The Effect of Sunscreen on Melanoma Risk

Jennifer S. Mulliken, MA, BA\textsuperscript{a}, Julie E. Russak, MD\textsuperscript{b,*}, Darrell S. Rigel, MD\textsuperscript{c}

INTRODUCTION

Exposure to UV radiation is a known risk factor for the development of melanoma and nonmelanoma skin cancers.\textsuperscript{1} Over time, sun exposure is known to cause DNA damage and systemic immunosuppression, which are factors for carcinogenesis.\textsuperscript{2–4} Total cumulative sun exposure is associated with the development of squamous cell and basal cell cancers, whereas intense intermittent sun exposure has been associated with the development of melanoma.\textsuperscript{5,6}

A history of sunburn in particular seems to be an important risk factor for the development of melanoma.\textsuperscript{7} The results of a meta-analysis conducted by Dennis and colleagues\textsuperscript{8} showed that sunburn carries a lifetime relative risk for melanoma of up to 1.6 across all age groups. In addition, the relationship between UV exposure and melanoma risk was found to be dose dependent. An increasing number of lifetime sunburns was associated with a linear increase in the risk of melanoma. It should be noted, however, that a history of sunburns might simply be a proxy for a strong history of recreational sun exposure because individuals who are infrequently exposed to UV radiation are more likely to burn when exposed to sunlight intermittently.

The cause of melanoma is multifactorial. In addition to genetic predisposition, phenotypic characteristics, such as fair skin, red hair, freckling, and proclivity to sunburn, all contribute to melanoma risk as does living in sunny locations or at high altitudes. Although exposure to UV radiation is the only known modifiable cause of melanoma, the role of sunscreen in melanoma prevention remains somewhat controversial.

KEYWORDS

- Cutaneous melanoma • Melanoma risk reduction • Sunscreen • UV protection • SPF

KEY POINTS

- While the etiology of melanoma is multifactorial, individuals who are exposed to intense sunlight intermittently are at highest risk for developing melanoma.
- Intermittent exposure to ultraviolet radiation is the only known modifiable cause of melanoma, but the role of sunscreen in preventing melanoma remains somewhat controversial.
- Evidence suggesting a positive association between sunscreen application and melanoma risk reduction is growing.
- Recent studies suggest that the regular use of sunscreen can prevent the development of melanoma by up to 10 years.
UV RADIATION AND THE PATHOGENESIS OF MELANOMA

UV light is classified according to its physical properties, namely wavelength. UV-A light occurs in the 320- to 400-nm wavelengths, UV-B light in 290- to 320-nm wavelengths, and UV-C light in 100- to 290-nm wavelengths. UV-C radiation is filtered by the ozone layer, whereas UV-A and UV-B radiation reach the earth’s surface and have been strongly implicated in the development of cutaneous melanomas.9,10

UV-A radiation is far more abundant in natural sunlight than UV-B radiation. The primary mechanism through which UV-A radiation injures cells is through the formation of free radical species. By causing oxidative DNA damage, UV-A light acts as a potential mutagen.11 UV-A radiation is also thought to have substantial immunosuppressive effects. Exposure to UV-A radiation in mice has been shown to prevent the local immunologic rejection of certain skin cancers.12 In other studies, UV-A radiation has been shown to induce the development of melanomas in opossums and in certain fish.13,14

Although only 5% to 10% of the UV radiation that reaches the earth’s surface falls in the UV-B spectrum, UV-B radiation is the major contributor to sunburn and is responsible for causing DNA damage. UV-B penetrates to the basal layer of the epidermis where it leads to the formation of pyrimidine (thymine) dimers in DNA.15–18 The incorrect repair of these DNA lesions can lead to mutations that alter cell function.11,16,18 The role of UV-B in the development of cutaneous melanoma has been demonstrated in melanoma-susceptible transgenic mice.18

Individuals who are exposed to intense sunlight intermittently are at the highest risk for developing melanoma. Melanoma is most common in persons with indoor occupations whose primary exposure to UV radiation is recreational, such as on weekends and vacations. This pattern of sun exposure in melanoma is further evidenced by the fact that melanoma tends to develop in areas of the body that are primarily subject to intermittent UV radiation. For example, men are typically affected on the back, whereas women are typically affected on the lower legs. In contrast to squamous cell and basal cell cancers, melanoma typically spares the face, hands, and forearms.

