Research Review
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An Update on Sunscreens IV

About the Commentators

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This review summarises recent research on the status of sunscreen as an adjunctive sun protection measure in the prevention of skin cancer and photoaging. Topics covered are sunscreen efficacy, adherence and application, and potential effect on vitamin D levels. Louise Reiche (New Zealand) and Adele Green (Australia) provide expert comment and recommendations.

Sunscreen efficacy: prevention of skin cancer and photoaging

Exposure to ultraviolet radiation (UVR) from the sun is the chief environmental risk factor for the three major types of skin cancer, basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma, as well as the skin tumours, actinic keratosis and melanocytic naevi, which are strong risk factors for skin cancer and melanoma. Considerably more common than skin cancer is photoaging (premature aging) of the skin, which also results from high cumulative solar UVR exposure. Given the common cause, i.e. UVR, it follows therefore that skin cancer and photoaging are largely preventable by avoiding or minimising excessive sun exposure.[1]

Exposure to UVR can be avoided by staying indoors during the hours of highest UVR intensity or reduced by wearing protective clothing, sunglasses, and a hat as well as seeking shade when outdoors. The application of sunscreen, as an adjunctive strategy to covering up and sun avoidance, is also widely used to protect against skin cancer and photoaging.[1,2]

A large, comprehensive, population-based case-control study demonstrated that, over the most recent two decades, optimal use of routine sunscreen was strongly associated with reduced risk of melanoma.[3] But due to being observational in design, epidemiological studies such as case-control studies are unable to clearly distinguish the main determinants of sunscreen use from those of skin cancer and photoaging and hence are somewhat uninformative.[1] Randomised controlled trials (RCT) provide more reliable evidence that sunscreen is a safe and effective strategy for the prevention of skin cancer, skin cancer tumours, and photoaging.[1]

The primary source of RCT evidence comes from the Nambour Skin Cancer Study, which was a field trial that enrolled adult residents (aged 25-75 years) from the Nambour community in Queensland, Australia, and to date is the only population-based intervention study to have examined the effects of SPF≥15 sunscreen use on skin cancer and photoaging end-points.[1] In the Nambour study, 1621 adults (aged 20-69 years when originally selected at random from the community electoral roll) participated in the trial between 1992 and 1996 that evaluated the effectiveness of daily versus discretionary application of SPF16 sunscreen on skin cancer and photoaging over a minimum follow-up time of 4.5 years.[4] After trial conclusion in 1996, the study participants were further followed-up for a decade, until 2006.[5,6]

Basal cell carcinoma

The Nambour study is the only RCT to have evaluated the role of sunscreen in the prevention of BCC and no statistically significant protective effect of regular sunscreen application as opposed to discretionary use (including no use) was demonstrated. Daily sunscreen use was not associated with a reduced incidence of people with newly acquired BCC either in the 4.5-year field trial period [rate ratio (RR): 1.03; 95% CI: 0.73-1.46][4] or in the extended 8-year follow-up period (1996-2004) after trial completion [RR: 1.02; 95%CI: 0.75-1.37 (**Table 1**)].[6] However, a tendency towards reductions in the incidence of first BCC (RR: 0.86; 95% CI: 0.59-1.26) and total number of BCC tumours (RR: 0.75; 95% CI: 0.49-1.14) was observed in the late follow-up period (2001–2004) in the daily sunscreen group compared with controls (**Table 1**).[6]

It was somewhat surprising that the Nambour study data did not support what would be predicted by epidemiological and direct evidence, i.e. a protective benefit of regular sunscreen use against BCC.[7] One explanation is the significant (upwards of 20 years) time lag between sun exposure and development of BCC, which brings into question the applicability of a 4.5-year study duration, and even an 8-year extended follow-up period, with respect to BCC risk when people have likely been accruing UVR damage for triple that amount of time with the median age at diagnosis being 67 years.[7]

