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Review

The challenge resulting from positive and negative effects of sunlight: How much solar UV exposure is appropriate to balance between risks of vitamin D deficiency and skin cancer?

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Abstract

There is no doubt that solar ultraviolet (UV) exposure is the most important environmental risk factor for the development of non-melanoma skin cancer. Therefore, sun protection is of particular importance to prevent these malignancies, especially in risk groups. However, 90% of all requisite vitamin D has to be formed in the skin through the action of the sun—a serious problem, for a connection between vitamin D deficiency and a broad variety of independent diseases including various types of cancer, bone diseases, autoimmune diseases, hypertension and cardiovascular disease has now been clearly indicated in a large number of epidemiologic and laboratory studies. An important link that improved our understanding of these new findings was the discovery that the biologically active vitamin D metabolite $1,25(OH)_2D$ is not exclusively produced in the kidney, but in many other tissues such as prostate, colon, skin and osteoblasts. Extra-renally produced $1,25(OH)_2D$ is now considered to be an autocrine or paracrine hormone, regulating various cellular functions including cell growth. We and others have shown that strict sun protection causes vitamin D deficiency in risk groups. In the light of new scientific findings that convincingly demonstrate an association of vitamin D deficiency with a variety of severe diseases including various cancers, the detection and treatment of vitamin D deficiency in sun-deprived risk groups is of high importance. It has to be emphasized that in groups that are at high risk of developing vitamin D deficiency (e.g., nursing home residents or patients under immunosuppressive therapy), vitamin D status has to be monitored. Vitamin D deficiency should be treated, e.g., by giving vitamin D orally. Dermatologists and other clinicians have to recognize that there is convincing evidence that the protective effect of less intense solar UV radiation outweighs its mutagenic effects. Although further work is necessary to define an adequate vitamin D status and adequate guidelines for solar UV exposure, it is at present mandatory that public health campaigns and recommendations of dermatologists on sun protection consider these facts. Well-balanced recommendations on sun protection have to ensure an adequate vitamin D status, thereby protecting people against adverse effects of strict sun protection without significantly increasing the risk of developing UV-induced skin cancer.
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Contents

1. Solar ultraviolet (UV) exposure and skin cancer

Historically, the connection between solar UV exposure and epithelial skin cancer was first described by Unna and Dubreuilh in the last decade of the 19th century (Unna, 1894; Dubreuilh, 1896). They observed actinic keratoses and squamous cell carcinomas (SCCs) in chronically sun-exposed skin from sailors and vineyard workers. Today, there is no doubt that solar UV exposure is the most important environmental risk factor for the development of non-melanoma skin cancer (Preston and Stern, 1992; Kricker et al., 1994; Elwood and Jopson, 1997; Armstrong and Kricker, 2001; Tilgen et al., 2005; Wang and Diepgen, in press). A connection between the risk of developing skin cancer and skin type has been shown. People with UV-sensitive skin types I or II are at a higher risk of developing skin cancer as compared to people with less UV-sensitive skin types (Tilgen et al., 2005; Wang and Diepgen, in press). Three main types of skin cancer can be distinguished: SCC (Rass, in press; Reichrath and Querings, in press), basal cell carcinoma (Reichrath and Querings, in press) and malignant melanoma (Gilchrest et al., 1999). Actinic keratoses are now considered to represent cutaneous SCCs in situ (Reichrath and Querings, in press). Actinic keratoses are more frequent in men, in sun-sensitive subjects exposed to chronic sun and in individuals who have a history of sunburn (Frost and Green, 1994). During the last decades, epidemiological data have demonstrated that painful sunburns are implicated in the pathogenesis of SCC (Green and Battistutta, 1990), basal cell carcinoma (Kricker et al., 1994) and malignant melanoma (Elwood and Jopson, 1997). Chronic sun exposure is the most important cause of SCC (Alam and Ratner, 2001), but may be less important for the development of basal cell carcinoma (Kricker et al., 1994). In addition, various reports analyzing sun exposure parameters have consistently demonstrated an association between the development of malignant melanoma and short-term intense UV exposure, particularly burning, in childhood (Osterlind et al., 1988). Many studies have shown that the incidence of malignant melanoma increases with decreasing latitude towards the equator (Green and Siskind, 1983). 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 malignant melanoma, and in fact has been found in some studies to be protective (Elwood et al., 1985; Elwood and Jopson, 1997; Kennedy et al., 2003). It may be speculated whether these connections may be an explanation for the finding of an increased risk of developing melanoma after sunscreen use, that was reported (Westerdahl et al., 1995). Recently, a large European case–control study investigated the association between sunbed use and cutaneous melanoma in an adult population aged between 18 and 49 years (Bataille et al., 2005). Between 1999 and 2001, sun and sunbed exposure was recorded and analyzed in 597 newly diagnosed melanoma cases and 622 controls in Belgium, France, The Netherlands, Sweden and the UK. In this study, 53% of cases and 57% of controls ever used sunbeds. There was a South-to-North gradient with a high prevalence of sunbed exposure in Northern Europe and a lower prevalence in the South (prevalence of use in France 20% compared to 83% in Sweden). The authors found that the dose and lag time between the first exposure to sunbeds and the time of study were not associated with melanoma risk, neither were sunbathing and sunburns (Bataille et al., 2005).

