Cancer Causes and Control **16**: 83–95, 2005.

The epidemiology of vitamin D and cancer incidence and mortality: A review (United States)

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Received 29 April 2004; accepted in revised form 27 July 2004

Key words: Vitamin D, calcium, colorectal cancer, prostate cancer, 25 (OH) vitamin D.

Abstract

In vitro and animal studies indicate that vitamin D may have anti-cancer benefits, including against progression and metastasis, against a wide spectrum of cancers. Supporting an anti-cancer effect of vitamin D is the ability of many cells to convert 25(OH)D, the primary circulating form of vitamin D, into $1,25(OH)_2D$, the most active form of this vitamin. No epidemiologic studies have directly measured vitamin D concentrations or intakes on risk of total cancer incidence or mortality. However, higher rates of total cancer mortality in regions with less UV-B radiation, and among African-Americans and overweight and obese people, each associated with lower circulating vitamin D, are compatible with a benefit of vitamin D on mortality. In addition, poorer survival from cancer in individuals diagnosed in the months when vitamin D levels are lowest suggests a benefit of vitamin D against late stages of carcinogenesis. The only individual cancer sites that have been examined directly in relation to vitamin D status are colorectal, prostate and breast cancers. For breast cancer, some data are promising for a benefit from vitamin D but are far too sparse to support a conclusion. The evidence that higher 25(OH)D levels through increased sunlight exposure or dietary or supplement intake inhibit colorectal carcinogenesis is substantial. The biologic evidence for an anti-cancer role of 25(OH)D is also strong for prostate cancer, but the epidemiologic data have not been supportive. Although not entirely consistent, some studies suggest that higher circulating $1,25(OH)_2D$ may be more important than 25(OH)D for protection against aggressive, poorly-differentiated prostate cancer. A possible explanation for these divergent results is that unlike colorectal tumors, prostate cancers lose the ability to hydroxylate 25(OH)D to $1,25(OH)_2D$, and thus may rely on the circulation as the main source of $1,25(OH)_2D$. The suppression of circulating $1,25(OH)_2D$ levels by calcium intake could explain why higher calcium and milk intakes appear to increase risk of advanced prostate cancer. Given the potential benefits from vitamin D, further research should be a priority.

Abbreviations: 25(OH)D, $1,25(OH)_2D$.

Introduction

The suggestion that sunlight exposure may lower risk of cancer was first made almost seven decades ago by Peller [1], and an inverse association between latitude and cancer mortality was first demonstrated by Apperly in 1941 [2]. Four decades later, Garland and Garland hypothesized that poor vitamin D status may contribute to a higher risk of colon cancer mortality, based on the premise that vitamin D is formed in the skin through solar UV-B radiation exposure [3]. Subsequently, Garland and colleagues proposed a similar association for breast cancer [4] and ovarian cancer [5], and Schwartz and colleagues hypothesized a similar relationship for prostate cancer [6, 7]. More recently, Grant has demonstrated that geographical mortality rates of numerous other cancers are associated inversely with regional UV-B radiation exposure [8].

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Linking the initial ecologic data on UV-B radiation exposure and cancer to vitamin D status was the discovery that many cell types [9–14] contain vitamin D receptors. When these receptors are activated by $1,25(OH)_2D$, the most active metabolite of vitamin D, they induce differentiation and inhibit proliferation, invasiveness, angiogenesis, and metastatic potential. Moreover, circulating 25(OH)D was also shown to be potentially beneficial because many cells types including cancer cells express 1-α-hydroxylase, and are thus able to convert 25(OH)D into $1,25(OH)_2D$. In addition, the vitamin D cancer hypothesis has been supported by studies that administer $1,25(OH)_2D$ to animals in various tumor models [15–17] and in small phase II clinical studies in humans that show that administration of $1,25(OH)_2D$ can slow the progression of advanced prostate cancer [18–20]. In various tumor models, including cancers of the lung [21–24], bone [25], colon [26], kidney [27], melanocyte [28], retina [29], breast [30] and prostate [10], vitamin D has activity against metastasis. Thus, *in vitro*, animal, and clinical data support a role for vitamin D activity against incidence or progression of a wide spectrum of cancers.

Despite this intriguing evidence, the vitamin D cancer hypothesis has received only limited epidemiologic study, and most of the focus has been limited to colorectal and prostate cancer incidence, and not to progression of many cancers. The potential influence of factors related to vitamin D status, such as age, skin pigmentation, obesity, and behaviors related to sunlight exposure, or nutrients, such as retinol, that may interact antagonistically with the actions of vitamin D, have not been considered in detail. This report will summarize major relevant findings from an epidemiologic perspective, and suggest various areas for research.

