Melanoma Epidemiology and Prevention

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Abstract

The epidemiology of melanoma is complex, and individual risk depends on sun exposure, host factors, and genetic factors, and in their interactions as well. Sun exposure can be classified as intermittent, chronic, or cumulative (overall) exposure, and each appears to have a different effect on type of melanoma. Other environmental factors, such as chemical exposures—either through occupation, atmosphere, or food—may increase risk for melanoma, and this area warrants further study. Host factors that are well known to be important are the numbers and types of nevi and the skin phenotype. Genetic factors are classified as

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high-penetrant genes, moderate-risk genes, or low-risk genetic polymorphisms. Subtypes of tumors, such as BRAF-mutated tumors, have different risk factors as well as different therapies. Prevention of melanoma has been attempted using various strategies in specific subpopulations, but to date optimal interventions to reduce incidence have not emerged.

Keywords

Epidemiology · Risk factors · Genetic factors · Host characteristics · Prevention

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1 Epidemiology

1.1 Introduction

Melanoma incidence has increased dramatically over the last 50 years, rising from 8.2 to 9.4 cases per 100,000 population in 1975 (females and males, respectively), age-adjusted, to approximately 24.2 and 35.4 per 100,000 in 2010 (females and males, respectively), in the USA. Mortality has increased also, with a plateau among females being reached recently, but with continued increase among males. This chapter is designed to bring the most up-to-date and accurate knowledge about the epidemiology of melanoma and current preventive practices. The focus is mainly on risk factors with less attention to prevention because, surprisingly, there is no clear path to melanoma prevention. Although reduction of intermittent sun exposure seems the most logical way to prevent the disease, it has not produced robust evidence of reduced incidence and mortality, even in Australia where the most widely applied preventive work has been done over time. Clearly, there are some things we have yet to learn about melanoma in order to reduce morbidity and mortality from this lethal disease.

1.2 Risk Factors for Melanoma

1.2.1 Sun Exposure

Sun exposure is the major environmental cause of melanoma [111, 112]. The proportion of melanoma attributed to sun exposure has been estimated to more than 90 % in Australia, Canada, Nordic countries, Switzerland, and the USA [5, 72, 98, 245] and between 78 and 90 % in several other European countries [5] including the UK with a recent estimate of 86 % of melanoma due to sun exposure [192].

Our knowledge of the complex association between sun exposure and melanoma comes mainly from case-control and cohort epidemiological studies. The geographic distribution of melanoma and the results of migration studies also provide evidence for the importance of *ambient sun exposure* [90].

Measurements of individual exposure vary between studies but are commonly classified as *intermittent* (short, intense sun exposure through activities such as sunbathing, outdoor recreations, and holidays in sunny climates), *chronic* (more continuous, primarily occupational exposure), and *total* sun exposure (the sum of intermittent and chronic exposure). Several case-control and cohort studies have investigated the association between individual sun exposure and melanoma risk. Meta-analyses of these studies show consistent results [65, 75, 76, 178] that continue to be supported by the results of studies published after the meta-analyses were undertaken [112]. There is strong evidence that an intermittent pattern of sun exposure increases melanoma risk. Chronic sun exposure shows no association, or a weak inverse association with melanoma risk. Total lifetime sun exposure is positively associated with melanoma risk, but the relationship is weaker than that for

intermittent sun exposure. *Sunburn* is a marker of an intermittent pattern of sun exposure, and there is a tendency for greater consistency of positive associations for sunburn than for intermittent exposure. The summary relative risks (RR) and 95 % confidence intervals (95 % CI) for highest versus lowest category of exposure in meta-analyses of more than 50 studies were RR 2.0 (95 % CI 1.7–2.4) for sunburn, RR 1.6 (95 % CI 1.3–2.0) for intermittent, RR 1.0 (95 % CI 0.9–1.0) for chronic, and RR 1.3 (95 % CI 1.0–1.8) for total sun exposure [75, 76]. Moreover, significantly higher risk was found for intermittent than chronic exposure among studies that published results for both exposures, RR 1.5 (95 % CI 1.2–1.8) and RR 1.1 (95 % CI 0.9–1.4), respectively.

The weak association with chronic sun exposure may be due to its promotion of epithelial thickening and this together with a tanning effect may offer a modest protection against later exposure to solar radiation. Some of the studies of chronic sun exposure reported risk estimates below 1.00 [75, 76], but these results should not be interpreted as a protective effect. Chronic exposure is mainly occupational exposure for outdoor workers, and in studies of the different types of sun exposure, the reference categories may have consisted of individuals with high intermittent exposure together with individuals with low sun exposure, thereby artifactually producing low-risk ratios in those with high chronic exposure [90]. A recent analysis of two large case-control studies found no association between occupational exposure and melanoma risk and no indication of confounding by recreational exposure [236]. Importantly, the presence of solar keratoses, a marker of high cumulative sun exposure, is consistently positively associated with melanoma risk [90, 186].

Melanoma risk differs not only by pattern of sun exposure, but also by *body site*, *age*, and *phenotype of the host* (Sect. 1.2.3). This indicates that melanoma may arise through multiple causal pathways [241]. Head and neck melanomas have been linked to chronic sun exposure, with older age at diagnosis and melanoma on the trunk and limbs to younger ages and intermittent exposure. Notably, the available evidence suggests that sun exposure can cause melanoma on all body sites, but risks tend to be higher for usually sun-exposed sites than occasionally exposed sites [47, 90]. For sunburn, strong positive associations have been found at all body sites (head/neck, trunk, arms, and legs) and with no significant site-specific differences in recent meta-analyses and pooled analyses [47, 186].

Early-life sun exposure, sometimes decades before diagnosis, is probably important. Migration studies have found that *childhood* is a sensitive period [90]. The current evidence also suggests that melanoma risk continues to increase with accumulating intermittent sun exposure. Meta-analyses have reported increased melanoma risk with increasing number of sunburns during *all life periods* (childhood, adolescence, adulthood, and lifetime) [59], with no significant differences between sunburns in childhood and adulthood [75, 76].

The entire ultraviolet (UV) spectrum is classified as carcinogenic to humans [82]. Since most of UVB (280–315 nm) and all UVC (100–280 nm) are removed by stratospheric ozone, about 95 % of the midday solar UV radiation reaching the Earth's surface is UVA (315–400 nm) and 5 % UVB. Because individuals are

exposed simultaneously to UVA and UVB when outdoors, it is difficult to distinguish between the effects of UVA and UVB in human studies. UVB is an established risk factor for sunburn, while both UVB and UVA may cause melanoma [112].

