

## Review Article

## Vitamin D Role in Prevention of Cancer: Overview

## Abstract

Vitamin D is the name given to a group of fat-soluble prohormones. Two major forms of Vitamin D that are important to humans are Vitamin D<sub>2</sub> or ergocalciferol and Vitamin D<sub>3</sub> or cholecalciferol. Vitamin D<sub>2</sub> is made naturally by the body when the skin is exposed to ultraviolet radiation (in particular, ultraviolet B [UVB] radiation) in sunlight. Vitamin D<sub>2</sub> and Vitamin D<sub>3</sub> can also be commercially manufactured. The active form of Vitamin D in the body is 1,25-dihydroxyvitamin D or calcitriol, which can be made from either Vitamin D<sub>2</sub> or Vitamin D<sub>3</sub>. Evidence suggests that Vitamin D helps in the prevention of various cancers such as breast cancer, colorectal cancer, prostate cancer, head and neck cancer, and other cancers. This review article briefs about the role of Vitamin D in the prevention of cancer.

**Keywords:** Cancer, Vitamin D, Vitamin D<sub>3</sub> (1,25-dihydroxycholecalciferol, calcitriol)

## Introduction

Vitamin D, unlike other vitamins, synthesis by the human body following exposure to ultraviolet rays. Hence, it is also called “Sunshine Vitamin.” It is a fat-soluble vitamin and stored in the body’s fatty tissue, which maintains serum calcium and phosphorus level. Vitamin D deficiency is considered the most prevalent nutritional deficiency in both developed and developing countries. Vitamin D deficiency is fast becoming pandemic, a global and national health concern. However, the bigger concern is that the population at large is not even aware of Vitamin D deficiency and its consequences. One-third of all cancers could be attributed to dietary deficiency.

Cancer has a poor prognosis despite improvements in surgery, chemotherapy, and radiotherapy and has increased the prevalence of morbidity and mortality. Cancer chemoprevention plays a very important role in preventing the deadly devastating disease of our society. In this fast-moving competitive world with sedentary lifestyle, habits have been changed. We are consuming adulterated food with less nutritious. Most of the time we stay indoors with less physical activities leads to obesity and because of workload results in decreased exposure

to sunlight. Use of sunscreen lotions, clothing to protect from sunlight, air pollution, and latitude all these factors which leads to decrease in Vitamin D (1,25-dihydroxyvitamin D) synthesis. The active form of Vitamin D in the body is 1,25-dihydroxyvitamin D or calcitriol, which can be made from either Vitamin D<sub>2</sub> or Vitamin D<sub>3</sub> after exposure to ultraviolet B (UVB) sunlight or ingested in the diet. To make the active form, Vitamin D<sub>2</sub> and Vitamin D<sub>3</sub> are modified in the liver to produce 25-hydroxyvitamin D (25 [OH] D), which travels through the blood to kidneys, where it is modified further to make 1,25-dihydroxyvitamin D. Vitamin D is involved in a number of processes that are essential for good health, including the followings:

- It helps improve muscle strength and immune function
- It helps to reduce inflammation
- It promotes the calcium absorption from the small intestine
- It helps maintain adequate blood levels of the calcium and phosphate needed for bone formation, mineralization, growth, and repair.<sup>[1-3]</sup> It can also be obtained through the diet, but very few foods naturally contain vitamin D. These foods include oily fish such as salmon, mackerel and sardine, fish liver oil, and eggs. Smaller amounts are found in meat and cheese. The most dietary Vitamin D comes from fortified

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foods such as milk, juices, yogurt, bread, and breakfast cereals. Vitamin D also can be obtained through dietary supplements. Dietary supplements and fortified foods usually contain either Vitamin D<sub>2</sub> or Vitamin D<sub>3</sub>.<sup>[2]</sup>