Anticancer actions of $1,25(OH)_2D$ and 25(OH)D

Fig. 1 illustrates the key reactions involved in vitamin D metabolism. Ultraviolet radiation (UV-B) is required for conversion of 7-dehydrocholesterol into vitamin D (cholecalciferol) in the skin [31]. Alternatively, vitamin D can be ingested through a few natural food sources, fortified foods, or from supplements. Vitamin D is then hydroxylated in the liver to produce 25(OH)D, which can then be converted by 1-α-hydroxylase into $1,25(OH)_2D$ [31, 32]. Circulating 25(OH)D concentration varies with exposure to sunlight or dietary intake and is considered the best indicator of vitamin D status. Circulating $1,25(OH)_2D$, which is several hundred-fold more active than 25(OH)D [33], is tightly regulated in the circulation largely by renal 1-α-hydroxylase activity

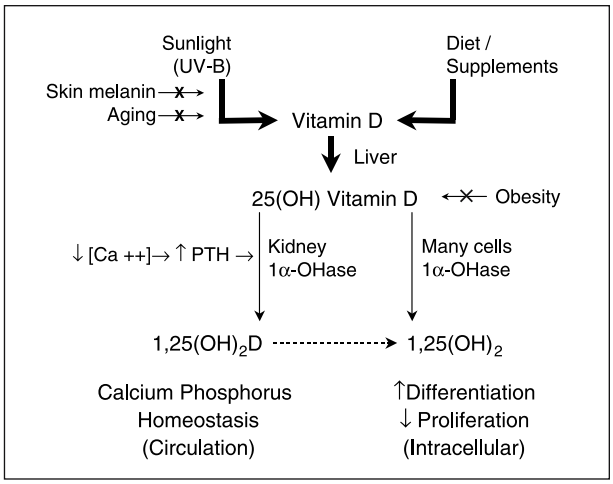

Fig 1. Proposed mechanism for vitamin D and cancer. The main sources of vitamin D are sunlight and diet or supplements. Darker skin, older age and obesity are associated with lower 25(OH)D. Anti-cancer effects may be largely due to conversion of 25(OH)D to $1,25(OH)_2D$ within cells, although circulating $1,25(OH)_2D$ may contribute.

[31, 32]. The concentration of circulating 25(OH)D is about 1000-fold that of $1,25(OH)_2D$. Both forms of circulating vitamin D may contribute to vitamin D activity, 25(OH)D because of its much higher concentrations and $1,25(OH)_2D$ because of its higher-activity.

Through the circulation, various cells can be exposed to either $1,25(OH)_2D$ or to 25(OH)D. If $1,25(OH)_2D$ is the most critical anti-cancer factor, then factors such as calcium concentration and parathyroid hormone (PTH) that influence renal 1-α-hydroxylase and thus circulating $1,25(OH)_2D$ concentration could be determinants of cancer risk. However, PTH and calcium do not appear to influence 1-α-hydroxylase activity in non-renal cells [34]. Regulators of 1-α-hydroxylase activity in various cell types are not well understood, but presumably if 25(OH)D is severely deficient, production of $1,25(OH)_2D$ would be impaired. Assuming cells have 1-α-hydroxylase activity, circulating 25(OH)D rather than $1,25(OH)_2D$ would be the more important determinant of intracellular $1,25(OH)_2D$. If circulating 25(OH)D is important for carcinogenesis, then factors that influence its levels may be predicted to affect cancer risk. Understanding the epidemiologic literature requires the consideration of determinants of $1,25(OH)_2D$ and 25(OH)D levels and activity.

Determinants of circulating $1,25(OH)_2D$ and 25(OH)D levels and activity

Circulating $1,25(OH)_2D$ is a hormone, and does not typically reflect vitamin D status, perhaps except at

extreme deficiency. Circulating $1,25(OH)_2D$ concentration is tightly regulated largely by renal 1-α-hydroxylase activity, so within normal ranges, 25(OH)D and $1,25(OH)_2D$ levels are not appreciably correlated. Excluding severe 25(OH)D deficiency, probably the major known readily modifiable determinant of $1,25(OH)_2D$ level is calcium intake [35]. Metabolic studies demonstrate a strong inverse association ($r = -0.76$) between change in calcium intake and change in $1,25(OH)_2D$ concentration in the circulation [36]. Within the normal dietary range in free-living populations, an inverse association has also been observed between calcium intake and $1,25(OH)_2D$ concentration [37, 38]. Other dietary and other modifiable determinants of $1,25(OH)_2D$ levels may exist [35], but these have not been clearly established to be relevant in free-living populations with typical diets.

Circulating 25(OH) is less tightly regulated than $1,25(OH)_2D$, and a number of factors contribute to its variation, including vitamin D intake, regional UV-B level, skin pigmentation, sunlight exposure behaviors, and adiposity. Skin in the elderly has a markedly decreased capacity to produce vitamin D [39]. However, age is not considered here because it is a strong predictor of cancers, incorporating the cumulative effect of many exposures and events, and cannot be used as a surrogate of vitamin D status with any reliability. Age is typically controlled for in epidemiologic studies of cancer rather than isolated as an independent factor. The important determinants of 25(OH) levels are discussed briefly next.

Vitamin D Intake: Vitamin D is contributed by a limited number of foods, including fish, eggs, and fortified milk products and breakfast cereals, and vitamin D-containing multivitamins and supplements. Besides fatty fish, few important (non-fortified) food sources exist. In the US, the recommended daily vitamin D intake is 200 IU for children and adults up to age 50 years, 400 IU for adults 50–70 years of age, and 600 IU and for individuals ≥70 years. However, based primarily on optimizing bone health, some experts have argued for a minimum of 1000 IU/day [39]. Such high intakes are required to achieve a 25(OH)D concentration in the range of 30–40 ng/ml (78–100 nmol/l), especially when sunlight exposure is minimal. The optimal intake for cancer prevention is unknown given the uncertainties regarding the role of vitamin D on cancer risk.

