REVIEW
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Melanoma Management

Skin cancer and vitamin D: an update

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Practice points

Skin cancer incidence, mortality, burden & cost

- Accurate incidence rates are hard to capture for the keratinocyte cancers, squamous cell carcinoma and basal cell carcinoma.
- Fatality rates for keratinocyte skin cancers are low, but approximately 55,000 deaths result from melanoma each year.
- Skin cancers cause a significant health burden and cost to healthcare systems.

UV radiation & skin cancer

- Exposure to UV-A radiation causes free radical production, resulting in oxidative damage.
- Exposure to UV-B radiation induces DNA damage; recent genetic studies confirm many UV 'signature mutations' in skin cancers, including both driver and bystander mutations.
- UV-induced immunosuppression results from irradiation in both UV-A and UV-B wavelengths and is an important factor in skin cancer development.

Vitamin D, skin cancer risk & prognosis

- Exposure to the sun causes both skin cancer and vitamin D production.
- Cutaneous production of vitamin D is initiated by exposure to UV-B radiation.
- Serum concentrations of 25-hydroxyvitamin D (25(OH)D) of 50 nmol/l or higher are classed as sufficient.
- Studies exploring the relationship between skin cancer risk and vitamin D show mixed results.
- Results from human studies are consistent in reporting that low levels of 25(OH)D are associated with thicker cutaneous malignant melanomas or a poorer prognosis.

What to tell skin cancer patients

- Caution should be taken to avoid harmful levels of sun exposure.
- It is important to maintain vitamin D levels above 50 nmol/l.
- Patients at high risk of skin cancer should routinely apply sunscreen to the face, hands and arms. Areas less frequently exposed to UVR may be exposed for short periods (e.g., 10 min) in the middle of the day when the UV-B levels are highest.

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SUMMARY Exposure of the skin to solar ultraviolet (UV) radiation has both risks and benefits for human health. Absorption of UV-B radiation by DNA results in mutations that underlie the development of skin cancers, as is apparent from genetic studies showing high occurrence of UV signature mutations within these tumors. UV-B radiation is also absorbed by 7-dehydrocholesterol to initiate vitamin D synthesis. In experimental studies vitamin D metabolites enhance apoptosis of malignant cells, inhibit angiogenesis and proliferation and increase differentiation, potentially reducing skin cancer development and improving prognosis after diagnosis. There are some supporting human data. We review the links between sun exposure, vitamin D and skin cancers.

KEYWORDS
• basal cell carcinoma
• keratinocyte cancer
• melanoma • squamous cell carcinoma • sun exposure
• vitamin D

Skin cancer incidence, mortality, burden & cost

Cutaneous malignant melanoma (CMM) and the keratinocyte cancers (KCs), predominantly basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), cause a significant public health burden. In 2012 there were approximately 230,000 new cases of CMM worldwide, with over 80% of these occurring in more developed regions of the world [1]. Although the 5-year survival is high, up to 90% in some countries such as Australia, there are approximately 55,000 deaths from CMM each year. The incidence of CMM has doubled each decade since the 1960s and this trend is likely to continue for at least the next two decades [2]. There are indications that incidence rates are plateauing or decreasing in younger age groups in some countries, possibly because younger cohorts have been exposed to public health messages from an early age [2]. Of note, however, a recent publication suggests that, an apparent decrease or stabilization of incidence is no longer apparent when the population denominator is adjusted to remove those at low risk of CMM, such as dark-skinned immigrants [3].

KCs have a very low case fatality rate, but a very substantial economic impact [4] as they are the most commonly occurring cancers in fair-skinned populations. However it is very difficult to capture accurate incidence rates and analyze geographic differences or temporal trends for a number of reasons. First, a tissue diagnosis may not be obtained for lesions that are treated destructively. Thus differences in management approaches between countries or changes over time could substantially affect international comparisons and trends. Second, there are few cancer registries that require mandatory reporting of KCs and there are very few high quality population-based studies. Finally, many people are diagnosed with multiple KCs either contemporaneously or sequentially, so calculation of person-based incidence rates results in a considerable underestimation of the KC burden. Despite these challenges, there is strong evidence that KC incidence has increased markedly in the last several decades. A recent analysis has shown that after adjustment for age, sex and the levels of ambient UV radiation, the average annual increases in SCC and BCC incidence were 4 and 1%, respectively [5].

