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Journal
Endocrine, 46(1)

ISSN
1355-008X

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Publication Date
2014-05-01

DOI
10.1007/s12020-013-0146-1

Peer reviewed

Published in final edited form as:
Endocrine. 2014 May ; 46(1): 29–38. doi:10.1007/s12020-013-0146-1.

Vitamin D and Cancer The Promise not yet Fulfilled

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Abstract

The negative association of the latitude where people live and the incidence of non cutaneous cancer in that population in North America has been demonstrated in many studies for many types of cancer. Since the intensity of UVB exposure decreases with increasing latitude, and UVB exposure provides the mechanism for vitamin D production in the skin, the hypothesis that increased vitamin D provides protection against the development of cancer has been proposed. This hypothesis has been tested in a substantial number of prospective and case control studies and in a few randomized clinical trials (RTC) assessing whether either vitamin D intake or serum levels of 25 hydroxyvitamin D (25OHD) correlate (inversely) with cancer development. Most of the studies have focused on colorectal, breast, and prostate cancer. The results have been mixed. The most compelling data for a beneficial relationship between vitamin D intake or serum 25OHD levels and cancer have been obtained for colorectal cancer. The bulk of the evidence also favors a beneficial relationship for breast cancer, but the benefit of vitamin D for prostate and skin cancer in clinical populations has been difficult to demonstrate. RTCs in general have been flawed in execution or too small to provide compelling evidence one way or the other. In contrast, animal studies have been quite consistent in their demonstration that vitamin D and/or its active metabolite 1,25 dihydroxyvitamin D ($1,25(OH)_2D$) can prevent the development and/or treat a variety of cancers in a variety of animal models. Furthermore, $1,25(OH)_2D$ has been shown to impact a number of cellular mechanisms that would be expected to underlie its anticancer effects. Thus there is a dilemma animal and cellular studies strongly support a role for vitamin D in the prevention and treatment of cancer, but the clinical studies for most cancers have not yet delivered compelling evidence that the promise from preclinical studies has been fulfilled in the clinic.

Keywords

vitamin D; vitamin D receptor; CYP27B1; CYP24A1; cancer

Introduction

The relationship between cancer and vitamin D remains controversial. The expert panel of the Institute of Medicine (IOM), after reviewing the data, declared that the data were inconclusive as to whether vitamin D had a protective role in cancer. As will be discussed the clinical data are indeed mixed, and definitive evidence from randomized clinical trials is lacking. Given the lack of pharmaceutical support for a sufficiently large trial, such evidence may be difficult to obtain in the near future in the current funding environment. On the other hand studies with animal models of various cancers have uniformly found benefit for either vitamin D supplementation or administration of $1,25(OH)_2D$ and its analogs. Moreover, numerous studies primarily with cell lines have elucidated a wide number of mechanisms by which $1,25(OH)_2D$ potentially could exert its anti tumor effects. In this minireview I will examine the epidemiologic evidence supporting (or not) the beneficial relationship between

vitamin D and cancer, describe the types of animal studies that have demonstrated this beneficial effect, and review a number of mechanisms by which this beneficial effect might be exerted. Given that thousands of papers have been published on this subject, this mini-review cannot hope to be comprehensive. Indeed the focus will be on four types of cancer: colorectal (CRC), breast (BCa), prostate (PCa), and non melanoma skin cancer (NMSC). This choice is based on the substantial number of studies focused on these cancers, the fact that these are epithelial cancers and might be expected to have similar mechanisms leading to cancer and/or response to vitamin D, and that the cells of origin of these cancers have the enzymatic machinery to produce $1,25(OH)_2D$ (CYP27B1), to catabolize it (CYP24A1), and to respond to it (vitamin D receptor (VDR)). Other tumors share some or all of these characteristics, but space does not allow their inclusion in this mini review.

