International Journal of Health Sciences and Research
Volume 14; Issue: 4; April 2024
Website: www.ijhsr.org
Review Article *ISSN: 2249-9571*

Vitamin D in Oncology: Beyond Bones to Battling Cancer - A Review Article

Dr Shashikant Adlekha[1], Dr Nagadharshan Devendra[2], Dr Shilpa Kakera[3]

[1]Associate Professor, Department of Pathology, Trinity Medical Sciences University, Saint Vincent and Grenadines
[2]Associate Dean Basic Sciences and Associate professor, Department of Biochemistry, Trinity Medical Sciences University, Saint Vincent and Grenadines
[3]Associate Professor, Department of Neurosciences and Anatomy, Trinity Medical Sciences University, Saint Vincent and Grenadines

Corresponding Author- Dr Shashikant Adlekha

DOI: https://doi.org/10.52403/ijhsr.20240471

ABSTRACT

Since the discovery of vitamin D, extensive research has been conducted to explore its physiological effects and the impact of its lack on human health. The body produces fat-soluble vitamin D when exposed to sunshine. Recent experimental studies suggest that exposure to sunlight and maintaining sufficient levels of circulating vitamin D can decrease the likelihood of developing cancer. Various in vitro and in vivo research indicate that vitamin D may be a beneficial supplement for both treating and preventing cancer.
However, sufficient clinical trials must be conducted to confirm the inhibitory effect of vitamin D on cancer occurrence. Therefore, comprehending the biological mechanics of vitamin D can be beneficial in preventing several chronic diseases. This review focuses on research studies indexed in MEDLINE and other databases, that have examined the impact of vitamin D on reducing cancer rates and its role in inhibiting the progression of cancer cells.
The correlation between vitamin D and cancer has been extensively researched, yielding inconsistent findings. There is no unanimity on whether vitamin D has a good anti-cancer impact. This review outlines the relationship between vitamin D and cancer risk, as well as the findings from clinical studies on vitamin D. It also delves into the factors that lead to the variability in study results. Single nucleotide polymorphisms (SNPs) that affect the effectiveness of vitamin D supplementation are emphasized. Comprehending these distinctions can tailor strategies to enhance the efficacy of vitamin D in reducing cancer risk.

Keywords: Vitamin D, Cancer, SNP, Chronic diseases

INTRODUCTION

Vitamin D, the "sunshine Vitamin" plays an active role in bone health and immune response modulation. In addition to regulating the correct bone density and protecting against various conditions related to bones, new research studies are beginning to increasingly highlight an interesting relationship between low Vitamin D levels and malignancy. Malignancy/Cancer can refer to one of the whole ranges of different diseases that primarily feature uncontrolled and rapid multiplication of cells by growth in localized areas, invasion of adjacent tissues or organs, and spread to other parts of the body, thus becoming remotely situated. This probable link of Vitamin D with cancer offers not only preventive measures but also

poses interesting questions about dietary and lifestyle choices.

Research on vitamin D has been widely generated and has documented the importance of this hormone for health and disease processes related to calcium absorption, immune function, and regulation of cell growth. We aimed to provide a holistic information review of the role of Vitamin D in cancer prevention and therapy, emphasizing its importance in oncology and public health.

We shall initiate with this attempt to understand the multifaceted roles of Vitamin D from its metabolic pathways and sources to its implications in cancer-preventive treatment, navigating in the scientific evidence that ties this nutrient into the complex world of malignancy.

Understanding Vitamin D

Vitamin D synthesis takes place in skin by sunlight and encompasses two important metabolic conversions in both the liver and the kidneys, thus producing its active form, 1,25 dihydroxycholecalciferol. This further interacts with nuclear receptors on cells themselves, modulating gene expression and cellular activities necessary for good health and prevention of disease.[1]

Deficiency and sources

Meanwhile, a deficiency is a common thing related to insufficient exposure to sunlight, dietary intake, and health conditions. It directly relates to many health issues, for instance, a much higher predisposition to specific cancers requiring the assurance of appropriate vitamin D either through natural exposure, diets, or supplements.[1]

Vitamin D and Cancer Prevention

The anti-cancer properties of Vitamin D are based on its competence in controlling cell growth, prompting cell differentiation, and modulating the immune system. All these mechanisms, according to Feldman et al. [2], point clearly toward a role that, to some extent, could prove protective from the development of malignant forms, especially colorectal, breast, and prostate cancers.