1.2.2 Indoor Tanning

Several case-control and a few cohort studies have investigated indoor tanning in relation to melanoma [32], and a causal positive association has been established [112]. The summary relative risk in the most recent meta-analysis of cohort and population-based case-control studies was 1.3 (95 % CI 1.1–1.4) for ever versus never use [32] and increased to 1.6 (95 % CI 1.4–1.9) when first use was before 35 years of age [33]. Furthermore, the risk is found to increase with the number of sessions [32, 136]. There is no indication that the risk associated with indoor tanning is substantially confounded by sun exposure [32, 96, 233].

Indoor tanning is popular in many countries and has become an important source of UV exposure. Up to 95–100 % of the body is exposed in a sunbed compared to 15–50 % during outdoor activities [22]. Measurements of modern sunbeds show UV irradiance higher than midday summer sun in Southern Europe and Australia, and exceeding the limits allowed by safety standards/regulations [106] (IARC [111, 112]; Gies et al. [84]; Nilsen et al. [185]; Tierney et al. 229). We still do not know which UV wavelengths actually increase melanoma risk. The irradiance from modern sunbeds is mainly in the UVA range with a fraction of UVB [67, 106] (Gies et al. [84]; Nilsen et al. [185]), and this is alarming in light of the increased focus on UVA as a carcinogen [82].

1.2.3 Other Environmental Factors

While the overwhelming majority of epidemiologic research has properly focused on the relationship between host characteristics (including genetics), exposure to UV radiation, and risk of cutaneous melanoma, findings from a number of relatively small studies have suggested that there may be other factors influencing risk of the disease.

Occupation and Melanoma

Several studies have suggested that exposure to polycyclic aromatic hydrocarbons, benzene, or other chemicals used in the printing industry [3, 41, 142, 163, 183] are associated with the development of melanoma. Similarly, studies of chemical workers have also shown elevated risks of melanoma [171, 179, 224]. Cohort studies of electrical and electronics workers [146, 203, 220] along with at least one case-control study [179] have also shown elevated risks for melanoma. It has been hypothesized that workers in occupations exposed to ionizing radiation might also be at increased risk of melanoma [3, 71, 218, 238, 252].

A number of investigations [29, 91, 94, 196] of airline pilots and cabin crew who might presumably be routinely exposed to cosmic radiation during high-altitude flight have also produced results suggestive of an increase in risk of melanoma.

However, several cohort studies among airline crews have also proved negative for melanoma [197, 250]. A more detailed review of findings from occupational and environmental studies of melanoma is found in Fortes and de Vries [70].

It should be noted that not all studies show elevated risk in any of these industries or occupations. In addition, workers in chemical, electrical, and electronics industries are potentially exposed to a large number of agents in the workplace, making it difficult or impossible to relate the elevated risks to one or more specific chemicals. Most of the elevated risk estimates are based on relatively small numbers of melanoma cases, as the studies to date have been predominantly cohort investigations designed to evaluate incidence or mortality due to common cancers, and melanoma is still a relatively rare disease in most populations. Finally, these occupational studies are usually based only on employment records and thus cannot adjust for the major known risk factors for the disease including phenotypic characteristics, nevus density, and UV radiation exposure.

PCBs

Relatively few studies have been conducted to look for specific environmental risk factors for melanoma, but among these, a number of studies have shown an elevated risk in individuals with suspected exposure to organochlorine compounds, such as polychlorinated biphenyls (PCBs) and some chlorine-based pesticides [1, 146, 161, 198, 203, 207, 208, 220, 240, 248]. As noted above, although these studies have some significant limitations, the results, with few exceptions, for implied industrial PCB exposure have been fairly consistently positive.

PCBs are aromatic compounds containing between one and ten chlorine atoms attached to a biphenyl structure. There are 209 reported congeners or variants, and PCBs—used commercially initially as dielectric fluids in electrical capacitors and transformers—contain mixtures of many of the congeners [134]. As potential adverse effects of PCBs became clear, most countries banned their production and use—the USA, Canada, and Australia in the 1970s and the European Union in the 1980s. However, PCBs are extremely persistent organic pollutants and survive in the environment for many years. PCBs are known to bioaccumulate in adipose tissue, and most human exposure in developed countries is through dietary intake of fish and animal products. Animal studies have shown evidence of malignant and benign tumors in the liver, lung, and oral mucosa in rats [176, 177] for a number of PCB congeners. However, melanoma was not among the tumors assessed in these studies, as a suitable animal model for melanoma has not yet been found.

A number of carcinogenic mechanisms [127], including formation of reactive oxygen species [69, 145, 157], endocrine disruption [80, 180, 204], and immune compromise [50, 147, 162, 173, 174, 209, 219], are known to be activated by PCBs. The evidence that PCBs can cause immune suppression is of particular interest because melanoma risk is known to increase between threefold and fourfold in individuals who are immunosuppressed due to agents given for organ transplantation [104, 117, 138].

One of the major drawbacks of human studies of melanoma and PCBs noted above is that no direct biological measures have been made in study subjects. A recent case-control study [73] evaluated blood levels of 14 PCB congeners and 11 organochlorine pesticides in 80 melanoma cases and 310 controls, and these investigators found significantly increasing trends in risk for melanoma with increasing blood levels of total PCBs, non-dioxin-like PCBs, and dioxin-like PCBs. Significant but more modest positive relationships were also seen with levels of some chlorine-based pesticide residues. These results persisted after adjustment for phenotypic factors, sun sensitivity, and sun exposure. Although the results of this preliminary study need confirmation in other investigations, they suggest that further, more detailed studies of organic chlorine compounds and melanoma may be productive. Recently, the International Agency for Research on Cancer (IARC) has reclassified PCBs from Group 2 "probably carcinogenic to humans" to Group 1 "carcinogenic to humans" [134].

The information to date from studies of non-ultraviolet radiation (UVR)-related factors in relation to malignant melanoma is not strong. However, the more recent studies showing elevated risks in those with significant exposure through the workplace or with relatively high blood levels indicate that other factors aside from UVR may play a part in the etiology of the disease.