Epidemiologic studies

The inverse relationship between solar exposure and cancer mortality in North America was first noted by Apperly [1] in 1941. This concept was popularized and linked to vitamin D as the protective element by the Garland brothers [2] in 1980 in their epidemiologic studies with colon cancer. With the exception of skin cancer this inverse relationship between solar exposure and cancer has been reported for many types of cancer in many countries as recently reviewed [3]. Subsequent studies have focused on the association of vitamin D intake or serum levels of 25OHD, generally using case control and cohort studies. The results differ depending on tumor type. Selected meta-analyses examining the association of vitamin D intake and/or 25OHD levels for colorectal, breast, and prostate cancer are summarized in table 1.

a. Colorectal cancer (CRC)

Ma et al [4] performed metaanalyses of 9 studies (8 cohort, 1 nested case control 6466 subjects) evaluating the relationship of vitamin D intake and CRC and 9 studies (7 cohort, 2 case control 2764 cases, 3948 controls) evaluating serum levels of 25OHD and CRC published between 1993 and 2010 from a variety of countries. They found an overall relative risk of 0.88 (CI 0.8–0.96) comparing the highest versus the lowest categories of vitamin D intake and a relative risk of 0.67 (CI 0.54–0.80) for the highest to lowest 25OHD levels. A 10ng/ml increment of 25OHD was calculated to reduce the risk of CRC to 0.74(CI 0.63–0.89). A similar conclusion was reached by Yin et al [5] who performed a metaanalysis on an additional 10 studies of serum 25OHD levels and CRC. In their analysis they found a relative risk of 0.82 (CI 0.69–0.97) for a 20ng/ml increase in 25OHD. When dietary calcium was taken into account (higher calcium is better) the risk reduction was increased. Moreover, metaanalyses of studies focused on the relationship between dietary calcium and CRC have found significant reductions in both CRC incidence [6], [7] and adenoma recurrence [8]. Vitamin D intake was not controlled for in these analyses. A calcium level around 1200mg per day appears to be optimal [7] [8]. These metaanalyses confirm previous results from the American Cancer Society cohort study (120,000 men and women) [9] and the National Institutes of Health (16,000 participants) [10] demonstrating a beneficial effect of vitamin D intake at least for males [9] or 25OHD level [10] on CRC. On the other hand, in the Women's Health Initiative, 400IU vitamin D per day did not show protection against CRC [11]. However, this trial had a number of problems including poor compliance and the low amount of vitamin D used. Moreover, the concomitant administration of estrogen may have reduced the vitamin D effect [12]. Thus at least for CRC there is a reasonably consistent set of data supporting the protective effect of vitamin D (and calcium) with respect to CRC incidence.

b. Breast cancer (BCa)

Shao et al. [13] reviewed 6 case control and 6 cohort studies evaluating the relationship of vitamin D intake on BCa development. In the largest case control study [14] a 34% decrease in BCa was found in those ingesting the highest level of vitamin D (>194 IU/day) versus those ingesting the lowest level (<60 IU/day). However, other smaller studies did not show this relationship. The largest cohort studies [15],[16] (Nurses Health Study with 88,891 participants and Womens Health Study with 31,487 participants) showed a reduction in risk (RR 0.72, CI 0.55–0.94 and 0.65, CI 0.42–1.00, respectively) but only in the premenopausal women. Of the 8 case control studies examining the association of serum 25OHD levels with BCa development, 5 showed a significantly lower relative risk. A metaanalysis of these studies demonstrated an OR of 0.55 (CI 0.38–0.80) comparing the highest quintile of 25OHD levels to the lowest [17]. In general these studies did not evaluate premenopausal and postmenopausal women separately. Chlebowski [18] performed a similar review of 10 case control and 10 cohort studies with respect to vitamin D intake and BCa and 4 case control and 6 nested case control studies with respect to 25OHD levels and BCa. A metaanalysis of 5 of the case control studies examining vitamin D intake failed to show a significant effect of vitamin D overall, but when only the premenopausal/perimenopausal women were included in the analysis a significant negative association between increased intake and BCa incidence was found (RR 0.83, CI 0.73–0.95) [17]. Of the 6 nested case control studies assessing the relationship of serum 25OHD and BCa only one study showed a significant negative association between high 25OHD levels and incidence of BCa, although 1 other study was close ((P=0.06). In a separate metaanalysis by Gandini et al. [19] a RR of 0.89 (0.82–−0.98) for a 10ng/ml increase in 25OHD was found when all studies were included and 0.83 (0.79–0.87) when only case control studies were pooled. As for CRC, the Womens Health Initiative did not show a protective role for vitamin D in breast cancer. Thus the epidemiologic data tend to support a protective role for vitamin D and BCa, but the data are not as compelling or consistent as for CRC.

