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ORIGINAL ARTICLE

Hope and challenge: The importance of ultraviolet (UV) radiation for cutaneous Vitamin D synthesis and skin cancer

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Abstract

Solar ultraviolet (UV)-radiation is the most important environmental risk factor for the development of non-melanoma skin cancer (most importantly basal and squamous cell carcinomas), that represent the most common malignancies in Caucasian populations. To prevent these malignancies, public health campaigns were developed to improve the awareness of the general population of the role of UV-radiation. The requirements of vitamin D is mainly achieved by UV-B-induced cutaneous photosynthesis, and the vitamin D-mediated positive effects of UV-radiation were not always adequately considered in these campaigns; a strict "no sun policy" might lead to vitamin D-deficiency. This dilemma represents a serious problem in many populations, for an association of vitamin D-deficiency and multiple independent diseases has been convincingly demonstrated. It is crucial that guidelines for UV-exposure (e.g. in skin cancer prevention campaigns) consider these facts and give recommendations how to prevent vitamin D-deficiency. In this review, we analyze the present literature to help developing well-balanced guidelines on UV-protection that ensure an adequate vitamin D-status without increasing the risk to develop UV-induced skin cancer.

Key Words: *Solar UV radiation, skin cancer, photoprotective, photodamage, VDES, supplementation*

Solar ultraviolet-B (UV-B)-radiation – a double-edged sword

At present, there is a controversial debate in many scientific and public communities on how much solar UV-exposure is appropriate to balance between positive and negative effects of sunlight [1]. We know today that at least some of the positive effects of UV-radiation are mediated via cutaneous photosynthesis of vitamin D. In this review, the present literature is analyzed to help developing well-balanced guidelines for skin cancer prevention and for UV-protection that ensure an adequate vitamin D-status.

Lack of UV-B-exposure results in vitamin D-deficiency – still a serious and under-recognized health problem

For more than 500 million years during evolution, phytoplankton and zooplankton have been producing vitamin D [2]. While the role of vitamin D in the physiology of lower non-vertebrate organisms is not well understood, it is well known that most vertebrates have to obtain an adequate source of vitamin D, in order to develop and maintain a healthy mineralized skeleton [2]. While up to 10 % of the human body's requirements in vitamin D can be obtained by the diet (under most living conditions in the US and Europe), approximately 90 % of all required vitamin D has to be synthesized from 7-dehydrocholesterol (7-DHC) in the skin through the action of the sun (UV-B) [2]. It has been estimated that approximately 1 billion individuals worldwide are vitamin D-deficient or -insufficient [2]. This causes a serious problem that is still widely under-recognized, since associations between vitamin D-deficiency and increased incidence and/or unfavourable prognosis of a broad variety of independent diseases including various types of cancer (e.g. skin-, colon-, prostate- and breast cancer), autoimmune diseases, infectious diseases, and cardiovascular diseases has been confirmed in a large number of studies [2]. Animal experiments, as well as epidemiological data from many countries relate risk for and survival of various malignancies including colon- and lung cancer with solar UV-exposure, latitude and vitamin D_3-synthesis in the skin [2,3]. Moreover, laboratory investigations analyzing the importance of the integrity of the

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vitamin D endocrine system for prevention of cancer pathogenesis and progression are in line with the so called vitamin D/cancer hypothesis. Notably, an increasing body of evidence now demonstrates an association between several vitamin D receptor (VDR) polymorphisms and cancer risk and progression [4,5].

