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CANCER (MF LEITZMANN, SECTION EDITOR)

Vitamin D_3 from Ultraviolet-B Exposure or Oral Intake in Relation to Cancer Incidence and Mortality

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Abstract

Purpose of Review This review summarizes the understanding of vitamin D_3's role in reducing risk of cancer incidence and mortality.

Recent Findings Recent randomized clinical trials and observational studies of participants who took part in vitamin D_3 supplementation studies provide increasing evidence that concentrations of serum 25-hydroxyvitamin D_3 [25(OH)D_3] up to ~ 60 ng/ml are inversely correlated with all cancer and some specific cancers' incidence and death, with a stronger effect on survival and death than on incidence. Mechanisms linking vitamin D_3 to effects on cellular proliferation, anti-angiogenesis, and anti-metastasis continue to be found.

Summary Vitamin D_3 reduces cancer risk causally. Maintaining 25(OH)D_3 in the range of 40–60 ng/ml reduces the risk of many cancers. Raising 25(OH)D_3 concentrations after diagnosis to that range increases survival rates and could significantly reduce the global burden of cancer incidence and death.

Keywords Vitamin D · Vitamin D deficiency · Cancer prevention · Mendelian randomization · Randomized controlled trials · Mechanisms

Introduction

The ultraviolet-B (UVB)—vitamin D—cancer hypothesis is nearing its 40th anniversary. Two beginning graduate students in public health proposed that hypothesis after seeing maps of cancer mortality rates and noticing an inverse correlation between colon cancer mortality rates and annual solar radiation exposure [1]. The hypothesis has received much support from other geographical ecological studies, observational studies, and studies of mechanisms [2–5]. However, in part, because of the concern that ecological and observational studies do not establish causality and because of limited support from randomized controlled trials (RCTs), the hypothesis has not received widespread support from the health care industry. With the results from some innovative observational studies and the most recent major vitamin D RCT, the support should increase.

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Justification for Using Vitamin D in Cancer Prevention and Treatment

Rates of cancer incidence are rising globally. Despite increasing awareness and early detection and diagnosis for some cancers, the disease remains a major concern for populations around the world. First, treating the disease with surgery, radiotherapy, and chemotherapy is costly. Such treatments—many of which are pharmacological medications—are not easily accessible to 85% of the world population that lives in low- to middle-income countries. Second, metastatic cancers almost always recur a few years later. Therefore, in the global attempt to fight cancer, finding options that could simultaneously serve as preventive and therapeutic measures is imperative. Such options would prevent the disease from

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occurring by regulating the cellular clock of growth not only by maintaining healthy genes, cellular components, and molecular microenvironment but also by maintaining the mechanisms that clear cellular damage functional. To be therapeutic, such options must be able to:

- Control the tumor microenvironment by blocking carcinogens or proliferation-inducing hormones at the cellular level,
- Limit angiogenesis to block the tumor's blood supply,
- Reduce inflammation in the tumor microenvironment,
- Permeate any resistant cancer stem cells in tumors, and
- Prevent transformed cancer cells from migrating, docking at and invading neighboring tissues.

Surgery is the first-line treatment for 60% of solid tumors, but surgery almost always requires radiation therapy and chemotherapy to ensure that tumor cells have not remained behind to survive and metastasize. Radiation therapies and chemotherapies usually target at least one of the preceding mechanisms, but few radiotherapy treatments or chemotherapy agents have pleiotropic abilities that target all mechanisms of cellular transformation, malignancy, or metastasis. All such available physical or pharmacological therapies often have adverse side effects. As a public health measure, it may therefore be beneficial to find natural agents that are relatively cheap and accessible to the general public and that could prevent malignancy, block metastasis, and treat the disease, independently or as an adjuvant measure to existing therapies.