Outcome and follow-up period	BCC			SCC		
	Daily sunscreen, incidence (no.)	No daily sunscreen, incidence† (no.)	Rate ratio* (95% confidence interval)	Daily sunscreen, incidence† (no.)	No daily sunscreen, incidence† (no.)	Rate ratio* (95% confidence interval)
Persons affected						
Trial + total follow-up period 1993–2004	1,296 (121)	1,270 (119)	1.02 (0.78-1.35)	546 (51)	811 (76)	0.65 (0.45-0.94)
Total follow-up period 1996–2004	1,516 (97)	1,494 (96)	1.02 (0.75-1.37)	625 (40)	934 (60)	0.65 (0.43-0.98)
Late follow-up 2001–2004	1,820 (55)	2,085 (63)	0.86 (0.59-1.26)	695 (21)	1,390 (42)	0.49 (0.28-0.83)
Total number of tumours						
Trial + total follow-up period 1993–2004	2,474 (231)	2,840 (266)	0.87 (0.64-1.20)	868 (81)	1,516 (142)	0.59 (0.38-0.90)
Total follow-up period 1996–2004	2,422 (155)	2,770 (178)	0.89 (0.64-1.25)	953 (61)	1,587 (102)	0.62 (0.38-0.99)
Late follow-up 2001–2004	2,548 (77)	3,408 (103)	0.75 (0.49-1.14)	960 (29)	1,952 (59)	0.49 (0.27-0.87)

*Rate ratios are given relative to the "no daily sunscreen" reference group, with 95% confidence intervals.
†Incidence per 100,000 person-years at risk.

Table 1. Summary of incidence of histologically-confirmed basal cell (BCC) and squamous cell (SCC) carcinoma in daily sunscreen versus discretionary sunscreen use groups from the Nambour study.[6]

Squamous cell carcinoma

The Nambour study is also the first RCT to assess the effect of regular sunscreen use on SCC. During the 4.5-year field trial, the incidence rate of people newly affected by SCC was reduced in the daily versus discretionary sunscreen use group but not significantly (RR: 0.88; 95% CI: 0.50-1.56), whereas the 40% reduction in SCC tumours in the daily sunscreen use group was statistically significant (RR: 0.61; 95% CI: 0.46–0.81).[4] In the extended 8-year follow-up period (1996–2004), both the incidence of people newly affected by SCC (RR: 0.65; 95% CI: 0.43–0.98) and SCC tumour incidence (RR: 0.62; 95% CI: 0.38–0.99) were reduced in the daily versus discretionary sunscreen use groups (**Table 1**).[6] Hence, regular sunscreen application provided ongoing protection against SCC, with the number of persons with SCC and the number of SCC tumours both being reduced in the long term by regular sunscreen use, up to 8 years after cessation of the intervention.

Melanoma

The total 15-year observation period of the Nambour study permitted evaluation of whether regular sunscreen use during the first 4.5 years of the study reduced the risk of primary cutaneous melanoma over the long term.[5] A total of 33 study participants were newly diagnosed with first primary melanomas (19 with in situ, 14 with invasive, none with metastatic melanoma) between 1993 and 2006. Ten years after the initial 4.5-year study period, 11 new primary melanomas had been identified in the daily sunscreen group versus 22 in the discretionary use group, which represented a non-significant reduction of the observed melanoma rate in those assigned to daily sunscreen use [hazard ratio (HR): 0.50; 95% CI: 0.24-1.02, p=0.51]. Despite there being no significant differences between the two groups with respect to *in situ* melanomas (HR: 0.73; 95% CI: 0.29-1.81), invasive melanoma was substantially reduced in the daily sunscreen group versus the discretionary group (3 vs 11; HR: 0.27; 95%CI: 0.08-0.97). Additionally, the average thickness of invasive melanomas (0.53mm) in the sunscreen group was non-significantly lower than in the discretionary sunscreen group (1.2mm).[5] Overall, these results suggest that regular sunscreen use in adults may prevent melanoma.

Actinic keratosis

Actinic (solar) keratoses (AK) are biomarkers of the skin having received high levels of UVR and their presence is associated with an increased incidence of BCC, SCC, and melanoma.[8,9] The Nambour study is not the only RCT to have investigated the effect of regular sunscreen use on the development of AKs. The results from the Nambour study[10] and three other RCTs,[11-13] including another Australian study,[13] indicate that regular sunscreen application protects against the development of actinic keratoses in adults. In the Nambour study, a 24% reduction in the ratio of AK counts in 1994 relative to 1992 with daily sunscreen use versus discretionary use was equivalent to the prevention of an average of one additional AK per person over that time. Interestingly, results from the other Australian study suggested an association between daily sunscreen use and remission of existing AKs, with 25% of AKs present at baseline remitting in the sunscreen group compared with 18% in the placebo group (adjusted odds ratio: 1.53; 95% CI: 1.29-1.80).[13] In the most recent of the four RCTs, Italian researchers demonstrated that a sunscreen containing DNA repair enzymes was more effective than a traditional sunscreen formulation in potentially preventing malignant transformation in patients with AKs.[11] These clinical findings appear to confirm experimental irradiation studies in which the addition of DNA repair enzymes (photolyase and endonuclease) to traditional sunscreens appeared to reduce UVR-induced molecular damage in the skin to a greater extent than sunscreens alone.[11]