UV radiation & skin cancer

There is considerable evidence showing that exposure to the sun causes skin cancer, including from observations of geographical variation in incidence, a higher risk in people with fair skin, an increased risk in people with markers of actinic damage such as actinic keratoses and the presence within tumors of 'UV-signature' genetic mutations (cytosine to tyrosine transitions at cyclobutane pyrimidine dimers).

Country of residence is an important determinant of the absolute risk of a CMM occurring in a fair-skinned person [6]. There is a clear latitude gradient of increasing incidence with decreasing latitude [7–10]. Within Australia the potential influence of latitude is clearly demonstrated in the decreasing incidence rates from north to south [7,11]. This is not the case in Western Europe, however, where the European national cancer registries report that the highest incidence rates are found in the Scandinavian countries [7,12]. This is probably because European populations at lower latitude have darker skin types, and also because people living in high latitude locations commonly take low latitude sunny holidays [13]. The latter argument is supported by the socioeconomic differences in CMM incidence that have been reported in Scandinavia [14].

Despite the difficulties in ascertaining the true incidence of KCs, there is a strong association between KC incidence and intensity of ambient ultraviolet radiation (UVR) [15]. In a recent quantitative review restricting the analysis to fair-skinned populations only, intensity of

ambient UVR accounted for almost 40% of the variability in incidence of SCC and BCC (with age, sex and calendar year additional important factors) [5].

Evidence for an important role for exposure to UVR in skin cancer risk also arises from its predilection for fair-skinned peoples [16–18]. For example, the highest incidence is in Australia (>1000 per 100,000 population) and the lowest in Africa (<1 per 100,000) despite generally higher levels of ambient UVR in the latter. In recent meta-analyses, fair skin phenotype or sun sensitive phototype was a key risk factor for CMM. The difference in incidence of skin cancers (including CMM and KC) between fair- and dark-skinned populations living in the same geographic location clearly illustrates the importance of skin type [19].

Recent meta-analyses have also confirmed that greater numbers of naevi and atypical naevi, and the presence of actinic damage and KC are strong risk factors for CMM [20–22]. In a recent report, there was a threefold increase in the risk of developing CMM after either SCC or BCC, even after adjustment for skin phototype [23].

Genetic studies show an increased risk of CMM in association with polymorphisms in genes determining skin phototype, for example *MC1R* [24]. Within CMM, characteristic UV-induced cytosine to thymine (C>T) mutations in tumor control pathways (e.g., *RAC1*, *STK19* and *PPP6C* genes) are found [25]. Both BCC and SCC show 'UV signature' mutations (C>T at cyclobutane pyrimidine dimers) in tumor suppressor genes, particularly the *TP53* gene [26–28]. For both CMM and KC, tumors from sun-exposed sites have the greatest mutation loads, and most of the mutations bear the 'UV signature' [28–31].

Despite these clear associations between exposure to the sun and all three tumor types, the patterns and timing of sun exposure that give rise to them differ. SCC appears to be most strongly linked to total lifetime sun exposure [32], but intermittent high dose exposure, as exemplified by a history of sunburn, appears to play an important role in development of BCC and melanoma [33]. Additionally, childhood sun exposure may be particularly important for CMM [34] and possibly BCC [35]. For melanoma, and possibly BCC, there may be added complexity, with the association with pattern and timing of sun exposure differing depending on the site of the tumor. CMMs occur on skin sites not commonly exposed to the sun, particularly in younger people and indoor workers, but have a predilection for sun-exposed sites in older populations. This finding has led to a 'divergent pathways' theory whereby melanomas of the head and neck are related to cumulative sun damage (consistent with their occurrence in older age groups), whereas CMMs of the trunk are associated with melanocyte proliferation due to skin phenotype, specific genetic mutations and intermittent sun exposure [36]. Similarly, chronic sun exposure may be more important for nodular BCC commonly found on the head and neck, and intermittent sun exposure more important for BCCs on the trunk [37].