c. Prostate cancer

Van der Rhee [3] summarized 14 prospective trials (not RTCs) examining the association between 25OHD levels and the development of prostate cancer. Eleven studies showed no association, and one study [20] showed a positive association with prostate cancer aggressiveness, although this was not seen in other studies [21]. A metaanalysis of 6 cohort/nested case control studies (8722 cases) examining the association of dietary vitamin D intake to PCa found a relative risk of 1.14 (CI 0.99–1.31) for an increase in dietary vitamin D of 1000 IU [21]. Similarly, a metaanalysis of 14 cohort/nest case control studies including 4353 cases examining the association of serum 25OHD and PCa found a relative risk of 1.04 (CI 0.99–1.1) for a 10ng/ml increase in 25OHD for all prostate cancers [21]. Likewise, no association was found for serum $1,25(OH)_2D$ levels [21]. Similar negative results were observed in the metaanalysis by Gandini et al. [19]. Although an initial clinical trial (ASCENT I) with high dose $1,25(OH)_2D$ and docetaxol seemed to show promise in the treatment of castration resistance PCa, this initial success could not be repeated in a larger trial (ASCENT II) potentially flawed by a change in the docetaxol only arm of the study [22]. Thus the clinical evidence weighs against vitamin D being beneficial in the prevention/treatment of prostate cancer.

d. Non melanoma skin cancer (NMSC)

Skin cancer is by far the most common cancer afflicting humankind. Over 1 million skin cancers occur annually in the United States, 80% of which are basal cell carcinomas (BCC), 16% squamous cell carcinomas (SCC), and 4% melanomas. Because UVB is the major etiologic agent for NMSC but is also the major means by which the body makes vitamin D, it has been difficult to separate out the beneficial effects of vitamin D on NMSC from the

deleterious effects of UVB exposure. Moreover, studies of the epidemiology of BCCs and SCCs are difficult in general to perform because most national registries exclude them, leaving no easily accessible database with which to track the development of these cancers. That said, a few epidemiologic studies have been published. An older study on vitamin D intake found no association between vitamin D and BCC risk [23]. However, some clinical studies of BCC patients show a potential beneficial role for vitamin D. In a nested case control study of 178 elderly men with NMSC compared to 930 without skin cancer enrolled in the Osteoporotic Fractures in Men (MrOS) study, men with the highest baseline serum 25OHD levels (30 ng/mL) had 47% lower odds of NMSC (CI 0.3–0.93) compared to those with the lowest baseline 25OHD levels [24]. On the other hand, a case control study from the Kaiser population found that higher prediagnostic 25(OH)D levels were associated with an increased risk of BCC [25] as did a subsequent study by Eide et al [26]. To date, there are limited epidemiologic studies on the effect of vitamin D or its metabolites on SCC prevention or treatment in humans. Therefore, although the animal studies are suggestive, additional work is needed to assess the suitability of topical or oral vitamin D3 for chemoprevention of either BCC or SCC in humans.

Animal studies

A number of animal studies have demonstrated an increased susceptibility to cancer in states of severe vitamin D deficiency or in disruption of vitamin D signaling by deletion of VDR. Moreover, vitamin D and/or VDR agonists (1,25(OH)2D and its analogs) have demonstrated effectiveness in preventing or treating cancers in a variety of models. A summary of selected studies examining the role of vitamin D signaling in the prevention or treatment of colorectal, breast and prostate cancer models is shown in table 2. Examples follow.

a. Colorectal cancer

Mice placed on a Western diet low in calcium and vitamin D spontaneously develop CRC that can be inhibited by supplementing the diet with calcium and vitamin D [27]. Chronic inflammation is a cause of CRC in both mice and humans. When VDR null mice are bred with mice lacking IL-10, a severe form of inflammatory bowel disease develops predisposing to CRC [28]. Similarly VDR null mice are particularly sensitive to the inflammatory effects of dextran sulfate sodium (DSS) [29]. Mice treated with the carcinogen azoxymethane (AOM) and DSS develop preneoplastic lesions that can be at least partially prevented with the administration of vitamin D or its active metabolites [30]. As will be discussed further when I discuss vitamin D regulated mechanisms for tumor development, activation of the wnt/β-catenin pathway is the major cause of CRC. A mouse model in which one of the regulators of this pathway, adenomatous polyposis coli (APC), has been mutated (APC^{min}) develop tumors spontaneously. Mice with this mutation develop tumors much faster on a Western diet [31], on a vitamin D deficient diet [32], or when bred with VDR null mice [33]. The addition of $1,25(OH)_2D$ to a vitamin D replete diet can reduce the tumor burden due to dietary deficiency in the APC^{min} mouse [32],[34].