Melanocytic naevi

One RCT has demonstrated sunscreen use to delay the formation of melanocytic naevi in light-skinned children, particularly in those with freckles.[14,15] Children in the sunscreen intervention group developed fewer naevi than did children in the control group (median counts, 24 vs 28; p=0.048) and modelling of the data suggested that freckled children assigned to the sunscreen group would develop 30-40% fewer new naevi than freckled children assigned to the control group. As naevi are an established risk factor for melanoma, with higher nevus counts being associated with the highest melanoma burden,[16] it follows by implication that a reduction in the number of naevi acquired in childhood might reduce the risk of melanoma in adulthood.

Skin photoaging

Sun-induced skin aging is clinically distinct from natural skin aging, with the accumulation of degraded elastotic material in the dermis, termed dermal elastosis, generally being accepted as the key distinguishing histological feature of sun-aged skin.[1]

In addition to the Nambour trial,[17] an earlier RCT also investigated the efficacy of sunscreen use in preventing or reducing skin aging in humans.[18] However, this earlier investigation of daily application of sunscreen for 24 months compared with placebo in older adults (mean age 63 years) showed no difference in dermal elastosis over time between the treatment groups after analysis that accounted for repeated measurements.[18] Moreover, only a small number of participants ended up completing the 24-month assessment and treatment adherence does not appear to have been assessed.[1] Perhaps more saliently, the lack of an effect of sunscreen use on photoaging demonstrated in this earlier investigation may have also been due to the advanced age of the study population.[1]

The Nambour study,[17] in contrast, restricted its evaluation of the effect of sunscreen use on photoaging to young and middle-aged adults because skin aging in this age range is caused mainly by photoaging rather than by photoaging in combination with natural aging changes. The Nambour study was able to show that the daily use of a sunscreen resulted in no detectable increase in skin aging (measured using the Beagley and Gibson microtopography scale, which has been validated for predicting the severity of dermal elastosis) after 4.5 years in healthy men and women aged <55 years (mean age 39 years): skin aging from baseline to the end of the trial was 24% less likely in the daily versus discretionary sunscreen use group (relative odds: 0.76; 95% CI: 0.59-0.98).

Sunscreen use: adherence and application method

The potential benefit of sunscreens in preventing the development of skin cancer and photoaging are only derived if users apply sunscreen adequately and regularly.

A reality of real-life use of sunscreen is that sunscreens may not be applied at the 2 mg/cm^2 thickness that provided the tested level of protection, with 0.5 mg/cm^2 being the amount more likely to be applied.[19,20] The relationship between SPF and the amount of sunscreen applied has been demonstrated to be non-linear, such that an SPF16 sunscreen is reduced to SPF2 when 0.5 mg/cm^{-2} is applied.[21] Even if the thickness of sunscreen applied is adequate, it is probable that not all exposed parts of the body will necessarily be protected by the sunscreen.[19,20] For example, UK surveys of sunscreen habits suggest that <50% of sunscreen users apply sunscreen to all uncovered body sites,[19] and the most frequently missed sites have been shown to be the neck, temples, and ears.[22] Furthermore, the frequency of re-application may be inadequate, especially if the user is sweating, swimming, or engaged in vigorous activity.[19,20]

Poor adherence to regular sunscreen use also compromises the effectiveness of sunscreen as an adjunctive sun protection modality.[2,23] Sunscreens that fail to meet consumer preferences in terms of fragrance, colour, appearance, and sensory profile, packaging, and cost may lead to sub-optimal use and hence poor UVR protection.[2]