2. Photocarcinogenesis of non-melanoma skin cancer

The solar UV spectrum consists of UV-C (wavelength below 280 nm), UV-B (280–315 nm) and UV-A (315–400 nm) bands (Rass, in press). The predominant part of the short-wave, high-energy and destructive UV

spectrum cannot reach the earth's surface, for the ozone layer of the outer earth atmosphere absorbs the shorter wavelength up to approximately 310 nm (UV-C and part of UV-B radiation; Rass, in press). In human skin, UV-light is absorbed by the different layers in a wavelength-dependent manner. UV-B is almost completely absorbed by the epidermis, only 20% of the UV-B energy reaches the epidermal basal cell layer or the dermal stratum papillare (Rass, in press). UV-A penetrates deeper into the dermis and deposits 30–50% of its energy in the dermal stratum papillare. These absorption characteristics explain at least in part why UV-B effects (skin cancer development) have to be expected predominantly in the epidermis and UV-A effects (solar elastosis, skin aging) in the dermis (Rass, in press). DNA is a major epidermal chromophore with an absorption maximum of 260 nm. Both UV-A and UV-B can induce structural damage to DNA. UV-B induces molecular rearrangements of the DNA with a characteristic formation of specific photoproducts (typically cyclobutane pyrimidine dimers or 6-4 photoproducts), which are known to be mutagenic. The genotoxic potential of UV-A is predominantly due to indirect mechanisms that include oxidative damage. Gene mutations that have been shown to be of importance for the pathogenesis of skin cancer include mutations in the p53 gene (actinic keratoses, SCCs) and in the patched (PTCH)/sonic hedgehog pathway (basal cell carcinomas). The UV-induced development of skin carcinomas has been analyzed using multiple model systems. Mutation-associated inactivation of the p53 tumor suppressor gene plays a critical role both in stages of initiation and progression of SCC (for a review, see Melnikova and Ananthaswamy, in press). Analysis of data on gene mutations in human premalignant actinic keratosis (AK) lesions as well as data from UV-induced carcinogenesis experiments in mice have suggested that the first step involves acquisition of UV-induced mutations in the p53 gene by epidermal keratinocytes (Melnikova and Ananthaswamy, in press). This defect diminishes sunburn cell formation and enhances cell survival allowing retention of initiated, precancerous keratinocytes (Melnikova and Ananthaswamy, in press). Second, chronic exposures to solar UV results in the accumulation of p53 mutations in skin, which confer a selective growth advantage to initiated keratinocytes and allow their clonal expansion, leading to formation of AK (Melnikova and Ananthaswamy, in press). The expanded cell death-defective clones represent a larger target for additional UV-induced p53 mutations or mutations in other genes, thus enabling progression to carcinomas. Concerning the pathogenesis of basal cell carcinomas, the importance of PTCH, SMOH and TP53 mutations has been demonstrated (Reifenberger et al., 2005). Suppression of the skin's immune system has been shown to be another one of the mechanisms by which solar UV radiation induces and promotes skin cancer growth, even at suberythemogenic doses (for a review,see Baron, in press). Immunosuppressive properties have been demonstrated for both UV-B and UV-A (Baron, in press). It has been speculated whether UV-B-induced production of vitamin D may be involved in UV-B-induced immunosuppression (Reichrath and Rappl, 2003).