In light of those requirements, vitamin D shines as a stellar candidate in the search for an anticancer agent. It is both preventive and therapeutic as well as an inexpensive and readily accessible natural biochemical agent. Mounting evidence indicates that higher serum 25-hydroxyvitamin D concentrations [25(OH)D] reduce the incidence and mortality rate of cancer. Moreover, vitamin D's multifaceted mechanisms of action can curtail several steps of cancerous transformation and malignancy simultaneously. Collectively, the body of evidence that we will present supports using vitamin D as a candidate in the global battle against cancer incidence, recurrence, and death.

This paper reviews recent advances in understanding how UVB exposure and vitamin D_3 affect cancer incidence, progression, and mortality.

Types of Studies

Geographical ecological studies investigate correlations between cancer outcomes and indices of solar UVB doses. Such studies are best conducted in mid-latitude countries that have large variations in solar UVB doses but small variations in other cancer risk-modifying factors, which are generally included in the analysis. Such studies have identified about 20 cancers that have mortality rates inversely correlated with solar UVB doses [2]. That vitamin D has more impact on cancer progression and death than on incidence is becoming apparent [6], which may help explain why observational studies of cancer incidence rates have not supported the findings of ecological studies to the extent expected.

Observational studies generally monitor cohorts for several years and compare 25(OH)D measured at enrollment with cancer incidence. However, 25(OH)D changes with season and time in general, so the longer the follow-up time, the less useful that value is. As a result, researchers using case-control studies, in which 25(OH)D is measured near the time of cancer diagnosis, find stronger inverse correlations between 25(OH)D and cancer incidence [7]. Although case-control studies are not widely accepted as a result of the assumption that reverse causality may be involved because of cancer's reduction of 25(OH)D, that assumption has not been verified and is probably incorrect. Findings from observational studies also indicate that 25(OH)D is directly correlated with survival rates for several cancers, including colorectal [8], lung [9], kidney, prostate, and melanoma [10], although lung cancer survival rate was poorer at higher 25(OH)D in Finland [10].

RCTs generally enroll people into a study in which half are randomly assigned to treatment such as vitamin D_3 supplementation, sometimes with calcium, whereas the other half are assigned a placebo. Unfortunately, most vitamin D_3 RCTs have been based on the model for pharmaceutical drugs, which assumes that the trial is the only source of the agent and that a linear dose–response relationship exists. Neither assumption holds for vitamin D_3: increases in 25(OH)D_3 decrease with vitamin D_3 supplementation as baseline 25(OH)D_3 increases, and 25(OH)D_3–health outcome relationships are nonlinear, with greater changes in outcome for changes at lower 25(OH)D_3. Other problems with vitamin D_3 RCTs include enrolling people with relatively high 25(OH)D_3, not measuring baseline or achieved 25(OH)D_3, and giving low doses of vitamin D_3. Vitamin D RCTs should be based on 25(OH)D, not vitamin D dose [11].

Two meta-analyses of RCTs investigating vitamin D supplementation and cancer incidence and mortality were reported recently. The first one included 24 studies of cancer incidence and 17 studies of cancer deaths [12]. The overall relative risk for cancer incidence from vitamin D treatment was 1.03 (0.91–1.15) while that for cancer death was 0.85 (0.70–1.04). The second one, published subsequently, used different criteria for inclusion and included only nine trials on cancer incidence and six trials on cancer death [13]. The overall relative risk for cancer incidence from vitamin D treatment was 0.99 (0.93–1.05) while that for cancer death was 0.88 (0.80–0.98). Although all of the RCTs included in both studies were based on vitamin D dose rather than 25(OH)D, so it

probably does not represent the true benefit of vitamin D supplementation on reducing cancer incidence and death, they do show that vitamin D has a greater impact on cancer death than on cancer incidence.

