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Vitamin D in the cancer patient

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Abstract

Purpose of review—To briefly review recent work within the vitamin D and cancer field, whereas also providing context relating how these findings may impact clinical care and future research efforts.

Recent findings—Vitamin D has now been convincingly shown both *in vitro* and in preclinical animal models to alter the differentiation, proliferation, and apoptosis of cancer cells. Whether vitamin D prevents cancer in humans or limits cancer progression, however, remain open questions. Epidemiologic and observational data relating circulating 25(OH)D levels and cancer risk suggest an inverse relationship for most cancers including breast, colorectal, leukemia and lymphoma, and prostate, although for each malignancy there also exist studies that have failed to demonstrate such an inverse relationship. Likewise, a more recent report failed to confirm a previously reported association of increased pancreatic cancer risk in patients with higher 25(OH)D levels. A large prospective study in which patients aged at least 50 years receive 2000 IU vitamin D3 daily for 5 years, with cancer as a primary endpoint, has recently been launched.

Summary—Although much effort has attempted to delineate a causal relationship between vitamin D and a wide array of human cancers, we await large-scale randomized controlled trial data for definitive answers.

Keywords

cancer; observational data; risk; vitamin D

INTRODUCTION

The central role of vitamin D in calcium homeostasis and skeletal health has been recognized for nearly 100 years. With the recent realization that hypovitaminosis D is much more pervasive than previously thought, few topics have engendered as much interest in the popular and medical press as the potential role of vitamin D as an easily modifiable mediator of a broad array of pathologic conditions, including multiple types of cancer. Herein, we will briefly review recent work within the vitamin D and cancer field, and provide context as to how these findings may impact current clinical care and future research efforts.

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Conflicts of interest

The authors declare no competing financial interests.

OVERVIEW OF VITAMIN D METABOLISM

Vitamin D exists as two biologically equivalent forms. Vitamin D₂ (ergocalciferol) is obtained from dietary vegetable sources or oral supplements; vitamin D₃ (cholecalciferol) is obtained either from skin exposure to ultraviolet B (UVB) irradiation, or via ingestion of oily fish, fortified foods, or oral supplements. Following intestinal absorption, both vitamin D₂ and D₃ are metabolized in the liver to 25-hydroxyvitamin D [25(OH)D], the storage form of vitamin D measured clinically to assess for vitamin D sufficiency. 25(OH)D undergoes subsequent conversion in the kidney and other tissues that possess 1- α -hydroxylase enzymatic activity to 1,25-dihydroxyvitamin D [1,25(OH)₂D], the active form of vitamin D. Notably, circulating 1,25(OH)₂D levels are approximately 1000-fold lower than 25(OH)D levels.

BREAST CANCER

Breast epithelial cells contain the enzymatic machinery to locally regulate 1,25(OH)₂D levels, as well as vitamin D receptors (VDRs). Although some (but not all) previous epidemiologic studies have demonstrated inverse relationships between circulating 25(OH)D levels and breast cancer development, recurrence risk, and mortality, studies that have examined vitamin D supplementation on breast cancer risk have provided inconsistent results.

A recent subset analysis of the Women's Health Initiative (WHI) study, in which 36 282 postmenopausal women in the USA were randomly assigned to receive either daily 1000 mg elemental calcium carbonate and 400 IU of vitamin D₃ or placebo, was only suggestive of a decrease in breast cancer risk in the treated patients [1]. In a recent case-control study that included 1585 breast cancer cases and 2940 controls, there was no association between serum 25(OH)D levels and overall breast cancer risk, although an inverse relation was observed in younger (age < 45 years) women and those premenopausal at enrollment, suggesting a potential protective effect of vitamin D in younger women [2]. Among women with breast cancer followed in the Women's Healthy Eating and Living Study, there was no relationship between serum 25(OH)D levels and breast cancer recurrence [3]. In the health, eating, activity, and lifestyle study, in which 25(OH)D levels were assessed in 585 breast cancer survivors followed for a median of 9.2 years, higher 25(OH)D levels were associated with overall but not breast cancer-specific survival, although multivariate adjustment attenuated the association [4].