During recent years, great progress has been made in laboratory investigations that searched for the "missing link" between the vitamin D and cancer. Of high importance was the discovery that in contrast to earlier assumptions, skin, prostate, colon, breast, and many other human tissues not only express the vitamin D receptor (VDR) but also express the key enzyme (vitamin D-1αOHase, CYP27B1) to convert 25(OH)D to its biologically active form, $1,25(OH)_2D$ [1,2,6]. This active vitamin D metabolite is considered as an not exclusively calciotropic hormone, but additionally as a locally produced potent seco-steroid hormone regulating various cellular functions including cell growth and differentiation [2,7]. As an example of its pleiotrophic effects, it has been shown that $1,25(OH)_2D$ is a direct regulator of antimicrobial innate immune responses [2,8,9]. $1,25(OH)_2D$ induces antimicrobial peptide gene expression in isolated human keratinocytes, monocytes and neutrophils, and human cell lines, and $1,25(OH)_2D$ along with lipopolysaccharides, LPS, synergistically induces cathelicidin antimicrobial peptide (camp) expression in neutrophils [2,8,9]. Moreover, it has recently been reported that Toll-like receptor (TLR) activation of human macrophages up-regulated expression of the VDR and the vitamin D-1αOHase (CYP27B1) genes, leading to induction of cathelicidin and killing of intracellular Mycobacterium tuberculosis. These data demonstrate a link between TLRs and vitamin D-mediated innate immunity [2,8,9]. Taken these data together, the effects of solar UV radiation on the innate and adapted immune system are not exclusively immunosuppressive, but also stimulate distinct immune responses.

Photocarcinogenesis of non-melanoma skin cancer and melanoma

Historically, the association between solar UV-exposure and non-melanoma skin cancer was first reported by Unna and Dubreuilh at the end of the 19th century [10,11] who recognized actinic keratosis (AK) and squamous cell carcinoma (SCC) in chronically sun-exposed skin areas of sailors and vineyard workers (notably, AK are now considered to represent cutaneous SCC *in situ* [12]. At present, it is scientifically accepted that solar UV-exposure represents the most important environmental risk factor for the development of AK, SCC and basal cell carcinomas (BCC) [1,13]. Epidemiological and laboratory data have convincingly shown that sunburns are implicated in the pathogenesis of SCC, BCC, and malignant melanoma (MM) [1,13,14]. Today, it is accepted that chronic sun exposure is the most important cause for the formation of SCC, but may be less important for the development of BCC [13]. AK is more frequent in men, in sun-sensitive individuals chronically exposed to solar UV, and in individuals who have a history of sunburn [13]. Concerning MM, numerous epidemiologic investigations analysing solar UV-exposure parameters have consistently reported an association between the development of MM and short-term intense UV-exposure, particularly burning in childhood [14]. It has been convincingly demonstrated by many investigators, that the incidence of MM increases with decreasing latitude towards the equator [1,14]. However, in contrast to short-term intense exposure, more chronic less intense exposure has not been found to be a risk factor for the development of MM and in fact has been found in several studies to be protective [1,14,15]. Berwick et al. evaluated the association between measures of skin screening and death from cutaneous melanoma in case subjects (n = 528) in a population-based study of cutaneous melanoma that were followed for an average of more than 5 years [16]. They found that sunburn, high intermittent solar UV-exposure, and solar elastosis were statistically significantly inversely associated with death from melanoma and concluded that solar UV exposure is associated with increased survival from melanoma [16].

Gass and Bopp have previously analyzed MM mortality rates in different occupational groups [17]. They concluded that indoor working males (including graduates and employees with commercial or technical education) have an increased risk affirming the association between melanoma risk and intermittent solar UV-exposure. In contrast, outdoor workers with chronic solar UV-exposure appeared slightly protected [17]. It may be speculated whether these associations may be an explanation for the finding of an increased risk to develop MM after sunscreen use, that was reported previously [18]. The hypothesis of an association between sunbed use and cutaneous MM was previously analyzed in a large European case-control study investigating an adult population aged between 18 and 49 years [19]. In that study in Belgium, France, The Netherlands, Sweden and the UK, solar UV and sunbed exposure was recorded and analyzed between 1999 and 2001 in 597 newly diagnosed MM cases and 622 controls. 53 % of cases and 57 % of controls ever used sunbeds. There was a South-to-North gradient with high prevalence of sunbed exposure in Northern Europe and lower prevalence in the South (prevalence of use in France 20 % compared to 83 % in Sweden). The authors concluded that dose and lag-time between first exposure to sunbeds and time of study were not associated with MM risk, neither were sunbathing and sunburns [19].

