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Vitamin D and Melanoma

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PURPOSE: Ultraviolet light from sunlight and other sources is the major environmental risk factor for melanoma of the skin. Humans also derive most of their vitamin D from exposure to sunlight. This article reviews current evidence that vitamin D might play a preventive role in the development of melanoma or affect tumor aggressiveness or melanoma patient outcomes.
METHODS: Literature review.
RESULTS: The vitamin D receptor has been identified in normal melanocytes as well as melanoma cell lines and primary tissue. A few studies have demonstrated relationships of functional polymorphisms in the vitamin D receptor with melanoma risk or tumor aggressiveness. Identifying an independent influence of vitamin D on melanoma risk is hampered by overwhelming confounding by the carcinogenic influence of ultraviolet radiation on skin melanocytes. Nonetheless an inverse association was suggested in a few studies with greater consumption of dairy foods or other dietary sources. Several lines of evidence are consistent with a potential influence for vitamin D on site-specific aggressiveness of skin melanomas, therapeutic response or patient survival.
CONCLUSION: Additional research is needed to determine whether vitamin D may have a preventive role in melanoma incidence or a salutary influence on melanoma patient outcome.
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KEY WORDS: Melanoma, Nonmelanoma skin cancer, Vitamin D, Vitamin D receptor, VDR, UVB, 1,25 dihydroxyvitamin D.

INTRODUCTION

Cutaneous malignant melanomas arise from epidermal melanocytes, the cells responsible for the production of the skin pigment melanin. The descriptive epidemiology of melanoma, including a strong north/south gradient in the United States and Europe and an opposite pattern in Australia, is consistent with a causal role of sunlight in melanoma, and epidemiologic studies have confirmed the association. The weight of evidence indicates that ultraviolet B in the solar spectrum (>280–315 nm) contributes to the development of melanoma and nonmelanoma skin cancers (NMSCs) (basal cell and squamous cell carcinomas [BCCs and SCCs, respectively]), though ultraviolet (UV) A (400–320 nm) is also likely to contribute to the incidence of skin cancer (1). There is an emerging body of evidence that adequate stores of vitamin D decrease the risk of many internal cancers through effects on cell proliferation, differentiation, cell death, and angiogenesis; these stores of vitamin D may also limit invasion and metastasis of tumor cells. The UV wavelengths responsible for photocarcinogenesis overlap with the action spectrum for the synthesis of vitamin D in the skin, creating a dilemma for public health professionals, medical care providers, and the public (2). This report summarizes the available evidence, mostly circumstantial, that vitamin D might contribute to the development or outcome of melanoma. Potential future directions for research are also reviewed.

CLINICAL AND EXPERIMENTAL EVIDENCE

Research in the early 1970s showed that calciferols can stimulate activity of tyrosinase, the principal enzyme involved in melanin synthesis, in cultured melanoma cells (3). Subsequently, the receptor for vitamin D was detected in cultured melanoma cells (4, 5) and in melanoma xenographs (6). Other studies confirmed the presence of the vitamin D receptor (VDR) in primary melanoma tissue (7).

Vitamin D metabolites have been shown to inhibit proliferation and induce differentiation in melanoma cells and tissues expressing the VDR (studies reviewed in Osborne and Hutchinson [8]). There is also evidence that 1,25-hydroxyvitamin D promotes cell survival and inhibits tumor invasion and angiogenesis (8). Albert et al. (9) reported that vitamin D analogues inhibit the growth of pigmented ocular tumors grown in transgenic mice, a model that closely resembles human choroidal melanomas.

The skin is an important target site for the actions of vitamin D (10). Photochemical reactions that produce the prohormone vitamin D_3 (cholecalciferol) takes place only

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Selected Abbreviations and Acronyms

NMSC = nonmelanoma skin cancer
BCC = basal cell carcinoma
SCC = squamous cell carcinoma
UV = ultraviolet
VDR = vitamin D receptor

in the skin, and it is now recognized that keratinocytes and other cells in the epidermis are capable of synthesizing the hormonally active vitamin D metabolite, 1,25-dihydroxyvitamin D (calcitriol) (11). Targets of locally produced calcitriol include keratinocytes, major structural cells in the epidermis and, in partnership with melanocytes, a principal component of the body's tanning response to sunlight. Locally produced active vitamin D also plays a role in the innate and acquired immunity in the skin, implicated in the defense against microbial invasion and the inflammatory responses to sun damage (12, 13). There is evidence that vitamin D may also be critical in the intrinsic defense against UV damage of cells in the skin (14, 15). In experimental systems, treatment with 1,25-dihydroxyvitamin D was shown to protect primary human keratinocytes against the induction of cyclobutane pyrimidine dimers, the principal mutation of UVB carcinogenesis (14). Survival of UV-treated keratinocytes was enhanced by 1,25-dihydroxyvitamin D while surviving cells exhibited significant reductions in signature UV photoproducts (15). Whether vitamin D may offer similar photoprotection in melanocytes has not been determined.

