About the Author

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Professor Young's research career has focused on the effects of sunlight on human health, which are beneficial as well as detrimental. Thus, it is important to understand the balance between the pros and cons of solar exposure, which vary with different Fitzpatrick skin types. An important part of this work has been on photoprotection by sunscreens and pigmentation. Most photobiology research has been done under laboratory conditions, often with solar simulated radiation, mainly because these are relatively easy to control. However, there is an increasing awareness that the laboratory does not necessarily predict what happens in the field, and this is especially true with sunscreens. In recent years, Prof. Young has been engaged with "holiday studies" to determine the effects of real sun on photobiological outcomes, including the effects of sunscreens. Prof. Young has been a regular contributor to meetings of the American and European Societies for Photobiology, as well as dermatology congresses. He is also a member of the United Nations Environment Programme (UNEP)—Environmental Effects Assessment Panel.

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Comparison of Skin Photoprotection by Pigmentation and Sunscreens

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Synopsis

Melanin, in people with naturally pigmented skins, offers a high level of photoprotection against the adverse molecular and clinical effects of solar ultraviolet radiation but, in contrast, has a modest inhibitory effect on vitamin D synthesis. Tanning in those with light skin offers relatively modest photoprotection. Sunscreens have the potential to offer high levels of protection in people who lack melanin. In theory, sunscreens can give protection comparable with that of deeply pigmented skin. This depends on the labeled sun protection factor (SPF) which in turn depends on how well the sunscreen is applied. In most cases, this will not achieve the desired SPF. The threshold dose for vitamin D synthesis is much lower than that for sunburn, such that vitamin D synthesis is still possible with sunscreen application.

INTRODUCTION

The adverse clinical effects of solar ultraviolet radiation (UVR ~ 295–400 nm) on human skin are well documented. Solar range UVR also has effects on the skin (1) and blood (2,3) transcriptomes. The only fully established benefit is vitamin D synthesis by UVB (280–315 nm) that is much more important than vitamin D intake from food sources. There is, however, increasing evidence of other benefits from solar exposure, such as a reduction in blood pressure (4). Cutaneous responses to sunlight are highly dependent on the Fitzpatrick skin type (FST) that ranges from I (very light) to VI (very dark); thus, FST I is much more prone to sunburn (erythema) and skin cancer than FST VI. The most probable reason for this is the amount of melanin in the epidermis. In other words, melanin is a very effective natural sunscreen. The presence of melanin is either constitutive or facultative; the former being the natural baseline level present in habitually sun-protected skin (i.e., buttock), whereas the latter is tanning in response to solar or other UVR exposure. Facultative pigmentation is also FST dependent.

Most photobiological research on human skin *in vivo* has been carried out on lighter FSTs ranging from I (e.g., Celtic) to IV (e.g., Mediterranean). Relatively little has been carried out on FST V (e.g., Indian subcontinent) and VI (e.g., African) (5). The most widely used

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acute endpoint to determine personal UVR sensitivity is erythema (i.e., sunburn), in particular the minimal erythema dose (MED). This is the lowest physical UVR dose (J/cm^2) that gives just perceptible skin redness about 24 h after exposure.

Melanocytes are dendritic cells that reside in the basal layer of the epidermis. They synthesize melanin that is transferred to epidermal keratinocytes that are the majority cell type. This process is enhanced (i.e., tanning) when the skin is exposed to UVR. Melanin is mostly concentrated in the lower epidermis and also presents as caps over nuclei of basal layer keratinocytes.

Several studies have attempted to enhance the tanning response with a view to improving photoprotection. Some have used sunscreen formulations that include 5-methoxypsoralen (5-MOP), which is a natural photosensitizing ingredient in bergamot (*Citrus bergamia*) oil (6). However, this approach is not viable because 5-MOP is a photocarcinogen (7). An important factor in tanning is the binding of α-melanocyte–stimulating hormone (α-MSH) to the melanocortin 1 receptor on melanocytes. Another approach has been to generate synthetic analogues of α-MSH to enhance tanning (8).

There is a melanin gradient with terrestrial UVB in indigenous populations. Melanin decreased as humans in prehistory dispersed away from tropical latitudes, and one driving factor for this loss is thought to be the need to maintain adequate vitamin D synthesis (9,10). Mass migration and travel in relatively recent history has meant people's skin color no longer matches the solar conditions under which it evolved. The need for photoprotection in normal healthy people depends on the FST, the intensity (irradiance) of the sun, and the time spent outdoors with uncovered skin. The World Health Organization has promoted the ultraviolet index (UVI) as means of estimating the sunburning capacity of solar UVR at any given location. The categories are low (1–2), moderate (3–5), high (6–7), very high (8–10), and extreme (11+). Photoprotection is recommended for light skin when the UVI reaches 3, but this has raised some controversy (11).