Research suggests that user preference is an important factor in encouraging regular use of sunscreen, as exemplified in the context of dermatological practice with patients typically preferring lighter cream-based emollient to greasier emollients.[24] For example, the cosmetic properties, sweat resistance, and usability of sunscreen (including non-irritation of the eyes), in addition to UVA/UVB performance, under outdoor working conditions were key factors in the overall acceptance of daily sunscreen use by outdoor workers in a German RCT.[25] Furthermore, at least in a clinical practice setting, shared decision-making and consideration of user choice, including individualising of sun protection advice, are also key components influencing adherence.[24]

Cost being a limiting factor in users applying sunscreen as often as necessary is suggested by a prospective RCT conducted in French beach resorts that assessed to what degree labelling and high cost account for the misuse of sunscreen.[26] Another French study, which analysed prices of sunscreens sold via the internet in Europe and North America, concluded that in situations of acute sun exposure (i.e. a week at the beach), the cost of sun protection appears acceptable if protective clothing is worn and low-cost, large-volume bottles of sunscreen are used.[27] In a sun-sensitive population requiring year-round protection, however, the annual budget is relatively high and compliance with sun protection guidelines may be compromised.[27]

Instructions on sunscreen packaging may also influence sunscreen use and application. In the French RCT that analysed the effect of SPF labelling on sunscreen use in addition to cost, sunscreen with explicit labelling increased the quantity of sunscreen applied and resulted in less sunburn.[26] The researchers concluded that difficulties in understanding the labelling hampers use and that more explicit labelling for the public would result in more optimal use of sunscreens.[26]

Another factor in non-adherence to sunscreen use appears to be simple forgetfulness. A multicentre cross-sectional study using a population-based survey of Australian adults and their knowledge, attitudes, and behaviour toward sun protection revealed that forgetfulness was the major barrier to sunscreen use.[28] In this study, a total of 85% of respondents did not apply a sufficient amount of sunscreen, only 32% reapplied sunscreen every 2 hours, and 20% never reapplied it.[28]

A potential means of improving adherence is cellular telephone text messaging, especially given evidence that forgetfulness is a factor in sunscreen non-adherence. In a RCT of the effect of an electronic text-message reminder system on adherence to sunscreen application conducted in the US, text-message reminders consisting of a 'hook' text detailing daily local weather information and a 'prompt' text reminding users (adults aged >18 years) to apply sunscreen resulted in significantly higher sunscreen adherence rate in recipients of the text message reminders versus non-recipients (56% vs 30%; p<0.001).[29] Similarly, an Australian RCT demonstrated that a theory-based, text message-delivered behavioural intervention (Healthy Text) targeting sun protection or skin self-examination behaviours produced significant improvements in sun protection behaviours among Queensland adults (aged 18-42 years).[30]

Sunscreen use: vitamin D

Skin conversion of 7-dehydrocholesterol to pre-vitamin D3 by UVB is the main source (>90%) of vitamin D,[20] which plays a physiological role beyond just bone health in humans.[31] It is perhaps not surprising therefore that concerns that regular use of sunscreen could compromise vitamin D synthesis in the skin, ultimately affecting general health, have been expressed since the mid-1980s[32,33] and more recently with greater awareness of vitamin D deficiency being a common though controversial health concern in Caucasian populations.[34]

Sunscreens could almost entirely block the solar-induced production of cutaneous pre-vitamin D3 on theoretical grounds or if administered under strictly controlled conditions; however, in practice, they have not been shown not to be associated with vitamin D deficiency.[20]

In prospective studies, normal levels of vitamin D were maintained in individuals who intensively avoided sun exposure by use of protective clothing and sunscreen when outdoors[36,37] and in individuals who regularly used sunscreen.[35,38,39] Of particular note, Marks et al. demonstrated that participants who applied SPF17 sunscreen daily during an Australian summer ended up with vitamin D biomarker serum levels that were similar to those in participants who used a placebo sunscreen, with no participant in either group having vitamin D biomarker serum levels outside of the reference ranges either at the start or end of the study (**Figure 2**).[35] In addition, Farrerons et al. not only showed no change in serum levels of bone biological markers during two years of daily SPF15 sunscreen use in elderly individuals (mean age 71 years) compared with controls,[38] but also no significant loss of bone mass in a 2-year follow-up report.[40] Reviews of the published literature have also concluded that use of sunscreen is not associated with lower-than-normal vitamin D levels.[41-43] In terms of comprehensive sun protection behaviour, a large study that measured vitamin D levels in 1113 adults in Nambour demonstrated that wearing a hat, long sleeves, sunglasses, and use of sunscreen or umbrella was not associated with vitamin D status, even after stratification by time spent outdoors.[37]