An introduction to vitamin D

The vitamin D precursor, 7-DHC, is present in the plasma membrane of epidermal keratinocytes. Shorter wavelength UV-B radiation breaks open the B ring of the steroid to form previtamin D_3, which subsequently undergoes thermal isomerization to form cholecalciferol, also called vitamin D_3. There are dietary sources of both vitamin D_3 and the form found in some fungi, vitamin D_2, although few foods are naturally rich in these nutrients. The active form of vitamin D, 1,25 dihydroxyvitamin D (1,25(OH)D), is produced following two separate hydroxylation reactions. The first occurs in the liver and produces the intermediary, 25-hydroxyvitamin D (25(OH)D) that is measured in serum to determine vitamin D status. The second occurs primarily in the kidneys, although other tissues express the enzymes needed to carry out this reaction, so that 1,25(OH)D can be produced within cells, including those of the skin [38].

Production of vitamin D_3 in the skin is influenced by factors that affect ambient levels of UV-B radiation: location (latitude, longitude and altitude), time of year and time of day and cloud cover [39]. At the individual-level, there is a nonlinear dose response between UV-B irradiation and vitamin D production that depends on the starting level of 25(OH)D [40,41]. Other factors that moderate the amount of vitamin D_3 produced following irradiation of the skin include the orientation to the sun (i.e., horizontal vs vertical) [42], and the amount of the body surface that is exposed [43]. Use of sunscreen at recommended levels (2 mg/cm^2) decreases the effectiveness of vitamin D production [44], but epidemiological studies suggest that frequent sunscreen users do not have lower levels of 25(OH)D than

infrequent users after taking account of the time spent outdoors [45–47]. The moderating effect of skin pigmentation (melanin density) is controversial, although most experimental studies using lamps with an output that is realistic for sun exposure at Earth's surface show that darker skin decreases the amount of vitamin D produced for any dose of UV-B radiation [40,42,48–53].

The actions of 1,25(OH)D are primarily mediated through ligation with a nuclear vitamin D receptor (VDR), resulting in genomic responses. In addition, there are membrane rapid response receptors that are distributed in most, if not all, human tissues [54]. Systemically produced 1,25(OH)D has a primary role in maintaining calcium homeostasis [55], and in recent years, vitamin D deficiency has been linked to an increased risk of a wide range of diseases [56,57]. Importantly, particularly for potential associations with skin cancer, the full vitamin D biosynthetic pathway can occur within the epidermis [38]. The 25-hydroxylase mRNA is not constitutively expressed but is induced by vitamin D_3 and UV-B radiation [58]. Active $1,25(OH)_2D$ can therefore be synthesized and act within the cell to have local effects. The VDR is expressed in melanocytes [59] and keratinocytes [60]. *In vitro*, within the epidermis, 1,25(OH)D, acting through the VDR, reduces the proliferation of keratinocytes and melanocytes and promotes differentiation, including of keratinocytes as they migrate outward from the basal layer to form the upper layers of the epidermis [38,61,62].

• Vitamin D & skin cancer risk

Identifying the role of vitamin D in the etiology of skin cancer in humans is extremely challenging, because exposure to the sun causes both vitamin D production and skin cancer. Much of the evidence arises from studies *in vitro* or in mouse models, with additional information from epidemiological and genetic studies in humans.

Recent studies *in vitro*, in mouse models, and in humans have explored the links between vitamin D metabolites and skin cancer development and progression. It is worth briefly examining the types of evidence arising from these different approaches.