b. Breast cancer

The carcinogen dimethylbenzanthracene (DMBA) causes breast cancers in rodents. The number of tumors is increased when the rats are fed a Western diet as is the case for CRC mentioned above [35]. Likewise, VDR null mice develop more tumors when treated with DMBA [36] or crossed into a MMTV-neu background [37] than do control mice. VDR agonists can prevent the growth of breast cancer xenografts whether ER negative or positive [38]. Bone metastases can be developed in mice using intracardiac injections of tumor cells. Dietary vitamin D deficiency enhances the growth of these metastases [39], and VDR agonists can reduce their growth [40].

c. Prostate cancer

Xenografts are commonly used models for evaluating prostate cancer. Vitamin D analogs can inhibit the growth of both androgen dependent and independent tumors in these models [41]. Similar to the method used to produce bone metastases, the growth of PC3 prostate cancer cells in bone was accelerated in mice on a vitamin D deficient diet [42]. The Nkx3.1;Pten mouse is a transgenic model that progresses from the stage of intraepithelial neoplasia (PIN) to frank adenocarcinoma. $1,25(OH)_2D$ slows the development of PIN [43]. On the other hand when the more aggressive transgenic model, LPB-Tag, is bred with VDR null mice, tumors developed more rapidly [43]. The TRAMP model (transgenic adenocarcinoma of mouse prostate) is also widely used for prostate cancer studies. High doses of $1,25(OH)_2D$ suppress the development of this tumor [44]. When bred with VDR null mice, these tumors develop enlarged vessels, signifying increased angiogenesis, that presumably contribute to their growth [45].

d. Non melanoma skin cancer

The two most common ways of inducing NMSC in animals are by chemical induction as with DMBA topically or orally often followed by repeated topical application of phorbol esters and by chronic exposure to UVB. When Zinser et al. [46] treated VDR null mice orally with DMBA, they observed that nearly all the VDR null mice developed skin tumors, mostly papillomas, whereas none of the wildtype controls did. These results have been confirmed by other groups including ourselves using topical administration of DMBA/phorbol esters [47] or UVB [48],[49]. In the latter case, SCC was the predominant cancer formed. Surprisingly, mice lacking the ability to produce $1,25(OH)_2D$ (CYP27B1 null) do not show increased susceptibility to tumor formation following either DMBA [48] or UVB [49]. Topical $1,25(OH)_2D$ is protective of some of the early effects of UVB [50], but its role in preventing NMSC development has not yet been shown. These results suggest that the VDR independent of its ligand $1,25(OH)_2D$ is exerting a protective effect against tumor formation, a conclusion that is only partially true as will be discussed when the mechanisms by which VDR and its agonists work to prevent tumor formation are explored in the following section.

Mechanisms by which vitamin D protects against tumor formation

$1,25(OH)_2D$ regulates the expression of hundreds if not thousands of genes, both those encoding mRNAs that are translated into proteins and those encoding RNAs that are not (miRNAs, lncRNAs). Indeed, regulation by $1,25(OH)_2D$ of many of the pathways discussed below were initially discovered using unbiased approaches such as microarrays. Different cell types have different profiles of genes that are regulated by $1,25(OH)_2D$, so generalizations are difficult to make. That said, there are a number of pathways that contribute to vitamin D regulation of cancer growth and metastasis that are found in several if not all the cancers discussed above. Thus, this section will be organized by mechanism and not by cell type. The mechanisms discussed below are summarized in table 3.

a. Antiproliferation

$1,25(OH)_2D$ is antiproliferative for most cells in which this has been examined. $1,25(OH)_2D$ typically causes arrest at the Go/G1 and/or G1/S transitions in the cell cycle. This is associated with a decrease in cyclins (varies with cell type) and an increase in the inhibitors of the cyclin dependent kinases (CDK) such as $p21^{cip1}$ and $p27^{kip1}$ again in a cell specific fashion [51],[52]. The effect of $1,25(OH)_2D$ on $p27^{kip1}$ levels has been shown to occur by decreasing its degradation by reducing its phosphorylation [53] or through miR181s [54]. The effect on $p21^{cip1}$ is more direct. Of interest is the observation by Liu et al.[55] that the antiproliferative actions of $1,25(OH)_2D$ and its induction of $p21^{cip1}$ in CRC cell lines is