The cutaneous vitamin D endocrine system (VDES) protects against UV-induced photocarcinogenesis

UV-B induces photochemical changes in the skin that may cause acute effects such as sunburn and immune suppression or chronic effects like premature skin aging and skin cancer [20]. Two important UV-B-mediated biological effects are the induction of apoptosis and the production of interleukin-6 (IL-6) [21–25]. Apoptosis, representing a mode of programmed cell death, is induced following UV-B-irradiation when cellular damage is too severe to be repaired [21–25]. To induce apoptosis, UV-B modulates a variety of important cellular signalling pathways that include various nuclear and cell surface death receptors and the formation of reactive oxygen species (ROS) [21–25]. Part of this process is the activation of a cascade of cystein proteases called caspases [21–25]. The final effector protease, caspase-3, mediates cleavage of several substrates, including poly (ADP-ribose) polymerase (PARP), which immediately results in apoptosis [21–25]. This cascade is considered to be crucial for executing apoptosis induced by UV-B [21–25]. Furthermore, it has been described that C-Jun-NH_2-terminal kinase (JNK), a member of the mitogen-activated protein kinases (MAPK), is required for UV-induced apoptosis via the induction of cytochrome c release [21–25]. It has been speculated that JNK-dependent apoptosis is mediated through mitochondrial cytochrome c release, which has also been observed as an early event in UV-mediated apoptosis in HaCaT cells [21–25].

On the other hand, UV-B-irradiation strongly induces IL-6 mRNA and release of IL-6 protein by human keratinocytes [21–25]. The cytokine IL-6 represents an important mediator of the sunburn reaction and of UV-B-dependent immune suppression [21–25]. Furthermore, IL-6 has been implicated in the tumorigenesis of BCC, a neoplasm that can be induced by UV-B radiation [21–25]. It has convincingly been shown that the biologically active vitamin D metabolite $1,25(OH)_2D$ protects human skin cells from UV-induced cell death and apoptosis [21–27]. In these studies, cytoprotective effects of $1,25(OH)_2D$ on UV-B-irradiated keratinocytes were seen morphologically and using a colorimetric cell survival assay [21–25]. Moreover, using an ELISA that detects DNA-fragmentation, it was shown that pretreatment with $1,25(OH)_2D$ suppresses UV-B-induced apoptosis by 55–70 % [21–25]. This suppression requires pharmacological concentrations of $1,25(OH)_2D$ and a preincubation period of several hours [21–25]. In addition, it was demonstrated that pretreatment with $1,25(OH)_2D$ also inhibits mitochondrial cytochrome C release (90 %), a hallmark event of UV-B-induced apoptosis [21–25].

Furthermore, it was demonstrated that $1,25(OH)_2D$ reduces two important mediators of the UV-response, namely, c-Jun-NH_2-terminal kinase (JNK) activation and interleukin-6 (IL-6) production [21–25]. As shown by Western blotting, pretreatment of keratinocytes with $1,25(OH)_2D$ diminishes UV-B-stimulated JNK activation by more than 30 %. Furthermore, $1,25(OH)_2D$ treatment reduces the UV-B-induced IL-6 mRNA expression and protein secretion by 75–90 %. Analyzing the cleavage of PARP further corroborated these observations. As mentioned before, PARP-cleavage is induced by UV-B-irradiation. It has been shown that pretreatment of keratinocytes with $1,25(OH)_2D$ (1 μmol/L, 24 h) inhibits efficiently, but not completely, this UV-B-induced PARP-cleavage [21–25].