Several recent studies have also examined the role of vitamin D in the skeletal response to breast cancer therapies, particularly in women receiving aromatase inhibitor therapy, in whom hypovitaminosis D is common [5]. A randomized, placebo-controlled, double-blinded study of the aromatase inhibitor exemestane as primary prevention of breast cancer in postmenopausal women found that 2 years of exemestane treatment significantly decreased bone mineral density at all skeletal sites examined despite calcium and vitamin D supplementation [6*]. The B-ABLE prospective cohort study of women receiving aromatase inhibitor therapy for early breast cancer, however, found that women with 25(OH)D levels at least 40 ng/ml had significantly less bone loss at the lumbar spine at 1 year compared with those with levels less than 30 ng/ml ($P = 0.005$) [7*]. Recent guidelines for the management of aromatase inhibitor-associated bone loss in postmenopausal women recommend inclusion of vitamin D, in addition to calcium and bone-targeted therapy, in the pharmacologic management plan in order to limit bone loss and reduce fracture risk [8].

Based on these above data, it remains unclear at present whether there exist optimal circulating 25(OH)D levels to reduce either the risk of breast cancer development or the risk

of recurrence. Given the importance of vitamin D in maintaining skeletal health, and the known detrimental effects of chemotherapeutics (including aromatase inhibitor therapies) on bone, assessment for and treatment of hypovitaminosis D in patients diagnosed with breast cancer and undergoing aromatase inhibitor therapy seems clinically prudent.

COLORECTAL CANCER

Like breast epithelial cells, cells of the colorectal tract contain both VDRs and the 1- α -hydroxylase needed to convert 25(OH)D to 1,25(OH) $_2$ D. Furthermore, 1,25(OH) $_2$ D has been shown to modulate colorectal cancer cell differentiation and proliferation *in vitro*.

A recent study reported on the association between circulating 25(OH)D and 1,25(OH) $_2$ D levels and colorectal cancer both in the Physician's Health Study, and in a meta-analysis of eight additional prospective studies [9]. Comparison of patients in the top 25(OH)D quartile to those in the bottom quartile demonstrated a significant inverse relation for colorectal cancer [odds ratio (OR) 0.66; 95% confidence interval (CI) 0.54–0.81], which was stronger for rectal (OR 0.5; 95% CI 0.28–0.88) compared with colon (OR 0.77; 95% CI 0.56–1.07) cancer. Consistent with this finding, a recent large nested case–control observational study of 1248 cases of incident colorectal cancer from Western Europe included as part of the larger EPIC study demonstrated a significant linear inverse relationship between 25(OH)D levels and risk for colorectal cancer development, with patients in the highest quintile having a 40% decreased risk when compared with those in the lowest quintile [10]. Other studies that have examined polymorphic variants of the VDR suggest that VDR polymorphisms may influence colorectal cancer risk [11], but not likelihood of adenoma recurrence [12].

In a recent randomized, double-blinded, placebo-controlled trial of patients with a previously confirmed colorectal adenoma, 6 months of daily treatment with supplemental calcium and/or vitamin D3 (800 IU) versus placebo induced changes in the expression of enzymes of vitamin D metabolism in the normal mucosa, although whether these changes impact risk for progression to colo-rectal cancer was not assessed [13].

Although both preclinical and observational studies suggest that vitamin D may be important in colorectal cancer, to date there remain scant data from randomized clinical trials [14] on how vitamin D supplementation affects the risk for colorectal cancer development or disease responsiveness following diagnosis. Thus, at present, the routine recommendation of vitamin D assessment and/or treatment for these indications is premature.

HEMATOLOGIC MALIGNANCIES

Although the majority of studies has examined the role of vitamin D in solid tumors, several recent studies have begun to examine the relationship between circulating vitamin D levels and hematologic malignancies.