Skin Pigmentation: The degree of skin pigmentation exerts a profound influence on vitamin D status. Melanin in the skin is a very effective filter against UV-B radiation. An individual with dark skin may require 10–50 times the exposure to UV-B radiation to produce an equivalent amount of vitamin D as does a light-skinned person [40]. Not surprisingly, African-Americans have much higher rates of vitamin D deficiency than whites. For example, based on the NHANES survey (1988–1994), the prevalence of hypovitaminosis D (≤37.5 nmol/l) was 42.4% among African-American women aged 15–49 compared to 4.4% among white women [41]. Note that this criterion for deficiency is about 3 times lower than that which may be optimal for bone health (up to 100 nmol/l) [39]. In addition, vitamin D levels decrease with age, so one may anticipate even lower levels in those over 50 years.

Body mass index: Higher body mass index or obesity have been consistently found to be associated with substantially lower concentrations of 25(OH)D. For example, in a nationally representative survey, for white women, the mean serum 25(OH)D (nmol/L) concentrations were as follows across the following BMI categories: <18.5 kg/m^2: 92.4; 18.5 to <25 kg/m^2: 88.9; 25 to <30 kg/m^2: 75.4; ≥30 kg/m^2: 65.3 [41]. A weaker gradient across BMI was noted among African-American women, but their overall mean concentration and variance was much lower (42.4 nmol/L on average). In another cross-sectional analysis including men and women, the correlation between BMI and 25(OH)D concentration was −0.4 ($p < 0.0001$) [42]. In an intervention study, BMI was inversely correlated with serum vitamin D concentrations after UV-B irradiation to the skin ($r = -0.55$, $p = 0.003$) and with peak serum vitamin D concentrations after vitamin D intake ($r = -0.56$, $p = 0.007$) [43]. The obesity-associated vitamin D insufficiency is probably due to decreased bioavailability of 25(OH)D due to its deposition in body fat compartments [43].

Sunlight exposure: UV-B radiation is the major source of vitamin D for most people because only a few food sources contain vitamin D. Being exposed to enough UV-B to cause a slight pinkness to the skin (1 minimal erythemal dose) produces vitamin D equivalent to an oral dose of 20,000 IU vitamin D; this is 100 times the RDA for adults under age 50 years [39]. A surrogate of vitamin D used in epidemiologic studies has been based on the average UV-B radiation in geographical region of residence. While informative, this variable is likely to be a crude surrogate because it does not take into account actual behaviors in seeking or avoiding sunlight, skin pigmentation, intake and other determinants. For example, elderly in nursing homes are likely to be vitamin D deficient even if they live in sunny regions. Interestingly, in a recent study of plasma vitamin D and colorectal cancer risk in the Nurses' Health Study [44], average UV sunlight (langleys/day) based on residence was more weakly

correlated with 25(OH)D concentrations ($r = 0.1$) than were other predictors such as BMI ($r = 0.17$), physical activity (presumably as a crude marker of outdoor exposure) ($r = 0.14$), and vitamin D intake ($r = 0.26$) (Diane Feskanich, personal communication).

Retinol: In the cell, $1,25(OH)_2D$ binds the vitamin D receptor (VDR), a member of the nuclear receptor superfamily. The VDR*$1,25(OH)_2D$ complex then interacts with the retinoid X receptor (RXR) to form a $1,25(OH)_2D$*VDR*RXR heterodimer complex, which then interacts with vitamin D responsive elements (VDRE). Retinoic acid receptors (RARs) also function as heterodimers with RXR proteins. Because both vitamin A (retinol) and D require RXR proteins for their actions, high doses of retinol may antagonize vitamin D actions [45, 46]. Animal and human evidence strongly support the existence for such antagonistic effects. For example, increasing intakes of retinol impaired vitamin D's ability to elevate serum calcium in rats, and had adverse effects on bone mass [45]. In humans, an intake of vitamin A corresponding to approximately one serving of liver per day antagonized the intestinal calcium response to vitamin D [46]. High retinol intake has been associated with a reduction in bone mineral density [47], and an increase in hip fractures [48, 49], and serum retinol levels have been correlated with an increased risk of fracture [50]. High intakes of retinol may plausibly antagonize any anti-cancer effects of vitamin D, but this hypothesis has not been addressed.

Epidemiologic evidence for vitamin D and total cancer incidence and mortality

The previous sections summarized briefly the rationale for a potential role for vitamin D on cancer incidence or progression, and summarized determinants of vitamin D status. This section summarizes the studies that have directly or indirectly examined vitamin D with risk of cancer incidence or progression. No study has examined prospectively circulating vitamin D concentrations or total vitamin D intake in relation to total cancer incidence or mortality. In fact, epidemiologic approaches have remained limited largely to refinements of examination of latitude as a surrogate of available UV-B radiation. Much of this recent work has been conducted by Grant, who used UV-B data to estimate that about 24,000 premature cancer deaths are attributable annually in the US to sub-optimal UV-B radiation exposure [8]. Grant found an inverse correlation between cancer mortality rates and regional UV-B for cancers of the breast, colon, rectum, ovary, prostate, stomach, bladder, esophagus, kidney, lung, pancreas, and uterus, as well as non-Hodgkin's lymphoma and multiple myeloma.