Apart from these effects, metallothionein (MT)-induction may be relevant for the anti-UV-B effects of $1,25(OH)_2D$. MT acts as a radical scavenger in oxygen-mediated UV-B-injury [21–25]. MTs are a class of small cysteine-rich proteins that bind and exchange heavy metal ions but also have clear scavenging properties for ROS [21–25]. Part of the UVB-induced damage to cells occurs through the formation of ROS and antioxidative agents such as MT have been reported to be photoprotective [21–25]. MT mRNA expression was clearly induced by $1,25(OH)_2D$.

+ Recently, the anti-apoptotic effect of $1,25(OH)_2D$ in keratinocytes was confirmed, using cisplatin and doxorubicin as apoptotic triggers [21–25]. In that study, it was demonstrated that $1,25(OH)_2D$ activated two independent survival pathways in keratinocytes: the MEK/extracellular signal regulated kinase (ERK) and the phosphatidylinositol 3-kinase (PI-3K)/Akt pathway [21–25]. Activation of ERK and Akt by $1,25(OH)_2D$ was transient, required a minimal dose of 10^{-9} mol/L and could be blocked by actinomycin D and cycloheximide. Moreover, inhibition of Akt or ERK activity with a PI-3K inhibitor (LY294002) or MEK inhibitors (PD98059, UO126) respectively, partially or totally suppressed the anti-apoptotic capacity of $1,25(OH)_2D$. Finally, $1,25(OH)_2D$ changed the expression of different apoptosis regulators belonging to the Bcl-2 family. $1,25(OH)_2D$ treatment increased levels of the anti-apoptotic protein Bcl-2 and decreased levels of the pro-apoptotic proteins Bax and Bad in a time- and dose-dependent way [21–25]. The authors concluded that $1,25(OH)_2D$ protects keratinocytes against apoptosis by activating the MEK/ERK and the PI-3K/Akt survival pathways and by increasing the Bcl-2 to Bax and Bad ratio.

These findings suggest a photoprotective effect of active vitamin D and create new perspectives for the pharmacological use of active vitamin D compounds in the prevention of UV-B-induced skin damage and carcinogenesis [21–25]. It is well known that photocarcinogenesis of skin cancer is caused largely by mutations at sites of incorrectly repaired DNA photoproducts, of which the most common are the cyclobutane pyrimidine dimers (CPDs) [20].

Recently, it has been demonstrated that 1,25$(OH)_2$D protects primary human keratinocytes against the induction of CPDs by UVB [21–27]. This protection requires pharmacologic doses of 1,25$(OH)_2$D and an incubation period of at least 8 h before irradiation.

It has been speculated that the anti-proliferative capacity of 1,25$(OH)_2$D underlies its protective effect against UVB-induced DNA damage [21–25]. De Haes et al. demonstrated that 19-nor-14-epi-23-yne-1,25$(OH)_2$D (TX 522) and 19-nor-14,20-bisepi-23-yne-1,25$(OH)_2$D (TX 527), two low-calcemic analogues of 1,25$(OH)_2$D, were even 100 times more potent than the parent molecule in inhibiting UV-B-induced DNA damage [21–25]. It was speculated that these molecules therefore may represent promising candidates for the chemoprevention of UV-B-induced skin cancer [21–25]. Other investigators showed that treatment with three different vitamin D compounds (1,25$(OH)_2$D; the rapid acting, low calcemic analog, 1α,25$(OH)_2$lumisterol-3 (JN) and the low calcemic but transcriptionally active hybrid analog 1α-hydroxymethyl-16-ene-24,24-difluoro-25-hydroxy-26,27-bis-homovitamin D3 QW-1624F2–2 (QW)) diminished the numbers of UV-induced pre-mutagenic CPDs from 0.5 h after cessation of UV radiation in all skin cell types. This may explain the enhanced survival of skin cells [26,27]. In these studies, the rapid response antagonist analog 1β,25$(OH)_2$D3 (HL) abolished the photoprotective effects of 1,25$(OH)_2$D whilst a genomic antagonist, (23S)-25-dehydro-1alpha-hydroxyvitamin D3–26, 23-lactone (TEI-9647), had no effect [26].