Mendelian randomization (MR) studies investigate links between variations of genes that affect 25(OH)D_3 and health outcomes such as cancer incidence. Such studies generally include the genes *CYP2R1*, which codes for a key enzyme in converting vitamin D_3 to 25(OH)D_3;*CYP24A1*, which destroys 1,25-dihydroxyvitamin D[1,25(OH)$_2$D]; *DHCR7*, which converts 7-dehydrocholesterol to cholesterol; and *GC*, which encodes the vitamin D binding protein. Variations in alleles of those genes account for 1–4% of the variation in 25(OH)D [14]. Sometimes baseline 25(OH)D_3 is measured. The correlation between cancer incidence and allele frequencies is used to determine whether vitamin D can be considered causally linked to the risk of particular cancers. To date, MR study results have been reported for incidence for many cancers. However, the only statistically significant result was for ovarian cancer in an Ovarian Cancer Association Consortium study involving 10,065 case patients and 21,654 control subjects of European ancestry, odds ratio (OR) = 1.27 (95% CI, 1.06–1.51) per 8 ng/ml decrease in 25(OH)D_3 [15]. In that same paper, the OR for high-grade serous epithelial ovarian cancer as determined from 4121 cases was 1.54 (95% CI, 1.19–2.01). No significant results were found for prostate cancer in eight studies, in agreement with findings of observational studies [16]. In a more recent paper involving 1031 ovarian cancer cases, the MR OR involving 11,096 cases was 0.85 (95% CI, 0.73–1.00) [17]. In that same paper, results were not significant for incidence of any other cancer, possibly because the numbers of cases were small, or for mortality from breast, colorectal, lung, pancreatic, or prostate cancer. However, all cancer mortality rate was found inversely correlated with genetically determined 25(OH)D, OR per 8 ng/ml lower 25(OH)D = 1.43 (95% CI, 1.02–1.99) [18].

Trying to understand why MR studies generally find no significant correlations between genetically determined variations in 25(OH)D and cancer incidence is a worthwhile endeavor. One reason for the lack of such findings may be that the genetic factors explain at most about 3.5% of 25(OH)D [17]. A second reason is that some studies do not include enough cancer cases to have the statistical power to find a significant effect. A third reason is that 25(OH)D varies with respect to, for example, season, age, and supplementation. In an analysis of results for observational studies of breast and colorectal cancer, the longer the follow-up period after blood draw, the nearer the OR was to 1.0. The effect was stronger for breast than for colorectal cancer, which was attributed to the fact that breast cancer can develop rapidly [7, 19].

Observational Studies of 25(OH)D on Cancer Incidence

Colorectal Cancer In a meta-analysis of 15 prospective observational studies and one case-control study, researchers found a pooled OR of 0.67 (95% CI, 0.59–0.76) for colorectal cancer incidence for high versus low baseline 25(OH)D [20••]. When the ORs were averaged for each step of 10 ng/ml, a nearly linear inverse relationship emerged from < 10 ng/ml to 50–60 ng/ml.

Breast Cancer The evidence that vitamin D reduces the risk of breast cancer incidence strengthened in 2018 because of findings from a pooled analysis of breast cancer incidence from two vitamin D RCTs (3325 women) and one observational study (1713 women) [21••]. Researchers measured 25(OH)D at baseline and after 1 year in the RCTs and every 6 months in the observational study. Participants in the RCTs took either 1100 or 2000 IU of vitamin D_3 per day plus 1.5 g of calcium per day or placebo, whereas participants in the observational study freely chose their doses of vitamin D_3 and calcium. Seventy-seven participants developed breast cancer during the 4- to 5-year study periods. A plot of breast cancer incidence rate versus 25(OH)D_3 resulted in a nearly linear reduction from 762 cases/100,000 population for 25(OH)D < 20 ng/ml to 134 cases/100,000 for 25(OH)D > 60 ng/ml. The hazard ratio (HR) for > 60 ng/ml versus< 20 ng/ml was 0.20 (95% CI, 0.05–0.82); $P = 0.03$. One strength of that study was that 25(OH)D ranged up to > 60 ng/ml. The HR for 40–59 ng/ml versus < 20 ng/ml was 0.48 (95% CI, 0.20–1.14); $P = 0.10$. Another strength was that seasonal variations in 25(OH)D were reduced because more than half of the women were taking reasonably large doses of vitamin D_3. It has been argued that case-control studies of breast cancer incidence were superior to prospective observational studies because breast cancer develops rapidly and both seasonal and long-term changes in 25(OH)D can reduce the long-term predictive value of 25(OH)D measured at baseline [7].