While caution is required in interpreting ecologic data, no strong alternative explanation to vitamin D has been offered. Moreover, these associations persisted even after adjusting for other risk factors, such as smoking, urban or rural residence, Hispanic heritage, poverty, dietary factors, and use of nonsteroidal anti-inflammatory drugs. A similar relationship between regional UV-B radiation and cancer mortality was seen in a multi-country ecologic study across European countries, where the potential (uncontrolled) confounders may differ [51]. Given that cancers have diverse risk factors, it is remarkable that the inverse correlation with regional UV-B radiation would be consistent across cancer sites. Although 24,000 cancer deaths appears to be a relatively modest (though important) fraction of the 556,500 annual cancer deaths in the US, if vitamin D status is indeed the relevant factor, this number would be a gross underestimation because regional sunlight intensity is only one determinant of vitamin D status, and does not take into account vitamin D intake, skin pigmentation, adiposity, and actual sunlight exposure.

Another recent study based on 115,096 cases and 45,667 deaths from breast, colon or prostate cancer diagnosed between 1964 and 1992 in Norway, found striking 30% reductions in fatality rates for cancers diagnosed in the summer and fall, when vitamin D levels are higher [52] compared to the winter. This finding suggests that a high level of vitamin D at the time of diagnosis, and possibly during cancer treatment, may improve the prognosis of at least the three malignancies considered. As discussed previously, late anti-cancer effects of vitamin D, such as reduction in metastases, are observed in numerous animal models. Some animal data suggest that vitamin D activity (using a vitamin D analogue) may improve tumor control by radiation treatment, in part by promoting apoptosis [30].

Obesity, which substantially lowers vitamin D concentrations, has been associated with increased mortality rate of numerous cancers [53]. Obesity has been suggested to be a poor prognostic factor for various cancer sites, including colon [54], breast [55], and prostate cancers [56, 57]. Among African-Americans, who also have much lower circulating 25(OH)D levels, males have a 40% higher mortality rate for total cancer and females have a 20% higher mortality rate compared to their whites counterparts [58]. These differences are not primarily due to differences in incidence. For total cancer, African-Americans have an advanced stage at presentation, and five-year survival rates are worse for almost all cancer sites, and across all stages. For breast

cancer, even corrected for grade, African-American women present with higher stage and more positive lymph nodes than white women [59]. Many factors have been considered as potentially explaining these differences, ranging from unequal access to medical care to differences in tumor biology. However, because consistently poorer survival is observed for cancer sites that are heterogeneous in regards to screening and treatment efficacy, access to treatment may not explain all of the differences.

Genetic epidemiology has allowed the consideration of polymorphisms in the vitamin D receptor as a complementary approach to examine the vitamin D cancer hypothesis. This endeavor may prove to be fruitful, but because of questions regarding the functionality of the specific polymorphisms, this approach has not as yet substantially helped in resolving the important questions regarding vitamin D status and cancer risk. To date, much of the research in this area has been focused on three adjacent restriction fragment length polymorphisms for BMI, ApaI and TaqI at the 3′ end of the vitamin D receptor gene [60]. These polymorphisms are probably non-functional, but may be in linkage disequilibrium with functional polymorphisms elsewhere in the vitamin D receptor gene. It is important for future research to identify new functional polymorphisms, and examine these in relation to cancer incidence and survival.

In summary, no epidemiologic studies have directly measured vitamin D concentrations or intake on total cancer incidence or mortality. However, higher rates of total cancer mortality in regions with less average UV-B radiation exposure, among African-Americans, and among overweight and obese people, each associated with lower circulating vitamin D, and a greater cancer mortality when individuals are diagnosed in the months when vitamin D levels are lowest are compatible with a benefit of vitamin D on cancer mortality. Table 1 summarizes the cancers that are related to these factors, and shows a strong correspondence across cancer sites influenced by these three factors which influence 25(OH)D levels. If vitamin D deficiency contributes to more aggressive tumor behavior across cancer sites, this would be consistent with this pattern. Alternative explanations are plausible, but given the strong biologic plausibility of a role of vitamin D against cancer progression, further study is important.

Table 1. Increased cancer mortality rate or poorer survival associated with lower UV-B radiation, obesity, and African-American race

Cancer site	Low UV-B radiation	Obesity	African-American
Colon	+	+	+
Rectum	+	+	+
Breast	+	+	+
Prostate	+	+	+
Esophagus	+	+	+
Liver	+	+	+
Pancreas	+	+	+
Stomach	+	+	+
Kidney	+	+	
Bladder	+		+
Uterus	+	+	+
Cervix	+	+	+
Ovary	+	+	
Lung	+		+
Non-Hodgkin's lymphoma	+	+	+
Multiple myeloma	+	+	+

Sources: Grant [8], Calle *et al.* [53], American Cancer Society [58].

Evidence for specific cancer sites

The vitamin D hypothesis may apply to multiple cancer sites, but the research focus has been primarily on colorectal, prostate, and breast cancers. Besides the inverse correlation with cancer mortality with average regional UV-B radiation, study for the other sites has been essentially non-existent or sporadic, and thus little can be said. Evidence for vitamin D and cancers of the breast, colorectum, and prostate will be reviewed here.