SUNSCREENS

Mechanism

UV light is a known carcinogen and, therefore, it is important to protect against the harmful effects of UV-A and UV-B radiation. Sunscreens are agents that temporarily block UV radiation absorption by the skin. Lotions, creams, protective clothing, umbrellas, sunglasses, and hats all qualify as sunscreen agents. Topically applied sunscreen agents are categorized as either organic or inorganic UV filters. Organic filters absorb UV radiation, whereas inorganic filters scatter and reflect UV radiation. There are advantages and disadvantages to both types of formulations. Most commercially available sunscreens contain a combination of organic and inorganic filters.

Inorganic UV filters, such as zinc oxide and titanium dioxide, were previously known as physical sunscreens. When photons of UV radiation contact submicroscopic sunscreen particles, they are dispersed in various directions. These agents do not break down over time and are generally well tolerated. Their major drawback is cosmetic; inorganic filters do not blend into the skin as easily as organic preparations and can result in a whitish discoloration of the skin.

Organic UV filters, previously known as chemical sunscreens, function by absorbing photons of UV radiation. These agents are highly effective and are typically more easily applied than inorganic agents because they are in the form of creams and lotions. Unlike inorganic agents, they tend to degrade with sun exposure and require frequent reapplication. In addition, organic sunscreens have the potential to penetrate the skin, resulting in systemic exposure.20,21 Finally, organic agents may cause a variety of adverse skin reactions, including allergic contact dermatitis, photoallergic dermatitis, irritant dermatitis, acne, and other aesthetic issues.22 These reactions occur infrequently, but the prominence of organic UV filters as allergens is increasing because of the increased use of soluble UV filters in daily face moisturizers.

The Sun Protection Factor System

The efficacy of a sunscreen should ideally be measured by the extent to which the sunscreen protects from skin cancer, but because these studies are difficult to perform, surrogate endpoints are used. The sun protection factor (SPF) system measures the ratio of time it takes to sunburn with sunscreen protection divided by the time it takes to burn without protection.23 When determining the SPF, a sunscreen application thickness of 2 mg/cm² is used. Because UV-B radiation causes sunburn, the SPF of a sunscreen measures protection from UV-B radiation only. For example, an SPF of 15 filters 94% of UV-B and an SPF of 30 filters 97% of UV-B. As SPF increases to more than
30, there are only marginal increases in the protection offered.24

UV-A protection is more challenging to measure because UV-A radiation is 1000 times less erythematogenic than UV-B radiation.25 The American Academy of Dermatology recommends that UV-A protection be determined by measuring the dose of UV-A needed to produce minimal persistent pigment darkening (PPD) at 2 to 24 hours.26,27 The UV-A protection factor of a sunscreen should reflect a 10-fold increase in the UV-A dose needed to induce a PPD. In addition, the ratio of UV-A/UV-B protection should be 1:3 at minimum, and only sunscreens that offer both UV-A and UV-B protection may claim broad-spectrum coverage. Generally speaking, an ideal sunscreen should protect against both UV-B and UV-A radiation and have an SPF of 30 or greater.26

There are several problems with the SPF system. For example, SPF is measured under ideal and controlled conditions. On average, 1 oz of sunscreen is required to cover the body, and it takes approximately 15 to 20 minutes from the time of application until a sunscreen becomes optimally effective.22 However, most people tend to underapply sunscreens, and the resulting SPF may attain only 20% to 50% of the labeled SPF.28 In addition, SPF tends to degrade 8 hours after application by about 55% with activity and by about 25% with indoor rest.29

There has been some question as to whether the maximum SPF on sunscreen labels should be limited to 50+ because products with SPF values more than 50 may not provide superior protection to products with SPF values less than 50. A 2010 study sought to compare the sun-protective effects of an SPF 50 sunscreen with an SPF 85 sunscreen by measuring the grade of erythema after an average of 5 hours of skiing or snowboarding.30 The results of this study demonstrated that sunscreens with an SPF higher than 50 (SPF 85) provided significantly better sun protection than SPF 50 sunscreens. Because people typically underapply sunscreens, higher SPF sunscreens may also offer a margin of safety over lower SPF sunscreens by maximizing the effective SPF.

**UV Filters in Sunscreens**

Organic sunscreens can be classified by whether they filter UV-B radiation, UV-A radiation, or both. Organic UV-B filters have been used since the 1970s when the first true sunscreen, para-aminobenzoic acid (PABA), became available.22 Since then, many other UV-B filters have become available; their properties are summarized in Table 1.