Epidemiological Evidence

Epidemiological studies, case-control studies, and meta-analyses strongly suggested a relationship between the level of Vitamin D and the risk for cancer, particularly in colorectal and breast cancers. Though studies have also shown an association between Vitamin D Deficiency and other malignancies like Ovarian cancer, Skin cancer, bone cancers and Head and Neck cancers. It is for these reasons that the finding of a considerable, significant reduction in serum 25(OH)D levels in cancer patients and optimizing the intake through fortified diets and multivitamin supplements could be useful in exploring the potential of Vitamin D in cancer prevention strategies.[3]

Relationship between Vitamin D and Certain Cancer Types

Breast Cancer

Studies show that Vitamin D has a preventive impact against breast cancer, indicating that higher levels of Vitamin D may lower the risk of acquiring the disease. Cell growth regulation and hormonal balance are important mechanisms for preventing breast cancer. [2]

New breast cancer cases as much as 2.3 million are identified each year, making it the primary cause of mortality for women globally.[4] Research has shown that a lack of 25(OH)D is prevalent in breast cancer patients, particularly affecting younger and obese individuals. [5] The study found a correlation between 25(OH)D insufficiency and more severe grade and ER-negative subtypes of breast cancer, suggesting a reduction in the preventive benefits of vitamin D and maybe further hormonal interactions. Additional research has elucidated the significance of Vitamin D Receptor (VDR) gene variations as potential risk factors for breast cancer in several ethnic groups, including North Indian women in New Delhi.[6] The researchers verified that females with high serum 25(OH)D levels are at a reduced risk and stage of breast cancer. Additionally, they showed that women with the polymorphic T (f) allele for the VDR Fok I site (genotype: CT/TT) have a higher likelihood of developing breast cancer compared to those with the wild C (F) allele (genotype: CC). The FokI polymorphism (rs2228570) is situated at the initiation codon in exon 2, leading to a modified translation start site and the production of an extended VDR variant consisting of 427 amino acids. This variant exhibits reduced gene activation efficiency compared to the wild type C allele, which has been demonstrated to enhance more vigorous anti-inflammatory reactions.[7] This specific mix of alleles may be responsible for the heightened susceptibility to breast cancer in women from North India, necessitating additional research.

Colorectal cancer

Studies have shown a considerable decrease in the incidence of colorectal cancer with increased levels of Vitamin D, making its function in prevention particularly convincing. Vitamin D is believed to have a protective effect due to its impact on cell differentiation and immunological function.[3]

Colorectal cancer originates from cells in the colon or rectum and affects approximately 1.9 million new cases worldwide each year [8]. A study by the Norwegian Women and Cancer Cohort involving 95,416 participants and 1774 cases of colorectal cancer revealed that individuals with higher vitamin D3 intake had a 17% lower risk of developing colorectal cancer in the proximal colon. The hazard ratio was 0.83 with a 95% confidence interval of 0.68–1.02. [9]

The results indicate that vitamin D deficiency might be linked to various areas of the colon, possibly due to the increased expression of VDR in the proximal colon.[10] Recent gene expression investigations in colorectal cancer tissue showed that both VDR and CYP3A4 were downregulated in the affected population.[11] CYP3A4 in the liver plays a role in metabolizing many drugs and is responsible for transforming and breaking down substances like vitamin D3 and D2 through hydroxylation processes.[12] So it's proposed that vitamin D metabolism could be compromised in the development of colorectal cancer.