A recent cross-sectional study found that supplementing with vitamin D_3 induces breast cancer–specific survival rate. The study was conducted in Ireland. Invasive breast cancer data for 5417 women aged 50–80 years were obtained from the National Cancer Registry Ireland database, and vitamin D supplement use was determined from national prescription data [22••]. For new vitamin D users, the HR was 0.80 (95% CI, 0.64–0.99); $P = 0.048$. For women who began taking vitamin D supplements within 6 months of diagnosis, the HR was 0.51 (95% CI, 0.34–0.74); $P < 0.001$. Results were similar for users versus nonusers and users supplemented with > 400 IU/d versus nonusers and users supplemented with < 400 IU/d.

Prostate Cancer For prostate cancer, the relation with respect to solar UVB doses and 25(OH)D is different from that for most internal organ cancers. For example, in the USA, prostate cancer mortality rates were highest in the northwest and lowest in the southeast from 1950 to 1994, whereas mortality rates for breast, colon, and many other cancers are highest in the northeast and lowest in the southwest [23].

Findings from a meta-analysis of individual participant data in 19 prospective studies indicated higher versus lower 25(OH)D associated with increased risk of nonaggressive disease [adjusted OR = 1.22 (95% CI, 1.13–1.31); $P_{trend} < 0.001$] [24]. However, for aggressive disease, adjusted OR = 0.95 (95% CI, 0.78–1.15). In a meta-analysis of prostate cancer–specific mortality rate based on seven cohort studies, researchers found a HR of 0.91 (95% CI, 0.87–0.97; $P = 0.01$) per 8 ng/ml increase in 25(OH)D [17].

African-Americans (AAs) have much higher rates of prostate cancer than European Americans do: incidence rates are higher by a factor of 1.7, whereas mortality rate is higher by a factor of 2.4, according to data from 2008 to 2012 [25]. A recent paper reported results of a cross-sectional study of 2322 control subjects and men who underwent prostate cancer biopsy (consisting of 1381 AAs, 715 European Americans, and 226 from other racial/ethnic backgrounds), the data of which were later reduced to a case-control study of 1657 men (699 prostate cancer patients and 958 control subjects) [26••]. For AAs, the association between high versus low calcium intake and aggressive prostate cancer was $OR_{Q1\ vs.\ Q4} = 4.3$ (95% CI, 1.7–10.8), whereas the association for high versus low vitamin D intake was $OR_{Q1\ vs.\ Q4} = 0.06$ (95% CI, 0.02–0.54) [26••]. Similar findings for calcium and vitamin D intake were reported for men with body mass index (BMI) < 27.8 kg/m^2 regardless of race but not for those with higher BMI.

Other Cancers Findings from recent observational studies also have indicated that 25(OH)D is inversely correlated with incidence of liver cancer in Europe [27] and Japan [28]. Reviews indicate that the evidence from observational studies for 25(OH)D are supportive for lung [9] and thyroid [29] cancer but weak for gynecological [30], (although supportive for ovarian cancer [31]), and pancreatic [32] cancers.

All-Cancer Incidence

In two recent observational studies, inverse correlations were found between 25(OH)D and all-cancer incidence [33••, 28]. One study that did not was from Germany, probably as a result of the low mean 25(OH)D (15.5 ng/ml) [34].