Breast cancer

An inverse association between regional sunlight exposure and breast cancer mortality has been observed in several analyses [4, 8, 61]. However, an analysis within the Nurses' Health Study did not find the expected geographic gradient for breast cancer incidence [62]. One nested case-control study based on 96 breast cancer cases found no association between prediagnostic $1,25(OH)_2D$ concentration and risk of breast cancer; circulating 25(OH)D, which could be the more relevant compound, was not examined. John *et al.* [63] analyzed data from NHANES I based on 190 women with incident breast cancer from a cohort of 5009 women. Several measures of sunlight exposure and dietary vitamin D intake were associated with a moderate reduction in breast cancer risk. In the Nurses' Health Study, vitamin D intake was examined prospectively in relation to breast cancer risk based on 3482 incident cases of breast cancer [64]. Total vitamin D intake (dietary plus supplements) was associated with a lower

risk of breast cancer (RR = 0.72; 95% CI = 0.55–0.94) for >500 *versus* ≤150 IU/day of vitamin D. Similar inverse associations were observed with other components of diary foods (lactose, calcium) so it was difficult to conclude definitively an independent effect of vitamin D. However, total vitamin D intake was more strongly associated with lower risk than was dietary or supplemental vitamin D intake individually, which is suggestive of an independent effect of vitamin D. Thus, the data for breast cancer incidence are suggestive of a benefit from vitamin D, but overall data are relatively sparse and inconclusive.

Colorectal cancer

The epidemiologic evidence that high vitamin D status may contribute to lower rates of colorectal cancer is strong and consistent [65]. The data linking average regional UV-B radiation and cancer mortality rates appear to suggest a stronger association for colorectal cancer than for other cancer sites. In the analysis by Grant, colorectal cancers constituted the largest group of cancers potentially preventable through an increase in UV-B radiation [8]. Grant estimated about 7000 premature deaths from colorectal cancer annually in the US due to inadequate doses of UV-B radiation. This estimate for colorectal cancer would account for about 30% of the total premature cancer deaths due to low UV-B whereas colorectal cancer mortality accounts for only about 10% of the total deaths from cancer.

Studies that have examined circulating 25(OH)D levels and subsequent risk of colorectal cancer or adenoma, the cancer precursor, have found a lower risk associated with higher 25(OH)D concentrations [44, 66–71], with one exception [72]. In the Washington County, Maryland cohort, an inverse relation between circulating 25(OH)D was observed in the first eight years after the blood sample collection [66], but no association was observed in cases diagnosed 10–17 years after the sample collection [72]. A study conducted in Finland found no relation between serum $1,25(OH)_2D$ concentration and colorectal cancer incidence, but an inverse relation was suggested for 25(OH)D level, particularly for rectal cancer [67]. A recent analysis in the Nurses' Health Study found a significant inverse association between 25(OH)D and colorectal cancer risk [44]. Several studies that have examined circulating vitamin D levels and risk of colorectal adenoma, cancer precursor, suggest an inverse association with 25(OH)D and possibly $1,25(OH)_2D$ [68–71, 73], particularly for advanced adenomas [71]. In regards to the required 25(OH)D level to reduce optimally colorectal cancer risk, no threshold was suggested in any of the studies. In the Nurses' Health Study [44], the largest relevant study of colorectal cancer, based on 193 incident cases, the RR decreased monotonically across quintiles, with a RR of 0.53 (CI, 0.27–1.04) for quintile 5 *versus* 1. The median 25(OH)D concentration in quintile 5 was 88 nmol/L.

When the relationships between colorectal cancer and dietary or supplementary vitamin D have been investigated in cohort studies of men [74, 75] and women [76–78] or both sexes [79, 80], and in case-control studies [81–88], the majority of studies suggested inverse associations for colon or rectal cancer, or both [74–77, 80, 82, 84, 86, 87]. Most importantly, all the studies of colorectal cancer that took into account supplementary vitamin D reported an inverse association. In these studies, the cutpoint for the top category was from approximately 500 to 600 IU/day, with an average of approximately 700–800 IU/day in this category. The risk reduction in the top versus bottom category was as follows: 46% [76], 34% [75], 58% [77], 24% [78], 30% [87], 29% male, 0% female [80], and 50% males, 40% females [88].

Milk and dairy products are sources of vitamin D in some populations that use fortification, and additionally, milk is an important source of calcium. Calcium intake influences the vitamin D requirements and increasing calcium intake lowers circulating $1,25(OH)_2D$ levels. Calcium intake had been hypothesized to decrease colorectal cancer risk [89], and there is now strong evidence [90] for a benefit of higher calcium intakes. For example, a recent meta-analysis found an inverse association for colorectal cancer for total dairy products (odds ratio (OR) = 0.62, 95% confidence interval (CI) 0.52–0.74 and for milk (OR = 0.80, 95% CI 0.68–0.95) based on published cohort studies [90]. Moreover, the meta-analysis did not include four recent supportive reports (from five distinct study populations) for calcium intake [79, 80, 91, 92]. Similar results have also been observed in a study of pooled data from large prospective studies [93]. Some of the studies also found calcium supplements reduced risk [80, 92], and data from randomized trials for adenoma risk among individuals with previous adenomas support a protective role for calcium [94, 95]. Some evidence indicates that calcium and vitamin D interact to lower risk [71, 96]. Although the precise dose-response relationship is difficult to assess, the recent prospective epidemiologic studies with the most comprehensive dietary assessments suggest that the benefit of calcium on colorectal cancer risk may be primarily in avoiding low intakes, and question whether a benefit exists beyond 800–1000 mg/day [80, 91–93].