### Role of Vitamin D in prevention of cancer

Women with higher solar UVB exposure in the third National Health and Nutrition Examination Survey had only half of the incidence of breast cancer as those with lower solar exposure,<sup>[4]</sup> whereas men in another national survey who had higher residential solar UVB exposure had only half the incidence rate of fatal prostate, colorectal, and breast cancer.<sup>[5]</sup> Fifty percent reduction in head and neck cancer after administration of Vitamin D<sub>3</sub>-treated animals.<sup>[11]</sup> The strong association of Vitamin D deficiency in diabetes, immunity, asthma, infections, high blood pressure, neuromuscular function, cancer, etc., was noted in contrast with the fact that Vitamin D receptors present in various organs and tissues of the human body, maintaining Vitamin D levels in blood above 30 ng/ml may ensure normal functioning of the body organs, and protect many from suffering from chronic ailments.<sup>[6,7,10]</sup> Vitamin D status in relation to 25(OH) D levels according to the US endocrine society classification as follows.<sup>[7]</sup>

Vitamin D deficiency, if serum level of 25 (OH) D level <20 ng/ml, Vitamin D insufficiency if serum level of 25 (OH) D level <21–29 ng/ml, Vitamin D sufficiency if serum level of 25 (OH) D level >30 ng/ml, and Vitamin D toxicity if serum level of 25 (OH) D level >150 ng/ml. The term deficiency of Vitamin D does not necessarily suggest explicit disease clinically, rather it means an increased risk for certain diseases and that also explains the seeming paradox that individuals who are ostensibly healthy today may nevertheless be deficient. As these diseases are multifactorial etiology, deficiency of Vitamin D, rather than being directly causal, acts by impeding the ability of tissues to adequately deal with physiological and pathological stimuli. However, these diseases will occur in the presence of optimum Vitamin D status; their risk will be lowered.<sup>[8]</sup> Improved understanding of the detrimental effects of Vitamin D insufficiency before the appearance of rickets led to a growing interest in these lesser degrees of Vitamin D deficiency and diagnosing this prerachitic, subclinical Vitamin D deficiency is important for non-skeletal health benefits.<sup>[23]</sup> Exposure of arms and legs to sunlight for 10–15 min between the hours of 10:00 am and 3:00 pm 3–4 times a week for people of dark color, longer, and more frequent exposure is recommended up to 30-min daily.<sup>[8]</sup>

The institute of medicine was able to set a recommended daily allowance (RDA) for Vitamin D. The RDA of Vitamin D for children and adults up through age 70 is 15 µg (equal to 600 international units [IU]) per day. The RDA is 20 µg (800 IU) a day for adults older than 70. The safe upper limit for adults was set at 100 µg (4000 IU)

per day.<sup>[9]</sup> Serum or plasma 25 (OH) D is the accepted biomarker for short-term accurate assessment of Vitamin D status, can arise from hydroxylation of either Vitamin D<sub>2</sub> or D<sub>3</sub>, it is recognized that many people have unexpectedly low levels. For those people, there are questions about how much Vitamin D it takes to raise the body's stores of it to healthy levels. It has been estimated that for every 100 IU of Vitamin D ingested; there is an increase in the blood level of 25 (OH) D of 1 ng/ml (2.5 nmol/L). Adequate exposure to UVB radiation or sunlight is more effective in raising blood levels of 25 (OH) D than 1000 IU Vitamin D<sub>3</sub> taken daily for adults of most skin types.<sup>[12,13]</sup>

Vitamin D induces anti-inflammatory by suppression of prostaglandin action through suppression of cyclooxygenase 2 expression, stress kinases, nuclear factor KB (NF-KB) signaling, and increasing tissue inhibitor of metalloproteinases 1 and E-cadherin response. Antiproliferation by decrease in cyclin-dependent kinases, cyclins, MYC and RB expression, and increase in P21 and P27 expression and intracellular kinase pathway modulations such as MAPK, ERK, P38 and P13 pathways. Apoptosis induction by inhibition of NF-kB signaling increases the expression of BAX proapoptotic gene and decrease in BCL-2 antiapoptotic gene. Induce differentiation by increase expression of casein, lipids, prostate-specific antigen, E-cadherin differentiation factors, adhesion of cancer, and normal cells through the regulatory mechanism. In addition, it affects growth factors by inhibiting IGF, EGF, and increased expression of growth inhibitor TGF-Beta, regulation of cell division, cytokine synthesis, signaling cell cycle control, and apoptosis pathway. Antiangiogenesis by decrease the activity of hypoxia-inducible factor alpha, vascular endothelial growth factor, interleukin-8, tenascin C, and prostaglandin E2 levels. Anti-invasion and metastasis by decreasing expression of matrix metalloproteinases-9, integrins, and plasminogen activator.<sup>[14]</sup> Calcitriol decreases the expression of aromatase, the enzyme that generally catalyzes the peripheral estrogen synthesis from androgens as well as in cancer tissue. Calcitriol downregulates the expression of estrogen receptors and further reduces estrogen signaling in cancer cells and its anti-inflammatory actions might play a role in for the prevention for cancer.<sup>[15,16]</sup>