dependent on the expression of the calcium sensing receptor, perhaps explaining why the combination of vitamin D and calcium on CRC is more potent than either alone. Forkhead box O (FoxO) proteins are transcription factors that control proliferation. $1,25(OH)_2D$ promotes the interaction between several of the FoxOs with VDR and FoxO regulators such as Sirt1 and protein phosphatase 1. This serves to keep FoxO dephosphorylated and in the nucleus where it can suppress genes involved with proliferation [56]. The levels of other genes linked to proliferation such as Myc, Fos, and Jun are also decreased by $1,25(OH)_2D$ [57]. Insulin like growth factor (IGF) as its name implies promotes the growth of a number of tumors. $1,25(OH)_2D$ stimulates the expression of IGF binding protein 3 (IGFBP3), that binds IGF I and II, limiting their growth promoting effects [58],[59]. TGFβ2 is an antiproliferative factor in epithelial cells. $1,25(OH)_2D$ stimulates the expression of TGFβ2 as well as the TGFβ receptors in a number of cell types including breast and prostate cancer cells [60], [61], [62]. Hedgehog (HH) signaling promotes proliferation, and its overexpression is a major cause of BCC [63]. In the skin of VDR null mice the HH pathway is up regulated, whereas the expression of components of the pathway such as Shh and Gli1 is suppressed by $1,25(OH)_2D$ [49]. $1,25(OH)_2D$ inhibits EGF promotion of proliferation by targeting the EGF/EGFR complex to endosomes [64] and inhibiting the expression of EGFR [65]. As noted in the discussion of CRC, mutations in Apc leading to over activation of the wnt/β-catenin pathway are the cause of most CRC. The role of vitamin D signaling in CRC prevention and treatment with respect to its impact on the wnt/β-catenin pathway has recently been reviewed [66]. When β-catenin binds to TCF/LEF sites in the nucleus proliferation is stimulated. $1,25(OH)_2D$/VDR competes with TCF/LEF for binding to β-catenin. Indeed binding of β-catenin to VDR may promote differentiation. Moreover, $1,25(OH)_2D$/VDR stimulates the expression and translocation (with calcium) of E-cadherin to the cell membrane where it forms a complex with β-catenin and other catenins again promoting differentiation. A similar mechanism exists in the skin, contributing to the ability of vitamin D signaling to protect against skin cancer [67]. In both tissues, the ability of $1,25(OH)_2D$ to increase intracellular calcium contributes to these actions of $1,25(OH)_2D$ by increasing E-cadherin expression and reducing the induction of cyclin D1 [68]. In addition to its ability to limit β-catenin access to the nuclear TCF/LEF response elements, $1,25(OH)_2D$ can up regulate the wnt inhibitor dickkopf (DKK)-1 [69] while inhibiting the wnt activator DKK-4 [70].

b. Apoptosis

$1,25(OH)_2D$ promotes the apoptosis of a number of cell types [71],[72]. These actions are accompanied by increased expression of the pro apoptotic genes GOS2 (Go/G1 switch gene 2) [52] and Bax [73] with suppression of the pro-apoptotic genes Bcl2 and Bcl-X_L [73]. Other pro-apoptotic genes induced by $1,25(OH)_2D$ include DAP (death-associated protein)-3, CFKAR (caspase 8 apoptosis-related cysteine peptidase), FADD (Fas-associated death domain) and a number of caspases (eg. caspase 3, 4, 6, and 8) [61]. $1,25(OH)_2D$ sensitizes cells to apoptosis induced by reactive oxygen species (ROS) and cytokines (eg. TNF-α) through both caspase dependent and independent pathways [74],[75]. By promoting both calcium influx and release from intracellular stores $1,25(OH)_2D$ induces apoptosis by activating the calcium dependent μ-calpain and calcium/calpain dependent caspase 12 [76]. Normal cells are protected by the presence of the calcium binding protein $CaBP_{28k}$, that acts as a calcium buffer in cells and that is less abundant in a number of cancer cells [76]. By inducing PTEN (phosphatase and tensin homolog) $1,25(OH)_2D$ inhibits PI3K and so reduces Akt activation increasing Bax activity and so promoting apoptosis [72]. Finally, $1,25(OH)_2D$ has been shown to stimulate autophagy [77] in some cancer cells in part by inhibiting the anti-autophagy gene mTOR and increasing the levels of the pro-autophagy gene beclin-1.