Chromium

As our understanding of the molecular changes that accompany melanomagenesis increases [14, 53], it has become apparent that in contrast to non-melanoma skin cancer, the singular role of UVR in melanomagenesis has become less certain [166, 167]. Not all of the attributable risk for cutaneous melanoma can be linked to UVR exposure, and the molecular pathology suggests that UVR alone may not be the etiologic agent [14]. Additionally, only about 10 % of melanomas have a strong Mendelian (heritable) component. Clearly, there are likely to be any number of cocarcinogens. A vexing and unexplained clinical observation is that Albino Africans develop multiple and often severe squamous cell carcinomas but very, very few melanomas [61], suggesting that melanin is necessary for the development of melanoma, and melanin interacts with heavy metals.

Chromium, specifically hexavalent chromium Cr(VI), has been classified as a class I human carcinogen for quite some time. Occupational epidemiology has strongly implicated exposure by welders and others as contributing to the pathogenesis of lung cancer [122, 123, 214]. There is also considerable data that document that Cr(VI) can cause lung tumors in mice [251] as well as a TH1-driven response indicative of type IV hypersensitivity [38].

The possible role of Cr(VI) in melanomagenesis was stimulated by participation in the CARET, in which it was demonstrated that β-carotene supplementation led to more, rather than fewer, lung cancers in smokers [187]. Redox metabolism is important in β-carotene and in melanocytes and melanoma cells; subsequently, the possible role of heavy metals was thus investigated as *a redox factor* [166].

Austin and Reynolds [8] were the first to point out the association between heavy metal exposure and an increase in risk for melanoma. Concern about the

effect of metal shedding, both local and systemically, led to a seminal epidemiologic meta-analysis study of other diseases in patients receiving hip-on-hip metal arthroplasties [188]. The crucial observation was that only melanoma was increased in these patients and in a time-related manner. A complex Nordic study also suggested a marked increase in both melanoma and prostate cancer [235]. However, a large (40,576 patients with hip replacement with metal-on-metal bearing surfaces and 248,995 with alternative bearings) but short-term (7 years) study of risk of malignant melanoma, hematologic malignancies, and prostate and renal tract cancers has demonstrated no increase in these malignancies [222].

Case and colleagues [122] conducted extensive studies in patients, and these have led to the following general observations [122, 132]: (1) Cr(VI) and cobalt (Co) were shed into the bloodstream of patients with prior metal-on-metal hip arthroplasties, but not in non-metal or knee arthroplasties (in which there is no direct metal–metal contact). (2) The concentration of Cr(VI) in the blood of these patients peaked at 6–12 years at 10 times "normal" levels and was measurable up to 10 years later. (3) Prospective follow-up also showed that there was also a statistically significant increase of both chromosome translocations and aneuploidy in peripheral blood lymphocytes at 6, 12, and 24 months after surgery. The changes were generally progressive with time, but the change in aneuploidy was much greater than that in chromosome translocations. However, no statistically significant correlations were found in secondary analyses between chromosome translocation indices and cobalt or chromium concentration in whole blood.

Experimental evidence shows that Cr(VI) may be involved in melanomagenesis [167]. Prolonged incubation of human melanocytes with a wide variety of metals at low non-toxic doses produced no effects. However, exposure to Cr(VI) resulted in morphological changes, aneuploidy was detected, and when cells from primary colonies were replated, secondary colonies formed. Additionally, exposure of human melanocytes to UVR and some metals causes bleaching of melanosomes and a pro-oxidant state [83]. Other physical evidence suggests a role in melanomagenesis as a wide variety of insecticides, PCBs, and metals (including chromium) have been identified bound to melanin [211]. These substances can convert the natural antioxidant to a pro-oxidant after UVR exposure. A separate piece of experimental evidence has emanated from the sequencing of a human melanoma [193]. The genomic results strongly indicated that both UV-induced and non-UV-induced DNA damages [a type associated with CR(VI)] were present. The evidence for a cocarcinogenesis role of hexavalent chromium in melanomagenesis is compelling and suggests that further investigation should lead to new etiologic and mechanistic insights.

1.2.4 Host Factors

Host factors greatly modify an individual's response to UVR, the principal environmental risk factor for melanoma. Host factors in this section refer to pigmentation characteristics: nevi; skin, hair, and eye colors; ability to tan; and propensity to burn.

Nevi

A major risk factor for melanoma is number and type of nevi. Nevi are benign collections of melanocytes, and the numbers of nevi have been implicated in numerous studies as the most important risk factor for melanoma, with an increased number of nevi associated with an increased risk of disease [15, 24, 158, 230]. A meta-analysis has shown that individuals with more than 100 normal nevi are at an almost seven times greater risk than individuals with few (≤15) nevi [75, 76]. The increase in risk is also thought to be incremental and proportional to the number of nevi present [158, 159]. It has been shown that the presence of 11–25 nevi conferred a 1.5-fold increase in risk compared with fewer than 10 nevi, and this risk doubled with each additional 25 nevi [158]. The size of the actual nevus also increases the risk of melanoma, especially those greater than 2.0 mm in diameter. The role of nevi as precursors of melanoma or markers of melanoma risk is controversial. They are, however, common adjacent to thin melanomas (those less than 1.70 mm) and less common among the thicker melanomas [210]. Approximately 50 % of melanomas less than 1.0 mm have adjacent neval remnants [221]. Still, many melanomas arise de novo; it is clear that individuals with many nevi are at high risk for developing melanoma [159].

Dysplastic or atypical nevi are also associated with an increased risk of melanoma. This subset of nevi are typified by cytological abnormality, with one definition requiring a macular component to at least one area of the lesion and at least three of either: an ill-defined border, an uneven contour, the presence of erythema, and variations in color or size greater than 5 mm [75, 76, 158]. Individuals with only one atypical lesion are already at a 1.6 times greater risk of melanoma, increasing to a tenfold greater risk with the presence of five or more atypical nevi [75, 76].

Atypical mole syndrome (also known as dysplastic nevus syndrome or familial atypical multiple mole and melanoma syndrome) is a rare phenotype characterized by at least two atypical nevi, high numbers (>100) of normal nevi and nevi on unusual body sites, such as the scalp, soles of the feet, buttocks, or breasts [15, 158]. Individuals with atypical mole syndrome, especially in conjunction with a family history of melanoma, are at an even greater risk of developing melanoma.