The results of a 5-year RCT does offer good evidence that vitamin D_3 reduces risk of total cancer. The VITamin D and Omega-3TriAL (VITAL) enrolled more than 25,000 participants, more than 5000 of whom were Black [35••]. Enrollees were given 2000 IU/d vitamin D_3 or placebo and 1 g/d omega-3 fatty acids or placebo. The mean baseline 25(OH)D was ~ 31 ng/ml and the baseline BMI was 28 kg/m^2. Participants were permitted to take up to 600 IU/d vitamin D_3 (800 IU/d if older than 70 years). For the entire group, the HR for cancer incidence was 0.96 (95% CI, 0.88–1.06). However, for those with BMI < 25 and ≤ 27.1 kg/m^2, the HR values were 0.76 (95% CI, 0.63–0.90) and 0.86 (95% CI, 0.75–0.99), respectively. The likely reason for a more beneficial effect for individuals with lower BMI is that the 2000 IU/d raises 25(OH)D more due to volumetric dilution with higher BMI [36]. Also, for Blacks, HR was 0.77 (95% CI, 0.59–1.01). According to that study's online supplement, the mean 25(OH)D for Blacks was 25.0 ng/ml, rising to 39.7 ng/ml at year one on the basis of a sample size of 154. Baseline and achieved 25(OH)D for those with BMI < 25 kg/m^2 were 33.3 and 45.9 ng/ml, respectively, whereas achieved 25(OH)D was 41.4 and 38.6 ng/ml for 25 kg/m^2 < BMI < 30 kg/m^2 and BMI ≥ 30 kg/m^2, respectively. Thus, the subgroup results are consistent with the importance of both baseline and achieved 25(OH)D, indicating that the group had either baseline 25(OH)D been lower or the vitamin D_3 dose higher, a significant reduction in all-cancer incidence would have been found. For the entire group, death from cancer was reduced non-statistically significantly in the treatment arm (HR = 0.83 [95% CI, 0.67–1.02]) but significantly in the analysis excluding the first 2 years (HR = 0.75 [95% CI, 0.59–0.96]).

Recommendations

From the evidence discussed here, as well as in other papers in the literature, keeping 25(OH)D in the range of at least 40–60 ng/ml would apparently provide optimal protection against most cancers. Vitamin D_3 can be obtained through sensible sun exposure, avoiding erythema (sunburn), and through supplements. In a recent intervention study, having 25(OH)D > 40 ng/ml greatly reduced the development of erythema under UV irradiation [37].

Mechanisms

Cell Proliferation, Survival, Apoptosis, and the Regulation of microRNAs

Cell proliferation, growth, and survival rely on several interlinked molecular signaling regulators that control the cell cycle and cellular turnover. In tumorigenesis, cell cycle control is dysfunctional, and the cell proliferates out of control in the absence of DNA repair rescue mechanisms, apoptosis, or

autophagy—processes that otherwise would sweep up faulty or worn-out cells. Several studies strongly support evidence that $1,25(OH)_2D_3$ or its analogues can suppress irregular cell proliferation, promote apoptosis, or activate cellular autophagy [38]. Findings in several cancer cell types collectively confirm that $1,25(OH)_2D_3$ has an effective preventive role in tumorigenesis by regulating different signaling pathways and stages of the cell cycle.

Treatment of HeLaS3 cervical cancer cells with $1,25(OH)_2D_3$ arrests the cell cycle at G_1 phase and increases expression of the tumor suppressor gene *p21*. This is associated with a repression in mRNA expression and protein levels of the human cervical cancer oncogene *HCCR-1* [39].

Treating MCF-7 breast cancer cell lines with $1,25(OH)_2D_3$ induces cell cycle arrest at the G_1/S transition phase by downregulating the synthesis or activity of cyclin and cyclin-dependent kinase (cdk) complexes cdk4, cdk6, and cdk2 through downregulating cyclin D1 and cyclin D3 complexes. This is accompanied by an upregulation of the tumor suppressor *p21* and downregulation of the downstream proto-oncogene *c-MYC* [40]. Similarly, in androgen receptor–positive prostate cancer cells, $1,25(OH)_2D_3$ treatment inhibits cdk2 activity and induces G_0/G_1 arrest [41].

Treatment with $1,25(OH)_2D_3$ can upregulate the expression of the protective gene breast cancer type 1 susceptibility protein (*BRCA1)* at the mRNA and protein levels in breast cancer cell line MCF-7 but not in the resistant cancer cell line MDA-MB-436. In MCF-7 and other breast cancer cell lines, estrogen receptor (ER) expression is correlated with increased sensitivity to the anti-proliferative effects of $1,25(OH)_2D_3$, indicating that $1,25(OH)_2D_3$ may be particularly effective in ER^+ breast cancer cell lines [42].

