Vitamin D, Sun Exposure and Skin Cancer

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Contributor: Alejandro Martin-Gorgojo

The current vitamin D deficiency epidemic is accompanied by an increase in endemic skin cancer. Ultraviolet (UV) exposure (neither artificial nor natural) is not the ideal source to synthesize vitamin D. There is conflicting epidemiological evidence regarding vitamin D, non-melanoma skin cancer (NMSC), and cutaneous melanoma (CMM), confounded by the effect of sun exposure and other factors.

Keywords: Cancer ; vitamin D ; vitamin D deficiency ; skin neoplasms ; melanoma ; cutaneous malignant melanoma ; basal cell carcinoma ; squamous cell carcinoma ; ultraviolet rays ; primary prevention ; prevention and control.

1. Introduction

Misnamed vitamin D is a true hormone that humans can synthesize upon sun exposure or through a balanced and healthy diet including vitamin D-rich foods or supplements. However, people's current predominantly indoor lifestyle with unhealthy, intense, and sporadic sun exposure, along with other factors (such as human migratory movements), have contributed to the vitamin D deficiency epidemic. Paradoxically, this epidemic is accompanied by an increase in endemic skin cancer [1].

Vitamin D shows anti-proliferative and pro-apoptotic effects in vitro on both melanocytes and keratinocytes. Ultraviolet (UV) exposure is the leading environmental risk factor for cutaneous malignant melanoma (CMM) and non-melanoma skin cancer (NMSC). Some studies have observed that vitamin D synthesis may protect against NMSC. However, the optimum vitamin D dose to reduce skin cancer risk has yet to be confirmed [2].

There are still multiple controversies regarding vitamin D and skin cancer, including the recommended serum levels and the limiting role that preventive measures against skin cancer may have on effective vitamin D synthesis.

2. “Sun-Related” Cancer: Magnitude of the Problem

Basal cell carcinoma (BCC), squamous cell carcinoma (SCC) —these first two are usually classified as NMSC–, and cutaneous malignant melanoma (CMM) are the three most frequent types of cutaneous cancer, which are considered “sun-related” (mainly UV-related) cancers.

A significant proportion of national tumor registries do not consider NMSC, given their high frequency and apparently low impact, as well as the fact that some cases are treated without histological confirmation. However, NMSC constitute the most commonly diagnosed cancers in North America, Australia, and New Zealand [3].

An estimated number of 1,042,056 new NMSC cases were diagnosed worldwide in 2018, with 65,155 deaths (approximately 6%) attributable to NMSC (mostly SCC) [3]. The incidence of SCC seems to be increasing, whereas mortality remains stable [4].

Cutaneous melanoma is considered the most lethal of the three main types of skin cancer. An estimated 287,723 cases of CMM were diagnosed worldwide in 2018, causing up to 60,712 deaths (21% mortality) [3]. CMM incidence has increased in most developed countries, mainly accounting for thinner lesions with better prognoses. Mortality tends to be stable among females in the United States (1.9 deaths per 100,000 attributed to CMM) but has been increasing over the years among males (from 2.88 per 100,000 in 1975 to 4.44 per 100,000 in the 2011–2015 period). These differences among male and female rates are controversial; behavioral, genetic, and hormonal factors may play a role [4].

3. Vitamin D Status and Supplementation in Carcinogenesis and Skin

Cancer

In vitro and preclinical animal models have shown that vitamin D alters cancer cell differentiation, proliferation, and apoptosis, making it a candidate agent for cancer regulation [5]. Whether vitamin D prevents cancer in humans or limits cancer progression remains unresolved [6].

The role of vitamin D in cutaneous carcinogenesis is most likely related to its effects on the regulation of growth, cell death, angiogenesis, and cell differentiation. The vitamin D receptor (VDR) is codified by a gene located on chromosomal region 12q13, has variants that are thought to alter its function [1], and is increasingly being considered as a tumor suppressor in the skin (with protective actions against UV-induced epidermal cancer formation) [7].

The protective actions of vitamin D against cutaneous cancer have been evaluated from the study of the relationship between vitamin D (levels, polymorphisms in the vitamin D receptor, and dietary supplementation) with the incidence and survival of various neoplasms [1].

It has been repeatedly suggested that sun exposure, through vitamin D production, may yield a protective effect on various internal cancers. However, from a nested case-control study of Swedish population-based registries comparing more than 100,000 patients with basal cell carcinoma (as a paradigmatic example of people with more sun exposure and vitamin D produced through it) with about 1 million control patients, it could be found that patients with BCC are at higher risk of having other cancers before BCC diagnosis. This evidence contradicts that vitamin D production via regular sun exposure has protective effects on internal cancers [8].

Attempts have been made to determine the most appropriate cancer-protective vitamin D daily intake. Daily doses of 1500 international units (IU) of vitamin D_3 were shown to reduce the male cancer mortality rate by 30% in the United States [1].

In recent years, many studies have made efforts to relate blood levels of vitamin D_3 (25-OH vitamin D) to the incidence of some cancers. For these studies, minimum values of 30–35 ng/mL (75–87.5 nmol/l) were used as a reference, which are considered optimal for obtaining the maximum beneficial effects of vitamin D. These persist even after adjustment for factors that could influence vitamin D levels, such as body mass index or age.