Leukemia

A recent prospective cohort study of 390 patients with newly diagnosed chronic lymphocytic leukemia evaluated the relationship between 25(OH)D levels and both overall survival (OS) and time-to-treatment (TTT), and compared these findings with a separate (validation) cohort of previously untreated patients from an observational study [15]. At a median follow-up of 3 years, patients with 25(OH)D levels deemed insufficient had reduced OS (hazard ratio 2.39; $P = 0.01$) and TTT (hazard ratio 1.66; $P < 0.01$), results that were confirmed in the validation cohort.

Lymphoma

Similar findings have now also been shown in non-Hodgkin lymphoma (NHL). A recent prospective cohort study of 983 newly diagnosed patients (mean age 62 year at diagnosis) with median follow-up of 34.8 months demonstrated that patients with 25(OH)D insufficiency had both inferior event-free-survival(hazard ratio 1.41; 95% CI 0.98–2.04) and OS (hazard ratio 1.99; 95% CI 1.27–3.13 [16]. A subsequent study of NHL patients by the same group, in which self-reported sun exposure was used as a surrogate for 25(OH)D levels, suggested that increased sun exposure during the teenage years was associated with significantly decreased NHL risk, an effect which was modified by germline polymorphic variation in the VDR [17].

Multiple myeloma – in a study of 148 patient with newly diagnosed multiple myeloma, serum vitamin D levels were correlated with International Staging System categorization, with 16% of patients in stage 1, 20% in stage 2, and 37% in Stage 3 having 25(OH)D levels in the deficient range, although 25(OH)D levels were not predictive of myeloma-associated bone disease [18]. Similarly high rates of vitamin D deficiency were seen in an independent cohort of myeloma patients [19]. Again, however, there was no significant correlation between vitamin D status and bone disease; further, when assessed at 1 year, vitamin D repletion was not found to impact the risk for myeloma relapse, bone disease progression, or survival.

Although thought-provoking, the above observational studies do not provide the prospective rigor needed to allow one to recommend for the routine assessment of the 25(OH)D levels in patients with leukemia, lymphoma, or myeloma. Whether vitamin D replacement improves survival in patients with leukemia and lymphoma, however, is a subject of active clinical investigation (clinicaltrials.gov –NCT01787409).

PANCREATIC CANCER

Like the other tissue types detailed, pancreatic islet cells have both 1- α -hydroxylase activity and express the VDR. Unlike epidemiologic/observational studies of other cancer types that have tended to show inverse associations between 25(OH)D levels and cancer risks, a nested case-control study of Finnish male smokers found a nearly three-fold (OR 2.92; 95% CI 1.56–5.48) increased risk of pancreatic cancer in patients in the highest compared with lowest quintile of 25(OH)D [20]. However, more recent work by this same research group, using a different large cohort of men and women aged 55–74 years at inception, failed to confirm this positive association (OR 1.45; CI 0.66–3.15; $P = 0.49$) [21].

Given these conflicting results and the paucity of other data, there is no current value in making recommendations either for or against vitamin D assessment and/or treatment in relation to pancreatic cancer.

PROSTATE CANCER

Prostate cancer cells also express both vitamin D metabolizing enzymes and the VDR, and *in vitro* studies have consistently shown that 1,25(OH)₂D affects both prostate cell differentiation and proliferation. Retrospective epidemiologic work has suggested an inverse relationship between circulating 25(OH)D levels and prostate cancer at lower levels, although at least one study demonstrated that high 25(OH)D levels may paradoxically be associated with increased prostate cancer risk [22].

