Vitamin D and Cancer Prevention

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Abstract Vitamin D and its potential role in the prevention of cancer have received widespread attention in recent years. A broad range of potential vitamin D-related mechanisms affecting carcinogenesis have been identified. Epidemiology now provides evidence for a cancer protective role of elevated levels of serum vitamin D, particularly for colorectal cancer, and less clearly for breast cancer, while for many other cancers, including cancer of the prostate, no associations have been demonstrated. There continues to be a gap between results from observational trials assessing vitamin D status and those from randomized trials of vitamin D supplementation that cannot be resolved easily. However, whether new randomized trials on vitamin D and cancer development should be conducted in the future remains debatable.

Keywords Vitamin D · Ultraviolet light · Supplementation · Cancer · Prevention · Epidemiology · Case–control study · Cohort study · Randomized controlled trial · Colorectal cancer · Breast cancer · Prostate cancer

Introduction

Evidence linking vitamin D (25[OH] cholecalciferol) (25[OH] vitamin D) to cancer risk has been accumulating over many decades. Scientific approaches from a variety of disciplines, including major contributions from cancer

epidemiology, are used in this research field. Geographical correlation, or ecological studies played a major role in the initial scientific discussion on vitamin D. The early ecological studies were conducted in the United States and provided evidence indicative of a north–south gradient in the risk of specific cancers. This prompted the hypothesis of a protective influence of vitamin D levels, modulated by the amount of average solar irradiation, on the risk of cancer at various sites, and also for other chronic conditions, such as cardiovascular and neurological diseases. UV irradiation, on the other hand, is well-known for its carcinogenic potential with regard to skin cancer—an effect not associated with vitamin D.

Vitamin D is necessary for human survival and has well-established supportive influences on bone formation and the neuromuscular system, mainly through its effect on calcium metabolism. Other functional properties of 25(OH) vitamin D and the physiologically active form, $1\alpha,25(\text{OH})_2$ vitamin D, include anticarcinogenic and anti-cell proliferative effects established in the laboratory. Vitamin D is synthesized through a chain of processes initiated by UV irradiation of the skin. In addition, there are food sources of vitamin D, as well as nutritional supplements and pharmaceutical preparations containing vitamin D. Some controversy exists as to the optimal serum levels of vitamin D, and these levels may well differ depending on the health outcome of interest [1].

This paper gives an overview of the physiology and characteristics of vitamin D, describes current data on vitamin D levels in various populations, and then examines the evidence from epidemiologic studies on vitamin D and cancer, with a focus on recent observational studies in large populations. The main theme of this paper is thus the question of whether high serum levels of vitamin D are associated with lower risks of cancer.

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Vitamin D

UVB skin exposure is the main source of vitamin D for most people, with foods such as fish and dairy products or vitamin D supplements providing the remainder. Some countries allow vitamin D food fortification. Skin exposure to UVB light photoisomerizes 7-dehydrocholesterol, a precursor substance, which leads to production of vitamin D₃ (Fig. 1). In turn, vitamin D₃ is metabolized to 25(OH) vitamin D in the liver and is stored or released into the bloodstream. The concentration of 25(OH) vitamin D serves as a biomarker for the vitamin D status of individuals. The kidney produces the biologically active form, 1,25(OH)₂ vitamin D.

A well-established function of the physiologically active form of vitamin D is the maintenance of calcium (and phosphorus) homeostasis by influencing both the intestinal uptake and the urinary excretion in the kidney. Both mechanisms aid in the mineralization of bones as well as in the functioning of neuromuscular processes. Because the calcium level in the body may only vary within a narrow range before problems, including muscular symptoms or, more severely, cardiac arrhythmias may occur, there is a finely tuned interplay with parathyroid hormone that ensures that

low calcium serum levels are increased through several mechanisms, including increased transformation of inactive into active 1,25(OH)₂ vitamin D [2].

With regard to cancer prevention, there is a growing body of literature linking in particular the active form of vitamin D to various aspects of cell proliferation and differentiation [3]. Most of these mechanisms have thus far only been established in vitro. The exact mechanisms concerning, for example, the inhibition of cell proliferation are under investigation and may vary between different types of tumors. However, current understanding includes direct regulation of genes responsible for cell proliferation as well as actions of vitamin D on growth-stimulating factors such as insulin-like growth factor (IGF), for example, through increased synthesis of IGF-binding protein. Other putative actions of vitamin D, including activation of immune responses and anti-inflammatory effects, are under investigation.