Ultraviolet radiation is thought to function as a complete carcinogen by damaging DNA and by suppressing protective cellular antitumoral immune responses (16). Shorter wavelength UVB (280–320 nm) was long thought to be the principal carcinogen in sunlight as UVB is efficiently absorbed by DNA; these wavelengths are associated with a characteristic mutation, cyclobutane pyrimidine dimers, found in 90% of squamous cell carcinomas (SCCs) and 50% of basal cell carcinomas (BCCs) (17) (and rarely in melanomas). However, emerging evidence indicates that longer wavelength UVA (320–400 nm) may also be carcinogenic in the skin. UVA is poorly absorbed by DNA, but it can generate reactive species that damage DNA. Moreover, UVA penetrates more deeply into skin than UVB (reviewed in Lund and Timmins [1]). In studies of human skin squamous cells, Agar and co-workers (18) demonstrated a preponderance of UVB-associated mutations (cyclobutane thymine dimers) in the superficial region of the epidermis and of UVA-associated mutations (8-hydroxy-2′-deoxyguanine adducts) in the basal region, which also corresponds to the stem cell compartment of the skin. Based on these observations, Halliday et al. (19) proposed that the UVA waveband of sunlight may be at least as important as UVB in causing skin cancer in humans. UVA, though not UVB, can penetrate to the approximate depth of the epidermal/dermal junction where melanocytes reside (1). This suggests that the widespread use of UVB-only excluding sunblocks, which also block vitamin D production in the skin (see below), may be of limited efficacy for reducing melanoma incidence. These results may have important implications for future public health initiatives for skin cancer prevention.

OBSERVATIONAL STUDIES IN SKIN CANCER

Sun exposure is a well-established environmental risk factor for melanoma and NMSC. Although sun exposure is an indisputable risk factor, the relationship is less direct for melanoma than for other types of skin cancer. BCCs and SCCs, which arise from keratinocytes in the epidermis (and are sometimes referred to as 'keratinocyte carcinomas'), invariably develop in chronically exposed skin. In contrast, melanoma has a tendency to develop on body sites that receive only intermittent sun exposure (and may develop at sites that receive virtually no exposure, including the eye and mucosa). Garland and associates (20) proposed in 1990 that vitamin D may have an ameliorating influence on the development of melanomas.

Epidemiologic evidence for a possible protective influence of sunlight/vitamin D on melanoma risk is suggested by studies showing lower than expected incidence rates in persons with outdoor occupations. It has been known for many years that professional or managerial occupations are associated with increased risk of melanoma, whereas farm workers, persons in the construction trade, and other persons working in primarily outdoor occupations are at lower risk (21). Although such observations may reflect a tendency for persons at higher risk for melanoma (e.g., with fairer skin or more prone to sunburn) to avoid outdoor work, the protective association for outdoor work is independent of constitutional risk factors (22). It should be noted that while outdoor workers have a lower overall incidence of melanoma, they are more likely than indoor workers to develop melanomas in chronically sun-exposed sites, including the head, neck, or face (23, 24). Outdoor workers would be expected to maintain higher systemic levels of 25-dihydroxyvitamin D (calcidiol), the main circulating form of vitamin D and depot for local production of the biologically active form of vitamin D, from their greater exposure to sunlight. A protective influence of a suntan against UV damage may account for the lower incidence of melanoma on the extremities and trunk in outdoor workers. However, it is also possible that lower rates of melanoma in outdoor workers reflect, at least in part, a level of protection afforded by their greater reserves of vitamin D.

A history of sunburn, which implies intermittent patterns of sun exposure, has consistently been linked to the risk of melanoma, whereas cumulative lifetime sun exposure appears not to be an important risk factor (21). These observations may be explained by the better recall of a discrete event, like sunburn, than time spent outdoors (a recent study that was based on the less subjective exposure of residential history demonstrated convincing associations with cumulative sun exposure (25)). Propensity to sunburn is also indicative of recent levels of sun exposure. Thus the risk associated with sunburn could reflect inadequate local or systemic levels of vitamin D and/or lack of photoprotection by a suntan.