Sufficient vitamin D serum levels confer protection against multiple malignancies. This is proved clinically in different tissues and in vitro in animal and cell culture studies. However, there is not enough epidemiologic evidence to support the positive role of vitamin D in preventing skin cancer, and there is even conflicting evidence [1][9]. As a matter of fact, a recent meta-analysis including 13 prospective studies suggested that vitamin D status is associated with greater risks of CMM and NMSC: each 30 nmol/L increment in 25(OH)-D_3 levels was associated with a 42%, 30%, and 41% increase in the risks of CMM, SCC, and BCC. These increases were probably confounded by sun exposure [10].

3.1. Vitamin D and Non-Melanoma Skin Cancer

Higher serum vitamin D_3 levels are associated with NMSC (OR: 2.07, CI: 1.52–2.80) [11][9], with a linear dose-response [10]. As previously stated, this is probably related to the dual effect of UVB, which allows vitamin D synthesis but, in turn, generates DNA damage causing skin cancer.

Even though xeroderma pigmentosum patients (with probably the highest risk of NMSC) have a high prevalence of vitamin D deficiency [12], current evidence regarding vitamin D and NMSC is controversial, and it is yet to be defined if vitamin D may decrease NMSC incidence or severity [2].

3.1.1. Basal-Cell Carcinoma (BCC)

Vitamin D inhibits the hedgehog pathway (the key tumor pathway in the development of BCC). However, current epidemiological evidence is conflicting, and ad hoc, prospective studies in humans are needed to know the true relationship between vitamin D serum levels and BCC risk [13].

Apart from the linear dose-response increase in BCC risk regarding serum levels, the previously referenced meta-analysis showed a slightly higher risk of BCC among those receiving at least 100 daily international units of either dietary or supplemental vitamin D (RR: 1.02, CI: 1.00–1.03, $p = 0.03$) [10]. The secondary analysis of a randomized clinical trial of supplementation with vitamin D and/or calcium also showed no benefit in preventing BCC (HR: 0.99; 95% CI: 0.65–1.51) [14].

Conversely, a study observed that maintaining serum vitamin D_3 levels above 25 ng/mL may significantly reduce recurrence rates of BCC [15].

3.1.2. Squamous-Cell Carcinoma (SCC)

Molecular studies have shown that the VDR is induced by the tumor suppressor gene p63, which (along with p53) is critical for keratinocytes to initiate the DNA repair process after UV exposure [13].

Despite the observed increase in SCC incidence in those with higher vitamin D serum levels, probably confounded by excessive photodamage [10], there is starting to be some epidemiologic evidence to believe that vitamin D and/or calcium) supplementation may be useful to prevent SCC (HR: 0.42; 95% CI: 0.19–0.91) [14].

Additionally, some studies have assessed the usefulness of vitamin D supplementation or topical application in different indications. An example is the intermittent supplementation of cholecalciferol, which has proven to be helpful to enhance photodynamic therapy to treat squamous cell carcinoma [16].

3.2. Vitamin D and Cutaneous Melanoma

The vitamin D pathway may play a role in melanoma since VDR expression is detected in different melanoma samples and cells. Calcitriol is shown to inhibit tumor invasion and angiogenesis in melanoma cell lines in animal models [13].

Adequate vitamin D levels are associated with diminished risk of melanoma occurrence (RR 0.62 [0.42–0.94]) [9], although there are heterogeneous and conflicting results in different studies with various risk measures [10][13].

Regarding melanoma prognosis, lower serum vitamin D_3 levels are significantly related to worse prognostic traits, namely Breslow thickness, along with poorer melanoma survival, even adjusting for inflammatory biomarkers [17]. Several studies have shown similar associations: one studied patients with variations in the gene coding for vitamin D-binding protein predisposing to lower serum vitamin D levels, with poorer melanoma-specific survival [18], and another confirming a significant association between vitamin D levels at diagnosis and location, tumor mitotic rate, and ulceration [19], and a more recent one observing vitamin D levels < 9.25 ng/mL as independent prognostic factor for overall survival in melanoma patients, linked to histologic ulceration [20]. Likewise, low vitamin D levels are related to increased susceptibility to melanoma, along with reduced melanoma survival [21]. However, several large-scale studies have not been able to prove the same associations [22].

Further investigation is warranted to determine whether supplementation of vitamin D could be of help for patients with or at risk of melanoma [17]. A study recently published in this journal confirmed the safety of vitamin D_3 supplementation (100,000 international units every 50 days) to stage II melanoma patients. It also observed that Breslow thickness influences both disease-free survival and the response (in terms of serum vitamin D levels) to supplementation [23]. Lower melanoma incidence has been observed in patients following a vitamin D-rich diet, but it has not been confirmed in case-control studies including individuals with a diet rich in vitamin D and patients receiving supplements. This may be related with polymorphisms of the VDR receptor, which influence the antitumor role of vitamin D [24]. There is additional conflicting evidence: a study observed that high vitamin D intake resulted in an increased risk of melanoma among men but had a protective effect against invasive melanoma in women [25].

In any case, it is reasonable to give vitamin D supplementation to those with insufficient vitamin D levels and to perform regular serum vitamin D re-screening among patients with or at risk of melanoma [26][27].

4. Take-home messages (extracted after narrative review completed in November 2021)

Current evidence is controversial, and there are no widely applicable strategies.

There are three practical recommendations. Firstly, sun protection recommendations should be kept among people at risk or with a personal history of skin cancer. Secondly, vitamin D should preferably be sourced through diet. Finally, in patients with melanoma or at risk of cutaneous cancer, serum vitamin D checks are warranted to detect and avoid its insufficiency.

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