Of particular interest with respect to potential antineoplastic properties of vitamin D is the finding that most cells, including many cancer cells, carry vitamin D receptors (VDR), thus making them targets for actions of vitamin D. VDR is a hormone receptor that, once activated through binding of the active form of vitamin D, exerts influence on gene regulation such that the expression of target genes is

Fig. 1 Sources, sites, and processing of vitamin D metabolites. GI, gastrointestinal. (From Zhang and Naughton [5]; redrawn with permission)

altered. VDR gene polymorphisms have been investigated in connection with numerous cancer sites, and although there is ample conflicting evidence, there are some indications of an association of VDR polymorphisms with, among others, breast and prostate cancer risk [4].

Population Vitamin D Levels

To understand the comparisons done in epidemiologic and clinical studies on vitamin D and cancer and the actual serum vitamin D levels studied, some knowledge on vitamin D serum levels in populations is required. Clinical vitamin D deficiency with 25(OH) vitamin D levels on the order of 25 nmol/L (10 ng/mL) or less leads to diseases such as osteomalacia and rickets. Serum levels below 50 nmol/L are common and are particularly prevalent in older adult populations and those at high latitude receiving limited hours of sufficient sunlight [5]. For the United States, recent representative data from the National Health and Nutrition Examination Survey (NHANES) mortality study indicate that 31.5% of participants had concentrations between 20 and 50 nmol/L, 42.5% had concentrations between 50 and 75 nmol/L, and 26% were found with levels of 75 nmol/L or greater. There are major variations with regard to ethnicity, gender, and other aspects, such as regular sun exposure and vitamin D intake through normal diet or supplements [6]. A recent US study estimated the vitamin D levels that children obtain from their usual sun exposure. According to this study, Caucasian children in northern US states could reach the recommended level of 600 IU/d of vitamin D3 in spring and summer only if they were not using sunscreen with the recommended sun protection factor of 15 or more [7]; for children with darker skin types, reaching recommended levels is even more difficult. In Germany, a national survey from 1998 showed that more than 50% of adult survey participants of both genders had levels below 50 nmol/L [8]; levels above 75 nmol/L were found in only 7% of migrant children, compared with 13% in the non-migrant population in a recent representative nationwide children and adolescent health survey [9]. However, whether vitamin D levels in the range above 30 nmol/L but below 50 or even 75 nmol/L are a matter of health concern is under some dispute [10, 11].

Evidence on Vitamin D and Cancer

Historically, initial considerations on the possible link between UV radiation exposure and cancer were derived from geographical correlation, or ecological studies. This type of study is based on aggregated data. Cancer incidence or mortality rates are compared between different regions,

counties, or provinces. Differences and trends in rates are investigated according to estimated solar radiation exposure of the areas, which differs according to latitude. Thus, the common feature of these studies is the absence of information on individual sun exposure and, more specifically, vitamin D levels.

In the United States, a marked north–south gradient, with incidence and mortality rates for colon cancer declining toward more southern states, was reported in 1980 by Garland and Garland [12]. Increasing levels of average UV radiation, and thus presumed vitamin D levels in the population, have been interpreted as potential explanations for these lower cancer rates. Similar studies have been conducted in other regions of the world, and suggestive evidence for associations between high solar irradiation and multiple cancer sites was presented [13]. In Europe, associations opposite to those from the US studies have been found for some cancers, with the highest cancer rates in countries with the highest reported average vitamin D serum levels. Incidentally, the situation with regard to the geographical distribution of vitamin D levels in Europe appears to be quite different from that in the United States, as populations in northern European countries have higher vitamin D levels than people living in southern Europe. Nutritional differences such as the more frequent consumption of fish are probably the reason for this observation, but other differences, including sun-seeking behavior, use of supplements, and other factors, may play a role. Thus, it appears obvious that lower vitamin D levels and increasing latitude do not generally equate, and other cancer risk factors also vary with latitude. Ecological studies are limited in taking account of these potential confounding factors and suffer from further difficulties, although methodologic advances, including much more detailed exposure assessment from meteorological data and approaches to confounder control, have been implemented [14]. These studies may be useful for guidance in hypothesis development as well as for cross-checking the plausibility of other studies, but they cannot provide a basis for causal inference.

Colorectal Cancer and Colon Adenoma

Colorectal cancer and colonic adenomas as precursors of colon cancer have been studied extensively for a potential association with low vitamin D levels, and evidence from many high-quality studies continues to accumulate in favor of a causal link.

In a 2008 summary report by the International Agency for Research on Cancer [2], joint analyses of the risk estimates from published cohort and case–control studies documented an inverse relationship between 25(OH) vitamin D levels and colon carcinoma, as well as adenoma of the

colon. For colorectal cancer, there was a 15% risk reduction (relative risk [RR], 0.85 [95% CI, 0.79–0.91]) for each 25-nmol/L increase in measured serum vitamin D level. The risk reduction was slightly less strong for adenoma (RR, 0.93 [95% CI, 0.88–0.99]).

