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Sunscreens and melanoma: the future looks bright

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Summary

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None to declare.

Background Meta-analyses of observational case–control studies have demonstrated no association between sunscreen use and the development of malignant melanoma.

Objectives To examine whether this observation is to be expected given the period during which the case–control studies were conducted, the sunscreens prevalent at that time, and how sunscreen is used and applied in practice. To predict whether modern sunscreens are likely to be effective as a preventative agent in melanoma.

Methods The protection against solar ultraviolet radiation delivered by sunscreens available prior to the early 1990s (when the data used in most published case–control studies were collected) was estimated by combining their absorption properties with the amount applied in a way reflecting common usage. Similar estimates were made for the protection offered by modern sunscreens.

Results It is not surprising that case–control studies have failed to find any association between sunscreen use and the risk of melanoma when consideration is given to the sunscreens in common usage at the time and the way in which sunscreen is applied in practice. Modern high Sun Protection Factor, broad-spectrum sunscreens, on the other hand, can be expected to be an effective measure in helping to prevent melanoma compared with sunscreens typical of those used 10–20 years ago.

Conclusions It is reasonable to suppose that the improvement in performance of modern sunscreens will lead to a worthwhile benefit as a preventative agent against melanoma, although these benefits may not be seen for several decades.

The observation that sunscreens protect against sunburn led to the common expectation that they will also protect against skin cancer, including malignant melanoma. Reports first appeared in the lay press in the early 1990s that this expectation may not necessarily be realized.[1] However, it was not until the results of 15 case–control studies were reviewed to evaluate the potential preventive effect of sunscreens against cutaneous melanoma that was there real cause for concern.[2] Of the 15 studies examined, four provided little evidence of an effect of sunscreen use on the risk of melanoma, three studies showed significantly lower risks for melanoma in sunscreens users compared with nonusers, while the remaining eight studies showed significantly higher risks in sunscreen users.

While the majority of studies reviewed could be taken to support a positive association between sunscreen use and melanoma, they were difficult to interpret because of problems of positive confounding (e.g. people who are at most risk of burning and most likely to develop melanoma are also most likely to use sunscreens) and negative confounding (e.g. sunscreen users may also use other methods of sun protection such as clothing and shade).

More recently, meta-analyses of observational case–control studies have demonstrated no association between sunscreen use and the development of malignant melanoma,[3,4] with failure to control adequately for confounding factors possibly explaining previous reports of a positive association linking melanoma to sunscreen use.

The controversy remains about the efficacy or otherwise of sunscreens in preventing melanoma,[5,6] with some going as far as suggesting that the hypothesis that sunscreen use does not prevent melanoma among people exposed to strong sunlight is implausible on the basis of animal and human models.[7] Yet if consideration is given to the period during which the data used in most case–control studies were collected, the ultraviolet (UV) absorbing properties of sunscreens prevalent at that time, and how sunscreen is used and applied in practice, then the observation that sunscreens appear to play little or no role in preventing melanoma is entirely to be expected.

Why sunscreens have not been shown to protect against melanoma

The most recent and largest systematic review by Dennis *et al.*[4] considered 18 heterogeneous case–control studies. Eleven of these studies collected data starting prior to 1990 and in the remaining seven studies sunscreen use was limited to the early 1990s.

In 1984, the median Sun Protection Factor (SPF) of sunscreen products used in Europe was 4–6,[8] but this had risen to 6–10[8] by 1987 and to about SPF15 by 1997, with a tendency for higher SPFs to be preferred in northern European countries compared with those in southern Europe (U Osterwalder, Ciba Specialty Chemicals, Basel; personal communication). So while not explicitly stated, it is likely that the respondents who took part in most, if not all, of these 18 studies were overwhelmingly using sunscreens with a typical SPF of about 8 and incorporating active UV filters limited largely to the UVB waveband as can be seen from Table 1, which shows that prior to 1990, sunscreens contained little in the way of effective UVA filters.[9,10]