Treating SCC25 head and neck squamous cell carcinoma cells with $1,25(OH)_2D_3$ can suppress *c-MYC*, *CDK4*, and *CCND2* expression and increase c-Myc cellular degradation in a vitamin D receptor–dependent manner. This process is associated with an upregulation of expression and stability of MAD1/MXD1, the c-Myc antagonist transcriptional repressor [43].

In colorectal cancers, $1,25(OH)_2D_3$ inhibition of proliferation occurs via JNK1 phosphorylation [44]. In adenoma and carcinoma colorectal cell lines (SW620, PC/JW, and HT29), treating cells with $1,25(OH)_2D_3$ increases the number of cells arrested at G_1 phase and the number of apoptotic cells by upregulating the proapoptotic protein Bak in a p53-independent manner [45]. Some p53-dependent apoptotic effects of $1,25(OH)_2D_3$ associated with upregulating the DNA damage repair factor GADD45 can also occur, as shown in human glioma cell lines [46].

Telomerase activity can promote survival of cancer cells by sustaining proliferative growth. Treating human ovarian cancer cell lines with $1,25(OH)_2D_3$ can downregulate telomerase activity by destabilizing and degrading human telomerase reverse transcriptase (hTERT) mRNA of the telomerase enzyme. This process, in turn, promotes apoptotic cell death in ovarian cancer cells. Further studies have shown that treating ovarian cancer cells with $1,25(OH)_2D_3$ blocks telomerase activity through increased expression of microRNA-498 (miRNA-498) [47]. Other miRNAs respond to $1,25(OH)_2D_3$ regulation, supporting a therapeutic inhibitory potential of vitamin D_3 in cancer treatment: miRNA-22, miRNA-627, miRNA-181a, miRNA-181b, miRNA-32, and miRNA-98 [48••].

Microenvironment, Oxidative Stress, Inflammatory Signaling, and Angiogenesis

Inflammation is a key hallmark of oncogenesis, contributing to malignant transformation, tumor growth, survival, and metastasis [49]. Oxidative stress and formation of reactive oxygen species and reactive nitrogen species produced by tumor-infiltrating immune cells can damage DNA or modify it epigenetically at important cell cycle control gene loci that can include tumor suppressor genes [50]. Inflammatory mediators such as interleukins (IL) and cytokines upregulate pathways that activate Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and signal transducer and activator of transcription 3 (STAT3) and restrict the activation of apoptosis needed for cellular control following oxidative stress. Such signaling can activate inhibitor kappa B (IκB) in tumor cells, promoting their sustained survival. Moreover, epithelial to mesenchymal transition promoting metastasis increases in the presence of inflammation in the tumor microenvironment. This process is associated with the increased expression of inflammatory cytokines such as transforming growth factor β (TGFβ) and tumor necrosis factor α (TNFα) and metastatic cell surface markers such as cadherin 11 and fibroblast-specific protein (FSP-1) [51]. The inflammatory involvement of IL-1, IL-6, and IL-8 has been documented in several cancers. IL-8 amplifies tumor-associated inflammation and promotes neovascularization toward tumors, thus promoting growth. IL-6 promotes tumor growth by upregulating the oncogenic K-ras pathway [52]. NF-κB mediates the expression of prostaglandin-endoperoxidase synthase-2/cyclooxygenase 2 (PGHS-2/Cox2), the rate-limiting enzyme involved in converting arachidonic acid to prostaglandin (PGE-2), which potentiates inflammatory response. PGHS-2 furthermore promotes secretion of vascular endothelial growth factor 1 (VEGF1), angiogenesis, and increased endothelial cell permeability to leukocytes and their recruitment to tumor sites, resulting in enhanced oxidative stress and formation of reactive oxygen species [53]. NF-κB activation can upregulate the cell cycle oncogenes *CCND1* and *c-MYC*, induce antiapoptotic changes by upregulating c-FLIP, Survivin, BcL-X_L, and upregulating cell adhesion molecules for homing and metastasis namely, ICAM-1, ELAM-1, and VCAM-

