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Review

Vitamin D and melanoma and non-melanoma skin cancer risk and prognosis: A comprehensive review and meta-analysis

Saverio Caini [a,*], Mathieu Boniol [b], Giulio Tosti [c], Serena Magi [d], Matelda Medri [d], Ignazio Stanganelli [d], Domenico Palli [a], Melania Assedi [a], Veronique Del Marmol [e], Sara Gandini [f]

[a] *Unit of Molecular and Nutritional Epidemiology, Institute for Cancer Research and Prevention, Florence, Italy*
[b] *International Prevention Research Institute, Lyon, France*
[c] *Division of Dermatoncological Surgery, European Institute of Oncology, Milan, Italy*
[d] *Scientific Institute of Romagna for the Study and Treatment of Cancer, Meldola, Italy*
[e] *Department of Dermatology. Hopital Erasme. Université Libre de Bruxelles, Brussels, Belgium*
[f] *Division of Epidemiology and Biostatistics, European Institute of Oncology, Milan, Italy*

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Abstract Vitamin D is formed mainly in the skin upon exposure to sunlight and can as well be taken orally with food or through supplements. While sun exposure is a known risk factor for skin cancer development, vitamin D exerts anti-proliferative and pro-apoptotic effects on melanocytes and keratinocytes *in vitro*. To clarify the role of vitamin D in skin carcinogenesis, we performed a review of the literature and meta-analysis to evaluate the association of vitamin D serum levels and dietary intake with cutaneous melanoma (CM) and non-melanoma skin cancer (NMSC) risk and melanoma prognostic factors. Twenty papers were included for an overall 1420 CM and 2317 NMSC. The summary relative risks (SRRs) from random effects models for the association of highest versus lowest vitamin D serum levels was 1.46 (95% confidence interval (CI) 0.60–3.53) and 1.64 (95% CI 1.02–2.65) for CM and NMSC, respectively. The SRR for the highest versus lowest quintile of vitamin D intake was 0.86 (95% CI 0.63–1.13) for CM and 1.03 (95% CI 0.95–1.13) for NMSC. Data were suggestive of an inverse association between vitamin D blood levels and CM thickness at diagnosis. Further research is needed to investigate the effect of vitamin D on skin cancer risk in

* *Corresponding author:* Address: Institute for Cancer Research and Prevention (ISPO), Unit of Molecular and Nutritional Epidemiology, Via delle Oblate 2, 50139, Florence, Italy. Tel.: +39 0557972548; fax: +39 0557972588.
E-mail address: s.caini@ispo.toscana.it (S. Caini).

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populations with different exposure to sunlight and dietary habits, and to evaluate whether vitamin D supplementation is effective in improving CM survival.

1. Introduction

Vitamin D is a pro-hormone that is synthesised in the keratinocytes from 7-dehydrocholesterol, in a reaction catalysed by ultraviolet (UV) radiation at wavelengths of 290–320 nm [1]. It can also be taken from the diet through the consumption of foods that are naturally rich in (like oily fish and cod liver oil) or fortified with it, or through supplementation [1]. Pre-vitamin D undergoes two hydroxylations to become biologically active [2]. The first occurs in the liver and transforms it into 25-hydroxyvitamin D (25[OH]D), which represents the circulating store of the vitamin. The second hydroxylation occurs in the kidney and leads to the formation of 1,25-hydroxyvitamin D (1,25[OH]D), the biologically active form.

The major biologic function of vitamin D is to regulate the homoeostasis of calcium and phosphorus [3]. Vitamin D has many other functions however, and its receptors may be found on a wide variety of cells [4].

Reduced serum levels of 25(OH)D have been reported correlated with several detrimental health effects [5–8], including worst prognosis of some cancers [9,10]. A meta-analysis of 35 independent case-control and cohort studies investigating the association of serum 25(OH)D levels with cancer showed a consistent inverse relationship between circulating 25(OH)D levels and colorectal cancer risk [11]; no similar conclusions could however be drawn for other cancer sites. Notably, so far none of the randomised, controlled trials has shown that vitamin D supplementation can prevent cancer [12,13] although the increase in vitamin D serum levels achieved in one of these trials, the Women's Health Initiative study, was probably insufficient [14].

In the skin, the active form of vitamin D can be completely produced by the keratinocytes [15]. The 1,25(OH)D thus produced has little influence on blood levels, but performs functions locally, as evidenced by the presence of vitamin D receptors (VDR) on keratinocytes and melanocytes [16]. *In vitro*, 1,25(OH)D inhibits the growth of malignant melanoma cell lines by regulating cell proliferation, differentiation and apoptosis, with an overall anti-tumour effect [17,18]. These effects are most likely mediated by the activation of VDR- and peroxisome proliferator-activated receptor-signalling pathways [19]. *In vivo*, the study of the effect of vitamin D on the risk of skin cancer is more difficult, given that (a) exposure to UV radiation is considered as the main risk factor for the development of both cutaneous melanoma (CM) [20,21] and non-melanoma skin cancer (NMSC) [22], and (b) the dietary intake of pre-vitamin D, either through food or vitamin supplements, has an uncertain association, if any, with its activity in the skin [1].

Evidence for the role of vitamin D in the pathogenesis of skin cancer is provided by findings on vitamin D receptor as well [23,24]. An impaired function of VDR predisposes to epidermal carcinogenesis by increasing cellular proliferation and decreasing differentiation of keratinocytes. The VDR play a crucial role in the DNA damage repair pathways as well [23].

The studies that tried to provide evidence on the effect of vitamin D on skin cancer risk have produced inconsistent results so far [25–28]. Other studies investigated the association of vitamin D blood levels with prognosis of CM, with results that, although inconclusive, seem to suggest a beneficial effect [29,30].

We present here a review of the literature and meta-analysis aiming at evaluating the effect of dietary intake (from food and/or supplements) and serum levels of vitamin D on the risk of developing a CM or a NMSC (basal cell cancer and/or squamous cell cancer), and the association with CM prognostic factors.

2. Materials and methods

2.1. Search of papers and inclusion criteria

A systematic literature search and quantitative analysis were planned, conducted and reported following MOOSE guidelines regarding meta-analysis of observational studies [31]. Published reports were obtained from the following databases using validated search strategies: PUBMED, Ovid Medline, EMBASE and ISI Web of Knowledge up to March 2013.

We searched independent studies published before 31st December 2013. We used different combinations of the following MESH terms to search eligible papers: vitamin D, skin cancer, cutaneous melanoma, basal cell cancer, squamous cell cancer, risk and prognosis. We obtained full copies of all articles that were considered as potentially eligible for inclusion in our meta-analysis; the reference lists of all papers retrieved at first stage were also inspected to find other eligible papers. Review articles not reporting original data were also excluded but checked for references. Two co-authors (S.C. and S.G.) independently read all the retrieved papers, decided on their inclusion in the final pool of papers to be used for the meta-analysis (based on inclusion and exclusion criteria listed below), and extract data into a dataset designed for the purpose.