Clinical implications arise from polymorphisms in the GC gene. Supplementing colorectal cancer patients with the GC rs4588 and rs2282679 polymorphisms with 2,000 IU of vitamin D was found to be less efficient in restoring 25(OH)D sufficiency [13].

Prostate Cancer

Research on the correlation between Vitamin D and prostate cancer yields inconsistent findings due to the complexity of the interaction. Data is indicating that Vitamin D might affect the risk and development of

prostate cancer, which justifies the need for more research. [2]

Prostate cancer is the predominant malignancy in males, with 1.4 million new cases identified annually. [14] A recent study indicates that the ApaI (A/C) polymorphism in intron 8 of the VDR gene could serve as a diagnostic and prognostic indicator for the stage of malignant prostate cancer in Egyptian men compared to those with benign prostatic hyperplasia.[15] The ApaI (A/C) polymorphism does not impact the encoded VDR protein. The reason for this connection is uncertain and may include intricate epistatic and/or gene regulatory effects.

An association was discovered between rs9393682 and the progression of localized prostate cancer, as well as the association between rsl378033 and the reduced progression of advanced prostate cancer. [16]

Ovarian Cancers:

Ovarian cancer, with a yearly global incidence of 313,000 new cases, is the leading cause of cancer-related mortality among gynaecologic tumours.[17] In a recent study, a meta-analysis was performed by researchers using searchable databases, including MEDLINE and the Web of Sciences, to examine the associations between dietary vitamin D intake, serum 25(OH)D levels, and the relative risk (RR) of ovarian cancer.[18] In 15 observational studies, individuals with elevated blood 25(OH)D levels exhibited a 37% reduced chance of ovarian cancer incidences when compared with lower levels (pooled RR=0.63). In contrast, the consumption of vitamin D had a modest negative correlation (RR=0.92). The strength of the adverse connection was found to be greater in case-control studies compared to prospective studies. In general, serum 25(OH)D levels have the potential to serve as a more reliable prognostic indicator for predicting the impact on ovarian cancer.

Bone Cancers:

Bone tumours are a diverse collection of abnormal growths that exhibit various radiological and histological characteristics. [19,20] Benign bone tumours are different from malignant tumours, which can be categorized as primary or secondary bone tumours, also known as metastases. Bone metastases are common and tend to occur more often in patients with breast, prostate, lung, thyroid, kidney, and bladder cancers. Primary malignant bone tumours have an unclear cause, unlike bone metastases.

Bone remodelling is a continuous and lifelong process that involves breaking down old or mechanically useless bone and replacing it with newly produced bone tissue. Cancer cells in the bone microenvironment significantly disrupt this balance. Cancer cells in bone manipulate indigenous osteoblasts and osteoclasts to create a favorable environment for their growth and development. Therefore, changes in the bone microenvironment have been associated with an elevated vulnerability of the skeletal system to cancer metastases. Vitamin D is crucial for maintaining a healthy and physiological metabolism of minerals and bone structure in the bone microenvironment. Thus, it is not unexpected that a lack of vitamin D has been shown to speed up the formation of tumors in bone.

Vitamin D deficiency has been found to increase the risk of developing cancer by enhancing tumour-related gene expression. [21,22] Research has shown that vitamin D plays a direct role in controlling cell growth, development, and cell death in several tissues, including cancerous tumors. VDR is commonly found in various cell types, including cancer cells, and multiple studies have shown a link between low VDR expression and increased tumour aggressiveness.

Research is actively exploring the possibilities of Vitamin D as a supplementary medication in cancer therapy. Research is investigating the potential benefits of Vitamin D supplementation in improving the effectiveness of traditional cancer treatments and enhancing patient outcomes. [23]

Challenges and controversies

The significance of Vitamin D in cancer prevention and treatment is a topic of contention, despite encouraging findings. Challenges related to Vitamin D toxicity and the interpretation of epidemiological findings complicate the direct use of Vitamin D supplementation in clinical settings. [1]

CONCLUSION

The complex connection between Vitamin D and cancer underscores the nutrient's potential in preventing and treating malignancies.