Two more recent overviews yielded similar findings, with an indication that the risk of rectal cancer is more strongly affected than the risk of colon cancer [15, 16]. For rectal cancer, a 59% risk reduction associated with an increase of 50 nmol/L of 25(OH) vitamin D was reported from this meta-analysis of prospective studies, and a 22% reduction for colon cancer was reported. A less marked effect of vitamin D (6% reduction of colorectal cancer risk) was reported from another large meta-analysis. Data from 60 observational studies were analyzed, and whereas vitamin D associations with colorectal cancer risk were of small magnitude, a marked risk reduction (up to 45%) associated with intake of calcium was reported [16]. All in all, results from observational studies on colon adenoma and colorectal cancer clearly suggest a protective role of high vitamin D levels.

These observational study results, however, are not supported by results from intervention trials on vitamin D supplementation. One of the largest studies to date is the Women's Health Initiative, a randomized, double-blind, placebo-controlled, multicenter study. More than 18,000 women receiving 10 µg (400 IU) of vitamin D₃ and 1,000 mg of elemental calcium daily over an average of 7 years did not show reduced colorectal cancer risk as compared with women receiving placebo [17]. Extensive sensitivity analyses left the main results unchanged. Although the study was reported to be adequately powered to detect a 22% risk reduction, the duration of 7 years was criticized as too short to allow firm conclusions to be drawn about the development of colorectal cancer. However, in a nested case-control study, cases identified during the trials were found to have significantly lower baseline vitamin D levels compared with controls, with a 2.5-fold risk increase in the lowest vitamin D level quartile (<31 nmol/L) as compared with the highest quartile (>58 nmol/L).

Breast Cancer

Laboratory studies underline the ability of high levels of vitamin D to suppress carcinogenesis directly in mammary tissue, and the mechanistic pathways were recently reviewed [18•]. In terms of epidemiology, breast cancer and its relationship to vitamin D have been studied in observational as well as randomized trials; however, the results were less consistent when compared with those for colorectal cancer. In a 4-year randomized clinical trial involving 1,179 women in Nebraska, the secondary outcome was all cancers, about one third of which were breast

cancers. Women in the intervention arm received a relatively high dose of 27.5 µg (1,100 IU) of vitamin D in combination with calcium. An inverse association between vitamin D and cancer, with 33% risk reduction for every 25-nmol/L increase in serum vitamin D level, was reported. Due to small numbers, no separate results for breast cancer were reported [19]. Uncertain compliance as well as issues regarding the statistical approach were discussed as problems involved with this trial [2], and the baseline vitamin D levels in control and intervention groups—above 70 nmol/L—were noted to be rather high. Specific results for breast cancer from the Women's Health Initiative trial (see above) after 7 years were negative, and the nested case-control study showed no differences between baseline vitamin D serum levels in case-control comparisons [20]. Several new randomized supplementation trials are currently under way.

Comprehensive meta-analyses of observational and clinical studies point to a modest reduction in breast cancer risk associated with higher levels of serum vitamin D. A recent report found a 27% risk reduction in the joint analysis of case-control studies [21]. However, the risk reduction was largely confined to case-control studies that measured serum vitamin D levels after diagnosis, whereas for case-control studies nested in cohorts with vitamin D measurements many years before diagnosis, the reduction was weak and nonsignificant. Chen et al. [22] also reported significant inverse relationships between both vitamin D intake and serum levels of vitamin D and breast cancer risk from a pooled analysis of 11 studies, but no associations for the studies relating circulating levels of the biologically active 1,25(OH)₂ vitamin D levels to breast cancer risk. In separate analyses, cohort and case-control studies yielded slightly different results. A significant risk reduction in the highest quartile of vitamin D intake was only found in the cohorts. A current comprehensive review of vitamin D and breast cancer additionally points out that several new cohorts from Scandinavian and other European countries have failed to show an association between vitamin D and breast cancer risk [23••]. Thus, the question of a vitamin D–breast cancer link appears still partly unresolved, and efforts to obtain more evidence from high-quality observational and perhaps intervention trials are warranted.