In vitro, epidermal cells or tissue are typically bathed in vitamin D metabolites or analogues and this may be at physiological or pharmacological doses that might not be relevant to typical epidermal levels. In mouse models, 1,25(OH)D or analogues are applied topically to explore the protective effect of higher local levels of 1,25(OH)D, that are thought to arise from local, epidermal, synthesis. Genetic knockout mice provide evidence related to systemic as well as local vitamin D deficiency, but are typically highly abnormal across a range of characteristics. Genetic studies of tumor cells compared with normal skin cells provide evidence of specific abnormalities that may indicate a role for vitamin D, such as within vitamin D pathway genes. In human studies, observational studies typically examine links between levels of 25(OH)D and skin cancer incidence or progression but it is difficult to tease out effects of vitamin D versus the effects of sun exposure, since the latter is a principal determinant of 25(OH)D levels. Candidate gene approaches and evidence in relation to dietary intake of vitamin D provide specific evidence of a vitamin D effect.

Pretreatment with high dose 1,25(OH)D decreased DNA damage and protected keratinocytes *in vitro* from UV-B-induced apoptotic cell death [63]. When 1,25(OH)D was topically applied in mice susceptible to UV-induced tumor development, the formation of cyclobutane pyrimidine dimers, apoptotic sunburn cells and the development of SCC following UV irradiation were reduced [64]. Some, but not all, melanoma cell lines are responsive to the antiproliferative effects of 1,25(OH)D [65,66], possibly through epigenetic pathways [67] and/or modulation of clusterin expression [68].

VDR knockout mice develop skin tumors following UV irradiation but mice lacking the *CYP27B1* gene (and thus unable to make 1,25(OH)D) do not [69]. This suggests that the VDR itself functions as a tumor suppressor in the skin (possibly through the hedgehog signaling pathways and β-catenin [70] via regulation of the expression of long noncoding RNAs [71]), rather than this being a pathway that involves 1,25(OH)D [72]. Notably, BCC, SCC and CMM cells express the VDR [72].

Melanoma in humans

Recent studies have explored the links between vitamin D status and CMM risk, with conflicting results. In a case–control study nested within the Alpha Tocopherol Beta-Carotene Cancer Prevention Study, there was no association between 25(OH)D levels and development of CMM at a median of 8.9 years of follow-up [73]. However, two recent prospective studies, from Denmark [74] and Australia [75], showed that higher 25(OH)D levels

at baseline were associated with higher incidence of CMM (and BCC) suggesting that 25(OH)D is a surrogate for sun exposure and that people with higher concentrations are at increased risk of skin cancer. Two recent meta-analyses, including these studies, support these findings, also showing an association of higher 25(OH)D concentrations with higher incidence of CMM [56,76].

In a recent meta-analysis, there was no evidence that vitamin D intake from food or supplements alters the risk of CMM, although there have been few studies and there was considerable heterogeneity [76]. Clinical trials may help to elucidate the effects of vitamin D intake on skin cancer risk, but there has been only one trial reported to date [77]. It found no overall effect of vitamin D and calcium supplementation on CMM risk, but among women with a history of KC there was a protective effect for melanoma.

In a recent meta-analysis of CMM risk in relation to polymorphisms in the *VDR* there was a modest increase in risk of CMM in association with the Ff and ff genotypes of the FokI polymorphism (compared with the wild-type; summary relative risk [SRR]: 1.21 [95% CI: 1.03–1.42] and 1.21 [95% CI: 0.95–1.54], respectively). There was a decreased risk of CMM with the Bb and BB genotypes (vs wild-type) of the BsmI polymorphism (summary relative risk: 0.78 [95% CI: 0.65–0.92] and 0.75 [95% CI: 0.59–0.95], respectively) [78]. Similar findings are reported from a case–control study [79]. In a hospital-based case–control study there was a significant decrease in risk of CMM in association with the Tt genotype (compared with TT) of the TaqI polymorphism of the *VDR* (adjusted OR [AOR]: 0.70; 95% CI: 0.54–0.90). However, in another case–control study of 305 CMM cases and 370 healthy controls there was no association between CMM risk and single nucleotide polymorphisms (SNPs) within the *VDR* or *CYP27B1* (encoding the 1α-hydroxylase enzyme that converts 25(OH)D to 1,25(OH)D), *CYP24A1* (encoding the 24-hydroxylase enzyme that breaks down 1,25(OH)D) or *VDBP* (encoding the vitamin D binding protein) [80].