Vitamin D serves as the precursor to calcitriol and plays a crucial role as a calciotropic hormone. Numerous analytical investigations have garnered significant interest in vitamin D's role in the pathogenesis and management of cancer. Several lines of evidence indicate a correlation between low serum level of vitamin D and an increased risk of cancers, as well as other chronic disorders. Calcitriol has a crucial role in the regulation of numerous genes that are involved in cellular processes, either directly or indirectly. Although numerous epidemiological studies have indicated a negative correlation between vitamin D and UV B status and the occurrence of cancer, this association has yet to be substantiated. To mitigate the risk of malignancy, individuals must maintain an adequate level of vitamin D.

Advancements in research will lead to a more detailed comprehension of Vitamin D's function, providing new cancer prevention and treatment opportunities. Continuing to study this connection highlights the need to maintain sufficient Vitamin D levels for overall health and wellness.

Declaration by Authors

Ethical Approval: Not Applicable

Acknowledgement: None

Source of Funding: None

Conflict of Interest: The authors declare no conflict of interest.

REFERENCES

1. Holick, M.F. (2007). Vitamin D deficiency. New England Journal of Medicine, 357(3), 266-281.
2. Feldman, D., Krishnan, A.V., Swami, S., Giovannucci, E., & Feldman, B.J. (2014). The role of vitamin D in reducing cancer risk and progression. Nature Reviews Cancer, 14(5), 342-357.
3. Garland, C.F., Gorham, E.D., Mohr, S.B., & Garland, F.C. (2009). Vitamin D for cancer prevention: global perspective. Annals of Epidemiology, 19(7), 468-483.
4. Arnold, M., Morgan, E., Rumgay, H., Mafra, A., Singh, D., Laversanne, M., Vignat, J., Gralow, J. R., Cardoso, F., Siesling, S., & Soerjomataram, I. (2022). Current and future burden of breast cancer: Global statistics for 2020 and 2040. The Breast, 66, 15–23.
5. Rosso, C., Fera, N., Murugan, N. J., & Voutsadakis, I. A. (2022). Vitamin D Levels in Newly Diagnosed Breast Cancer Patients according to Tumor Sub-Types. Journal of Dietary Supplements, 20(6), 926–938.
6. Chakraborty, M., Arora, M., Ramteke, A., Yadav, V., Naaz, H., Muntakhab, M., Tripathi, P., & K, N. C. (2023). FokI polymorphism of Vitamin D receptor gene and deficiency of serum Vitamin D increases the risk of breast cancer in North Indian women. Endocrine, 81(1), 168–174.
7. Van Etten, E., Verlinden, L., Giulietti, A., Ramos-Lopez, E., Branisteanu, D., Ferreira, G., Overbergh, L., Verstuyf, A., Bouillon, R., Roep, B., Badenhoop, K., & Mathieu, C. (2007). The vitamin D receptor gene FokI polymorphism: Functional impact on the immune system. European Journal of Immunology, 37(2), 395–405.
8. Rawla, P., Sunkara, T., & Barsouk, A. (2019). Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. Gastroenterology Review, 14(2), 89–103
9. Paulsen, E. M., Rylander, C., Brustad, M., & Jensen, T. E. (2023). Pre-diagnostic intake of vitamin D and incidence of colorectal cancer by anatomical subsites: the Norwegian Women and Cancer Cohort Study (NOWAC). British Journal of Nutrition, 130(6), 1047–1055
10. Lu, R., Wu, S., Xia, Y., & Sun, J. (2012). The Vitamin D Receptor, Inflammatory Bowel Diseases, and Colon Cancer. Current Colorectal Cancer Reports, 8(1), 57–65.