The exact nature of the role of nevi in melanoma development and progression is yet to be fully understood. This is likely to be, in part, because the factors affecting nevus expression and development are also complex and yet to be fully elucidated. A twin study found that the contribution of genetic factors to nevus expression was mediated by sun exposure and that with age, the component due to sun exposure declined greatly, increasing the proportion of nevus expression due to genetics [16]. Nevi on body sites regularly exposed to the sun had a smaller genetic contribution to variance than nevi on sun-protected sites, suggesting a greater environmental effect of sun exposure on the development of nevi on exposed body sites.

An interaction between sun exposure and nevi has been observed in various other investigations [24]. A study of Australian children found that increased sun exposure in childhood was significantly associated with an increased number of

nevi [97]. A separate study of German adults found that intense, intermittent sun exposure in childhood or adolescence, characterized by sunburn, was significantly associated with high nevus counts and the occurrence of atypical nevi [77]. The authors suggested that sun exposure might induce nevus development, which subsequently affects risk of melanoma [77].

As noted earlier in this chapter, Whiteman et al. [242] have put forward a hypothesis for two divergent pathways for melanoma development on differing body sites. They propose that some individuals are prone to melanoma due to chronic sun exposure and are therefore more likely to develop melanoma on body sites regularly exposed to the sun, like the face. Alternatively, other individuals with a propensity for melanocytic instability are at risk of developing melanoma via a proliferative melanocytic pathway, characterized by atypical nevi or high numbers of nevi [24, 242]. The authors predict that melanoma development in the latter group of individuals is instigated early in life by sun exposure and then driven by other risk factors. They are therefore more likely to develop melanoma on body sites not chronically exposed to sunlight, such as the trunk, perhaps due to unstable melanocytic development. Supporting this theory are findings from an Italian study [49]. These studies found individuals with melanoma on the head or face significantly more likely to have fewer nevi and, conversely, individuals with melanoma on the trunk more likely to have high nevus counts.

Other Pigmentation Factors

Pigmentation characteristics are well-established host risk factors for melanoma, with skin, eye, and hair colors all known to be associated with susceptibility. An inverse relationship has been consistently demonstrated between melanoma risk and degree of skin pigmentation [6, 24, 159]. Fair-skinned individuals have a much higher risk for developing melanoma than dark-skinned individuals, such that risk estimates in individuals of non-European descent, who are typically darker-skinned, are up to 10–20-fold less than those in individuals of European descent, who are typically lighter-skinned [15, 230].

Skin reaction to the sun is also a predictor of melanoma risk. Skin that freckles easily has a tendency to burn or an inability to tan, showing an increased propensity for the disease [37, 159, 230]. Some authors have hypothesized that skin reaction contributes less to melanoma risk than actual skin color, while others have postulated that skin reaction is a better predictor of risk than skin color [6, 159]. Analytically, skin reactivity has been shown to be a strong, independent predictor of susceptibility to melanoma and may also be a more robust measure of pigmentation due to the issues surrounding accurate measurement of skin pigmentation within and across studies [6, 230].

A pooled analysis of 10 case-control studies [30] showed that both fair skin types and a high degree of freckling were associated with a twofold increase in risk of developing melanoma, independent of each other, hair color and number of nevi. The effect of freckling on risk was notably mediated by age, with a much higher risk found in those less than 40 years of age. This could be related to the stronger predictive effect of sun exposure in childhood and adolescence, with degree of

freckling acting as a marker for degree of sun exposure as well as an indicator of melanocyte instability.

This pooled analysis, along with numerous other epidemiological studies [158, 230], found an increased risk of melanoma among individuals with red or blonde hair, or blue or green eyes. While Bliss et al. [30] found hair and eye colors to be independent risk factors for melanoma, Gandini et al. [75, 76] have questioned whether the association between these traits is completely independent of skin color. While clearly associated with melanoma, they argue that it cannot be a causal relationship and that they appear to be risk factors for the disease simply due to their correlation with skin pigmentation. As a result, a number of investigators have formed indexes to avoid collinearity in pigmentation characteristics and risk. Furthermore, as eye and hair colors are less prone to misclassification or recall bias than measurements of skin color or skin reaction to the sun, they may represent a more accurate marker of overall pigmentation traits, strengthening their association with melanoma susceptibility [75, 76].

As with many factors affecting melanoma risk, the relationship with pigmentation characteristics is complicated and still not clearly understood. Further complexities lie in the known and potential underlying genetic variants associated with pigmentation.

1.2.5 Germline Genetic Factors and Genome-Wide Association Studies (GWAS)

Melanoma sometimes develops within families (about 10 % of people with melanoma report a first- or second-degree relative with melanoma [99]), but this occurrence may be due to relatives sharing either genetic risk factors or environmental risk factors such as excessive sun exposure, or both. A population-based study of Australian twins estimated that 55 % of the variation in susceptibility to melanoma is due to genetic influences [215]. Genetic factors have also been shown to contribute as much or more to melanoma risk prediction than classical risk factors, over and above pigmentary effects [57]. The discovery of melanoma susceptibility genes can improve our knowledge of the biological pathways involved in melanoma development. This knowledge can be translated into potential new targets for future therapies and more accurate melanoma prediction tools which can improve our identification of people at high risk for melanoma who might benefit from screening or targeted prevention strategies [57].

High-Penetrance Gene Mutations

CDKN2A on chromosome 9p21 was identified in 1994 as the first high-penetrance melanoma susceptibility gene [119, 165]. *CDKN2A* encodes two distinct proteins, p16INK4A and p14ARF, which are involved in cell cycle control, tumor suppression, and melanocyte senescence [165]. The p16INK4A protein binds to the cyclin-dependent kinases CDK4 and CDK6, inhibiting phosphorylation of the retinoblastoma protein and progression of the cell through the G1 cell cycle checkpoint. The p14ARF protein induces cell cycle arrest or apoptosis via the p53

pathway. Mutations in the *CDK4* gene are also associated with very high risk of melanoma, and the activities of *CDK4* and p16 have similar downstream effects [99]. However, *CDK4* mutations are very rare and only found in a handful of melanoma families worldwide [99].

