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Current perspective

Skin cancers are the most frequent cancers in fair-skinned populations, but we can prevent them.

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ABSTRACT

Cancers of the skin are the most commonly occurring cancers in humans. In fair-skinned populations, up to 95% of keratinocyte skin cancers and 70–95% of cutaneous melanomas are caused by ultraviolet radiation and are thus theoretically preventable. Currently, however, there is no comprehensive global advice on practical steps to be taken to reduce the toll of skin cancer. To address this gap, an expert working group comprising clinicians and researchers from Africa, America, Asia, Australia, and Europe, together with learned societies (European Association of Dermato-Oncology, Euromelanoma, Euroskin, European Union of Medical Specialists, and the Melanoma World Society) reviewed the extant evidence and issued the following evidence-based recommendations for photoprotection as a strategy to prevent skin cancer. Fair skinned people, especially children, should minimise their exposure to ultraviolet radiation, and are advised to use protective measures when the UV index is forecast to reach 3 or higher. Protective measures include a combination of seeking shade, physical protection (e.g. clothing, hat, sunglasses), and applying broad-spectrum, SPF 30 + sunscreens to uncovered skin. Intentional exposure to solar ultraviolet radiation for the purpose of sunbathing and tanning is considered an unhealthy behaviour and should be avoided. Similarly, use of solaria and other artificial sources of ultraviolet radiation to encourage tanning should be strongly discouraged, through regulation if necessary. Primary prevention of skin cancer has a positive return on investment. We encourage policymakers to communicate these messages to the general public and promote their wider implementation.

1. Ultraviolet radiation and skin cancer

The aim of this article is to summarize the current knowledge on ultraviolet (UV) radiation as a cause of skin cancer and to provide medical recommendations for photoprotection as a prevention strategy. These photoprotection recommendations have been agreed by international experts from Africa, America, Asia, Australia and Europe, and by the scientific societies involved: European Association of Dermato-Oncology, Euromelanoma, Euroskin, European Union of Medical Specialists, and the Melanoma World Society.

The principal cause of cutaneous melanoma and keratinocyte cancers (basal cell carcinomas and cutaneous squamous cell carcinomas) is solar ultraviolet (UV) radiation. This relationship is well established on several levels.

First, epidemiological studies since the 1950 s have shown that the incidence and mortality of melanoma in fair-skinned populations is significantly higher in regions near the equator than at higher latitudes [1]. Fair skin is defined by skin types I-IV according to Fitzpatrick [2]. Per unit area of skin, the highest densities of melanoma occur on sites with highest sun exposure such as the face, head, and neck. The association between UV radiation and the development of melanocytic nevi is also well established [3]. Increasing frequency of sunny vacations is associated with a large increase in melanocytic nevi in children. A high number of melanocytic nevi is associated with an increased risk of developing melanoma. Similarly, keratinocyte cancers have higher incidence rates in sun-sensitive individuals with lighter skin tones compared to those with less sun-sensitive skin and darker skin tones. They typically occur on the most sun-exposed body areas, being associated with a history of excessive recreational or occupational sun exposure, sunburns and signs of actinic skin damage [4]. The risk for keratinocyte skin cancers rises with increasing ambient solar radiation and decreasing latitudes.

Second, studies on somatic mutations confirms the causal role of UV radiation in the development of keratinocyte cancers and cutaneous melanoma. These tumours have the greatest tumour mutation burden among all solid cancers [5]. Characteristically, C>T or CC>TT transitions, that are typical UV signature mutations, account for more than 80% of these mutations.

Third, UV radiation induces skin cancer in animal models, both squamous cell carcinoma, and more recently, melanoma [6].