A pooled analysis of two studies with 880 cases and 880 controls demonstrated that individuals with serum 25 (OH) D<sub>3</sub> of approximately 52 ng/ml had a 50 percent lower risk of breast cancer than those with levels of 13 ng/ml.<sup>[17]</sup> A case-control study on 1394 postmenopausal breast cancer patients and 1365 controls confirmed that the 25 (OH) D level was significantly associated with lower breast cancer risk, particularly at levels above 20 ng/ml.<sup>[18]</sup> Another population-based randomized controlled trial found that calcium plus Vitamin D supplementation decreased cancer incidence as a secondary outcome and the dose of 1100 IU/day increased serum 25 (OH) D from 29

to 38 ng/ml. After 4 years of treatment, the supplemented group showed a 60% lower risk of developing cancer than the placebo group.<sup>[19]</sup> The study has to confirm the benefit of using calcium and Vitamin D supplement than using Vitamin D supplement alone. Women in the women's health initiative who were Vitamin D deficient (25 (OH) D <12 ng) had a 253% increased risk for developing colorectal cancer during the 8 years of the study compared with women who were Vitamin D sufficient at the beginning of the study.<sup>[20]</sup>

Potential toxic effects of Vitamin D overdosage, such as bone demineralization, hypercalcemia, hypercalciuria, or nephrocalcinosis with renal failure are encountered rarely, only when the daily dose exceeds 10,000 IU of Vitamin D on a chronic basis. However, no known health risks are associated with dosages of Vitamin D in normal range of intake 2000 IU/day which is affordable in preventing many types of cancer.<sup>[21,22]</sup> In patients with liver, kidney, and gastrointestinal disease, people taking medicines that affect Vitamin D (1,25-dihydroxyvitamin D) levels such as certain antiepileptic medication, rifampicin, isoniazid, and glucocorticoids and people with dark skin are more predispose to many types of cancer.<sup>[23]</sup>

A clinical trial comprised 16 patients with newly diagnosed head and neck squamous cell carcinoma (HNSCC) being untreated and 16 patients being treated with 1,25(OH)<sub>2</sub> D<sub>3</sub>(Vitamin D<sub>3</sub>) during a 3-week interval between cancer diagnosis and surgical treatment. The HNSCC tissues of patients who received treatment with 1,25(OH)<sub>2</sub> D<sub>3</sub>(Vitamin D<sub>3</sub>) had increased levels of CD4+ T-cells. The results of this study demonstrate that the patients treated with 1,25(OH)<sub>2</sub> D<sub>3</sub>(Vitamin D<sub>3</sub>) had a lengthier time to tumor recurrence compared with patients who were not treated before the surgery.<sup>[24-26]</sup>

Vitamin D has a complex interaction between parathyroid hormone and calcium, diet and genetic modification need to be understood. Regular estimation of Vitamin D status by serum 25 (OH) D levels is important for prevention and treating effects of extraskeletal effects caused by subclinical Vitamin D deficiency. Certain lifestyle modifications with supplementation or fortification of food can go longway to our main motto in prevention is better than no cure for this enigmatic disease in later stages.

## Conclusion

Vitamin D is the name given to a group of fat-soluble prohormones. Two major forms of vitamin D are vitamin D<sub>2</sub> or ergocalciferol and vitamin D<sub>3</sub> or cholecalciferol is an active form of vitamin D. Vitamin D is a naturally occurring vitamin and receptors of Vitamin D are present in all cell types of our body to perform various functions. Eighty percent of populations are deficient in Vitamin D because of change in lifestyle. Vitamin D deficiency is a global health concern predisposes to various diseases such as cancer. Vitamin D helps in prevention of various

cancers by reducing inflammation, antiapoptotic, and antiproliferative and decreasing aromatase activity, but there is no universal protocol for Vitamin D administration depending on patient age, weight, and location.

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## Conflicts of interest

There are no conflicts of interest.

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