In the Prostate Cancer Prevention Trial, in which nutritional risk factors for prostate cancer were assessed in 9559 men in the USA and Canada, no nutrient or supplement (including

vitamin D) was associated with overall prostate cancer risk [23]. This is consistent with another recent prospective nested case–control study in which 25(OH)D levels were not associated with overall prostate cancer risk; in that same study, however, comparison of the highest 25(OH)D quartile to the lowest quartile revealed a 57% reduction (OR 0.43; 95% CI 0.24–0.76) in lethal prostate cancer risk [24]. In contrast, a recent study of 943 men from Sweden suggested a weak positive nonlinear association between 25(OH)D levels and prostate cancer risk [25], a result not seen in another recent study including 1447 men with prostate cancer [26]. Reasons for discrepancies in findings between the studies are not readily evident, but are consistent with the prior variability seen in observational studies relating vitamin D and prostate cancer.

In study of 52 men with low-risk prostate cancer, 1 year of daily supplementation with 4000 IU of vitamin D3 did not impact prostate specific antigen (PSA) levels, but was associated with a decrease in the number of biopsy-positive cores in over half of the evaluable patients [27]. Consistent with this, a randomized double-blind trial of 66 men treated with oral vitamin D3 prior to radical prostatectomy demonstrated that daily treatment with 40 000 IU of vitamin D3 raised prostate tissue 1,25(OH)₂D levels, which were shown to be inversely correlated with prostate tissue levels of the cellular proliferation marker Ki67 [28]. In contrast, a small trial of 18 men with castration-resistant prostate cancer failed to demonstrate an effect of weekly intra-venous 1,25(OH)₂D in combination with dexamethasone on either clinical or PSA response [29], whereas the addition of 1,25(OH)₂D to docetaxel in a randomized open-label phase III trial of 953 men with castration-resistant prostate cancer decreased OS when compared with the arm receiving docetaxel and prednisone [30].

Thus, like previous malignancies already discussed, the lack of long-term well controlled randomized trials of vitamin D in prostate cancer limits our current knowledge of whether there exist optimal 25(OH)D levels to reduce the risk of prostate cancer development or recurrence. It is noteworthy, however, that like women who undergo accelerated aromatase inhibitor-induced bone loss, men undergoing androgen deprivation therapy (ADT) for prostate cancer similarly lose bone rapidly [31]. Further, given that prostate cancer prevalence increase with age, many men with prostate cancer already have underlying (and often unrecognized) osteopenia or osteoporosis even prior to initiation of ADT, thus, further increasing their fracture risk. Accordingly, although no recent trials have examined the effect of vitamin D in skeletal health in men with prostate cancer, given the well recognized role of vitamin D in bone metabolism and the known negative effects of ADT on the skeleton, the routine assessment for and treatment of hypovitaminosis D in patients with prostate cancer seems clinically prudent.

SKIN CANCER

The causal relationship between sunlight (ultraviolet light) exposure and both melanoma and non-melanoma skin cancers is well recognized. However, the majority of previtamin D in humans is produced via skin exposure to UVB irradiation, and like the other cancers described, an inverse relationship between 25(OH)D levels and malignant melanoma has been described [32].

A recent study prospectively evaluated the association of incident squamous cell carcinoma (SCC) or basal cell carcinoma (BCC) and 25(OH)D levels in 4641 women as part of the Nurse's Health Study. Consistent with increased sun exposure as the basis both for increased 25(OH)D levels and skin cancer risk, a positive association was seen between 25(OH)D levels and both SCC (OR 3.77; 95% CI 1.70–8.36) and BCC (OR 2.07; 95% CI 1.52–2.80) when women in the highest quartile were compared with those in the lowest [33].

Given that sun exposure is the primary risk factor for the development of both melanoma and nonmelanoma skin cancer, and given our present belief that vitamin D obtained orally is biologically equivalent to that obtained through skin exposure to UVB irradiation, it seems prudent to ensure adequate vitamin D intake primarily through oral sources, which are readily absorbed, inexpensive, and readily available.

CLINICAL TRIALS WITH VITAMIN D ANALOGUES

Multiple *in vitro* and animal model studies have examined vitamin D analogues, either alone or in combination with other chemotherapeutic agents, and demonstrated anticancer activity. Despite such preclinical findings, however, the results of human trials (Phase I and II) of vitamin D analogues across a variety of cancers, including prostate cancer [34], breast and colorectal cancer [35], and other solid tumors [36] have been disappointing for clinical efficacy. Few trials examining vitamin D analogues in cancer are ongoing.