**PABA derivatives**

Although PABA is an effective UV-B absorber, it is rarely used in sunscreens because of its potential to cause allergic contact dermatitis and phototoxic dermatitis.27 It is also known to stain clothing. PABA derivatives, such as padimate O, are less effective than PABA at filtering UV radiation, but they are also less likely to cause hypersensitivity reactions or stain clothing.31

**Cinnamates**

As their name implies, cinnamates are derivatives of cinnamon. They are chemically related to balsam of Peru and cocoa leaves, and individuals who are sensitized to these items may cross-react to sunscreens that contain cinnamates.22 Because cinnamates are comprised of polar oils, sunscreens that contain cinnamates may leave a greasy sensation on the skin when applied.32

Octinoxate, a cinnamate, is currently the most commonly used UV-B filter in the United States.27 A weak absorber of UV-B radiation, octinoxate is frequently combined with other UV filters in sunscreens to achieve adequate sun protection. Cinoxate is another cinnamate derivative that is rarely used in modern sunscreen formulations.

**Salicylates**

Salicylates are photostable agents with high substantivity; as a result, they are frequently incorporated into water-resistant products and combined with photolabile UV-A filters, such as avobenzone.24,31 Octisalate, homosalate, and trolamine salicylate are commonly found in sunscreens. Trolamine salicylate is also often used in hair products as a UV filter.33

**Octocrylene**

Octocrylene lacks substantivity, but it is frequently used with the UV-A filter, avobenzone, as a photostabilizer.34

**Ensulizole**

As a water-soluble agent, ensulizole is commonly used as a component in cosmetic moisturizers.31

Protection from UV-B has historically been the focus of sunscreen development. However, as the role of UV-A radiation in photocarcinogenesis, phototoxicity, and photaging has been better understood, UV-A filters have increasingly been incorporated into commercial sunscreens. UV-A is classified as either UV-A-2 (320–340 nm) or UV-A-1 (340–400 nm) depending on wavelength, and these filters vary in their absorptive properties along the UV-A spectrum. The UV-A filter agents are summarized in Table 1.
Table 1
Available sunscreen agents

<table>
<thead>
<tr>
<th>Sunscreen</th>
<th>UV Spectrum</th>
<th>US Availability</th>
<th>Peak Absorption (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organic Filters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PABA</td>
<td>UV-B</td>
<td>Yes</td>
<td>283</td>
</tr>
<tr>
<td>Padimate O</td>
<td>UV-B</td>
<td>Yes</td>
<td>311</td>
</tr>
<tr>
<td>Octinoxate</td>
<td>UV-B</td>
<td>Yes</td>
<td>311</td>
</tr>
<tr>
<td>Cinoxate</td>
<td>UV-B</td>
<td>Yes</td>
<td>289</td>
</tr>
<tr>
<td>Octisalate</td>
<td>UV-B</td>
<td>Yes</td>
<td>307</td>
</tr>
<tr>
<td>Homosalate</td>
<td>UV-B</td>
<td>Yes</td>
<td>306</td>
</tr>
<tr>
<td>Trolamine salicylate</td>
<td>UV-B</td>
<td>Yes</td>
<td>260–355</td>
</tr>
<tr>
<td>Octocrylene</td>
<td>UV-B</td>
<td>Yes</td>
<td>303</td>
</tr>
<tr>
<td>Ensulizole</td>
<td>UV-B</td>
<td>Yes</td>
<td>310</td>
</tr>
<tr>
<td>Parsol SLX</td>
<td>UV-B</td>
<td>No</td>
<td>312</td>
</tr>
<tr>
<td>Uvasorb HEB</td>
<td>UV-B</td>
<td>No</td>
<td>312</td>
</tr>
<tr>
<td>Univil T150</td>
<td>UV-B</td>
<td>No</td>
<td>314</td>
</tr>
<tr>
<td>Meradimate</td>
<td>UV-A</td>
<td>Yes</td>
<td>340</td>
</tr>
<tr>
<td>Avobenzone</td>
<td>UV-A</td>
<td>Yes</td>
<td>357</td>
</tr>
<tr>
<td>Ecamsule</td>
<td>UV-A</td>
<td>Yes</td>
<td>345</td>
</tr>
<tr>
<td>Univil A Plus</td>
<td>UV-A</td>
<td>No</td>
<td>354</td>
</tr>
<tr>
<td>Neo Helioplan AT</td>
<td>UV-A</td>
<td>No</td>
<td>334</td>
</tr>
<tr>
<td>Oxybenzone</td>
<td>UV-A/UV-B</td>
<td>Yes</td>
<td>288 and 325</td>
</tr>
<tr>
<td>Sulisobenzone</td>
<td>UV-A/UV-B</td>
<td>Yes</td>
<td>366</td>
</tr>
<tr>
<td>Dioxybenzone</td>
<td>UV-A/UV-B</td>
<td>Yes</td>
<td>352</td>
</tr>
<tr>
<td>Silatriazole</td>
<td>UV-A/UV-B</td>
<td>No</td>
<td>303 and 344</td>
</tr>
<tr>
<td>Biscotrizole</td>
<td>UV-A/UV-B</td>
<td>No</td>
<td>303 and 344</td>
</tr>
<tr>
<td>Bemotrizinol</td>
<td>UV-A/UV-B</td>
<td>No</td>
<td>305 and 360</td>
</tr>
<tr>
<td><strong>Inorganic Filters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zinc oxide</td>
<td>UV-A/UV-B</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Titanium dioxide</td>
<td>UV-A/UV-B</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>