UV radiation increased p53 expression in human skin cells and concurrent treatment with 1,25$(OH)_2$D further enhanced this effect several fold, at 3 h and 6 h after UV radiation [26]. Combined with previously reported lower nitrite levels in the presence of 1,25$(OH)_2$D, it has been speculated that this increased p53 expression may favour DNA repair over apoptosis [26,27]. Additionally, it has convincingly been shown that topical application of 1,25$(OH)_2$D or QW suppressed solar simulated UV (SSUVR)-induced pyrimidine dimers in the epidermis of irradiated hairless Skh:HR1 mice, measured 24 h after irradiation [26,27]. Furthermore, UV-induced immunosuppression in the mice was markedly reduced by topical application of either 1,25$(OH)_2$D or QW [26,27]. Taken these data together, a protective effect of vitamin D compounds against UV-B-induced photodamage was convincingly shown in vitro and in vivo. It is tempting to speculate that the UV-B-induced cutaneous production of vitamin D may represent an evolutionary highly conserved feedback mechanism that protects the skin from the hazardous effects of solar UV-radiation.

The molecular basis of the photoprotective effect of vitamin compounds is the expression of the VDR and other key components of the VDES in skin cells [6,28]. Therefore, it is not surprising that distinct VDR polymorphisms have recently been identified as potential risk factors for carcinogenesis of non-melanoma skin cancer and melanoma [29,30].

Skin cancer prevention campaigns: should they continue to recommend strict protection against solar and artificial UV-radiation?

While the incidence of skin cancer has dramatically increased during the last decades, it is now accepted that the reasons for this development are multifactoral [20]. It has been speculated that besides the age pyramid and other factors, cultural changes that result in increased UV-exposure, may be of particular importance [20]. Notably, it has been assumed that socio-economical and cultural changes in the behaviour of large groups of society may have resulted in an increase of UV-exposure in those individuals. These changes may include more recreational activities and holidays spent in the sun as well as frequent exposure to artificial UV in sunbeds. The wellness-movement with tan advocating the current ideal of beauty may have supported this development as well. However, one has to keep in mind that the reported increase in skin cancer incidence may be due to other factors independent from solar UV-radiation. As an example, it has been recently published that the large increase in reported melanoma incidence is likely to be due to a diagnostic drift which classifies benign lesions as stage 1 melanoma [31]. In that study, this conclusion could be confirmed by direct histological comparison of contemporary and past histological samples. The authors concluded that these findings should lead to a reconsideration of the treatment of 'early' lesions, a search for better diagnostic methods to distinguish them from truly malignant melanomas, re-evaluation of the role of ultraviolet radiation and recommendations for protection from it, as well as the need for a new direction in the search for the cause of melanoma [31].

To counteract the increasing incidence of skin cancer, public health campaigns were developed and introduced, with the aim to improve the knowledge of the general population regarding the role of artificial and solar UV-radiation for the development of skin cancer. However, it has to be noted that positive effects of UV radiation were not adequately considered in most of these campaigns that in general proposed a strict "no sun policy" [1]. The first of the campaigns were introduced and established in Australia in the early 1980s, containing messages and slogans which were easy to remember, including the "Slip (on a shirt), Slop (on some sunscreen), Slap (on a hat)" initiative [32]. Afterwards several international consensus meetings profited from Australian experiences and renewed similar aims in the primary prevention of skin cancer [32]. The World Health Organisation (WHO) started a Global UV Project called INTERSUN [33], which aimed to