The SPF of a sunscreen is assessed after phototesting *in vivo* at an internationally agreed[11,12] application thickness of 2 mg cm^{-2}. Yet a number of studies have shown that consumers apply much less than this,[13] typically between 0·5 and 1·0 mg cm^{-2}. Application thickness has a significant effect on protection with most users probably achieving a mean value of between 20% and 50% of that expected from the product label as a result of common application thickness.[14] That the protection achieved is often less than that expected depends upon a number of other factors apart from amount applied such as uniformity of application, cosmetic 'feel' of sunscreen, resistance to water immersion and sand abrasion, and when, where and how often sunscreen is re-applied.[13] Furthermore, studies of sunscreen use by beachgoers highlight other important behavioural considerations including failure to apply sunscreen prior to exposure and failure to apply to all exposed skin.[15]

By considering the absorbing properties of commonly used sunscreens prior to the early 1990s (Fig. 1a), it can be shown that a sunscreen of nominal SPF8 when applied at a typical thickness of 0·5–1·0 mg cm^{-2} will result in an effective SPF of only 2–3, and a total solar UV radiation (UVA + UVB) dose to the skin of somewhere between 70% and 90% of that received by unprotected skin exposed for the same time. Hence with such a small impact of this generation of sunscreens on modifying the solar UV exposure of skin, it is not surprising that case–control studies have failed to find any association between their use and the risk of melanoma. Furthermore, there is some epidemiological evidence that suggests that sun exposure in childhood and adolescence may be a critical period in the initiation of melanoma.[16] If this were the case, then effective sunscreens would not have been available (or sunscreens were not used at all) in the early years of life by the adults who participated in these case–control studies.

What of the future?

During the 1990s, new UV filters became available that exhibited high molar extinction often combined with peak absorption in the UVA region (Table 1). This availability coupled with a rapid, *in vitro* assay for assessing the UVB and UVA protection provided by sunscreens,[17] allowed formulators to develop a new generation of much more effective sunscreens (Fig. 1b).

There has been a trend in recent years towards high SPFs across all the major brands and estimates are that just over

Table 1 Molar absorption coefficients (ε_{max}) and absorption maxima (λ_{max}) of common organic sunscreens available commercially in Europe and/or the U.S.A.

UV filter	INCI name[a]	λ_{max} (nm)	ε_{max} (M^{-1} cm^{-1})
Commonly used pre-1990			
PABA	Para-aminobenzoic acid	283	15 300
MBC	4-Methylbenzylidene camphor	300	24 500
OCT	Octocrylene	303	12 600
PBSA	Phenylbenzimidazole sulphonic acid	305	26 000
EHS	Ethylhexyl salicylate	307	5000
OD-PABA	Ethylhexyl dimethyl PABA	311	27 300
EHMC	Ethylhexyl methoxycinnamate	311	23 300
BP3	Benzophenone-3	325	9400
MA	Menthyl anthranilate	338	5600
Rarely/not used pre-1990			
DEBT	Diethylhexyl butamido triazone	311	114 900
BEMT	Bis-Ethylhexyloxyphenol methoxyphenyl triazine	341	48 000
TDSA	Terephthalyidene dicamphor sulphonic acid	345	47 000
BMBM	Butyl methoxydibenzoyl methane	358	34 720

[a]International Nomenclature of Cosmetic Ingredients.