11. Sadeghi, H., Hashemnia, V., Nazemalhosseini-Mojarad, E., Ghasemi, M. R., & Mirfakhraie, R. (2022). Correlated downregulation of VDR and CYP3A4 in colorectal cancer. Molecular Biology Reports, 50(2), 1385–1391
12. Wang, Z., Lin, Y. S., Zheng, X. E., Senn, T., Hashizume, T., Scian, M., Dickmann, L. J., Nelson, S. D., Baillie, T. A., Hebert, M. F., Blough, D., Davis, C. L., & Thummel, K. E. (2011). An Inducible Cytochrome P450 3A4-Dependent Vitamin D Catabolic Pathway. Molecular Pharmacology, 81(4), 498–509.
13. Muindi, J. R., Adjei, A. A., Wu, Z. R., Olson, I., Huang, H., Groman, A., Tian, L., Singh, P. K., Sucheston, L. E., Johnson, C. S., Trump, D. L., & Fakih, M. G. (2013). Serum Vitamin D Metabolites in Colorectal Cancer Patients Receiving Cholecalciferol Supplementation: Correlation with Polymorphisms in the Vitamin D Genes. Hormones and Cancer, 4(4), 242–250.
14. Wang, L., Lu, B., He, M., Wang, Y., Wang, Z., & Du, L. (2022). Prostate Cancer Incidence and Mortality: Global Status and Temporal Trends in 89 Countries From 2000 to 2019. Frontiers in Public Health, 10.
15. El-attar, A. Z., Hussein, S., Salama, M. F. A., Ibrahim, H. M., AlKaramany, A. S., Elsawi, M. K., Hemeda, M., & Algazeery, A. (2022. Vitamin D receptor polymorphism and prostate cancer prognosis. Current Urology, 16(4), 246–255
16. Lin, V. C., Huang, S. P., Ting, H. J., Ma, W. L., Yu, C. C., Huang, C. Y., Yin, H. L., Huang, T. Y., Lee, C. H., Chang, T. Y., Lu, T. L., & Bao, B. Y. (2017). Vitamin D receptor-binding site variants affect prostate cancer progression. Oncotarget, 8(43), 74119–74128.
17. Huang, J., Chan, W. C., Ngai, C. H., Lok, V., Zhang, L., Lucero-Prisno, D. E., Xu, W., Zheng, Z. J., Elcarte, E., Withers, M., & Wong, M. C. S. (2022). Worldwide Burden, Risk Factors, and Temporal Trends of Ovarian Cancer: A Global Study. Cancers, 14(9), 2230.
18. Jung, S., Jin, S., & Je, Y. (2023). Vitamin D Intake, Blood 25-Hydroxyvitamin D, and Risk of Ovarian Cancer: A Meta-Analysis of Observational Studies. Journal of Women's Health, 32(5), 561–573
19. Guise, T. A., & Mundy, G. R. (1998). Cancer and Bone*. Endocrine Reviews, 19(1), 18–54.
20. Flanagan, A. M., & Lindsay, D. (2017). A diagnostic approach to bone tumours. Pathology, 49(7), 675–687
21. Feldman, D., Krishnan, A. V., Swami, S., Giovannucci, E., & Feldman, B. J. (2014). The role of vitamin D in reducing cancer risk and progression. Nature Reviews Cancer, 14(5), 342–357.
22. Tagliabue E, Raimondi S, Gandini S. Vitamin D, Cancer Risk, and Mortality. Adv Food Nutr Res. 2015; 75:1-52.
23. Trump, D. L., Hershberger, P. A., Bernardi, R. J., Ahmed, S., Muindi, J., Fakih, M., Yu, W. D., & Johnson, C. S. (2004). Anti-tumor activity of calcitriol: pre-clinical and clinical studies. The Journal of Steroid Biochemistry and Molecular Biology, 89–90, 519–526

How to cite this article: Shashikant Adlekha, Nagadharshan Devendra, Shilpa Kakera. Vitamin D in oncology: beyond bones to battling cancer - a review article. *Int J Health Sci Res.* 2024; 14(4):559-564. DOI: *https://doi.org/10.52403/ijhsr.20240471*

******