Interestingly, a contribution of the skin vitamin D system to the pathogenesis and prognosis of malignancies including malignant melanoma has been demonstrated (Osborne and Hutchinson, 2002). We have characterized the expression of key components of the vitamin D endocrine system (vitamin D receptor (VDR), vitamin D-25OHase, 25(OH)D-1αOHase, 1,25$(OH)_2$D-24OHase) in cutaneous SCCs, basal cell carcinomas and malignant melanoma (Reichrath and Rappl, 2003; Reichrath et al., 1999; Reichrath et al., 2004a, b; Mitschele et al., 2004; Seifert et al., 2004). Our findings provide supportive evidence for the concept that endogeneous synthesis and metabolism of vitamin D metabolites as well as VDR expression may regulate growth characteristics of basal cell carcinomas, cutaneous squamous cell carcinomas and malignant melanoma (Reichrath and Rappl, 2003; Reichrath et al., 1999; Reichrath et al., 2004a, b; Mitschele et al., 2004; Seifert et al., 2004). An association of Fok 1 restriction fragment length polymorphisms of the VDR with occurrence and outcome of malignant melanoma, as predicted by tumor (Breslow) thickness, has been reported (Hutchinson et al., 2000). The same laboratory demonstrated that a polymorphism in the promotor region of VDR (A1012G, adenine–guanine substitution -1012 bp relative to the exon 1a transcription start site) is related in melanoma patients to thicker Breslow thickness groups and to the development of metastasis (Halsall et al., 2004). The authors concluded that polymorphisms in the VDR gene, which can be expected to result in impaired function of biologically active vitamin D metabolites, are associated with susceptibility and prognosis in malignant melanoma. By using array CGH, amplification of the 1,25$(OH)_2$D-metabolizing enzyme 1,25$(OH)_2$D-24OHase was recently detected as a likely target oncogene of the amplification unit 20q13.2 in breast cancer cell lines and tumors (Albertson et al., 2000). It has been speculated that overexpression of 24OHase due to gene amplification may abrogate 1,25$(OH)_2$D-mediated growth control.

Additionally, amplification of the 25(OH)D-1αOHase gene has been reported in human malignant glioma (Diesel et al., 2005). The significance of these findings remains to be investigated. We have analyzed metastases of malignant melanomas and found no evidence of amplification of 1αOHase or 24OHase genes using Southern analysis (Reichrath et al., 2004b). However, we detected various splicing variants of the 25(OH)D-1αOHase gene in cutaneous malignancies (Diesel et al., 2005). The clinical significance of this finding remains to be elucidated.

3. Sun protection recommendations

During the last decades, public health campaigns have improved our knowledge regarding risk of UV radiation for skin cancers. However, it can be speculated that positive effects of UV light were not adequately considered in most of these campaigns, which in general proposed a strict "no sun policy". Strict sun protection recommendations still represent a fundamental part of public health campaigns and prevention programs aimed at reducing UV radiation-induced skin damage and skin cancer. These sun protection recommendations include use of sunscreens, protective clothing and avoidance of sunlight. Clothing is extremely effective in absorbing all UV-B radiation, thereby preventing any UV-B photons from reaching the skin (Holick, 2003; Matsuoka et al., 1992). Most sunscreen products combine chemical UV-absorbing sunscreens and physical inorganic sunscreens, which reflect UV, to provide broad-spectrum protection. Nowadays, most sunscreen products protect against both UV-B and UV-A light. It has to be noticed that the need for sun protection may vary between individuals depending on their skin type and other factors. The very skin types most resistant to the harmful effects of UV radiation are also the ones most associated with diseases of vitamin D deficiency.