These observations that regular use of sunscreen does not affect vitamin D levels are likely explained by sub-optimal application of sunscreen[19,20] and the fact that sunscreens do not block all UVR; they allow the transmission of a fraction of incident UVB, equal to 1/SPF.[20] For example, use of an SPF30 sunscreen will allow one-thirtieth, or 3.3%, of the erythemal UVR, the majority of which is UVB, to be transmitted.[20]

Regarding one of the likely explanations being that sufficient light is received by the skin despite sunscreen use, Marks et al. demonstrated that, at least during an Australian summer, sufficient light is received via the sunscreen itself and the lack of total skin cover at all times to allow adequate vitamin D synthesis to occur in regular users of sunscreen.[35] Indeed, exposure of just 10% of skin surface for about 3-7 minutes per day (depending on geographical location) during a New Zealand summer was shown to be sufficient to maintain normal vitamin D levels while being insufficient to produce erythema.[44] In addition, different racial groups (Asian, European, Maori, and Pacific peoples) with different skin types demonstrated little difference in sun exposure time to generate adequate vitamin D.[44] Furthermore, whether due to delayed diagnosis or other factors, greater melanoma thickness, and hence likely worse outcomes, observed in Maori and Pacific peoples compared with Europeans,[45,46] suggests that all racial groups/skin types will benefit from sun protection and sunscreen use since it would reduce skin cancer risk without reducing vitamin D levels.

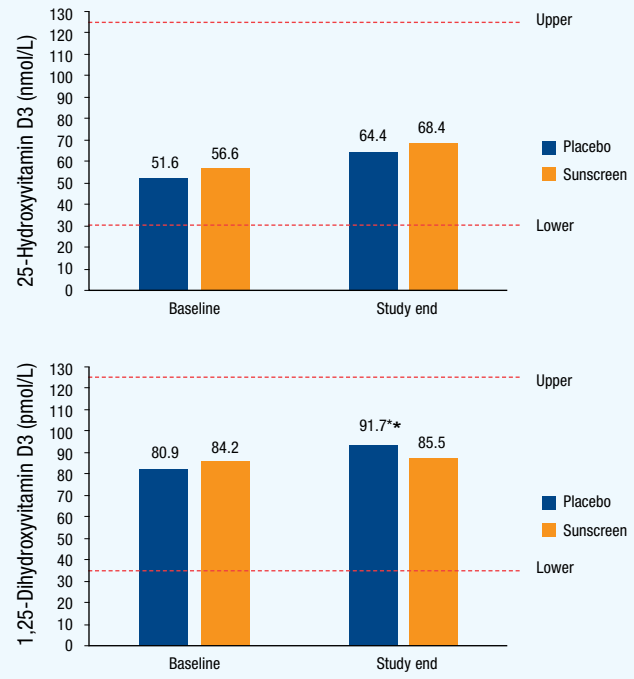

Figure 2. Effect of sunscreen use on vitamin D biomarker serum levels during an Australian summer as measured at study start (baseline) and study end (7 months) in a randomised placebo-controlled trial.[35] Red dashed lines = biomarker reference range; *p=0.0009 versus baseline.

EXPERT COMMENTARY – *Dr Louise Reiche*

In my clinical practice, the ability of the skin to repair sun damage, once protected, is impressive. The sooner patients start, the quicker and more extensively the recovery is seen. But it is never too late. Octogenarian life-long outdoor workers, regularly covering up and applying daily sunscreen throughout the year, slowly and progressively reduce the production of scaly actinic keratoses and extent and frequency of skin cancers over the subsequent 3-5 years. This reduces morbidity and financial burdens considerably and could have a great impact on health budgets if universally undertaken. Furthermore, wrinkling and mottled pigmentation lessen, so rejuvenating sun protectors. I am observing the broader spectrum higher SPF (30-50) sunscreens are reaping the results better, so would anticipate if the same Nambour studies were repeated with sunscreens meeting the Australia/New Zealand standards updated in 2013, and observed over a longer time period, the statistical results in skin cancer reduction would be more compelling. Arguably, it is UVA exposure that contributes more to photoaging and perhaps melanoma and SCCs. So, better UVA protection provided by modern compliant sunscreens are likely to yield superior protection. Visible light may have an additive effect so tinted sunscreens or addition of a powdered mineral foundation make-up is advocated for photoaging reversal.

