6.36 (95% CI 3.80–10.33). It was estimated that 42% of melanomas are attributable to having ≥ 25 common naevi, corresponding to 121,800 patients newly diagnosed with melanoma from an annual worldwide total of 290,000 new cases. Moreover, approximately 25% of melanoma cases are attributable to the presence of one or more atypical naevi, corresponding to an estimated number of 70,000 new cases in 2018. High total body naevus counts (≥ 50 common naevi) account for approximately 27% of melanoma cases, whereas individuals with few common naevi (0–10) account for only 4% of melanoma cases.

Naevi yield similar relative risks in the UK and Australia, suggesting that genetic factors are important despite different environmental exposure. Multiple naevi might also be an indicator of excessive sun exposure, and thus be associated with an increased risk of CM. A study of Australian children found that increased sun exposure in childhood was significantly associated with an increased number of naevi (65). A separate study of more than 11,000 European children found that sunburns and holidays in the south were significantly associated with high naevus counts and the occurrence of atypical naevi (66). However, it is likely that sun exposure influences smaller naevi on chronically sun-exposed sites and to a lesser extent, larger atypical lesions on intermittently exposed sites, which have more probably a genetic basis (67, 68).

Total naevus count was found to be more strongly associated with CM on intermittently sun-exposed skin (i.e. trunk and legs) than CM on chronically exposed skin (i.e. the head/neck and arms) (37). This may be related to BRAF somatic mutations, which are also more common in CM originating on trunk and legs compared with the head and neck.

A previous prospective cohort study conducted in Australia (64) found that the characteristic most strongly associated with invasive melanoma was self-reported naevus density at age 21 years [many vs. no moles HR 4.91 (95% CI 2.81–8.55)].

Looking at melanoma-related deaths in USA, a recently published prospective study using data from the Nurses' Health Study ($n=77,288$ women) and Health Professionals Follow-up Study ($n=32,455$ men) investigated cutaneous naevi and risk of melanoma death (69). During 26 years of follow-up, 2,452 melanoma cases were histologically confirmed and 196 patients died from melanoma. An increased number of naevi was associated with melanoma death: HR for ≥ 3 naevi compared with no naevi was 2.49 (95% CI 1.50–4.12) for women and 3.97 (95% CI 2.54–6.22) for men. Among melanoma cases, increased number of naevi was associated with melanoma death in men, but not in women. Similarly, the number of naevi was positively associated with

Breslow thickness in men only (p -value for trend 0.01). A possible explanation is that male patients with melanoma and high naevus counts might tend to have their melanomas diagnosed at later stages or may be related to different prevalence of melanoma body sites in men and women. Indeed, melanoma more frequently occurred in men at the head and neck or trunk (sites associated with poorer survival), while it occurred more frequently at the extremities in women (69). The observed differential associations by sex might also reflect other aetiological mechanisms: for instance, the number of naevi had been identified as a phenotypic marker of plasma sex hormone levels, with more naevi associated with higher levels of oestradiol and testosterone (70).

SUNSCREEN USE

Studies have been inconclusive regarding sunscreen use and the development of naevi among children, with a single randomized trial showing evidence of benefit (71), while other studies have shown a positive association between sunscreen use and naevus prevalence (66, 72–74). An Italian large observational study on 1,512 children and adolescents found that sunscreen users were more likely to develop naevi compared with non-users. Moreover, unlike other paediatric analyses (75), a higher frequency of daily application of sunscreen was associated with a higher naevus count, suggesting that this association cannot be due only to residual confounding. On the other hand the use of high sun protection factor (SPF) (>30) sunscreens exclusively, compared with the use of sunscreens with $\text{SPF} \leq 30$, adequately protected skin during sun exposure and significantly reduced naevus burden. These results were confirmed by subsequent studies (76–78).

The possible explanation of these findings may be interpreted in the light of 2 considerations. First, children who apply more sunscreen are probably fair-skinned subjects with freckles who tend to be burnt by the sun easily and, consequently, lower skin-phototypes have a greater tendency to develop sunburn and naevi. Secondly, the anti-erythematous effect and a false sense of protection against sunburn conferred by frequent application of sunscreen may lead children to spend more time in the sun and to expose themselves in the middle of the day when ultraviolet rays are stronger (79).

Sunscreen use is recommended for sun protection in addition to clothing and shade (80). Sunscreen can decrease the risk of sunburn and SCC (82).

Meta-analyses of observational studies showed no effect of sunscreens on melanoma risk, but the results of the studies are difficult to interpret due to lack of adjustment for potential confounders (82).

The only randomized controlled trial showed a decreased melanoma risk of subjects who used sunscreen daily compared with discretionary sunscreen use (78).

However, this trial was conducted among subjects who lived in Australia, a country with very high ambient solar radiation and high awareness of skin cancer.

Recently, the Norwegian Women and Cancer Study (83), a prospective population-based study of 143,844 women and 722 cases of melanoma, showed that sunscreen users reported significantly more sunburns and sunbathing vacations and were more likely to use indoor tanning devices. However, $\text{SPF} \geq 15$ sunscreen use was associated with significantly decreased melanoma risk compared with $\text{SPF} < 15$ use. The estimated decrease in melanoma (PAF) with general use of $\text{SPF} \geq 15$ sunscreens by women age 40–75 years was 18% (95% CI 4–30%).

Primary skin cancer prevention behaviours, focusing on reducing the amount of UVR reaching the skin, include covering sun-exposed skin, wearing a hat and sunglasses, and sunscreen use. There is no high-quality experimental evidence on the efficacy of sunscreen to prevent melanoma; however it is important that patients and consumers do not stop protecting their skin until better-quality evidence emerges. The important message is that sunscreen should not be an excuse to prolong intentional sun exposure.

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