4. Vitamin D deficiency—a serious health problem

Approximately 90% of all requisite vitamin D is formed within the skin through the action of the sun—a serious problem, for a connection between vitamin D deficiency and various types of cancer (e.g., colon, prostate and breast cancer) has been confirmed in a large number of studies (Gorham et al., 1990; Garland et al., 1989, 1991; Grant, 2002). The idea that sunlight and vitamin D inhibit the growth of human cancers is not new (for a review, see Schwartz, 2001). When Peller noticed an apparent deficit of non-skin cancer among US Navy personnel, who experienced an excess of skin cancer, he concluded in 1936 that skin cancers induce a relative immunity to other types of cancer (Peller, 1936). Consequently, he advocated the deliberate induction of non-melanoma skin cancers, which were easy to detect and to treat, as a form of vaccination against more life-threatening and less treatable cancers. It was in 1941 when the pathologist Frank Apperly published geographic data that demonstrated for the first time an inverse correlation between levels of UV radiation in North America and mortality rates from non-skin cancers (Apperly, 1941). Apperly concluded that "the presence of skin cancer is really only an occasional accompaniment of a relative cancer immunity in some way related to exposure to ultraviolet radiation." "A closer study of the action of solar radiation on the body", he reasoned, "might well reveal the nature of cancer immunity." Since the time of Apperly's first report, an association between increased risk of dying from various internal malignancies (e.g., breast, colon, prostate and ovarian cancer) and decreasing latitude towards the equator has now been confirmed (Grant, 2002). A correlation of latitudinal association with sun exposure and decreased vitamin D serum levels has been demonstrated (Garland et al., 1989; Grant, 2002). Interestingly, black men, who are at an increased risk of developing vitamin D deficiency, have also an increased risk for prostate cancer and develop a more aggressive form of the disease. Moreover, it has been reported that sun exposure is associated with a relatively favorable prognosis and increased survival rate in various other malignancies, including malignant melanoma (Berwick et al., 2005). It has been speculated that these findings were related to UV exposure-induced relatively high serum levels of vitamin D. Berwick et al. recently evaluated the association between measures of skin screening and death from cutaneous melanoma in case subjects ($n = 528$) from a population-based study on cutaneous melanoma, who were followed for an average of more than 5 years (Berwick et al., 2005). They found that sunburn, high intermittent sun exposure and solar elastosis were statistically significantly inversely associated with death from melanoma and concluded that sun exposure is associated with increased survival from

melanoma (Berwick et al., 2005). Cell and animal experiments reported in the literature, as well as epidemiologic data from some countries relate survival of various malignancies, including colon cancer, with sun exposure, latitude and vitamin D_3 synthesis in skin (Moan et al., 2005).

It can be summarized that the evolution of our understanding of the role of vitamin D in cancer parallels our understanding of the importance of vitamin D for rickets (Holick, 2003). In both diseases, epidemiologic observations about consequences of sun exposure preceeded experimental observations and were subsequently validated by them. Apperly's insightful observations on sunlight exposure and cancer, like those of Theobold Palm on the protective effects of UV radiation on rickets half a century earlier (Palm, 1890), passed virtually unnoticed for many years, only to be rediscovered by epidemiologists decades later. During recent years, great progress has been made in laboratory investigations that searched for the "missing link" between vitamin D and cancer. Of high importance was the discovery that in contrast to earlier assumptions, skin, prostate, colon, breast and many other tissues express the enzyme to convert 25(OH)D to its active form, $1,25(OH)_2D$ (Schwartz et al., 1998; Reichrath, 2001; Lehmann et al., 2004). Therefore, $1,25(OH)_2D$ is now not exclusively considered as a calciotropic hormone but also as a locally produced potent hormone regulating cell growth (for a review, see Lehmann et al., 2004).

5. Rigorous sun protection increases the risk of vitamin D deficiency

We recently analyzed whether patients that need to protect themselves for medical reasons from sun exposure are at risk of developing vitamin D deficiency. Serum 25(OH)D levels were analyzed in renal transplant patients with adequate renal function and in an age- and gender-matched control group at the end of winter. All renal transplant patients had practised solar UV protection after transplantation. Serum 25(OH)D levels were significantly lower in renal transplant patients than in controls (Querings et al., 2006). In another pilot study, we have analyzed basal $25(OH)D_3$ serum levels in a small group of patients with xeroderma pigmentosum ($n = 3$) and basal cell nevus syndrome ($n = 1$) at the end of wintertime (February–March). $25(OH)D_3$ levels in all four patients were markedly decreased with a mean value of 23.75 mmol/l (9.5 ng/ml; normal range 37.5–225 nmol/l (15.0–90.0 ng/ml)). In conclusion, we demonstrate reduced serum $25(OH)D_3$ levels in sunlight-deprived risk groups (Querings and Reichrath, 2004).