Only about 2 % of all melanoma cases in the population carry a *CDKN2A* mutation, but the probability is much higher when a strong family history of melanoma or multiple primary tumors are present [26, 87]; as such, *CDKN2A* mutations are estimated to account for approximately 40 % of familial cases [87]. Carriers of a *CDKN2A* mutation have a substantial lifetime risk of developing cutaneous malignant melanoma; population-based estimates indicate that around 30–50 % of mutation carriers will develop melanoma by 80 years of age [20, 58], whereas lifetime risk estimates derived from clinic-based sampling (of families with multiple cases of melanoma) range from 58 to 90 % penetrance by 80 years of age [27].

Intermediate-Risk Gene Variants

The melanocortin-1 receptor (*MC1R*) gene, which encodes the melanocyte-stimulating hormone receptor, was identified as the first low- to medium-penetrance gene associated with melanoma risk [99, 232]. It is one of the major genes that determine skin and hair colors, although there is evidence that it acts via pigmentary and non-pigmentary pathways to influence melanoma development [56, 120, 201]. There are many common variants of *MC1R* [121], but only six of them are usually referred to as "red hair color phenotype" or "R" variants (associated with red hair, fair skin, freckling, poor sun sensitivity) and are associated with a greater-than-twofold increased risk of melanoma [56, 201, 243, 244]. The other *MC1R* variants (usually referred to as "r" or "non-RHC") generally have a relatively weak association with red hair color phenotype and have a weaker association with melanoma risk [56, 201, 243, 244]. Although each variant individually is associated with a small increase in risk of melanoma, some people carry more than one variant and the combined effect can be large (e.g., more than fourfold increased risk of melanoma for people carrying 2 "R" alleles compared to wild-type alleles). Also, since the prevalence of *MC1R* variants conveying elevated risk in populations of European origin is very high (ranging up to about 70 %) [56, 120], as a group they account for a substantial proportion of disease in the population [243, 244]. It is estimated that approximately 21 % of the familial aggregation of melanoma among those developing melanoma under the age of 40 is explained by MC1R variants, assuming a multiplicative polygenic risk model [56].

More recently, *MITF*, the microphthalmia-associated transcription factor, was identified as a medium-penetrance melanoma susceptibility gene through a candidate gene approach in individuals affected with melanoma and renal cell carcinoma [21] and whole-genome sequencing of melanoma-prone families [249]. *MITF* regulates several other genes whose functions in melanocytes range from development, differentiation, survival, cell cycle regulation, and pigment production [249]. The *MITF* E318K variant allele is relatively uncommon in the population (about 1 % prevalence) but is associated with a 2–3-fold increased risk of

melanoma, which is higher for those with multiple primary melanomas [249]. The presence of the E318K variant allele is associated with a higher nevus count and non-blue eye color.

Of interest, it has been shown that variation in *MC1R* and *MITF* is more strongly associated with melanoma in people with darker phenotypic traits than those with fairer complexions [25, 56, 120] and that risk of melanoma among carriers with "low-risk" phenotypes was as great or greater than among those with "at-risk" phenotypes with few exceptions [25].

Low-Penetrance Gene Variants

Since 2008, a series of genome-wide association studies (GWAS) has led to a substantial increase in our understanding of melanoma genetics [2, 13, 28, 39, 135, 149]. While the discovery of high- and medium-penetrance susceptibility genes has used genetic linkage and candidate gene approaches in families with a strong family history, the discovery of low-penetrance susceptibility genes relies on large, often unselected case-control studies.

As expected, these GWAS have identified or confirmed variants in or near pigmentation genes as being associated with melanoma risk, including *MC1R*, *TYR*, *ASIP*, *SLC45A2*, *IRF4*, and *TYRP1*. Risk variants for melanoma also lie in or near *MTAP*, *PLA2G6*, and *IRF4*, *TERT/CLPTM1L*, loci that have been shown to be associated with nevus count variation. However, one of the most important developments to come from the GWAS approach is the identification of susceptibility genes that do not act via pigmentation pathways but instead are involved in other cellular processes such as DNA repair and cell cycle control; these include genes in or near *ATM*, *CASP8*, *CCND1*, *MX2* [2, 13, 135, 149], and *FTO*, which appear to have a broader function than its obesity-related effects [113]. The minor allele frequencies for these genomic variants are in the range of 1–49 %, and the risk of melanoma associated with the risk allele is in the range of a 1–2-fold increased risk [135]. On their own, each of these variants only slightly increases risk of melanoma; however, carrying several variants can significantly increase melanoma risk, which may also be further modified by environmental factors such as UV exposure.

Future Directions

Future directions in this field include determining which are the causal variants associated with melanoma risk, determining the biological mechanisms underlying the non-pigmentary associations, evaluating the gene–gene and gene-environment interactions, and incorporating genetic variants into melanoma risk prediction models and testing their effect on motivating risk-reducing behaviors as a cancer prevention strategy.

1.2.6 Somatic Genetic Factors: Tumor Subtypes

Another direction related to genetic analyses is based on tumor, or somatic, alterations. Melanoma is a heterogeneous disease with a variety of histologic subtypes

and complex epidemiology. Age-specific incidence patterns display early- and late-onset peak frequencies for trunk and face/ear melanomas, respectively [130, 131], consistent with hypotheses that melanoma arises from more than one causal pathway and contain distinct melanoma genotypes [241]. *NRAS* and *BRAF* mutations, mutually exclusive of each other, are found, respectively, in 10–30 and 25–60 % of primary melanomas [60, 63, 64, 93, 228]. Less frequently, melanomas contain *KIT* mutations, particularly mucosal melanoma or melanomas arising on acral or on sun-damaged sites [53]. *GNAQ* and *GNA11* mutations were discovered in uveal and CNS melanomas, defining additional molecular melanoma subgroups [81, 129, 200]. Frequently, melanomas also contain *PTEN*, *CDKN2A*, *CDK4*, and *CCND1* copy number alterations that help to define molecular subgroups [54, 55].

Newer high-throughput sequencing methods for tumors have allowed studies to identify many additional somatic mutations in melanomas [103, 110, 128, 156, 239], including *NF1* and *RAC1* mutations (5 % of cases) and *BRAF* gene fusions [35, 110]. Recently, it was also discovered that 30–40 % of melanomas harbor mutations in the promoter region of the telomerase reverse transcriptase (*TERT*) gene, and these *TERT* promoter mutations were found to occur more frequently in *BRAF*-mutant melanomas [101, 105, 108, 107]. The contribution of these newly discovered mutations to melanoma subclassifications remains to be fully elucidated.