encourage countries to take action to reduce UV-induced health risks. Additional goals were the development and use of an internationally recognized UV Index (UVI) to facilitate sun protection messages related to daily UV-intensity and special programmes for schools to teach children and teachers about sun protection [32]. Until today, strict recommendations for protection against artificial and solar UV-radiation still represent a fundamental part of public health campaigns and prevention programmes aimed at reducing UV-radiation-induced skin damage and skin cancer [1,32]. These recommendations include the use of sunscreens, protective clothing and avoidance of artificial and solar UV-exposure. Appropriate clothing is extremely effective in absorbing all UV-B radiation thereby preventing any UV-B photons from reaching the skin [34]. Most sunscreen products combine chemical UV-absorbing sunscreens and physical inorganic sunscreens, which reflect UV, to provide broad spectrum protection. At present, most sunscreen products protect against both UV-B and UV-A radiation.

Solar UV-protection increases the risk to develop vitamin D-deficiency

We recently analyzed whether patients that have to protect themselves from solar and artificial UV-exposure for medical reasons are at an increased risk to become vitamin D-deficient. We investigated the serum 25(OH)D concentration in renal transplant patients with adequate renal function and in an age- and gender-matched control group at the end of winter [35]. Due to their increased risk to develop UV-induced skin cancer, all renal transplant patients had been advised to protect themselves against solar and artificial UV-radiation after transplantation. The serum concentrations 25(OH)D were significantly lower ($p = 0.007$) in renal transplant patients ($n = 31$, geometric mean 27.3 nmol/L [with 95 % confidence interval 20.5 nmol/L – 35.8 nmol/L]) as compared to age- and gender-matched controls ($n = 31$, 50.0 nmol/L [39.3 nmol/L – 63.8 nmol/L]) [35]. Similar findings were made in another pilot study, where we measured the basal serum 25(OH)D concentrations in a small group of patients with Xeroderma Pigmentosum (XP, $n = 3$) and basal cell nevus syndrome (BCNS, $n = 1$) [36]. Concentrations of 25(OH)D- were markedly decreased in all four patients (mean value: 23.8 nmol/L), as compared to the normal interval (50.0–225.0 nmol/L) [36]. Thus, in these two investigations we demonstrate a reduced serum 25(OH)D concentration in these risk groups that have to protect themselves against artificial and solar UV-radiation [35,36].

How much vitamin D do we need?

At present, there is an ongoing debate on how much vitamin D we need to achieve a protecting effect against cancer and other diseases. From the historical point of view, the U.S. Recommended Dietary Allowance (RDA) of vitamin D from 1989 is 200 IU [37]. Yet, investigations in the last decades have shown that oral intake of 200 IU vitamin D daily has no effect on bone status [38]. In consequence, it was recommended by some experts in the field that adults may need, at least, five times the RDA, or 1,000 IU, to be adequately protected against bone fractures, some cancers and derive other broad-ranging health benefits [37]. In conclusion, the 1989 RDA of 200 IU is antiquated, but the newer 600 IU Daily Reference Intake (DRI) dose for adults older than 70 is still not adequate [37]. Some experts even suggested that daily doses of 2,000 IU orally, previously considered to represent the upper tolerable intake (the official safety limit), does not deliver the amounts of vitamin D that may be optimal [37]. To evaluate putative risks that may be associated with vitamin D-supplementation, one should first look at the physiological capacity of the human skin to synthesize vitamin D. On a sunny summer day, total body sun exposure produces in the skin approximately more than 10,000 IU vitamin D per day [37]. Considering this fact, concerns about toxic overdose with dietary supplements that exceed 800 IU vitamin D are poorly founded. Moreover, it has been speculated that a person would have to consume almost 67 times more vitamin D than the previously recommended intake for older adults of 600 IU to experience symptoms of overdosage [37]. Reinhold Vieth believes people need 4,000-10,000 IU vitamin D daily and that toxic side effects are not a concern until a 40,000 IU/day dose [37]. Reports of other experts in the field are in line with these findings. It has been suggested by several experts that older adults, sick adults, and "perhaps all adults" would need 800–1,000 IU vitamin D daily and it has been indicated that daily doses of 2,400 IU—four times the recommended intake–can be consumed safely [37]. According to recent estimations an intake of 1,000 IU daily would bring 25(OH)D serum concentrations of at least 50 % of the population up to advantageous ranges of 75 nmol/L [39]. Thus, higher doses of vitamin D are needed as oral supplements, at least for those individuals who do not reach the desired status.