Melanomas are etiologically diverse and may develop through different pathogenetic mechanisms some that could involve a preventive role for vitamin D. Whereas NMSCs, especially SCCs, develop as a result of cumulative direct sun exposure with progressive loss of p53 and clonal expansion of apoptosis-resistant cells (26), melanomas appear to evolve by several alternative pathways in which sunlight plays a variable role (27). Recent evidence has demonstrated that the majority of melanomas that occur on body sites receiving only intermittent sun exposure (trunk and extremities) exhibit mutations in *BRAF* and/or N-*ras*, whereas melanomas that arise on skin that is chronically exposed to the sun (head or neck) or on acral skin or mucosal membranes seldom exhibit these mutations (28–30). Oncogenic mutations in *BRAF* or N-*ras* is also reported in a large proportion of melanocytic nevi (30, 31), an important melanoma risk factor. It is not known whether vitamin D is a mediator of any of the alternative pathways to melanoma. However, the predilection for melanomas to occur at sites that receive limited sun exposure is consistent with the possibility that inadequate local production of vitamin D could be a cofactor in the development of *BRAF*-associated melanomas.

The majority of studies have not demonstrated a protective association between the regular use of sunscreens and the risk of melanoma. In a recent quantitative review of 17 studies published from 1966 to 2007 (32), Gorham et al. reported no overall association between regular use of sunblocks and melanoma risk; four of the studies indicated a statistically significant inverse association, six studies indicated no association, and seven studies demonstrated a statistically significant positive association. Several explanations have been proposed to explain why a protective association of sunblocks with melanoma has not been demonstrated (33). One plausible explanation is that by preventing sunburn, use of sunblocks results in more prolonged exposure to UVA, which does not produce erythema, is not excluded by most sunblocks, and may be an important contributor to the onset of melanoma (1). Sunscreens used over the period of the studies included in the review by Gorham et al (32) blocked mainly UVB (34), wavelengths that also trigger the production of vitamin D in the skin. Use of sunscreens has been shown to modestly reduce circulating vitamin D levels (35–37); full body application in controlled circumstances can completely block endogenous vitamin D production (38). It is possible that vitamin D–suppressive effect of sunblocks and/or their failure to block UVA could help account for the failure of these agents to reduce incidence of melanoma.

Most research suggests that use of sunbeds for tanning is moderately associated with melanoma, particularly for regular or long-term exposure (39). Most of the evidence comes from retrospective case-control studies. A positive association of sunbed exposure with melanoma risk was also demonstrated in a large prospective study (40). Until the late 1970s, sunbeds emitted primarily UVB, whereas modern devices emit approximately 95% UVA (41). As noted, UVA may contribute to melanoma and other skin cancers (1). In large powerful tanning units, the UVA irradiation intensity may be 10 to 15 times higher than that of midday sun (42). UVB that is emitted in sunlamps could potentially afford some protection through the production of vitamin D. If so, it could be speculated that high levels of UVA overwhelm protective influences of vitamin D and/or tanning produced by UVB in sunlamps.

Vitamin D occurs naturally in only a few foods (fish and organ meats), while fortification of liquid milk provides an additional dietary source (43). Few studies have examined vitamin D from diet in relation to melanoma incidence. In a small case-control study (165 cases, 209 controls), vitamin D from dairy foods and nutritional supplements had no association with melanoma risk (44). In a larger study (502 cases, 565 controls), persons in the highest quintile of vitamin D intake were at significantly reduced risk (45). Some studies (46), though not all (47,48), have reported inverse associations with the consumption of fish, an important dietary source of vitamin D.

POLYMORPHISMS IN THE VDR

The gene encoding the VDR (MIM 601769) maps to chromosomal region 12q13 and contains numerous common variants, some that are hypothesized to influence the expression and/or function of the VDR protein. Several common polymorphisms in the VDR have been studied in relation to melanoma risk, aggressiveness, or prognosis (case-control results summarized in Table 1) (49–54).

The most commonly studied single variant is the Fok I restriction site (F/f) in exon II. This variant is of interest because it results in an altered translation start site. The shorter encoded protein (F) is thought to be more active

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TABLE 1. VDR polymorphisms and cutaneous melanoma incidence: published case-control studies