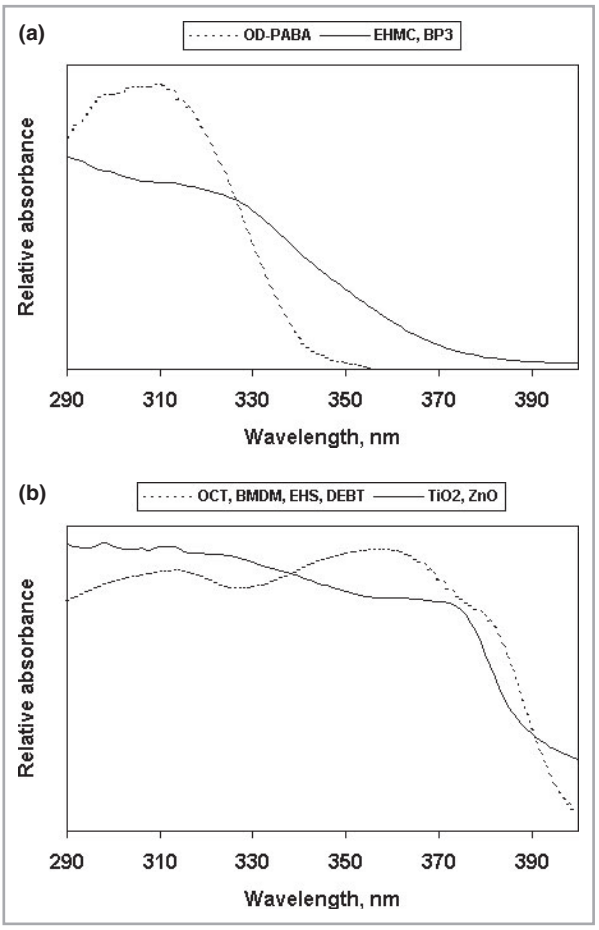

Fig 1. (a) Absorption profiles of typical pre-1990 sunscreens. (b) Absorption profiles of typical modern sunscreens.

one-half of all sunscreens sold in the UK in 2002 were SPF15 or above.[18] Consumers have learnt about sun protection through the media, manufacturers and retailers. Although it is generally recognized that SPF15 is the dermatologists' recommended minimum, many brands market sun protection products with far higher SPFs. In 2002, sunscreens with SPFs between 20 and 29 were the most popular in the UK, while sales of SPF30 and higher were increasing faster than any other SPF category and sales were up 27% on the previous year.[18]

In terms of formulation, creams have lost popularity, due to the fact that they rub less easily into the skin and can leave a white film, which many consumers find unacceptable. High SPF products, which could previously only be found in cream formulations, now include lotions, milks, gels, sticks and sprays.

In addition to the trend for higher SPFs, there have been publications of guides concerning dosage[19,20] and re-application[21] and it is to be hoped that with greater consumer awareness of the gap between expectation and realization of sunscreen SPFs,[22,23] the effective SPFs of currently applied products will move closer to the labelled SPF.

Consequently, a modern, broad-spectrum sunscreen of SPF25 (typical of the most popular SPF) applied at an average thickness of about 1·0 mg cm^{-2}, will result in an effective SPF of about 8–10 and a total solar UV radiation (UVA + UVB) dose to the skin of somewhere between 20% and 30% of that received by unprotected skin exposed for the same time. In other words, modern sunscreens can be expected to be about fourfold more effective in preventing melanoma than sunscreens typical of those used 10–20 years ago.

This conclusion is based on the cautious premise that all wavelengths of UV radiation are equally effective in initiating and promoting melanoma. There are *in vivo* and *in vitro* biological data suggesting a potential role for broad-spectrum (UVA + UVB) UV radiation in the pathogenesis of melanoma, and evidence from epidemiological and clinical observations, while inconclusive, is consistent with this hypothesis.[24] On the other hand, a recent study[25] using a hepatocyte growth factor/scatter factor transgenic mouse model of UV-induced melanoma concluded that, within the constraints of this animal model, UVB is primarily responsible for the induction of mammalian cutaneous malignant melanoma.

Although this finding may well point to a similar relevance in humans, it is evident that we still remain ignorant of the precise role of different wavelengths of UV radiation in initiating and promoting melanoma in humans. Yet whatever the action spectrum for melanoma induction in humans, it is clear that modern sunscreens can be expected to be about four times as effective as older sunscreens.

It is reasonable to suppose that this improvement in performance will lead to a worthwhile benefit of modern sunscreens as a preventative agent against melanoma, although this may be compromised to some extent by the reported observation that recreational use of high-SPF sunscreen can prolong the amount of time people spend in the sun.[26] That a randomized controlled trial of a broad-spectrum SPF30 sunscreen in children showed that the sunscreen group developed fewer naevi (a surrogate end-point for the risk of developing melanoma) than the control group[27] is cause for optimism. However, even if modern sunscreens prove to be effective, these benefits, in terms of a falling incidence of melanoma, may not be seen for several decades.[28]

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