**Benzophenones**
Oxybenzone, sulisobenzone, and dioxybenzone are UV-A filters that are commonly incorporated into sunscreens. Of these, oxybenzone is the most commonly used. Although these agents primarily offer protection in the UV-A-2 range, a second protective band is found in the UV-B range. Oxybenzone is the most common cause of contact phototoxicity among sunscreens, however, and its use in sunscreens is limited by its allergic properties and by its photolability.

**Avobenzone**
Avobenzone is currently the only filter approved by the Food and Drug Administration (FDA) and has a peak absorbance in the UV-A-1 spectrum. Although avobenzone has a broad absorbance spectrum, its use has historically been limited by its photolability. Today, avobenzone is frequently incorporated into sunscreens with more photostable agents, such as octocrylene, salicylates, and oxybenzone. The results of recent studies have suggested that combining avobenzone with octocrylene provides the most effective UV-A protection available in the United States.

**Meradimate**
Meradimate’s absorption spectrum lies within the UV-A-2 range. Overall, it is a weak UV-A filter and is rarely used.

**Ecamsule**
Ecamsule is a recently approved sunscreen agent in the United States. Compared with other agents, ecamsule is a photostable and efficient UV-A filter.
Inorganic sunscreens, such as zinc oxide and titanium dioxide, provide protection in the UV-A and UV-B ranges, but overall they tend to be less efficient at filtering UV radiation than the newer organic agents. Inorganic sunscreens have historically tended to be cosmetically unappealing; they may leave a whitish discoloration on the skin, stain clothing, and be comedogenic. Micronized formulations are now more commonly used; because particle size has decreased, these newer formulations are able to protect against shorter UV wavelengths.

The agents discussed previously differ in their UV protective wavelengths, and a combination of several filters is often required to achieve the desired level of protection. In addition, there are several broad-spectrum UV-A and UV-B filters available outside of the United States. Bisocetizole (absorption peaks: 303 nm and 344 nm) and bemo-trizinol (absorption peaks: 305 nm and 360 nm) are examples of 2 broad-spectrum agents available in Europe that are currently undergoing approval in the United States.

**SUNSCREEN AND MELANOMA RISK REDUCTION**

A variety of factors are known to increase an individual’s risk of developing skin cancer, including exposure to UV radiation, decreased skin pigmentation, positive family history, and geographic location. As awareness of the sun’s potentially harmful effects has grown, skin-protection efforts have also become more widespread. Sunscreens, protective clothing, and sun avoidance have all been used to modify individual skin cancer risk.

The role of sunscreens in the prolonged prevention of actinic keratoses and squamous cell carcinomas has been well established. However, although exposure to UV radiation is a known and modifiable cause of melanoma, the ability of sunscreens to reduce the risk of developing melanoma remains controversial. In recent decades, many studies have attempted to establish a link between sunscreen application and the incidence of melanoma, but no consensus has been reached.

The results of 15 case-control studies conducted by the International Agency for Research on Cancer were indecisive regarding the effect of sunscreen on the development of melanoma. Of these studies, 4 showed no association between melanoma and sunscreen use, 3 suggested a lower risk of melanoma with sunscreen use, and 8 suggested a higher risk of melanoma with sunscreen use. Other studies have postulated that because sunscreen prevents symptoms of sunburn, it also permits more time sunbathing; therefore, sunscreen users could be at an increased risk of developing melanoma. An increased risk of melanoma with sunscreen use has also been suggested at high altitudes where sunscreens may allow overexposure to UV-A radiation.

As others have previously noted, the studies that found a positive association between sunscreen use and melanoma failed to control adequately for confounding factors. For example, individuals with fair skin who burn easily are the most likely to use sunscreen, but these individuals are also the most likely to develop melanoma in the first place. In addition, those studies that found a lower risk of melanoma with sunscreen use may have overlooked the fact that sunscreen users may be more likely to use other methods of sun protection, including clothing, umbrellas, and tree cover.