Keratinocyte cancers in humans

The epidemiological evidence for a role of vitamin D in KC risk is similarly contradictory, but perhaps more heavily weighted toward a positive association between higher 25(OH)D levels and higher KC risk.

In a nested case–control study of older American men in the Osteoporotic Fractures in Men Study, men in the highest quintile of 25(OH)D (≥75 nmol/l) had a 46% lower odds of a history of KC (self-reported at 5 year follow-up) compared with the lowest quintile (<40 nmol/l; AOR: 0.54, 0.31–0.96) [81]. There was no significant association for incident KC, although the numbers of these were quite small (n = 100). Similarly, the median serum level of 25(OH)D was significantly higher in the control group compared with the patients with BCC (29.5 vs 24.2 ng/ml, p = 0.003) in another study, although here blood samples were collected 2 weeks postdiagnosis [82].

Most other studies show the opposite: an increased risk of KC in association with higher 25(OH)D levels. In a case–control study, women in the highest quartile of serum 25(OH)D concentration (compared with the lowest quartile) had an increased risk of BCC (AOR: 2.07; 95% CI: 1.52–2.80) and SCC (AOR: 3.77; 95% CI: 1.70–8.36) [83]. Similarly in nested case–control studies from northern California [84], Denmark [74] and Australia [75], higher 25(OH)D levels were associated with increased risk of BCC. Interestingly, in the Australian study, there was a nonsignificant lower risk of SCC in association with 25(OH)D >75 nmol/l cf. ≤75 nmol/l [75]. Recent meta-analyses including these studies show an association of higher 25(OH)D concentrations with higher incidence of KC [56,76] and no association between vitamin D supplementation or dietary vitamin D and KC incidence [56,76].

In a genetic study, the presence of the TT genotype in the Fok1 polymorphism of the *VDR* gene was associated with a greater than tenfold increase in the risk of BCC (OR: 10.14, p < 0.001). Other VDR polymorphisms were also associated with increased BCC risk, but not so strongly [82]. The Fok1 polymorphism corresponds to a C/T substitution in exon 4 leading to a new translation initiation site and a longer VDR protein that is less transcriptionally active. In an Australian study, homozygous genotypes of the Taq1 polymorphism, TT/tt, were associated with an increased risk of developing solar keratosis, compared with VDR heterodimers, for example, Tt [85]. One study showed that the expression of the VDR was significantly higher in BCCs of the patients than in the healthy skin of the controls [82].

Vitamin D & prognosis after skin cancer diagnosis

Cultured melanoma cells express the 25-hydroxylase enzyme that converts 25(OH)D to 1,25$(OH)_2$D [86]. However, recent evidence

suggests that many melanoma cell lines are resistant to the antiproliferative effects of 1,25(OH)D [66]. In one study using immunosuppressed mice with human solid xenograft melanoma lines, administration of pharmacological doses of $1,25(OH)_2D$ suppressed the growth of the CMM and inhibited metastasis in one line but not another [87]. Reduction in expression of the *VDR* [88] and *CYP27B1* [89] within CMM is correlated with more aggressive and advanced tumors and lower survival, suggesting that 1,25(OH)D may play a role in prognosis.

Results from human studies are generally relatively consistent in showing that low 25(OH)D levels are associated with thicker CMM, later stage or worse prognosis (summarized in Table 1). However, in all of the studies published to date vitamin D status was measured several months after diagnosis, so reverse causality – more aggressive CMM causing greater ill health and resulting in lower sun exposure and therefore vitamin D production – cannot be ruled out (see Table 1).