Clinical Characteristics of Tumor Subtypes

BRAF- and *NRAS*-mutant melanomas have been examined in several studies in relationship to their clinical characteristics. *BRAF*-mutant melanomas are associated with young age at diagnosis, intermittently sun-exposed sites such as the trunk, superficial spreading subtype, absence of solar elastosis, and presence of mitoses [17, 60, 63, 64, 93, 144, 155, 228]. *NRAS*-mutant melanomas are associated with older age at diagnosis, but less associated with specific anatomic location, are more likely to be nodular subtype, and show increased Breslow thickness and presence of mitoses [60, 63, 64, 86, 139, 228, 231, 234]. Interestingly, *RAC1*-mutant melanomas are more common in older men on the head and neck location [128], while *TERT* promoter mutations in melanomas are associated with older age, increased Breslow thickness, nodular subtype, and tumor ulceration [101].

BRAF-mutant melanomas were found to be more common in patients with increased numbers of nevi [93, 228] and with the presence of nevi adjacent to the melanomas [63, 195]. These findings are plausible as approximately 70 % of nevi contain *BRAF* mutations [194]. *BRAF* mutations were associated with the ability to tan but not with freckling or hair or eye color [93, 228]. *TERT* promoter mutations in melanoma were not associated with hair, skin, or eye color or number of nevi [101].

Sun Exposure and Tumor Subtypes

The mechanistic contribution of sun exposure to melanomagenesis remains to be elucidated. Most studies note indirect evidence, such as associations between mutations with anatomic site, to infer a relationship to UV exposure; however, body site alone may influence mutational status. Studies examining sun exposure

questionnaire data found that *BRAF*-mutant melanoma was associated with high early-life ambient [228] and individual self-reported childhood sun exposure [144] and was less likely to occur in people with high cumulative sun exposure [92]. However, these results remain to be replicated. Of note, while the majority of *BRAF*-mutant melanomas harbor a single base change resulting in *BRAF*V600E alteration, approximately 10 % of *BRAF* mutations in melanoma contain two adjacent base changes, tandem mutations [226] that have not been found in *BRAF*-mutant tumors of other types, such as colon and lung cancers. It is possible that these tissue-specific tandem mutations arise related to UV exposure [227]. The *BRAF*V600K tandem mutation has engendered particular interest. Among a cohort of Australian patients with metastatic melanoma, the frequency of non-*BRAF*V600E, including V600K, mutations increased with older age and histologic solar elastosis at the primary melanoma site [164]. In a North European cohort, participants with *BRAF*V600K-mutated melanoma were significantly older at diagnosis than those with *BRAF*V600E-mutated melanoma [118]. In an Austrian cohort, *BRAF*V600K mutations were more frequent than *BRAF*V600E mutations in in situ lentigo maligna melanomas [223]. However, we are not aware of a study that has examined *BRAF*V600K-mutant melanoma in relationship to reported sun exposure.

A variety of evidence suggests that UVB exposure might be responsible for mutations in melanoma tumor suppressor genes. *PTEN*, *CDKN2A*, and *P53* harbor higher rates of UVB signature mutations than oncogenic *BRAF* and *NRAS* variants, and *TP53* and *CDKN2A* harbor higher rates of UVB signature mutations than non-skin cancers [102]. Furthermore, *PTEN* mutations occur in approximately 50 % of melanomas from xeroderma pigmentosum patients, who are susceptible to UV mutagenesis, while *BRAF*, *NRAS*, and *KIT* mutation frequencies were lower than *PTEN* [160]. Next-generation sequencing has more recently identified UVB signature hot spot mutations in putative oncogenes, including at *PPP6C* R264C, *STK19* D89N, and *RAC1* P29S [103, 128]. In addition, *TERT* promoter mutations in melanoma, also UVB signature mutations, are more frequent at both chronically and intermittently sun-exposed than non-exposed sites, although these mutations were not associated with reported sun behavior [101]. Additional work will be necessary to collect epidemiologic evidence, including from sun exposure questionnaires, as to whether these mutations are associated with ambient exposure, sun behaviors, and patterns of UV exposures.

Melanocortin-1 receptor (*MC1R*), which is a highly polymorphic gene whose variants are associated with red hair, fair traits, and melanoma risk, was found to be strongly associated with *BRAF*-mutant melanoma on non-chronically sun-damaged skin in US and Italian cohorts [133] and regardless of signs of chronic solar damage in a separate Italian cohort [68]. However, studies conducted in North Carolina and Australia found no association between carriage of *MC1R* variants and *BRAF*-mutant melanoma [93, 228], while a study conducted in Germany found *BRAF*-mutant melanoma to be less frequent among *MC1R* variant carriers than non-carriers, with the effect dependent entirely upon the nodular subtype [212]. A recent study in Spanish and Austrian populations found no association of *MC1R*

status with *BRAF*-mutant melanoma across all tumor sites but a non-significant association for truncal melanoma and a significant inverse association between *MC1R* variants and *BRAF*-mutant melanomas of the head and neck [92]. Additional larger—perhaps international—studies seem necessary to provide any real understanding of the association of *MC1R* variants with *BRAF*-mutant melanoma in the context of possible anatomic site and histologic subtype dependencies.

In conclusion, it has become clear that *BRAF*, *NRAS*, *KIT*, *GNAQ*, and *GNA11* mutations in melanoma contribute to the definitions of melanoma subgroups. Additional mutations recently identified in tumor suppressor genes and oncogenes are expected to refine this classification. Much work is anticipated to determine the associations of these mutational subgroups with genetic risk factors, sun exposure, and outcomes. Understanding the risk based on mutation subgroups is ultimately expected to contribute to our understanding of how to design targeted prevention messages.

1.2.7 Gene-Environment Interaction

The interactions revealed through the Genes Environment and Melanoma study (GEM) analyses will identify some of the "missing heritability" that GWAS have not found [253]. Few new studies address the gaps or the need to identify risk for melanoma among those without traditional risk factors. Our GEM analysis of a rare MITF mutation shows significant interactions with low nevus density and dark hair color [25]. GWAS of melanoma have identified additional genetic risk factors but unfortunately have not yet been useful for public health interventions. It is critical to identify genetic factors in concert with the environmental factors, mainly UV exposure, and to be able to control for moderators, such as pigmentation and number of nevi, as did Thomas et al. [228] with risk in GEM for BRAF mutations. Approximately 10–15 % of individuals diagnosed with melanoma can expect to die from their disease. At this point in time, there are no reliable biomarkers to distinguish aggressive melanoma from a more indolent lesion. Exciting progress in treatment has been made in the last few years—using immunotherapy (anti-CTLA-4, anti-PD-1, chimeric antigen receptor therapy); however, life has not been significantly prolonged by treatment and still only one-third of patients respond. Researchers are largely clueless as to why more don't benefit [52]. If we could identify lesions that are aggressive at early stages of the disease, we could make a huge impact on disease-specific mortality.