17. NF-κB also exacerbates the aggressive invasive nature of tumor cells through upregulated metalloproteinase gene expression and urokinase-type plasminogen activator (*uPA*) [54, 55]. IL-1 is produced by several cells in the tumor microenvironment, including tissue-specific tumor cells, stromal cells, immune cells infiltrating the tumor site, and endothelial cells. IL-1 can mediate several functions promoting malignancy, including upregulating PGHS-2/Cox2 and angiogenesis [56]. Several studies show that $1,25(OH)_2D_3$ can exert anti-inflammatory effects and counteract the effects of many of the preceding proinflammatory interleukins and cytokines as well as downregulate their downstream genes [57].

$1,25(OH)_2D_3$ inhibits prostaglandin action by inhibiting the expression of PGHS-2/Cox2, its receptor on cells, and promotes the degradation of the proinflammatory mediator by upregulating gene transcription of 15-hydroxyprostaglandin dehydrogenase (15-PGDH) [58••]. In primary prostatic cell cultures of normal epithelial and adenocarcinoma cells, treating cells with $1,25(OH)_2D_3$ decreases prostatic inflammation by reducing IL-6 expression. This occurs through upregulation by $1,25(OH)_2D_3$ of mitogen-activated protein kinase phosphatase 5 (MKP-5), which inhibits p38 MAPK. MKP-5 dephosphorylates the stress-activated protein kinase p38, which in turn suppresses the downstream transcription of IL-6. $1,25(OH)_2D_3$ also attenuates IL-6 production and overrides carcinogenic challenge of these cells with TNFα or UV stimulation.. This finding highlights the protective and preventive role of $1,25(OH)_2D_3$ in prostate cell lines. However, in metastatic cell lines such as DU145 and PC3, which constitutively express high levels of IL-6, the data indicate that $1,25(OH)_2D_3$ may be effective against external proinflammatory stress and may play a role in prostate cancer prevention in a dose-dependent manner. A defined time window of treatment and use of a higher concentration of $1,25(OH)_2D_3$ (> 50 ng/ml in the treatment medium) may be needed to be effective in metastatic prostate cancer cells [59].

The anti-inflammatory effect of $1,25(OH)_2D_3$ through suppression of interleukin-mediated inflammation and angiogenesis mentioned above has been documented in several in vitro studies. Treating several cancer cell lines with $1,25(OH)_2D_3$ can suppress expression of IL-8, IL-1β, IL-6, IL-10, IL-17, and TGFβ and associated proinflammatory downstream signaling [48••, 60, 61, 62••].

Metastasis and Cell Adhesion Molecules

Epithelial to mesenchymal transition (EMT) is an important process of cellular change that initiates tumor cell metastasis. EMT is accompanied by changes in the microenvironment of the tumor and cellular changes within transformed cancer cells. Treatment with vitamin D_3 can have several anticancer effects on molecules regulating angiogenesis, invasion, and metastasis in vitro and in vivo [63]. In squamous cell carcinoma cells, $1,25(OH)_2D_3$ upregulates the cell surface adhesion marker E-cadherin, which is important in maintaining epithelial cell–cell junctions and suppressing transition from benign to metastatic malignant lesions. Treatment also downregulates the expression and secretion of matrix metalloproteinases MMP-2 and MMP-9 needed for invasion as documented both in migration assays and in experimentally induced tumor mouse models [64].