UV radiation is classified as a Group 1 carcinogen by the International Agency for Research on Cancer, comparable to smoking in producing high tumour mutation burdens [4]. How much UV radiation is required to induce mutations in skin cells? UVB dose is usually expressed in units of minimum erythema dose - the dose that triggers initial redness of the skin and incipient sunburn. DNA photolesions are triggered directly by UVB radiation, that induce the formation of pyrimidine cross-links, such as pyrimidine dimers, between neighbouring DNA base pairs. These can be visualized using immunofluorescence techniques. Additionally, UVA exposure causes oxidative DNA damage through the release of reactive oxygen species [4]. Studies performed in hairless mice aimed to determine the exact UV dose that triggers mutations in skin cells [7]. They found that as little as 10–20% of the minimum erythema dose is sufficient to trigger mutations. Sunburns are not necessary for the development of skin cancer. While high SPF sunscreens are effective at reducing epidermal photodamage in human volunteers when applied properly under controlled conditions, most people apply insufficient quantities of sunscreen, and also incompletely cover their exposed skin. Therefore, most people sunbathing will receive sufficient doses of UV radiation to induce detectable photodamage, even after applying sunscreen.

In fair-skinned populations, it is estimated that up to 95% of keratinocyte skin cancers and 70–95% of cutaneous melanomas are caused by UV radiation [4,8,9]. Therefore, a significant proportion of skin cancers can be prevented by reducing unnecessary, excessive UV

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exposure through effective UV photoprotection.

The increasing incidence of melanoma can best be studied by analysing the long-term trends. For example, in 1950, the Danish Cancer Registry documented one case per 100,000 inhabitants, rising to three cases per 100,000 in 1970, then to ten cases in 1990, 25 cases in 1990 and 50–70 cases predicted for 2036 [10]. The 50-fold increase in less than 90 years is unique among all cancers, and the incidence trend for keratinocyte cancer is very similar [10]. Similar trends have been reported in other populations with predominantly European ancestry, indicating the rise in melanoma is a global phenomenon.

2. Evidence-based ultraviolet radiation protection recommendations

The scope of this article is to formulate clear, globally valid practical recommendations for the primary prevention of skin cancer. Systematic literature searches were carried out for all practical recommendations. The recommendations were agreed by the authors at a consensus conference in Rome on November 3rd, 2023.

Intentional exposure of the skin to UV radiation for tanning including sunbed use should be considered as an unhealthy behaviour. Adequate UV protection includes a combination of the following measures in order of importance: avoiding intense or high solar UV exposure by seeking shade, avoiding use of indoor tanning devices, physical protection with clothing, wide-brimmed hat and sunglasses, and use of sunscreens for uncovered skin. These measures are particularly important for children and adolescents and remain valid for life. Advice for the general population is summarized in Table 1.

Avoidance of high/intense UV exposure constitutes the first pillar in UV protection. The UV index quantifies the intensity of solar UV radiation reaching the Earth surface, on a scale from 1 to 11 + . According to the World Health Organization, sun protection measures are advised starting from UV index 3 (moderate). UV intensity is highest 2 h before and after solar noon and responsible for 50–75% of daily UV flux (Fig. 1). Therefore people are advised to seek shade during these hours of the day (for UV index 3–7) or to stay indoors (UV index 8 or more) (Fig. 2) [11]. The UV index is communicated by meteorological services and is available through various apps.

Indoor tanning devices are a further avoidable source of strong UV exposure. Legislation banning use of commercial tanning facilities is in place in Brazil, Australia and Iran, and is being considered in other jurisdictions as a cost-effective policy intervention that can reduce melanoma and other skin cancers.

Physical protection by clothing, a hat and sunglasses are the second pillar in UV protection. Epidemiological studies have repeatedly found a reduced risk of sunburns, development of nevi in children and melanoma through sun protection by clothes as compared to sunscreens[12]. The protective properties of clothes vary with fibre type (polyester, nylon > wool, silk > cotton), the density of the weave, colour (colorants contribute to UV blocking), design (e.g. long sleeves, a collar) and the incorporation of UV absorbers. Clothing with high UV Protection Factor is particularly useful in high UV exposure conditions such as outdoor sports and water sports. Hats should have wide brims to protect the head, face, neck and ears.