Author	Cases/ Controls	Cdx2 rs11568820 5' promoter	A-1012G rs4516035 5' promoter	FokI rs10735810 M1T	BsmI rs1544410 intronic	TaqI rs731236 I352I
Hutchinson et al (2000) [49]	316 / 108			Ff (OR: 1.60; CI: 0.97,2.64) ff (OR: 1.90; CI: 0.89,4.27)		Tt (OR: 1.28; CI: 0.74,2.22) tt (OR: 1.28; CI: 0.59,2.89)
Halsall et al (2004) [50]	176 / 80		AG (OR: 2.5; CI: 1.1, 5.7) AA (OR: 3.3; CI: 1.4, 8.1)			
Han et al (2007) [51]	219 / 873	GA (OR: 1.03; CI: 0.74,1.44) AA (OR: 0.57; CI: 0.22,1.48)		Ff (OR: 1.01; CI: 0.72,1.41) ff (OR: 1.37; CI: 0.87,2.14)	Bb (OR: 0.89; CI: 0.64,1.24) BB (OR: 0.81; CI: 0.51,1.30)	
Li et al (2007) [52]	602 / 603			Ff (OR: 1.32; CI: 1.03,1.68) ff (OR: 1.03; CI: 0.71,1.51)		Tt (OR: 0.70; CI: 0.54,0.90) tt (OR: 0.71; CI: 0.50,0.99)
Povey et al (2007) [53]	596 / 441		AA/AG (OR: 1.88; CI: 1.18, 3.00) persons ⩽50 years			
Santonocito et al (2007) [54]	101 / 101		AG (OR: 0.98; CI: 0.43, 2.26) AA (OR: 0.69; CI: 0.29, 1.62)	Ff (OR: 0.78; CI: 0.41,1.47) ff (OR: 0.81; CI: 0.31,2.09)	Bb (OR: 0.74; CI: 0.40-1.39) BB (OR: 0.29; CI: 0.12- 0.71)	

VDR = vitamin D receptor; OR = odds ratio; CI = confidence interval

(55). A total of four studies have examined associations of this variant with cutaneous melanoma, three providing suggestive evidence that carriers of the less active f allele may be at modestly elevated risk (49, 51, 52). A fourth Italian study including 101 cases and 101 controls did not support this association (54).

Other studies have considered the restriction fragment length polymorphisms, BsmI in intron 8 and TaqI in exon 9. The TaqI and BsmI variants, along with a third variant in this cluster (ApaI) are in linkage disequilibrium, resulting in two common haplotypes, BAt and baT. Persons homozygous for the b, a, or T alleles demonstrate significantly lower VDR mRNA levels than those exhibiting the BB, AA, or tt genotypes, whereas heterozygotes have intermediate values (56). Two studies were concordant in demonstrating significant inverse association for BB in BsmI and carriers of the t allele in TaqI (52). A nested case-control study within in the Nurses' Health Study cohort was also consistent with a possible inverse association for the B allele in BsmI (51), whereas a fourth study suggested a modest positive association with the TaqI t allele (49).

Two other variants studied, designated Cdx2 and A-1012G in the promoter region, are of unclear functional significance (discussed in Halsall et al. (50)). Interestingly, two studies (50, 53) found significantly increased risk in carriers of the A allele for A-1012G polymorphism. A third investigation (54) did not replicate the finding, though the study was small. The Cdx2 polymorphism was examined in one study with null results (50).

MELANOMA STAGING AND OUTCOME

Polymorphisms in the VDR have been associated with tumor aggressiveness (49, 50, 54) or metastasis (50) in a few studies. All reports were based on limited series (number of melanoma cases ranging from 101–316), and no associations have yet been replicated in independent studies.

Melanoma incidence rates are low among non-Caucasians in the United States (57). However, 5-year survival rates are appreciably higher in whites (93%) when compared to blacks (75%) (58). Blacks are more likely to be diagnosed with acral subtypes of melanoma and are diagnosed at a later stage of disease (57). While these differences, in addition to genetic factors, may contribute to the noted disparities in melanoma-specific survival, a poorer outcome has been demonstrated in blacks even after adjusting for differences in melanoma stage at diagnosis (57). Vitamin D insufficiency is more prevalent among African Americans than other Americans (59) because of the interference of melanin with photochemical reactions that promote vitamin D synthesis in the skin. It is unclear whether lower plasma 25-dihydroxyvitamin D concentrations might contribute

to tumor aggressiveness or poorer outcome in African American patients.

Fears and Tucker (60) presented data showing that melanoma survival rates in the United States have no relation to variation in 'UVB flux', a measure of the ambient biologically effective dose of UVB. This finding suggests that exposure to ambient UVB in sunlight (and hence exposure to vitamin D–producing wavelengths) is not related to melanoma survival. However, data provided by Berwick et al. (63) suggested a different conclusion (response to Fears and Tucker). In an analysis of international data, these investigators demonstrated a positive relationship between melanoma survival rates and incidence rates, a finding which implies that persons who live in sunny climates, where incidence rates are highest, are less likely to die of the disease. The relationship was linear to an incidence of about 15 per 100,000, above which survival rates had no relation to incidence rates. All of the populations in Fears and Tucker's U.S.-based analysis (60) had incidence rates for melanoma equal to or greater than the threshold incidence of 15 per 100,000, a possible explanation for the lack of association of UV with melanoma survival in the analysis of U.S. data by Fears and Tucker.