In summary, the data for vitamin D intakes and 25(OH)D concentrations and UV-B exposure for colorectal cancer and adenoma, and on UV-B are generally consistent with a protective effect for higher 25(OH)D. Estimated optimal intakes are in the range of at least 700–800 nmol/day, and optimal serum 25(OH)D at least 90 nmol/L. However, as no plateau could be identified, optimal intakes and levels may be higher. In addition, higher intakes of calcium and milk appear to be protective.

Prostate cancer

For prostate cancer, the results regarding vitamin D are generally non-supportive. In populations where severe vitamin D deficiency is uncommon, higher 25(OH)D level has not been associated with a reduced risk [97–101]. Only two studies [102, 103], which were conducted in Nordic countries, supported an inverse association for 25(OH)D, though one of these studies also found an increased risk in men with the highest 25(OH)D values [103]. Because of the high latitude and reduced sunshine exposure in Nordic countries, 25(OH)D levels were quite low, and $1,25(OH)_2D$ synthesis is impaired only when 25(OH)D is seriously deficient [104–107]. Thus, it is possible that the 25(OH)D levels were low enough to influence substrate availability for $1,25(OH)_2D$, though $1,25(OH)_2D$ was not measured in these studies. Regarding $1,25(OH)_2D$, one study [97] is supportive, while another is suggestive [98] for an inverse association for circulating $1,25(OH)_2D$ and aggressive prostate cancer, particularly in older men. Interestingly, in a case-control study conducted in the UK, where vitamin D deficiency is relatively common in the elderly [108], regular foreign holidays, higher sunbathing score, and higher exposure to UV radiation were associated with a reduced risk of prostate cancer [109]. However, in the study by Grant [8], average regional UV-B radiation was only weakly related to prostate cancer mortality. A recent nested case-control study did not support a reduced risk of prostate cancer associated with higher $1,25(OH)_2D$ or 25(OH)D [100], but the vast majority of cancers were organ-confined and detected through PSA elevation in this study. Another recent small study based on 83 cases from the National Prevention of Cancer Trial found no association between plasma 25(OH)D or $1,25(OH)_2D$ and total prostate cancer risk [101].

In contrast to colorectal cancer, none of the four studies that have evaluated whether dietary or supplemental vitamin D is related to risk of prostate cancer support a protective association [38, 110–112]. In one cohort, vitamin D intake was found to be inversely associated with colorectal cancer risk [75], but not with prostate cancer risk [110]. This finding suggests the effect of dietary vitamin D may differ between prostate and colorectal cancer.

For prostate cancer, a different pattern from colorectal cancer emerges for calcium and milk intake. Countries with greater per capita consumption of milk, especially the non-fat portion of milk [113], have higher prostate cancer mortality rates [114, 115]. A number of case-control [111, 112] and prospective cohort [37, 110, 116, 117] studies have shown positive associations between calcium intake and prostate cancer risk, especially for advanced disease [110–112, 116] and at higher doses taking supplements into account [110, 116]. Other studies are non-supportive [38, 118–120] or only suggestive of an association with calcium [121, 122]. In many case-control studies, men consuming high levels of milk and other dairy products are at an either statistically significant increased risk [112, 123–128] or borderline significant ($p \leq 0.1$) increased risk of prostate cancer [121, 122, 129, 130], though several studies have not supported an association [131, 132]. A recent meta-analysis of eleven case-control studies published between 1984 and 2003 found a combined odds ratio of 1.68 (95% CI = 1.34–2.12) [133]. Most prospective cohort studies [37, 117, 118, 134–136] but not all [38, 137–139] support an association between higher intake of milk or dairy products and risk of prostate cancer. The magnitude of the relative risks comparing the high and low categories of milk or calcium intakes has varied across studies; the relative risk has been two-fold or higher in some studies [110–112, 117, 123, 125, 126], and from about 1.5-fold to less than two-fold in others [116, 122, 124, 127, 128]. In the remaining supportive studies, the relative risks have been about 1.3 to 1.4-fold [37, 121, 134, 135].

Although not entirely consistent, these data are compatible with the hypothesis that low $1,25(OH)_2D$ and very low 25(OH)D, which could lower $1,25(OH)_2D$, may increase risk of prostate cancer incidence or progression. Vitamin D intake does not appear to be appreciably associated with risk of prostate cancer, though studies are relatively sparse. High calcium and milk intakes appear to increase risk of aggressive or advanced prostate cancer.