The application of high protection sunscreens to uncovered areas of the skin represents the third pillar of UV protection. Two community-based, prospective, randomized trials conducted in Australia

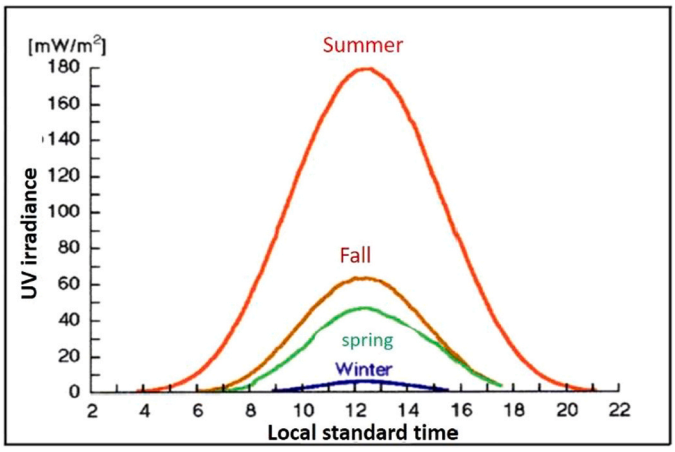

Fig. 1. Diurnal and seasonal variation of solar ultraviolet radiation. This graph shows the time of solar noon at 12 am, but during the summer months in the northern hemisphere (around June), the solar noon occurs around 1:00 PM to 2:00 PM local time for cities in Central European Time such as Berlin, Paris, and Madrid. Adapted from Institute of Medical Climatology, Christian-Albrechts-University of Kiel: www.uni-kiel.de/med-klimatologie/uvinfo.html.

demonstrated that daily sunscreen application on the head and arms unprotected by clothing, reduced the development of actinic keratoses at 7 months and squamous cell carcinoma at 4.5 years [13,14]. Follow-up after 10 years also revealed a significantly lower number of melanomas in the sunscreen group [15]. In contrast, observational epidemiological studies repeatedly found a moderately increased risk of sunburns, nevi, and melanoma associated with sunscreen use as compared to protection by clothes [16]. In conditions of intentional sun exposure (sunbathing, indoor tanning, outdoor activities), the use of a sunscreen may promote risky behaviour by increasing sun exposure duration and intensity [17]. There are no studies showing that sunscreens protect against skin cancer when used in sunbathing.

In conclusion, when the UV index is forecast to reach 3 or above, it is recommended that broad-spectrum (UVB+UVA) sunscreens (Sun Protection Factor of 30 + - 50 +) is applied every day to the face, ears, scalp if uncovered, neck and all parts of the body not covered by clothing. Ideally, this would form part of the morning routine. This protects the skin from the harmful effects of everyday sun exposure [18].

These recommendations apply for all fair-skinned populations, including different risk groups such as children, outdoor workers and persons with high risk for skin cancer (e.g. personal history, over 100 nevi, chronic immune suppression). Babies under the age of 6 months should not be exposed to direct sunlight [19]. For outdoor workers, prevention measures should be standardly provided by employers including shifting labour hours and breaks, and providing shade, protective clothing and sunscreen to minimize UV exposure.

Similar recommendations have been made in reviews and other articles in the past [20]. Those focused on reducing UV exposure, while we go further and recommend avoiding sunbathing and tanning. This recommendation is more radical and clearer.

Primary prevention of skin cancer has a positive return on investment [21,22] Policymakers should communicate strong UV protection messages to the public and discourage the use of commercial tanning

Table 1
Advice for ultraviolet radiation protection for fair skinned populations.

- Avoid sunbathing and tanning
- Do not use sunbeds
- Use UV protection measures when UV index is moderate or higher:
- Use clothing, a wide-brimmed hat and sunglasses as the main protection measures;
- Use a sunscreen with sun protection factor 30 + - 50 + and UVA label for all skin areas that cannot be protected by clothing;
- Avoid direct sun exposure at solar noon (2 h before / after).