As more studies are showing minimal but regular outdoor exposure generates sufficient vitamin D (for all skin types), routine (rather than discretionary) application of sunscreen would benefit the entire population. Novel technology educating and reminding consumers of optimal use is promising to correct inadequate application issues. Better long-term outcomes are anticipated. Sunscreens that are pleasant and easy to apply, effective, long-lasting, economical, and without adverse effects become ever more important.

EXPERT COMMENTARY – *Professor Adele Green*

When Europeans first inhabited Australia and New Zealand they were very aware of the effects of sun exposure. They knew sun-exposed skin became sunburnt or brown which was unwelcome when smooth white skin and creamy complexions were sought-after as indicators of wealth and leisure. Furthermore, fashions of the time dictated large-brimmed hats, gloves and long-sleeves be worn as a matter of course. Sunscreen was unknown, but so was the need for sunscreen. Skin cancer was rare and melanoma even rarer, occurring mostly in men occupationally sun-exposed like sailors and farm labourers.

In the early 20th century, a gradual shift in cultural mores began in Europe and in populations of European heritage like Australia and New Zealand. After World War I, sun exposure was increasingly associated with good health due to growing beliefs in the tonic effect of sunlight (e.g. used as tuberculosis treatment) alongside fresh air and nature in promoting strong healthy bodies. Brown skin was now considered the sign of wealth, summer clothing-cover was minimal and community sun exposure was high. Skin cancer and melanoma incidence rates increased to almost epidemic proportions. In response to the realisation that sun exposure (specifically solar ultraviolet (UV) radiation) was driving these increases, Australia and New Zealand began vigorous sun awareness campaigns in the 1980s and these have continued. Central to these campaigns is the advice to stay in shade when possible and return to our forebears' customs of wearing large-brimmed hats and long-sleeves in the sun as a matter of course. Today sunscreen use is also a key component of comprehensive sun protection and thus skin cancer prevention because it is highly cost-effective compared to other cancer prevention strategies, and harmful side-effects are few.

Both asbestos and solar UV are classified as "Type 1 Carcinogens" i.e. they are scientifically-proven causes of cancer in humans. These days no-one would voluntarily expose themselves to asbestos, yet many people voluntarily expose themselves, without protection, to strong sunlight. People even pay to be exposed to yet another Type 1 Carcinogen, artificial UV radiation in the form of solaria and sunbeds, to acquire brown skin and in doing so risk accelerated signs of photoaging: coarsened and lined skin with patches of discolouration, as well as skin cancer. Regular sunscreen application can slow photoaging, and this message can be used to enhance the appeal of long-term prevention behaviours, especially in young people. Billions of dollars are spent each year on anti-aging face creams and treatments, when all that was required was sun-protecting hats and long-term use of sunscreen of SPF 15+ or more, applied with adequate thickness and re-applied regularly after sweating or swimming. Prevention is better than cure and nowhere is this more evident than for sun-induced skin aging and cancers.

Take-Home Messages

- The results of a the large Nambour RCT that compared daily sunscreen use with discretionary use demonstrated that regular sunscreen use:
  - Provides ongoing protection against the development of SCC.
  - Appears to have no clear benefit in reducing BCC tumour, although use of a higher protection sunscreen and a younger study population to see the maximum potential effect of long-term sun protection may have revealed a clear benefit.
  - May prevent melanoma.
  - Can delay photoaging of the skin.
- The results of the Nambour RCT, and three other RCTs, demonstrated that use of sunscreen provides protection against the development of AK.
- RCT evidence, although limited, supports beneficial effects of sunscreen use on the occurrence of skin cancers and skin photoaging and, as such, is an effective adjuvant to wearing protective clothing and sun avoidance.
- Non-adherence and sub-optimal application remain a barrier to the effectiveness of sunscreen in protecting against skin cancer.
- Current evidence indicates that use of sunscreen is not associated with vitamin D deficiency.

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