A hypothesis to explain divergent results between colorectal and prostate cancers

Fig. 2 broadly summarizes the divergent pattern, as just discussed, for factors related to vitamin D and calcium for risks of colorectal and prostate cancer. Given the *in vitro* and *in vivo* evidence supporting a benefit of

Vitamin D, Calcium and Cancer: Summary of Relationships from Epidemiologic Studies			
	Colorectal	Prostate	
Ecologic (UV-B)	↓↓	↓	(weak)
Vitamin D Intake	↓↓	0	
Circulating 25(OH)D		↓ *	
$1,25(OH)_2D$	0	↓	(aggressive)
		0/↑	(non-aggressive)
Calcium / Milk Intake	↓↓	↑↑	(aggressive)
		0	(non-aggressive)

↓↓ = strong protection ↓ = suggestive protection
↑↑= strong increased risk
* perhaps only for clinically low 25(OH)D levels

Fig. 2.

vitamin D for both these cancers, what can account for these quite different patterns? One possible factor to consider is the capacity of cells to convert 25(OH)D to $1,25(OH)_2D$ via 1-α-hydroxylase. An important recent finding is that whereas normal prostate cells possess 1-α-hydroxylase activity, prostate cancer cells have profoundly reduced 1-α-hydroxylase activity, and thus respond to $1,25(OH)_2D$ but not to 25(OH)D treatment [140, 141]. This finding seems to be robust for many prostate cancer primary cultures and cell lines. The defect in enzyme activity appears to caused by decreased promotor activity [140]. In one study, transfection of 1-α-hydroxylase cDNA in LNCaP cells restored the inhibitory effects of 25(OH)D [142]. A recent study concluded that diminished 1-α-hydroxylase activity in prostate cancer cell lines occurs through decreased gene expression, whereas decreased activity in primary cultures occurs through post-translational means [143].

If intracellular $1,25(OH)_2D$ levels are relevant for cancer risk, we might consider two distinct patterns based on whether 1-α-hydroxylase activity is present or not (illustrated in Fig. 3). Because colorectal cancer cells generally retain normal or perhaps exhibit even elevated 1-α-hydroxylase activity [144, 145], sunlight, vitamin D intake and circulating 25(OH)D levels would be predicted to be important, whereas circulating $1,25(OH)_2D$ may be largely irrelevant because cells could make $1,25(OH)_2D$ from 25(OH)D. In contrast, due to loss of 1-α-hydroxylase activity, prostate cancer cells may become insensitive to circulating 25(OH)D and thereby more dependent on circulating $1,25(OH)_2D$. Circulating $1,25(OH)_2D$ levels are tightly regulated, and although 25(OH)D is the substrate for $1,25(OH)_2D$, the concentrations of $1,25(OH)_2D$ and 25(OH)D are not correlated except when 25(OH)D is seriously deficient [104–107]. For prostate cancer, such consistency for 25(OH)D or its determinants (sunlight, intake) is not observed, and in fact, some studies suggest circulating $1,25(OH)_2D$ itself [97, 98] or only levels of 25(OH)D sufficiently low to reduce $1,25(OH)_2D$ availability [102, 103] may be relevant, at least for aggressive prostate cancer.

The loss of 1-α-hydroxylase activity could not only explain the weak findings for sunlight [8], vitamin D intake [38, 110–112] and circulating 25(OH)D [97–100,

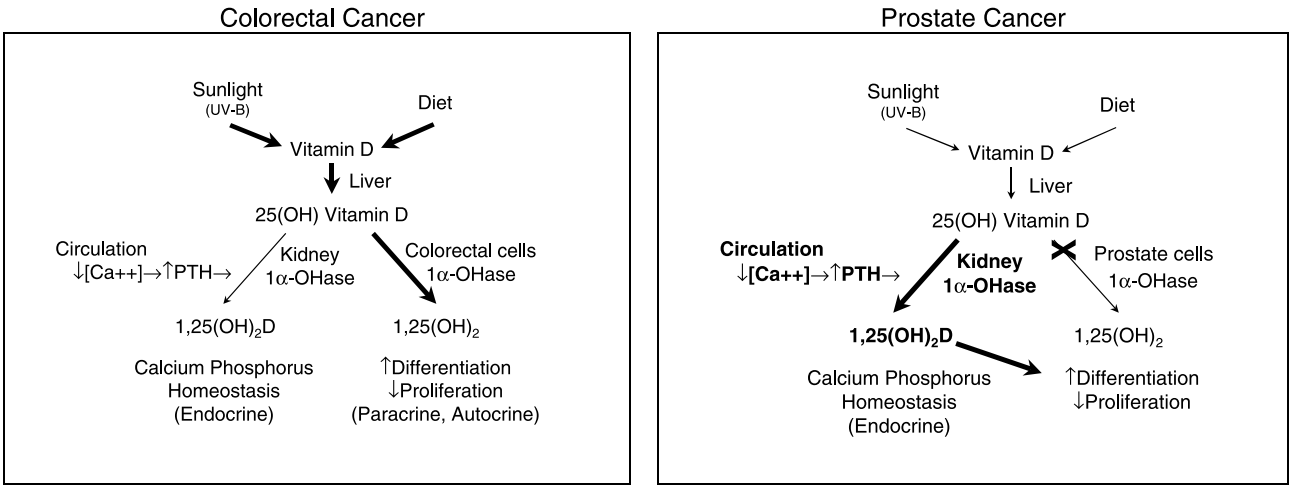

Fig. 3. Proposed mechanism for why vitamin D influences prostate and colorectal cancer differently: For colorectal cancer, cells maintain 1-α-hydroxylase activity and the predominant influence is from paracrine or autocrine $1,25(OH)_2D$ produced intracellularly from 25(OH)D. For prostate cancer, loss of 1-α-hydroxylase activity reduces paracrine or autocrine influence and reliance on total circulating 25(OH)D and increases influence of circulating $1,25(OH)_2D$, which is tightly regulated by calcium and phosphorus status (e.g., calcium intake).