It is important to note that there is no evidence that vitamin D supplementation postdiagnosis improves prognosis, and Hutchinson and colleagues suggest it may even have adverse effects, for example through immune suppression [94].

Vitamin D or an independent effect of sun exposure?

Several of the studies cited above show that the ranking of serum 25(OH)D levels remains stable over several years and is highly correlated with recent sun exposure – individuals with higher exposure to the sun have higher 25(OH)D levels and vice versa. In recent years, there has been considerable interest in possible independent effects of sun exposure on health, particularly immune-mediated effects that are not occurring through a vitamin D pathway [95]. Here we consider this issue in relation to skin cancer development and prognosis.

One of the first studies to raise a question about a possible beneficial effect of sun exposure on melanoma prognosis, was that of Berwick and colleagues, who reported that higher (compared with lower) self-reported intermittent lifetime sun exposure was associated with a lower risk of death from CMM within 5 years of diagnosis (HR: 0.6; 95% CI: 0.3–1.0; p = 0.04) [96]. Serum 25(OH)D levels were not measured. In their more recent study, however, these findings were not replicated, and sun exposure prior to diagnosis was not associated with survival after melanoma diagnosis [97]. A study of European patients with CMM found that those who reported more sunny vacations prior to diagnosis had better survival [98]. The assumed pathway has been through the protective effects of higher vitamin D status but vitamin D intake has not been shown to alter CMM risk or prognosis. Notably, in many locations, the higher 25(OH)D levels in those with markers of better prognosis are likely to primarily reflect recent sun exposure rather than vitamin D intake, given that dietary intake and use of supplements is generally low. While the findings from genetic

Table 1. Studies showing a link between 25(OH)D level and markers of melanoma prognosis.

Study (year)	Measure of prognosis	Sampling of 25(OH)D	Outcome	Ref.
Randerson-Moor *et al.* (2009)	Breslow thickness	At least 3–6 months after diagnosis	Inverse correlation between 25(OH)D level and Breslow thickness	[90]
Gambichler *et al.* (2013)	Breslow thickness	At baseline (up to 6 months after diagnosis) and 6 months later	Lower Breslow thickness was a predictor of high 25(OH)D concentration	[91]
Nurnberg *et al.* (2009)	CMM stage at diagnosis	Sampling between October and April (time between diagnosis and sampling highly variable)	Serum 25(OH)D levels significantly lower in stage IV vs stage 1 CMM	[92]
Newton-Bishop *et al.* 2009	Breslow thickness; relapse-free survival	Sampling 3–6 months after diagnosis	Significant trend toward lower 25(OH)D levels in association with higher Breslow thickness and lower relapse-free survival	[93]

25(OH)D: 25 hydroxyvitamin D; CMM: Cutaneous malignant melanoma.

studies (reviewed above) do suggest that vitamin D is important, an additional independent effect of sun exposure cannot be ruled out.

What do I tell my skin cancer patients?

There remains considerable controversy around the optimal level of 25(OH)D that is necessary for good health. Some suggest the optimal serum level of 25(OH)D should reflect the concentration necessary to suppress the parathyroid hormone, but this level has been reported to vary widely from 20 nanomoles per litre (nmol/l) to 110 nmol/l [99–101]. Many observational studies link low 25(OH)D levels with increased risk of a range of internal cancers [102]. However, based on a review of associations with a wide range of disease outcomes, the United States Institute of Medicine recommended that there was sufficient evidence of a causal association only in relation to requirements for bone health, and recommended that a serum 25(OH)D level of 50 nmol/l should be considered sufficient [103]. Further, while there was a general consensus that less than 25 nmol/l was classed as deficiency [104,105], the Institute of Medicine concluded that less than 30 nmol/l constituted risk of deficiency [103]. A further challenge lies in the wide variability in measurement results dependent on the assays and laboratory techniques used [106–108].