The vitamin D–cancer dose–response relations have been investigated in several studies. A meta-analysis of five observational studies of serum 25(OH)D concentrataions found that it takes about 1,500 IU of vitamin D3 per day to reduce the risk by 50 % for colorectal cancer, based on the assumption that 25(OH)D- concentrations of the population are low [40]. In a cohort study of male health professionals, it was found that taking daily 1,500 IU of vitamin D3 should reduce all-cancer mortality rates by approximately. 30 % for males in the United States [41,42]. For breast cancer, based on two studies of serum 25(OH)D concentrations and breast cancer

risk, it was concluded that it takes about 4,000 IU/day for a 50 % reduction in risk for breast cancer [43]. At present, many experts in the field agree that the evidence to date suggests that daily intake of 1,000–2,000 IU/day of vitamin D could reduce the incidence of vitamin D-deficiency-related diseases with minimal risk in Europe, the US, and other countries.

The benefit of an increased vitamin D status in reducing the economic burden of disease in western Europe has been estimated [44]. In that study, vitamin D dose-disease response relations were estimated from observational studies and randomized controlled trials. The reduction in direct plus indirect economic burden of disease was based on increasing the mean serum 25(OH)D concentration to 100 nmol/L, which could be achieved by a daily intake of 2,000–3,000 IU of vitamin D [44]. For 2007, the reduction was estimated at 187,000 million Euro/year. The estimated cost of 2,000–3,000 IU of vitamin D3/day along with ancillary costs such as education and testing might be about 10,000 million Euro/year. The authors suggested that sources of vitamin D could include a combination of food fortification, supplements, and natural and artificial UVB- irradiation, if properly acquired [44].

How much sunlight do we need?

There is no doubt that UV-radiation is mutagenic and is the main reason for the development of non-melanoma skin cancer. Therefore, excessive solar UV-exposure has to be avoided, particularly burning in childhood. To reach this goal, the use of sunscreens as well as the wearing of protective clothes and glasses is absolutely important. Additionally, sun exposure around midday should be avoided during the summer in most latitudes. However, it has been assumed that the net effects of solar UV-B-radiation on human health, in the US and in most countries in Europe, are beneficial at or near current levels [42,45]. It has been speculated that the beneficial (protective) effect of less intense solar radiation outweighs its negative (mutagenic) effect. In agreement with this assumption, some authors concluded that many lives could be prolonged through careful exposure to sunlight or more safely, vitamin D-supplementation, especially in non-summer months [45,46]. Previously, the economic burdens of insufficient UV-B-irradiation and vitamin D insufficiency as well as excess UV-irradiation for related diseases and conditions have been estimated in the United States [46]. It was estimated that approximately 50,000–63,000 individuals in the United States and 19,000–25,000 in the UK die prematurely from cancer annually due to insufficient vitamin D [46]. The US economic burden due to vitamin D insufficiency from inadequate exposure to solar UV-B-irradiance, diet, and supplements was estimated at $40–56 billion in 2004, whereas the economic burden for excess UV-irradiance was estimated at $6–7 billion [46]. The authors concluded that increased vitamin D through UV-B-irradiance, fortification of food, and supplementation could reduce the health care burden in the US, UK, and elsewhere [46].