1.3 Survival and Melanoma

1.3.1 Ecologic Studies

Ecologic studies are subject to many unknown biases. However, they can also provide insights into scientific problems and so have utility. In the area of melanoma mortality, there are few large studies that have been conducted, so the large databases maintained by the US SEER program and the WHO database can be helpful

to evaluate trends over time and by latitude. Some time ago, Lemish et al. [141] observed that survival from melanoma increased with increasing melanoma incidence among several populations and suggested that high levels of ambient sun exposure might induce a more biologically benign type of melanoma. Recent data evaluating a very large number of populations support this association of the positive temporal and geographic association with incidence and survival [7].

Conflicting analyses, however, exist. For example, two studies have found no association between latitude or other measures of UV exposure and mortality from melanoma in the USA [116, 130, 131]; however, others have reported a positive association between increasing latitude (decreasing UV) and increasing melanoma mortality rates [46, 216] or a negative association between increasing latitude and melanoma mortality [34, 66, 78].

A different measure of previous sun exposure derived for ecologic study is season of diagnosis. Seasonality of diagnosis has been shown to be associated with melanoma mortality in one study. Boniol et al. [31] found that in Australia, those diagnosed in the summer had a significantly reduced risk of dying from melanoma compared to those diagnosed in the winter with a hazard ratio (HR) of 0.72 (95 % CI 0.65–0.81). Again, there are conflicting data. A report from Spain [172] showed a significant association between diagnosis in July and August (the Spanish summer) and mortality from melanoma. Finally, another report from Australia [115] found no association between season of diagnosis and survival from melanoma in Victoria. Clearly, the weight of the evidence for melanoma in these ecological studies does not support a role for diagnosis during the summer and improved survival.

So, in summary, the ecologic studies are mixed in their results, but the weight of the evidence no longer supports a strong positive association between latitude and UV exposure.

1.3.2 Analytic Studies

Unfortunately, few analytic studies have interviewed patients for sun exposure and residential histories and then followed subjects for mortality. Berwick et al. [23] reported an inverse association between measures of solar exposure and melanoma mortality. The authors suggested that this provocative finding might indicate a beneficial effect of sun exposure in relationship to survival with melanoma mediated by vitamin D produced by sun exposure. Alternative hypotheses were also offered that previous sun exposure might induce more indolent melanomas through increased melanization and DNA repair capacity.

Interestingly, Heenan et al. [100] published a somewhat similar analysis finding that solar elastosis was of borderline significance (P for trend = 0.07) and inversely associated with death from melanoma.

Rosso et al. [206] have also suggested that intense intermittent sun exposure prior to the diagnosis of melanoma is associated with an improved survival. A study from the UK measured serum vitamin D at diagnosis and found that those with the highest level of serum vitamin D had the best survival [181].

To add to the confusion, Berwick and colleagues [25] have now analyzed survival data from a very large international cohort of melanoma patients and find that there is little association between sun exposure prior to diagnosis and melanoma survival. This seems like a reasonable conclusion given the mixed evidence presented above.

In summary, the analytic studies evaluating mortality in relationship to solar exposure prior to diagnosis have quite mixed results. The discrepancy among studies is worthy of further investigation. Analytic studies are generally considered to be more valid than ecologic studies and could come up with different interpretations of data because they may suffer less from misclassification of solar UV. In addition, measures of individual sun exposure are likely to be more precise than those estimated by latitude or UV exposure, regardless of how measured.

2 Prevention and Evaluation of Efficacy

Prevention of sunburn and reduction of time spent in the sun has been the aim of many sun safety interventions. These interventions have focused on children and adults in settings ranging from childcare facilities, schools, and outdoor recreation sites to workplaces and community-wide campaigns that attempt to reach at-risk populations in a variety of venues. Interventions have primarily relied on training, education, and communication, with a few including distribution of sun protective products (e.g., sunscreen) and organizational actions and policies.

Metrics for both sunburn and time spent in the sun have varied. Sunburn has been measured as either any sunburn or number of sunburns. Time in the sun has been assessed through reported amount of time outdoors, with some studies focusing simply on time spent sunbathing for the purpose of getting a suntan and others distinguishing intentional exposure such as sunbathing from incidental sun exposure associated with outdoor recreation. Observational methods for assessing sun exposure have been used which include assessment of skin color change, measures of UV from polysulfone badges worn by respondents, and counts of melanocytic nevi. Unfortunately, there is no "gold standard" for assessing changes in solar UV exposure, rendering comparison of results from different prevention studies difficult.

The public commonly assumes that sunscreen is a good preventive measure against skin cancer, including melanoma. This assumption was confirmed by a randomized controlled trial (RCT) of regular sunscreen use among 1621 people aged 25–75 in Queensland, Australia, and demonstrated a 50 % reduction (hazard ratio 0.50; 95 % CI 0.24–1.02; $P = 0.051$) in melanoma incidence, particularly invasive melanomas (hazard ratio 0.27; 95 % CI 0.08–0.97) at a 10-year follow-up. This finding was echoed in an observational study [137] where they found that routine use of sunscreen and other sun protection methods was higher among controls than among cases ($P = 0.03$) and other sun protection methods ($P = 0.006$). However, in this study, the authors are cautious about the results as few used sunscreen routinely and the measures of other sun protection methods lacked specificity.

2.1 Interventions in Childcare and School Settings

Studies that evaluated sun safety interventions for children in childcare and school settings have provided mixed results on the effectiveness of these. In childcare settings, two studies reported no change in sun exposure measured by parent reports or by change in melanocytic nevi in the children's skin [18, 19, 246], but one study did find that children spent less time outdoors during peak sun hours at childcare centers with sun protection policies [124]. One study also failed to produce changes in sunburn prevalence after an educational intervention with parents [18, 19].