SUNSCREENS

Sunscreens are topical formulations that contain synthetic organic UVR filters and/or mineral and/or organic nanoparticles (12). They work by absorbing solar UVR and also by some scattering in the case of pigments. Ideally, they should remain on the surface of the skin, but there is increasing evidence that they can penetrate into the systemic circulation because they or their metabolites can be detected in blood and urine (13). Sunscreen efficacy is measured by their ability to prevent erythema ~24 h after exposure to solar simulated radiation (SSR). The index for this is the sun protection factor (SPF) when the test product is applied at 2 mg/cm^2 skin. Essentially, this is a ratio of the MED with and without sunscreen application (14). SSR does not contain visible light (400–700 nm), and sunscreens are not designed to protect in this region. It has been suggested the laboratory-determined SPF may underestimate protection against erythema because of not taking visible radiation into account (15).

COMPARISONS OF PHOTOPROTECTION BY MELANIN AND SUNSCREENS

Melanin, especially constitutive melanin, has the advantage of being always present. Furthermore, its presence increases after exposure to sunlight. Sunscreens, on the other hand,

have to be applied before intended sun exposure behavior and reapplied during exposure. No study has directly compared photoprotection by melanin and sunscreens. In fact, this is conceptually difficult because the results would be biased by the amount of melanin and the SPF of the sunscreen and its application thickness. The approach taken as mentioned in the following text is to compare the results of studies on melanin and sunscreens on important markers of solar damage and benefit. The main conclusions are summarized in Table I.

DNA DAMAGE, ERYTHEMA, AND SKIN CANCER

DNA is an important UVR-absorbing chromophore in the epidermis, and the presence of UVR causes DNA damage, such as cyclobutane pyrimidine dimers (CPDs), that can be detected in human skin after UVR exposure in the laboratory (16,17) and in skin or urine after holidays in adults (18,19) and children (20). DNA photodamage probably plays a major role in erythema and certainly has a major role in photocarcinogenesis (21). This can be demonstrated by the very high incidence of skin cancer in xeroderma pigmentosum patients who lack DNA repair capacity (22).

Recent studies have shown the importance of location when assessing protection by constitutive melanin against photodamage to epidermal DNA. Comparisons of FST II versus VI show that protection by melanin varies with epidermal zone, such that the protection factor by melanin in the basal layer is about 60 but only five in the upper epidermis (23). This difference has biological significance because the basal layer contains keratinocyte stem cells and melanocytes, whereas keratinocytes in the upper epidermis are approaching the final stages of terminal differentiation. Skin cancer is much more common in FST

Table I
Comparison of Protection by Pigmentation (Melanin) and Sunscreens for Adverse and Beneficial Effects of Solar UVR

	Type and level of protection		
Endpoint	Constitutive pigmentation	Facultative pigmentation	Sunscreen
DNA damage (CPD)	Very high protection factor of ~60 in basal layer of the epidermis when comparing FST VI with II (23).	Modest, with protection factors in the region of 2–4 (29).	Depends on the SPF and application thickness (39). May be very high with high SPF sunscreen (40).
Erythema	About 6- to 8-fold when comparing FST VI with II (25,26).	Modest, with protection factors in the region of 2–4 (27–29).	Depends on the SPF in laboratory studies but no data on the "real-life" SPF. Very effective when used correctly on holiday (18).
Skin cancer	High (5).	Unknown	Low (42–44).
Vitamin D synthesis	Low, with an estimated inhibitory factor of 1.3 when comparing FST VI with II (51).	Unknown	Low but very few data from intervention studies (52–54). Studies needed on high SPF intervention (55).

I/II versus V/VI, and interestingly, the difference in the incidence of basal cell carcinoma (BCC), the most common type of skin cancer, is about 60 (23).

There is an inverse relationship between the increasing FST and the MED on habitually sun-protected skin. However, there is considerable overlap of the MED between FST I and IV. The difference in the MED between FST II and IV on sun-protected skin is about two, which is very modest in SPF terms (24). There have been fewer studies with FST V and VI, but comparisons between I/II and VI show a protection factor of melanin against erythema of about 6–8 (25,26). This is about the same as the protection factor against DNA photodamage for the whole epidermis (23).

Studies to determine the protective properties of facultative tanning in FST I–IV have shown this to be modest against DNA damage and erythema. Field and laboratory studies have shown protective factors to be in the region of 2–3 (27–29). Other factors such as stratum corneum thickening as a result of solar exposure may be important, but they are poorly understood (30).

It is relatively simple to determine the SPF under very controlled laboratory conditions, one of which is the application of the sunscreen at 2 mg/cm^2 on skin (14). In practice, people apply very much less with a commensurate typically linear reduction in the SPF (12). For example, one study on Danes on holiday in Egypt showed an average application thickness of 0.79 mg/cm^2 (31). This can result in overestimation of protection and, therefore, overexposure and sunburn (32,33). In general, people do not apply sunscreen very well (34). Correct application of a sunscreen can prevent erythema during a week's sun holiday with maximal UVI of 9 (18).