c. DNA repair

The skin is exposed to DNA damage both by UVB that damages DNA directly [78] and by UVA that damages DNA through oxidative stress [79]. The latter is the major cause of DNA damage in tissues other than the skin. UVB induced DNA damage includes the formation of cyclobutane pyrimidine dimers (CPD) and pyrimidine (6-4)pyrimidone photoproducts (6-4PP). If these lesions are not repaired C to T or CC to TT mutations result, the UVB "signature" lesion [80]. Preventing DNA damage from producing DNA mutations is the role of DNA damage repair (DDR), operating through mechanisms involving damage recognition, repair and signal transduction. The epidermis of VDR null mice is slow to clear CPDs and 6,4PPs following UVB [49],[81]. Moreover, $1,25(OH)_2D$ topically applied protects the skin from UVB induced photodamage including increased clearance of CPDs, decreased apoptosis, increased survival, and increased expression of p53 [50]. Poly-ADP-ribose polymerase (PARP) is involved with DNA breaks, and is activated by UVB. $1,25(OH)_2D$ reduces PARP activity in keratinocytes [82]. In other tissues vitamin D deficiency is associated with increased frequency of chromosomal damage due to oxidative and other stresses [39]. In humans vitamin D deficiency is associated with increased levels of 8-OH-2′-deoxyguanosine (8-OHdG), a marker of oxidative DNA damage, whereas vitamin D supplementation reduces these levels [83]. Moll et al. [84] found that $1,25(OH)_2D$ induced two genes important for DDR: XPC (xeroderma pigmentosum complementation group C) and DDB2 (damage-specific DNA binding protein 2 also known as XPE). VDR agonists also induce the DNA repair protein GADD45 (growth arrest and DNA-damage inducible) [85]. Protection against oxidative DNA damage is mediated by a variety of $1,25(OH)_2D$ induced antioxidant enzymes including thioredoxin reductase 1 [60], superoxide dismutase [60], glucose-6 phosphate dehydrogenase [86], and glutathione peroxidase [52]. Oxidative DNA damage is increased in the colonic epithelium of VDR null mice [87] and reduced in the colons of humans given 800 IU vitamin D as daily supplements [83].

d. Prostaglandin metabolism

Prostaglandin (PG) production is associated with cancer growth and metastasis [88]. The enzymes responsible, cyclo-oxygenase (COX) 1 and 2 are induced by a variety of tumor promoters [89]. On the other hand $1,25(OH)_2D$ at least in some cancer cell lines suppresses COX2 expression synergistic with NSAIDs and that of PG receptors while increasing the expression of 15-PGDH (hydroxyprostaglandin dehydrogenase 15-NAD), the enzyme that inactivates PGs [44].

e. Angiogenesis

Angiogenesis is critical for tumor growth and metastasis. VEGF (vascular endothelial growth factor) is the major stimulator of angiogenesis. VEGF production is generally induced in hypoxic states by HIF (hypoxia induced factor) 1α. $1,25(OH)_2D$ inhibits the proliferation of endothelial cells and reduces VEGF-induced endothelial cell sprouting and elongation resulting in tumors with decreased vascularization [90]. As noted earlier the TRAMP model in a VDR null background shows enlarged vessels and increased vessel volume along with increased expression of HIF-1, VEGF, and angiopoeitin [45]. $1,25(OH)_2D$ reduces hypoxia induced expression of VEGF in a variety of cancer cell lines [91] at least in part by reducing the expression of HIF-1.

f. Inhibition of metastasis

In addition to reducing the blood supply to the tumor, which also serves as a conduit for metastasis, $1,25(OH)_2D$ reduces the migration and invasion capacity of tumor cells [92]. This is facilitated by down regulation of the matrix protein laminin and its receptors α6 and

β4. The induction of E-cadherin discussed earlier reduces the ability of cancer cells to bind to endothelial cells, necessary for their ability to metastasize. $1,25(OH)_2D$ also reduces the expression of CEACAM1 (carcinoembryonic antigen-related cell adhesion molecule 1) by endothelial cells again reducing metastasis [93]. Degradation of the matrix by enzymes produced by cancer cells facilitates their ability to metastasize. $1,25(OH)_2D$ limits the activity of matrix metalloproteinases and cathepsins by inducing their inhibitors [94].