Meta-analyses of case-control studies have shown no association between sunscreen use and the development of melanoma, although the conclusions that can be drawn from these data are also limited. For example, some of these studies used data collected before 1990 when the median SPF of sunscreen products was less than 10. In more recent years, median SPF trends have been increasing. As a result, the outcomes of many earlier studies may no longer be applicable.

The SPF of a sunscreen is assessed at an application thickness of 2 mg/cm². Most consumers, however, only apply sunscreen at a thickness of 0.5 to 1.0 mg/cm². A sunscreen of SPF 8 applied at a thickness of 0.5 to 1.0 mg/cm² will result in an effective SPF of 2 to 3. Given how minimally earlier-generation sunscreens modified UV exposure of the skin, it is not surprising that some case-control studies failed to find any association between sunscreen use and melanoma risk.

More broad-spectrum modern sunscreens, on the other hand, provide an effective SPF of around 8 to 10 when applied at an average thickness of 1.0 mg/cm². Total UV-A and UV-B exposure to the skin with these sunscreens is about one-third of that with earlier-generation sunscreens.

Overall, epidemiologic studies of melanoma prevention have been limited by insufficient statistical power, recall bias, and the fact that people tend to be poor historians when reporting prior sunscreen usage. The main determinants of sunscreen use are the same as those of melanoma: susceptibility to sunburn, high sun exposure, and a positive family history. There is also a 10- to 50-year latency period between the initial period of sun exposure and the development of melanoma. As a result, it has been difficult to ascertain whether any association exists between sunscreen use and the incidence of melanoma.
Although melanoma incidence reduction through sunscreen use has not been proven, evidence suggesting a positive association between sunscreen application and melanoma risk reduction is growing. For example, the total number of nevi is an important risk factor for the development of melanoma, and the use of sunscreens has been found to attenuate the formation of nevi in light-skinned children. In addition, hepatocyte growth factor/scatter factor transgenic mice treated with sunscreen demonstrated significantly less UV-induced DNA damage (as measured by thymine-thymine dimmer concentration) and fewer UV-induced melanomas than control mice.

Most recently, the first randomized controlled trial to evaluate the association between sunscreen use and melanoma risk has suggested that regular application of sunscreen may, in fact, prevent the development of melanoma for up to 10 years. This trial provides the strongest evidence to date that the regular use of sunscreen can prevent the development of primary cutaneous melanomas. Long-term follow-up showed that, among adults aged 25 to 75 years, daily application of SPF 15 sunscreen to the head and arms for 5 years was associated with a reduced incidence of new primary melanomas over a 10-year period. After 15 years of follow-up, a 73% reduction in invasive melanomas was also seen with daily sunscreen application. The results of this study have led others to comment on the positive long-term effects of reminding patients to use sunscreen regularly.

NEW DEVELOPMENTS

UV exposure undeniably causes skin damage, and the use of sunscreen or sun-protective clothing is critical in protecting from cutaneous cancers and premature aging. To help consumers select and use sunscreens appropriately, the FDA released a series of sunscreen labeling guidelines in June 2011. Under these guidelines, which will become effective in June 2012, all over-the-counter sunscreen products will be subject to a standard test that will determine which products provide protection against both UV-B and UV-A radiation. Products that pass the test will be labeled as broad spectrum. In addition, only those broad-spectrum sunscreens that have an SPF value of 15 or higher can claim to reduce the risk of skin cancer and premature skin aging if used as directed with other sun-protection measures. Manufacturers will no longer be able to claim that a sunscreen is waterproof or sweat proof because these claims overstate a sunscreen’s effectiveness. Unless manufacturers submit data to the FDA for approval, sunscreens will also not be able to claim immediate protection after application or for more than 2 hours after application. Finally, water-resistance claims on sunscreen labels must indicate whether the sunscreen’s SPF remains effective for 40 minutes or 80 minutes after swimming or sweating, based on standard testing.

SUMMARY

A strong history of intermittent sun exposure is a well-known risk factor for melanoma. In addition, persons with a fair complexion, red hair, freckles, and inherited gene mutations are also at an increased risk of developing melanoma. As a result, sun protection is extremely relevant in these individuals. Although the role of sunscreen in melanoma prevention remains somewhat controversial, the 2011 study by Green and colleagues provides the strongest evidence to date that the regular use of sunscreen can prevent the development of melanoma for up to 10 years. The daily application of sunscreen to exposed skin can be expensive and time intensive, so counseling about sun-protection efforts should start early to encourage good habits. Given the known role of UV radiation in the pathogenesis of melanoma, it seems foolish not to encourage the regular use of sunscreen in all individuals and especially in those individuals already at increased risk.

REFERENCES

The Effect of Sunscreen on Melanoma Risk