Sunscreens are effective at preventing epidermal CPDs (35), which would be expected because erythema and epidermal CPDs have similar action spectra in the solar UVR range (36). CPDs can be caused by suberythemal exposure, and such DNA damage (as well as erythema) accumulates with such exposure daily because epidermal CPDs have a half-life of 33 h (i.e., slow repair) (37). Daily application for 11 d of a low SPF sunscreen, before suberythemal SSR exposure, was shown to be effective at reducing cumulative CPDs and erythema (38). A more recent study, which detected CPDs by immunostaining and quantitative high pressure liquid chromatography with tandem mass spectrometry, has shown that an SPF 50+ sunscreen was very effective at preventing DNA damage by very high doses of acute and repeated (five consecutive days) SSR exposure (39). This study also showed that DNA protection, in acute and repeat SSR exposure cases, was dependent on sunscreen application thickness. Significant protection was observed even with application at 0.75 mg/cm^2 (equivalent to an SPF of 21), typical of consumer use. Studies have not been designed to determine a DNA protection factor (DNA-PF). A new approach has been recently reported in which an SPF 50+ sunscreen had a DNA-PF of 98.2 [95% confidence interval (CI) of 51.6–187.2] (40).

There is considerable evidence that the CPD plays a major role in skin cancer, especially keratinocyte cancers (21). Thus, they would be expected to have a beneficial effect against human skin cancer as has been reported in studies on mouse models (41). Studies show that sunscreen use can inhibit skin cancer (42). The best prospective evidence is from long-term intervention studies in Nambour, Queensland, Australia (discussed in the article by A. Green in the same issue). The most robust conclusion from these studies is that a 4.5-y randomized controlled intervention with an SPF 16 product significantly reduced the incidence of melanoma (43) and squamous cell carcinoma (SCC), but not BCC (44). This reduction is very important clinically, but less so numerically; for example, the rate

ratio (intervention sunscreen vs. discretionary use sunscreen) for SCC in trial and total follow-up (1993–2004) of 0.65 (95% CI 0.45–094), representing a cancer protection factor of ~1.5. In this context, it should be remembered that the real SPF of the product was likely to have been much less than 16 because of the way people typically apply sunscreens. Furthermore, given that the mean age of entry into the study was about 50 y, this rural population will have had a high level of baseline UVR-induced DNA mutations in keratinocytes. It is probable that one of the reasons for the benefits of long-term sunscreen use in this study was the immunoprotective effects of sunscreens (45). Photoimmunosuppression is thought to play an important role in skin cancer (46). There is considerable mouse evidence that the CPD initiates the antigen-specific cutaneous immunosuppression when a given antigen is presented to the skin after UVR exposure (47). Interestingly, organ transplant patients on drug immunotherapy, which is not antigen-specific, are very prone to skin cancer, especially SCC (48). It would be reasonable to suppose that earlier sunscreen intervention, especially in areas of high insolation, would have greater long-term benefits.

VITAMIN D SYNTHESIS

Vitamin D is important for bone development and maintenance, but there is increasing, though controversial, evidence that vitamin D has many other health benefits (49). It is well documented that people with pigmented skins have less good vitamin status than those, at comparable latitudes, with lighter skins. This is usually attributed to an inhibitory effect of melanin. Laboratory research on the effect of melanin on vitamin D synthesis has given conflicting results (50). A recent laboratory study on FST II–VI has shown that melanin has a very modest effect on vitamin D synthesis. Comparisons of FST II versus VI showed that the melanin inhibition factor was <1.5 (51), but this may be sufficient to explain the epidemiological data. It is also likely that cultural and behavioral factors may also explain differences in vitamin D status in different ethnic groups. The most likely reasons for the differences with the DNA protection data is the spatial relationship between melanin and the UVR target. In the basal layer, nuclei are largely under the melanin, whereas the precursor for vitamin D is throughout the epidermis with high concentrations in the upper less melanized epidermal layers.

Two recent reviews concluded that sunscreen use has little or no impact on vitamin D synthesis (52,53). A weeklong field study in Tenerife, under a cloudless sky with a maximum UVI of 9, showed a high level of vitamin D synthesis even when optimal application of an SPF 15 sunscreen (>2.0 mg/cm^2) prevented erythema (54). This intervention group was in contrast to a discretionary sunscreen use group that had a higher level of vitamin D synthesis but presented with sunburn on multiple body sites. Thus, sunscreens may inhibit vitamin D synthesis, but they still allow considerable synthesis with suberythemal exposure. It should be noted that we lack data on the effect of a high SPF sunscreen, especially in temperate climates (55). Sunscreens can enable vitamin D synthesis because the threshold UVR dose for this process is much lower than that for erythema.

CONCLUSIONS

Constitutive melanin in deeply pigmented skin is very effective at preventing basal layer DNA photodamage, erythema, and skin cancer. Protection against DNA damage and

erythema is much lower by facultative tanning in white skin types. A comparison of FST II versus VI shows that melanin has a very modest inhibitory effect on vitamin D photosynthesis. Melanin protection/inhibition against a given target depends on spatial relationships within the epidermis. Sunscreen protection against erythema depends on its the SPF and application thickness. Used correctly, sunscreens will inhibit erythema in "real-life" situations. There is good experimental evidence that sunscreens will inhibit DNA photodamage and skin cancer. However, to get the equivalent of constitutive protection against skin cancer, it is likely that FST I/II would need an SPF about 60. Sunscreens have a relatively modest effect on vitamin D synthesis. Better sunscreen protection would be achieved with better use.

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