To summarize, it is important that recommendations of health campaigns on sun protection represent a balanced view of positive and negative effects of solar UV-exposure. As Michael Holick reported previously [2,47], we have learned that at most latitudes such as Boston, USA, very short and limited solar UV-exposure is sufficient to obtain "adequate" vitamin D- concentrations. Exposure of the body in a bathing suit to one minimal erythemal dose (MED) of sunlight is equivalent to ingesting at least about 10,000 IU of vitamin D and Holick estimated that exposure of less than 18 % of the body surface (hands, arms, and face) two to three times a week to a third to a half of an MED; (about 5 min for skin-type-2 adult in Boston at noon in July) in the spring, summer, and autumn is more than adequate. Anyone intending to stay exposed to sunlight longer than recommended above should apply a sunscreen with a sufficient sun protection factor to prevent sunburn and the damaging effects of excessive exposure to sunlight.

How to treat and prevent vitamin D deficiency?

What conclusions do we draw from the findings reported above, most importantly the demonstration of an association between vitamin D-deficiency and the occurrence of numerous independent diseases, including various types of cancer? The important take home message for dermatologists and other clinicians is that health campaigns promoting strict sun protection procedures to prevent skin cancer may increase the severe health risk of vitamin D-deficiency. Especially dermatologists have to know about the importance of an adequate vitamin D-status if solar UV-exposure is seriously curtailed.

It has to be emphasized that in groups that are at high risk of developing vitamin D-deficiency (e.g. nursing home residents; patients with skin type I, transplant recipients or other patients under immunosuppressive therapy), vitamin D-status needs to be monitored subsequently. As a consequence of the severe health risks that are associated with vitamin D-deficiency, vitamin D-deficiency has to be treated, e.g. by giving vitamin D orally as recommended previously [2]. It has been shown that a single dose of 50,000 IU vitamin D once a week for 8 weeks is efficient and safe to treat vitamin D-deficiency [2]. Another means of guaranteeing vitamin D-sufficiency, especially in nursing home residents, is to give 50,000 IU of vitamin D once a month [2]. To prevent vitamin D deficiency in the

general population, at present, most experts in the field agree that the evidence to date suggests that daily intake of 1,000–2,000 IU/day of vitamin D could reduce the incidence of vitamin D-deficiency-related diseases with minimal risk in Europe, the US, and other countries [2].

If we follow the recommendations discussed above carefully, they will ensure an adequate vitamin D-status, thereby protecting us against adverse effects of strict solar UV-protection. Most importantly, these measures will protect us sufficiently against the multiple negative effects of vitamin D-deficiency on health without increasing our risk to develop UV-radiation-induced skin cancer. To reach this goal it is important that health campaigns transfer this information to the general population and to every clinician, especially to dermatologists.

Questions and answers

R Vieth, Canada

I was hoping to hear more about the ability of the skin to both 25 hydroxylate and produce $1,25(OH)_2D3$ locally. If these are agents which can potentially affect the skin then the skin, by acquiring UV light, is also able to handle its own vitamin D metabolism and perhaps affect the proliferation of cells.

J Reichrath

I would love to do studies on this aspect but it is not technically possible for me. It is very hard to measure the generation of these compounds in the skin.

G Jones, Canada

Do you see any possibility that because this is a skin cancer, you might be able to treat it with vitamin D analogues by topical administration or do you think this is just a pipe dream?

J Reichrath

At present I would say it is most unlikely. In cases where such treatment might be feasible, surgery is certainly the best option. In those critical cases where surgery is not possible, then vitamin D would not help either.

R Vieth, Canada

I think there is a controversial issue in Dermatology in that the pharmaceutical industry is unwilling to promote the use of vitamin D, since it is a non-proprietary compound and it is not in their interest for it to be used. Unfortunately, Dermatology has been driven by the analogue production companies. The skin has a completed endocrine system to enable it to synthesise $1,25(OH)_2D3$ but as far as I am aware, nobody has looked at whether cholecalciferol applied to the skin might benefit the skin.

J Reichrath

We have done some very basic experiments, which did show some positive effects, but these were not statistically significant.

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