There is considerable evidence to suggest that, following a diagnosis of skin cancer, sun exposure and vitamin D status fall (e.g., Idorn *et al.* [109]). As a diagnosis of skin cancer increases risk of subsequent skin cancers, it may be appropriate to recommend that people with a history of skin cancer avoid the sun as much as possible and ensure adequate vitamin D status through supplementation. This would apply especially to people who have had multiple skin cancers or who have undergone organ transplants and are at particularly high risk of KC. For people with a first skin cancer diagnosis it may be possible to minimize risk of subsequent skin cancers and maintain vitamin D without supplementation, but finding the balance is currently difficult for several reasons.

Firstly, calculating the time required in the sun to deliver a given dose of vitamin D relies on the existence of an accurate action spectrum. The International Commission on Illumination (CIE) has published an action spectrum for the production of previtamin D [110] but recent work suggests that it may not be accurate [111]. In addition, models generated to estimate the dose-response between UV irradiation and change in 25(OH)D levels have used nonsolar simulated irradiation sources, or have included only very small numbers of participants of a narrow age range or skin type. At this stage there is insufficient evidence on the dose-response for individuals of different age and skin type, to make recommendations on the optimal time in the sun.

Vitamin D production is induced only by UV-B radiation and thus occurs most efficiently when the UV-B intensity is highest [39]. UV-B intensity is well reflected by the UV Index (UVI) [112,113]. The differences between the CIE previtamin D action spectrum and the CIE action spectrum for erythema mean that, to maximize vitamin D production while minimizing the risk of erythema, it is best to seek sun exposure when the UVI is high (e.g., at noon), rather than low as is currently recommended.

The greater the skin surface area that is exposed to the sun, the greater the production of vitamin D_3 [41]. On the contrary, for erythema it is the dose to any piece of skin or epidermal cell that causes DNA damage and increases risk of skin cancer. Thus, the message for optimal vitamin D production would be to expose as much skin as possible for a short time when the UVI is high. The risk in implementing such a message is that, despite the ratio between vitamin D_3 production and erythema being optimal at high UVI, the absolute difference in the time required to achieve the two outcomes is small. As an example, based on current dose-response models and CIE action spectra, when the UVI index is 12 it takes less than 5 min to make an acceptable daily dose of vitamin D with the face and arms exposed, but only about 15 min for somebody with type 2 skin to experience erythema [112]. While extreme caution would be required to avoid harmful levels of sun exposure, the appropriate strategy for people at high risk of skin cancer may be to routinely apply sunscreen to the hands, face and arms [114], but to deliberately expose less frequently exposed areas of skin for a short time at a high UVI.

Conclusion

It is difficult, on the evidence to date, to provide any definitive answers on whether vitamin D has any protective role in skin cancer development or prognosis. Higher 25(OH)D levels postdiagnosis and higher sun exposure prediagnosis have been associated with thinner CMM

and better prognosis, but it is impossible to tell how indicative the postdiagnostic 25(OH)D levels are of the prediagnostic situation. On the other hand, there is clear evidence that sun exposure increases the risk of all types of skin cancers. On the basis of the evidence reviewed here, it is prudent to avoid high dose sun exposure leading to sunburn, to always protect the face and hands when in the sun, and to use sun protection when outdoors for other than short periods of time when the UVI is 3 or higher. It is important to maintain 25(OH)D levels of around 50 nmol/l or higher, and in many locations this should be achievable with short periods of sun exposure during the middle of the day in most seasons, with additional intake of vitamin D possibly required in winter in some locations.

Future perspective

Ideally, the question of the role of vitamin D in skin cancer would be resolved by clinical trials of vitamin D supplementation at appropriate levels for a sufficient duration. Such trials are unlikely to ever be possible for CMM because it is uncommon, although a large enough study, undertaken in a high risk group (e.g., living in a high ambient UVR location), may provide evidence to support or refute a role of vitamin D. Current trials underway in elderly people, primarily looking at other end points such as all-cause mortality, may generate enough KC outcomes for this end point also to be examined.

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