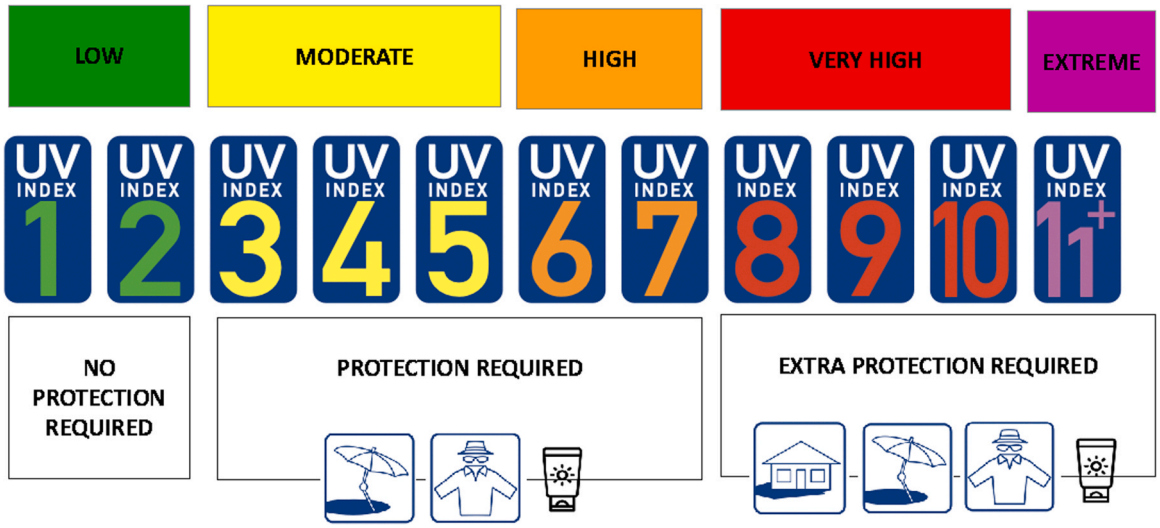

Fig. 2. Ultraviolet Radiation Index-dependent recommendation of photoprotection
Adapted from WHO [11].

facilities, through strict regulation or preferably a ban. They should ensure population-wide communication and education about daily UV index, e.g. with weather reports, and creating outdoor shade facilities in schools and recreational areas.

3. Open questions

Does consistent UV protection cause vitamin D deficiency? Some studies suggested that consistent photoprotection is associated with vitamin D deficiency. However, there is no general agreement on how to define vitamin D deficiency and which are the normal serum levels. Randomized trials on vitamin D oral supplementation to improve melanoma or other cancers prognosis have not shown any positive effect [23].

How can we change behaviour to optimize UV protection? There is a widely-proven gap between the major progress made in recent decades in raising awareness and informing the general public about the harms associated with excessive UV exposure, and the modest changes achieved in UV exposure behaviours [24]. A crucial research priority is to identify the most effective intervention and communication strategies by which consistent UV-protection behaviours are promoted, particularly in high-exposure groups including frequent sunbathers/tanners and outdoor workers. In parallel, special attention should be given to policies providing widely accessible tree shade/ shade structures.

Can sunscreens cause harm through systemic absorption? Maximal topical use of organic UV filters induced persistent elevated plasma levels, and some organic filters have been linked with estrogenic effects in animal studies [25]. It is still unclear whether there are the biological consequences of these high plasma levels on human health, and if they are actually attained in real-life. Further safety analysis is envisioned by the regulators in US and EU. The introduction of nano- technologies in the production of UV filters has raised concerns regarding the potential increased skin penetration and systemic absorption of these products. So far there is no evidence from human studies backing these concerns, and several nano-particles UV filters, both inorganic and organic are deemed safe for use on the skin, with some size and concentration limitations, by EU and other territories regulators [26].

Is the addition of natural antioxidants to sunscreen formulations dangerous? Natural antioxidants, like vitamins E, C, or coQ10 have been added to sunscreen formulations for their putative role in protection against UVR-induced oxidative damage and visible-light induced pigmentation. Yet, recent studies have raised the concern of metastasis-promoting effects of antioxidants in mice melanoma models [27]. Furthermore, their benefits in topical sunscreen formulations remain to be determined, especially in patients with actinic damage or field cancerization.

Do UV-filter residues from sunscreens harm the environment? UV filters residues that wash off in large amounts from tourist coastal areas into marine waters may contaminate natural and drinking water, and they have been found within various species of fish worldwide [28]. In the laboratory setting, at concentrations higher than those detected in sea water, some organic UV filters showed toxic effect on corals and fish reproduction. More research into their impact on human health from marine exposure or food contamination, as well as on marine life is needed.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

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