Treating glioma C6 cells with $1,25(OH)_2D_3$ downregulates the extracellular matrix protein tenascin-C, thus blocking cell migration of transformed cells, angiogenesis, and metastatic invasion [65]. The dose-dependent anticancer effect of $1,25(OH)_2D_3$ on tenascin-C also has been documented in normal and malignant mouse and human mammary epithelial cell lines [66]. In experiments with breast cancer cells, both the ER^+ cell line MCF-7 and ER^-cell line MDA-MB-231, treatment with $1,25(OH)_2D_3$ has a very effective dose-dependent ability in blocking cytoskeletal changes, migration, and metastatic invasion. In a dose-dependent manner, $1,25(OH)_2D_3$ upregulates tumor suppressor molecule PDZ-LIM domain–containing protein 2 (PDLIM2) involved in cytoskeletal stability, modulation of focal adhesion, and cell movement and hence suppresses tumorigenicity of cells. In MCF-7 cells, this is accomplished after 12-h treatment with vitamin D_3. In MDA-MB-231 cells, this is accomplished by 48 h of treatment, indicating that dose-dependent effects are important when considering treatment with vitamin D_3 as well as the presence of different molecular mechanisms that could be targeted in both carcinomas [67].

Recent findings in 143B osteosarcoma cell lines show that vitamin D_3 treatment can suppress gene expression of several genes involved in cell invasion and metastasis in a Runx2-mediated fashion. Those genes include genes that support metastasis, such as fibroblast growth factor 1 and 2 (*FGF1* and *FGF2*), bone morphogenic protein 1 (*BMP-1*), *Integrin β4 (ITGB4)*, *MMP-1* and *MMP-28*, kallikrein-related peptidase-7 (*KLK7*), and matrix extracellular phosphoglycoprotein (*MEPE*) [68]. Similar findings of MMP inhibition have been documented in other cancer cell lines, such as prostate cancer [60, 63].

Autophagy

In the battle against cancer, prevention is as important as cure. Autophagy is a preventive way to protect the body from the accumulation of damaged cells affected by stresses such as oxidative stress. It is a mechanism by which cells of the immune system clear out damaged or worn-out cells that cannot be repaired by DNA excision repair or other mechanisms. $1,25(OH)_2D_3$ can modulate autophagy and increase cellular survival in both healthy tissues and cancer cells. Recent

studies have shown that expression of the vitamin D receptor can regulate autophagy in normal breast mammary glands and in MCF-7 luminal epithelial breast cancer cells. This mechanism both has a preventive effect and is useful when using vitamin D_3 as an adjuvant during chemotherapy to promote the clearance of chemotherapy-affected cells [69••].

Future Considerations for the Use of Vitamin D_3 that Need Further Investigation

Recent studies by Dimitrov and colleagues showed that in human but not mouse tumor cells, treatment with $1,25(OH)_2D_3$ upregulates the mRNA expression of programmed death ligand-1 (*PD-L1*) in epithelial and myeloid cells. PD-L1, in turn, activates PD-1, thus subduing and suppressing the cytotoxic T cell response of killer T cells needed to activate antitumor immune activity [70]. Such recent initial yet controversial findings compel us to approach the effects of vitamin D_3 on the immune system with caution. Because vitamin D_3 affects the innate and adaptive immune system phases differently, further studies are needed to address using vitamin D_3 in cancer prevention and therapy in a tissue-specific, time-dependent, and dose-dependent manner.

However, several studies have indicated that when used as an adjuvant to chemotherapy, vitamin D_3 may be important in potentiating the effects of classical chemotherapeutic agents. Vitamin D_3 can act to potentiate chemotherapies by promoting apoptosis, decreasing angiogenesis, and promoting anti-inflammatory palliative effects that help clear chemotherapy- and radiotherapy-sensitized tumor cells [71–74].

Conclusion

Vitamin D_3's role in reducing risk of cancer incidence and death has been increasingly supported in the past few years by the findings of RCTs and observational studies conducted on participants in vitamin D_3 supplementation studies. Mechanisms that explain how vitamin D_3 does so are well known. For optimal reduction in risk and survival, $25(OH)D_3$ in the range 40–60 ng/ml is recommended.

Compliance with Ethical Standards

Conflict of Interest William B. Grant has received research funding from Bio-Tech Pharmacal, Inc. (Fayetteville, AR).

Meis Moukayed declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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