6. How much vitamin D do we need?

How much vitamin D do we need to achieve a protecting effect against cancer and other diseases? The US Recommended Dietary Allowance (RDA) of vitamin D from 1989 is 5 μg (200 IU; Subcommittee on the Tenth Edition of RDAs, Commission on Life Sciences and and National Research Council, 1989). Yet, studies have shown that 5 μg (200 IU/day) has no effect on bone status (Dawson-Hughes et al., 1995). It has been recommended that adults may need, at a minimum, five times the RDA, or 25 μg (1000 IU), to adequately prevent bone fractures, protect against some cancers and derive other broad-ranging health benefits (Vieth, 1999). In conclusion, the 1989 RDA of 5 μg (200 IU) is antiquated, and the newer 15 μg (600 IU) daily reference intake dose for adults older than 70 is still not adequate (Dawson-Hughes et al., 2005). It has been suggested that even the 50 μg (2000 IU) upper tolerable intake, the official safety limit, does not deliver the amounts of vitamin D that may be optimal (Dawson-Hughes et al., 2005). On a sunny summer day, total-body sun exposure produces approximately 250 μg (10,000 IU) vitamin D per day. As a result, concerns about toxic overdose with dietary supplements that exceed 20 μg (800 IU) are poorly founded. It has been speculated that a person would have to consume almost 67 times more vitamin D than the current 15 μg (600 IU) recommended intake for older adults to experience symptoms of overdosage (Vieth, 1999). Vieth believes people need 100–250 μg (4000–10,000 IU) vitamin D daily and that toxic side effects are not a concern until a 1000 μg (40,000 IU)/day dose (Vieth, 1999).

Other researchers agree with these findings. They suggest that older adults, sick adults and "perhaps all adults" need 20–25 μg (800–1000 IU) daily. They indicate that daily doses of 60 μg (2400 IU)—four times the recommended intake—can be consumed safely (Vieth, 1999).

7. Conclusions

What conclusions do we draw from these findings, most importantly the demonstration of an association between vitamin D deficiency and the occurrence of various types of cancer? The most important take-home message, especially for dermatologists, is that strict sun protection procedures to prevent skin cancer may induce the severe health risk of vitamin D deficiency. There is no doubt that UV radiation is mutagenic and is the main reason for the development of non-melanoma skin cancer. Therefore, excessive sun 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 is absolutely important. Additionally, sun exposure around midday should be avoided during the summer in most latitudes. However, the dermatological community has to recognize that there is convincing evidence that the protective effect of less intense solar radiation outweighs its mutagenic effect. In consequence, many lives could be prolonged through careful exposure to sunlight or more safely, vitamin D supplementation, especially in non-summer months. Therefore, recommendations of dermatologists on sun protection should be moderated. As Michael Holick reported previously (Holick, 2001), we have learned that at most latitudes such as Boston, USA (41°N), very short and limited solar exposure is at certain times of the year sufficient to achieve "adequate" vitamin D levels. Exposure of the body in a bathing suit to one minimal erythemal dose (MED) of sunlight is equivalent to ingesting about 250 μg (10,000 IU) vitamin D and it has been reported 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. Although further work is necessary to define the influence of vitamin-D deficiency on the occurrence of melanoma and non-melanoma skin cancer, it is at present mandatory that especially dermatologists strengthen the importance of an adequate vitamin D status if sun 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 or patients under immunosuppressive therapy who must be protected from the sun exposure), vitamin D status should be monitored subsequently. Vitamin D deficiency should be treated, e.g., by giving vitamin D orally as recommended previously (Holick, 2001; Vieth, 1999). It has been shown that a single dose of 1250 μg (50,000 IU) vitamin D once a week for 8 weeks is efficient and safe to treat vitamin D deficiency (Vieth, 1999). Another means of guaranteeing vitamin D sufficiency, especially in nursing home residents, is to give 1250 μg (50,000 IU) of vitamin D once a month. If we follow the guidelines discussed above carefully, they will ensure an adequate vitamin D status, thereby protecting us against adverse effects of strict sun protection recommendations. Most importantly, these measures will protect us sufficiently against the influence of vitamin D deficiency on the occurrence of various malignancies without increasing our risk of developing UV-induced skin cancer. To reach this goal, it is of high importance that this information is transferred to every clinician, especially to dermatologists. Otherwise dermatologists will not be prepared for the moderation of sun protection recommendations, which are necessary to protect us against vitamin D deficiency, cancer and other diseases.

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