VITAMIN D AND NEUROPSYCHIATRIC DISORDERS IN CANCER

Mood disorders, including depression, are highly prevalent in cancer patients and may have implications for treatment outcomes [37]. Although vitamin D deficiency has been implicated in depression, studies have shown mixed results. Vitamin D deficiency and insufficiency are common in depressed populations and may contribute to the onset and persistence of depression [38]. These association data and the observation that vitamin D receptors exist in both neuronal and glial cells including regions of the brain that have been implicated in the pathophysiology of depression [39] have spurred interest in pursuing vitamin D supplementation for the prevention or treatment of depression. A study on the effects of vitamin D supplementation on depression in overweight/obese patients without cancer found improvement of depression scores measured by the Beck Depression Inventory in patients randomized to 20 000 or 40 000 IU vitamin D weekly for 1 year [40]. However, longer term and larger scale studies of daily or intermittent high dose vitamin D failed to show an effect on multiple indicators of mood and well being [41,42]. As such, the inconsistent results of causal studies currently fail to clarify whether vitamin D is an antecedent risk factor or instead a consequence of lifestyle factors in depressed patients in general, and cancer patients in particular.

VITAMIN D AND NEUROPATHY

Even less clear is whether vitamin D is important for peripheral nerve health in cancer patients, in whom chemotherapy induced peripheral neuropathy (CIPN) can frequently be a treatment limiting factor. Reports of an association between vitamin D insufficiency and neuropathy in diabetes mellitus [43] and Sjogren's syndrome [44] contrast with a non-significant increase in the rate of neuropathy after chemotherapy in patients with vitamin D sufficiency versus insufficiency [45]. Although nutra-ceuticals cannot be recommended for prevention or treatment of CIPN at this time [46], the role of vitamin D in peripheral nerve health in cancer patients remains largely unexplored.

VITAMIN D – BEYOND CANCER

Although the exact role of vitamin D in cancer remains rather murky in nearly all instances in which the relationship has been examined, vitamin D has a well described role in the maintenance of optimal skeletal health, a critical component of care in the cancer patient which is all too frequently neglected. Although vitamin D deficiency is particularly common in the elderly, in whom limited sun exposure, reduced dietary intake, and renal impairment are common, it is important to recognize that vitamin D supplementation is both inexpensive

and easy to achieve as for most patients, with daily intake of approximately 800–1000 IU of vitamin D sufficient to prevent hypovitaminosis D.

CONCLUSION

Although beyond the scope of this review, currently available evidence strongly supports the role for vitamin D in the maintenance of skeletal health, which can be adversely impacted by cancer and related treatments. To date, nearly all studies which have examined the role of vitamin D in cancer have been plagued by methodological shortcomings, including in particular observational rather than interventional approaches, confounding by concurrent calcium supplementation, or dosing that would not achieve sufficient 25(OH)D levels as currently defined. Thus, at present, the role for vitamin D in either limiting cancer development or for assuaging aggressiveness following cancer diagnosis remains limited for all cancer types examined, owing to a dearth of well controlled, prospective, long-term randomized controlled trials with cancer as a primary outcome. Optimism remains that the recently launched VITamin D and Omega-3 Trial (VITAL) trial, a large randomized, double-blinded, placebo-controlled trial in which 20 000 patients aged at least 50 years will receive 2000 IU of vitamin D3 daily for 5 years and in which cancer is a primary prespecified endpoint [47^{***}], will enlighten the current muddled landscape.

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KEY POINTS

- Vitamin D deficiency is very common in cancer patients.
- Vitamin D impacts skeletal health, an often overlooked aspect of cancer care.
- Definitive evidence that vitamin D affects cancer risk or progression is lacking.
- A randomized prospective clinical trial with cancer as a primary endpoint is underway.