Several studies (61–63), though not all (64), have reported a more favorable prognosis, and one has shown a delayed age at onset (65) in persons whose melanomas arise in chronically sun-exposed skin (e.g.,. where there is histologic evidence of solar elastosis at the involved site (65)). Several explanations have been proposed for these observations (63), including a potentially ameliorating influence of locally produced 1,25-dihydroxyvitamin D on melanoma outcome. As sun exposure occurred prior to melanoma diagnosis (and sun exposure before diagnosis is not indicative of exposure after diagnosis as persons with melanoma tend to avoid sun exposure (66)), these results suggest that high local levels of 1,25-dihydroxyvitamin D are associated with the development of less aggressive tumors. However, such an interpretation is not consistent with the observation that patients with melanoma on the scalp or neck, a chronically sun-exposed site, have significantly worse survival than patients with melanomas that develop on the trunk or extremities (67). In their study, Berwick et al. (63) also found evidence of a protective association with sun exposure prior to melanoma diagnosis. These authors followed up patients formerly enrolled in a melanoma case-control study and found a strong independent protective association for indices of chronic and intermittent sun exposure, associations that were independent of tumor stage. If not due to chance, these results suggest that systemic vitamin D status may have an impact on melanoma survival rates. Taken together, the limited evidence available suggests that vitamin D may be involved in the earliest stages of tumor metastasis.

A recent study published in abstract form suggested that higher serum concentrations of 25-dihydroxyvitamin D may have a favorable impact on melanoma outcome (68). In a series of 212 patients with melanoma of all stages, the authors reported significantly lower rates of 'progression' in patients with higher baseline levels of 25-dihydroxyvitamin D.

SUMMARY AND IMPLICATIONS

Melanoma of the skin is currently the sixth most common cancer diagnosis in the United States, contributing about 28,000 new cases in women and 35,000 new cases in men. Approximately 8,400 deaths will be attributed to melanoma of the skin in 2008 (58). Sunlight is an important risk factor for melanoma, and current public health recommendation to avoid excess sun exposure should be heeded, especially by those persons predisposed to sunburn or with a personal or family history of melanoma. However, as vitamin D status is easily modified by changes in diet, as well as relatively minimal exposure to sunlight, it would be useful to establish whether vitamin D plays any role in melanoma risk reduction or outcome. Whether serum concentrations of 25-dihydroxyvitamin D, an indicator of vitamin D status, influence melanoma survival rates is an important question; serological studies could be conducted that relate baseline concentrations of 25-dihydroxyvitamin D to melanoma progression and patient survival. Efficacy of vitamin D analogues for the treatment of cancer is currently limited by the tendency for these agents to cause hypercalcemia, although synthetic VDR ligands with reduced calcemic potential are in active development (69). Given the grim outlook for patients with metastatic melanoma, prevention should remain the focus. Studies of dietary intake provide an option for investigating a preventive role of vitamin D in melanoma. Only a limited number of foods naturally contain vitamin D, and most dietary supplements contain only the current adult recommended dietary allowance (400 IU), which is considered by most authorities to be too low (70). Therefore large studies are needed to ensure a sufficient number of persons with intakes of vitamin D that are likely to be protective (70). The outcome of UV exposure with respect to melanoma incidence and outcome most likely depends on a balance between beneficial and harmful effects of UV. Genetic variants in the VDR (or other genes involved in vitamin D signaling) could have an impact on this balance, and more definitive studies focused on VDR polymorphisms would be valuable. Chemoprevention studies are also feasible and could be targeted to high-risk patients (e.g., with a personal history of melanoma or multiple risk factors) followed up prospectively for incidence of melanoma or preinvasive lesions. Evidence that UVA may contribute to the development of melanoma has

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coincided with the growing awareness that UVB produces a variety of health benefits through the production of vitamin D. A greater understanding of the wavelengths that produce melanoma is therefore important for the development of appropriate photoprotection strategies (71). Sufficient levels of vitamin D can be obtained from relatively minimal exposure to sunlight (UV-induced synthesis is maximal at suberythemal UV doses [2]), so skin cancer avoidance and vitamin D 'nutrition' from moderate, safe levels of sun exposure need not be at odds.

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