Mechanisms by which cancer blocks vitamin D action

A number of cancers no longer express VDR [95]. The transcription factors Snail 1 and 2 are expressed in CRC and other cancers, and they inhibit VDR expression [96]. Wildtype p53 increases expression of VDR, but mutant p53 suppresses it and blocks its function [97]. miR125b, increased in some cancer cell lines, inhibits VDR expression [98]. CYP27B1 expression, while generally expressed in the early stages of tumor development, is often lost as the cancer becomes more aggressive [99], whereas the levels of CYP24A1 may remain elevated [100], effectively reducing the levels of $1,25(OH)_2D$ in the tumor.

Summary and Future Directions

The promise of vitamin D in the prevention and treatment of cancer is at least 33 years in the making. Most if not all normal cells and most tumor cells at least in their early stages of development express the VDR. Moreover, many normal cells and the tumors from which they originate express CYP27B1, the enzyme producing $1,25(OH)_2D$. Thus by providing these tumors with 25OHD, the substrate for CYP27B1, which is readily achieved in vivo with vitamin D either through the natural process of vitamin D production in the skin or by supplementation of the diet, it should be possible to prevent or control most tumors expressing VDR and CYP27B1. However, as reviewed here this has best been achieved for CRC and to some extent for BCa, but for PCa and NMSC the efforts have been less successful. However, the compelling data from animal studies and the numerous potential mechanisms elucidated by cell based studies indicate that the promise of vitamin D and/or its active metabolites/analogs in the management of cancer remains intact. We need bigger studies and better study designs to determine whether the promise will be realized. Meanwhile the IOM recommendations including a safe range of vitamin D intake from 600–4000IU per day to achieve 25OHD levels from 20–50ng/ml (50–125nM) are reasonable and are likely broad enough to provide at least some protection against malignancy when and if that is clearly demonstrated. Unfortunately, much of the world's population does not even achieve the lower end of this range. Thus future directions include developing those long term large RTCs that will help determine optimal 25OHD levels for the prevention of malignancy, RTCs addressing the role of vitamin D supplementation with other forms of cancer treatment with attention focused on those pathways regulated by $1,25(OH)_2D$ that can serve as targets in various malignancies, and finally ensuring that vitamin D insufficiency is recognized for the world wide problem that it is and treated appropriately.

Acknowledgments

I appreciate the administrative assistance of Aaminah Khan and Vicky Lee and financial support from NIH RO1 AR050023, DOD CA1110338, and VA Merit Review

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Table 1
Meta-analyses of human epidemiologic studies

The meta-analyses of colorectal cancer by Ma et al (4) pooled the results from 9 prospective trials with respect to diet and an additional 9 studies with respect to 25OHD levels. There were approximately 1 million participants including 6,466 cases in the dietary study and 2,767 cases and 3.948 controls in the 25OHD level studies. Vitamin D intake and serum 25OHD levels were generally divided into quartiles or quintiles (one was reported in deciles) with relative risk determined between the highest and lowest category. Vitamin D intake was reported in mg/d, and serum 25OHD levels in ng/ml. The meta-analysis by Yin et al. (5) included 10 studies focused on serum 25OHD levels and colorectal cancer risk. It included 3539 cases and 4115 controls. The 25OHD levels, reported in ng/ml, were divided into quartiles or quintiles, and the relative risk reported for the highest level compared to the lowest level. The meta-analyses by Chen et al (12) included 11 studies (5 case-control, 6 cohort) examining the relationship of vitamin D intake to breast cancer and 7 studies (4 case-control, 3 nest case-control) examining the relationship of 25OHD levels to breast cancer. Vitamin D intake was reported in IU/day or mg/day, serum 25OHD levels in nM. The results were reported in quartiles or quintiles with relative risk determined between the lowest and highest levels. The meta-analyses by Gandini et al. (19) included 10 studies (5 case-control, 1 cohort, 4 nested case-control) with 6,175 cases examining the relationship of serum 25OHD levels (reported in ng/ml) to breast cancer and 11 cohort or nested case-control studies with 3,956 cases examining the relationship of serum 25OHD levels to prostate cancer. In most of the studies the results were reported in tertiles, quartiles, or quintiles with comparisons between the lowest and highest groups, although some studies compared results of those above or below the median. The Gilbert et al. (21) meta-analyses included 13 studies of dietary vitamin D intake and 14 studies of serum 25OHD levels and prostate cancer, including several studies including aggressive prostate cancer. In the dietary meta-analysis there were 8,722 total prostate cancer cases including 3,046 aggressive prostate cancer cases. In the serum 25OHD meta-analysis there were a total of 4,353 prostate cancer cases including 871 aggressive prostate cancer cases. Dietary vitamin D intakes were reported in IU/day; serum 25OHD levels in ng/ml, which for nearly all studies were divided into quartiles or quintiles. Relative risks were reported for each quartile or quintile, and overall relative risk given in this table for a 1000IU increase in vitamin D or 10ng/ml increase in serum 25OHD.