Prostate Cancer

Prostate cancer is one of the most common cancers in men, and its etiology remains largely unclear. Ecological studies have repeatedly pointed out inverse associations between solar UV levels and prostate cancer risk. Conversely, observational studies generally have not shown protective effects of vitamin D. A new pooled analysis of 11 studies found no associations between vitamin D and prostate cancer risk (RR

per 25-nmol/L increase, 0.99 [95% CI, 0.95–1.03]) [24]. Similar null results were obtained in an even more extensive systematic review and meta-analysis [25•], which also included a recent study nested in the randomized, placebo-controlled Prostate Cancer Prevention Trial. This study also showed no association between risk of prostate cancer and intake of vitamin D or any other nutrient [26]. Current epidemiologic evidence thus does not support a link between vitamin D and prostate cancer. There is at least one reason for caution, however: all available studies focus on vitamin D serum levels or vitamin D intake in adulthood. Whether vitamin D levels in childhood or adolescence are important for prostate cancer risk late in life cannot be assessed from current studies.

Other Cancer Sites

Many other cancers have been investigated with regard to vitamin D. A major initiative to collect and jointly analyze the evidence on rarer cancers is the Vitamin D Pooling Project of Rarer Cancers (VDPP) [27, 28]. Ten cohorts from heterogeneous populations were pooled to conduct studies on seven cancer types, including gastric, pancreatic, and kidney cancer, as well as non-Hodgkin's lymphoma. Overall, there was no association between serum vitamin D levels and any of the cancers. For pancreatic cancer, very high levels of vitamin D (> 100 nmol/L) seemed to increase risk by a factor of two [29].

Vitamin D for Cancer Patients

Beyond the question of a primary preventive role of vitamin D, the question of whether vitamin D is useful for cancer patients with regard to reducing recurrence and mortality has also received attention recently [30, 31]. A small body of evidence suggests that low serum vitamin D levels may be predictive of a worse outcome in some cancers; however, much more research will be needed to inform clinical practice. For prostate cancer, several intervention trials have not shown any benefit of vitamin D supplementation. A joint analysis of data from three studies found no improved survival for supplement users; major heterogeneity between the trials was noted [30].

Conclusions

The interest in vitamin D as a potential chemopreventive agent in cancer prevention has virtually exploded during the past decade. This can be interpreted as a late response by the scientific community to early reports by Garland and

Garland [12], who were the first to point out a potential role for vitamin D in colorectal cancer prevention. Prevention studies have moved from ecological approaches to analytical observational trials and in some cases to randomized intervention studies, and from studies attempting to quantify vitamin D intake to investigations relying on serum measurements. On the other hand, there is a continuous flow of new findings from experimental studies showing a myriad of potential mechanisms through which vitamin D and its metabolites could play a role in cancer development. As can be expected in such a rapidly developing research arena, there is conflicting evidence with regard to many of the issues under investigation, but some consistency begins to emerge.

First, based on the accumulating evidence from many different observational studies, colorectal cancer and adenoma of the colon are strong candidates for a preventive role of high levels of vitamin D. The one missing piece of support relates to intervention trials, which have not shown the same effects as the observational trials. Although this may be related to the individual characteristics of the available trials, Gandini et al. [24] proposed an alternative line of thought—that the vitamin D level may be indicative of the propensity of an individual to develop colorectal cancer rather than being a cause in itself. Lifestyle factors, including smoking, physical activity, and nutrition, would be associated with this propensity. An improved scientific understanding of the conflicting observations is likely to be achieved only through new studies or data obtained from extending the existing longitudinal studies.

Second, for other cancers, the evidence on the preventive potential of vitamin D is less convincing. The second-best candidate is breast cancer, but if a risk reduction exists, it may be of lower magnitude than that for colorectal cancer. Prostate cancer studies, on the other hand, have resulted in null findings in the majority of cases. This includes the use of vitamin D supplementation for prostate cancer patients. Similarly, the search for a causal role of vitamin D levels in other, rarer cancers has not yielded results that strongly indicate preventive potential. For some authors, however, the reliance on randomized trials or analytical observational studies seems unwarranted, as they consider evidence from geographical correlation studies sufficient to recommend a general increase in vitamin D levels for cancer prevention and reduction of overall mortality [32]. Thus far, however, many scientists remain cautious regarding changed recommendations on vitamin D levels. The well-known harms of increased exposure to UVB as one way of increasing vitamin D levels further complicate matters [33].

In summary, vitamin D, the “sunshine vitamin,” continues to be an interesting topic for cancer prevention studies, and no doubt new molecular pathways and mechanisms will be identified that contribute to an improved understanding of vitamin D action. Are large-scale randomized trials the

only way to provide more conclusive answers on vitamin D in cancer prevention? Although the idea is scientifically intriguing, caution is warranted given the costs and the restricted scope of randomized clinical trials [28]. Finally, in considering the importance of vitamin D for health, its effects on other health end points and on overall mortality also should be included in a comprehensive assessment.

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