102, 103] for prostate cancer, but also suggests that high milk and calcium intake could be deleterious because these lower circulating $1,25(OH)_2D$ levels [35]. For example, in the Physicians' Health Study, men who consumed >600 mg calcium/day from skim milk had a $1,25(OH)_2D$ level of 30.06 pg/ml compared to 35.64 pg/ml in men with an intake of <150 mg/day ($p = 0.005$). Thus, low calcium intake was associated with about a 20% increase in $1,25(OH)_2D$ levels compared with high intakes. While a change of this magnitude may appear relatively modest, within an individual, $1,25(OH)_2D$ level is tightly regulated, so this difference could be important. Moreover, because the half-life of $1,25(OH)_2D$ is about 3–6 h, this 20% difference, based on a single random measurement, is likely to substantially underestimate the difference in time-integrated $1,25(OH)_2D$ concentration. Further support that this seemingly moderate 20% difference in $1,25(OH)_2D$ concentration could have an important physiologic influence on prostate cancer is provided by studies that demonstrate that administration of $1,25(OH)_2D$ can slow the rate of rise of PSA in patients with advanced prostate cancer [18–20]. For example, in one study, $1,25(OH)_2D$ increased from 43.4 to 52.9 pg/ml, a 22% increase after $1,25(OH)_2D$ treatment; nonetheless, this treatment significantly slowed the rate of rise in PSA for recurrent prostate cancer [20]. This rise in $1,25(OH)_2D$, comparable to the 20% higher level in men with low dietary calcium intakes compared to those with higher intakes [37], is thus biologically important.

Conclusions and implications

In vitro, animal and clinical studies strongly indicate that vitamin D may have anti-cancer benefits, including against progression (such as metastasis) against a wide spectrum of cancers. Thus, vitamin D could be potentially beneficial against either incidence or mortality, or both. High-risk groups for hypovitaminosis D include individuals with low intakes, who live in regions with low sunlight intensity, who avoid sunlight or thoroughly use sunscreen, who have darker skin, who are old, who live in a nursing home, and who are overweight or obese. No epidemiologic studies have directly measured vitamin D concentrations or intakes on risk of total cancer incidence or mortality. However, higher rates of total cancer mortality in regions with less UV-B radiation, and among African-Americans and overweight and obese people, each associated with lower circulating vitamin D, and a greater cancer mortality when individuals are diagnosed in the months when vitamin D levels are lowest are compatible with a benefit of vitamin D on cancer mortality. The similarity in the cancer sites associated with evidence of increased mortality or aggressive behavior related to obesity, dark skin, and residence in low UV-B region is intriguing, and deserves further investigation.

The only individual cancer sites that have been examined in relation to vitamin D in some detail are colorectal, prostate and breast cancer. For breast cancer, some data are promising but far too sparse to support a conclusion. The evidence that higher 25(OH)D levels, through sunlight exposure or dietary or supplement intake, inhibits colorectal carcinogenesis is substantial. The biologic evidence for an anti-cancer role of 25(OH)D is also strong for prostate cancer, but the epidemiologic evidence has not been supportive. Although not entirely consistent, some evidence suggests that higher $1,25(OH)_2D$ may be more important than 25(OH)D for protection against prostate cancer, and only for aggressive, poorly-differentiated cancers. A possible explanation for these divergent results is that unlike colorectal tumors, prostate cancers lose the ability to hydroxylate 25(OH)D to $1,25(OH)_2D$, and may rely on the circulation as the main source of $1,25(OH)_2D$. The suppression of circulating $1,25(OH)_2D$ levels by calcium intake could explain why higher calcium and milk intakes are associated with increased risk of advanced prostate cancer.

For bone health, for which the benefits of vitamin D are more established, substantially higher-levels than are achievable through current recommendations are required. Some experts recommend at least 1000 IU vitamin D/day, which is five times higher than levels recommended for younger people (<50 years of age). For optimal colorectal cancer prevention, similarly high intakes are likely to be required. Another consideration may be the potentially antagonistic effect of high retinol intakes in vitamin D actions, which has been established for calcium homeostasis and bone health. In the US, supplements with vitamin D usually contain retinol, which may somewhat offset the potential benefit from vitamin D.

The available data on vitamin D and cancer incidence or mortality are intriguing but far from complete, and the following important questions remain: (1) do higher vitamin D levels lower cancer risk in humans; (2) what cancer sites are affected; (3) what stage in the natural history is vitamin D most important, and is the influence primarily on incidence or mortality; (4) if beneficial, what is the optimal intake and circulating concentration; (5) does high calcium intake, which suppresses circulating $1,25(OH)_2D$, have an adverse effect on prostate cancer because prostate cancer cells lose 1-α-hydroxylase activity, and if so, what calcium intake is optimal to balance

pros and cons; (6) could excessive retinol intake counter the potential benefit from vitamin D on cancer risk; and (7) are higher cancer mortality rates in overweight and obese individuals, African-Americans, and residents of the Northeastern US related to the higher prevalence of hypovitaminosis D in these groups? Given the potential benefits from this vitamin against a wide spectrum of malignancies, further research should be a priority.

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