Several interventions directed at primary school-aged children have resulted in reduced sun exposure measured by self-reports, UVR (UV)-sensitive dosimeters, skin color change, or development of fewer melanocytic nevi [43, 44, 45, 51, 109, 126, 140, 169, 170], but a few did not affect sun exposure [85, 109, 205]. These interventions involved instructional materials inserted into the school curriculum or had dermatologists talk with staff and parents.

A limited number of interventions have been evaluated with secondary school-aged children. One intervention using instructional materials inserted into the school curriculum reduced sun exposure or sunbathing [213], but another study using school-based instruction did not [44, 45]. Also, a recent study of an Internet-delivered curriculum did not improve the frequency of sunbathing [40].

Interventions containing appearance-focused messaging or photo-aging information, including UV imaging, have reduced college students' time in the sun [114, 150], although regional differences have been seen in this effect [152]. Some interventions have failed to influence time in the sun [143, 151, 154, 202] or actually produced increased sun exposure on some measures [48]. In some of these interventions, college students were provided with sunscreen and UV monitors, too [48, 114, 202].

Studies on interventions in schools have also produced some evidence that they can reduce sunburn. Sunburn incidence has been reduced with interventions in primary schools [42], secondary schools [40], and college [143]. However, studies in these contexts have also failed to report change in sunburn [18, 19, 51, 175, 199], and one study found increased sunburn frequency post-intervention [48].

2.2 Interventions in Occupational Settings

Interventions targeting sun exposure and sunburn in workplaces have been less common than those delivered in school settings; however, they have generally been effective at improving both outcomes. Specifically, one study of a 10-year follow-up to yearly education and mandatory sun protection policy with road workers found reduced sun exposure measured by skin tanning and solar keratosis [247]. Another study on ski area employees found reduction in sunburns by employees immediately [42] although this reduction was no longer evident in the following summer [4] or when the intervention was distributed throughout the North American ski industry [4]. Finally, the sun protection program at ski areas did not affect sunburn prevalence among guests [237].

Likewise, an intervention for swimming pools that included signage, program guidebooks, and instructions on training lifeguards to teach sun safety to children reduced sunburns among lifeguards in a randomized trial [79]. This intervention remained effective at decreasing sunburns among lifeguards when disseminated nationwide to pools where lifeguards also reported the presence of pool policies to promote sun safety to children and parents and teaching sun safety to children [95].

2.3 Interventions in Outdoor Recreation

Sun safety interventions in outdoor recreation settings have able to reduce sun exposure and sunburn. One study delivering photo-aging information, photograph of UV damage, and free sunscreen did find some reduction in sunbathing but not in incidental sun exposure [153]. Another study on a similar intervention with beach visitors reduced their frequency of sunbathing and prevalence of sunburn at a 2-month follow-up but only sunbathing and not sunburn prevalence at a 1-year follow-up [191]. A third study conveying risk information and UV photographs did not affect sun exposure [190]. However, a fourth intervention that included information on the harms of sun exposure and benefits of protection on sunscreen labels decreased sunburn prevalence but not time in the intense sun [182].

2.4 Interventions on Dermatology Patients

Two recent evaluations have explored whether interventions with dermatology patients can decrease sun exposure and sunburns. One study in China did report decreased sun exposure following clinic-based education and provision of sunscreen [108, 107], but another study in the USA intervening with melanoma patients with the aim of improving protection of their children found no overall impact on children's time outdoors or sunburn [89]. Parents at moderate to high risk of developing skin cancer limited their time in the sun following an intervention using printed information and telephone contact but did not change their children's sun exposure [125].

2.5 Community-Wide Interventions

Finally, a small number of studies have examined the effect of community-wide interventions that convey sun protection messages through a variety of venues. The longest intervention is the SunSmart campaign in Australia. The latest time series evaluation showed that time spent outdoors in the sun and incidence of sunburn had declined over the years of the campaign [62]. A community-wide intervention in Falmouth, Massachusetts, also reported a reduction in painful sunburns in children but no change in their sun exposure [168]; however, this intervention was limited

by the cross-sectional nature of the evaluation, so that the individuals responding at baseline were not the same individuals responding after the intervention.

2.6 Does Sun Safety Increase Time in the Sun?

A few studies mentioned earlier found that time in the sun increased following the prevention intervention, which raises concerns that people use sun protection and exposure to prolong intentionally their time in the sun. This same concern has been advanced in studies showing that population that used sunscreen had greater melanocytic nevi, an indicator of sun exposure [9, 10, 11, 12, 18, 19, 148], although a recent study from Canada found that sunscreen reduced nevi in a randomized prospective design [74]. The negative effects of sunscreen may be most evident when individuals choose to be outdoors in the sun rather than when their time in the sun is determined by factors out of their control such as work schedules. However, it is also possible that this effect arises from confounding by indication, where individuals who need and use sunscreens the most have sun-sensitive light skin and are at highest risk of more nevi, regardless of their amount of sun exposure. Individuals who engage in other sun safety practices may be able to spend extended time outside without obtaining high doses of solar UVR [36]. Also, sun exposure can have benefits, including the production of vitamin D. The aim is to achieve the right balance.

2.7 Limitations

A few limitations to the research on interventions to prevent sunburn and reduce time in the midday sun are worth noting. Some studies had poor-quality designs (e.g., lack of a control group, small samples). Many studies relied on self-report measures of sunburn and time in the midday sun. There is evidence that self-reports on sunburns can be valid [36, 189, 225], but an expert panel recommended that measures define sunburn (e.g., red and/or painful from exposure to the sun) and provide a specific recall period (e.g., past three months) [217]. Observational measures of time in the sun by colorimeter assessments of change in skin color have limitations, too (e.g., color can fade; precise amount of exposure is difficult to measure).

3 Conclusions

There is a great deal known about melanoma; however, there is much still to understand. A current trend is to evaluate "gene–environment interactions." There are new genetic discoveries every day, and these may help to understand the etiology and factors important for melanoma progression. Environmental exposure is extremely difficult to measure, but measurement is likely an important problem

that investigators may solve in the future. The best advice that can be given for prevention is the "precautionary principle," that is, individuals should avoid extreme exposure to UV light including tanning beds. Skin examination is a second piece of important advice for secondary prevention of melanoma, which is covered in the next chapter. Individuals should become "aware" of their skin—any unusual spots or nodules deserve the attention of a primary care physician or a dermatologist. Together, caution in the sun and awareness of one's skin are today the best advice for melanoma prevention.

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