Cancer	Author	n Studies/Analysis	Pooled Relative Risks (RR)
A. Colorectal	Ma et al.[4]	9	0.88 (0.8–0.96) Vit D Intake
			0.67 (0.54–0.80) 250HD levels
	Yin et al.[5]	10	0.82 (0.69–0.97) 250HD levels
B. Breast	Chen et al [12]	11	0.91 (0.85–0.97) Vit D intake
		8	0.55 (0.38–0.80) 250HD levels
	Gandini et al [19]	10	0.83 (0.79–0.87)[a] case control (5) 250HD levels
			0.97 (0.92–1.03)[b] prospective (5)
C. Prostate	Gandini et al [19]	11	0.99 (0.95–1.03) 250HD levels
	Gilbert et al [21]	13	1.14 (0.99–1.31) Vit D Intake
		14	1.04 (0.99–1.10) 250HD levels

Table 2

Animal Studies

Cancer	Author	Study Design	Results
A. Colorectal	Newark et al[27]	Western Diet	Ca+ D prevents
	Murillo et al[30]	Chemical induced	D prevents
	Yang et al [31]	APC^{min} + Western Diet	Ca+ D prevents
	Xu et al[32]	APCmin + D Deficient Diet	D+1,25$(OH)_2$D prevents
	Zheng et al[33]	APC^{min} in VDRKO	↑ cancers
	Huerta et al[34]	APC^{min} + D Deficient Diet	1,25$(OH)_2$ D prevents
B. Breast	Lipkin et al[35]	DMBA + Western Diet	Ca+ D prevents
	Zinser et al[36]	DMBA + VDRKO	↑ cancers
	Zinser et al[37]	MMTV-neu + VDRKO	↑ cancers
	VanWeelden at al[38]	MCF-7 xenografts	EB1089 ↓ growth
	Ooi et al[39]	Tumor inspections	D deficiency ↑
	El Abdaimi et al[40]	Xenograft breast cancer	EB1089 ↓ growth
C. Prostate	Bhatia et al[41]	Xenograft prostate cancer	EB1089 ↓ growth and mets
	Zheng et al[42]	PC3 cells in bone	Deficiency ↑ growth
	Mordan-McCombs et al[43]	LPB-tag model	1,25(OH)2 D ↓ progression
	Krishnan et al[44]	TRAMP model	1,25(OH)2 D ↓ growth
	Chung et al[45]	TRAMP model +VDRKO	↑ angiogenesis

Table 3

Mechanisms of Vitamin D tumor Suppression

Cancer	Author
A. Antiproliferation	1. Arrest of cell cycle: Go/G1 and G1/S
	2. Dephosphorylation of FOXO
	3. ↓ levels of myc, fos, jun
	4. ↓ activity of growth factors: IGF-1, IHH, EGF
	5. ↑ activity of TGFβ
	6. ↓ activity wnt/β-catenin signaling
B. Apoptosis	1. ↑ expression GOS 2 and Bax, ↓expression Bc12 and Bc1-XL
	2. ↑ expression DAP-3, CFKAR, FADD, ↓ caspases
	3. ↑ expression PTEN
	4. ↑ autophagy
C. DNA Repair	1. ↑ clearance of CPDs and 6,4-PPs (in UVB irradiated skin)
	2. ↓ oxidative DNA damage by ↑ expression antioxidant enzymes
	3. ↑ expression of DNA repair enzymes XPC and DDB2
D. Prostaglandin Metabolism	1. ↓ COX2 expression
	2. ↓ PG receptors
	3. ↑ 15-PDGH expression
E. Angiogenesis	1. ↓ proliferation of endothelial cells
	2. ↓ VEGF expression
F. Metastasis	1. ↓ cell migration and invasion capacity
	2. ↓ expression of laminin and its receptors
	3. ↑ expression of E-cadherin
	4. ↓ expression of CEACAMI