Review Article

Vitamin D and Malignancies: A Review of Plausible Role

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Abstract:
The vitamin D endocrine system plays a primary role in the maintenance of calcium homeostasis as well as exerting a wider range of biological activities including the regulation of cellular differentiation and proliferation, immunity, and reproduction. The biologically active metabolite of vitamin D, 1,25(OH)2D3, affects mineral homeostasis and has numerous other diverse physiological functions including effects on growth of cancer cells and protection against certain immune disorders. solid tumors such as prostate, breast and colon cancers are another increasing area of vitamin D research. The article aims at reviewing vitamin D association with cancer risk.

Key words: Cancer, Diet , Malignancy, Vitamin D.

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Introduction:

Vitamin D from the diet or dermal synthesis is biologically inactive and requires enzymatic conversion to active metabolites. Vitamin D is converted to 25-hydroxyvitamin D, which is the major circulating form of vitamin D, and then further to 1,25-dihydroxyvitamin D, the active form of vitamin D, by enzymes in the liver and kidney. 1,25-dihydroxyvitamin D binds to the intracellular vitamin D receptor and activates vitamin D response elements within target genes. The half-life of 1,25-dihydroxyvitamin D is four to six hours, compared with two to three weeks for 25-hydroxyvitamin D and 24 hours for parent vitamin D.[1]

Vitamin D exerts a wider range of biological activities including regulation of cellular differentiation and proliferation, immune function, and reproduction. The metabolism

of vitamin D to its active form 1,25 dihydroxyvitamin D (1,25D) provides a mechanism to act in a paracrine or autocrine fashion. The contemporary Non-renal metabolism of vitamin D model does not go with the currently accepted model of the vitamin D endocrine system. 1,25D has many actions on bone cells, albeit with an unclear physiological significance.[2] The deficiency of vitamin D is known mainly for its association with fractures and bone disease.[3-5] Apart from the above mentioned aspects, most recent paradigm is the newly recognized association of vitamin D with risk of several types of cancer.[6-8] The high prevalence of vitamin D deficiency, combined with the discovery of increased risks of certain types of cancer in those who are deficient, suggest that vitamin D deficiency may account for several thousand premature deaths from colon[9] breast,[10,11] ovarian,[12] and prostate cancer[13] annually.[14] These findings creates a new impetus for ensuring adequate vitamin D intake in order to reduce the risk of cancer.

Vitamin D Metabolism

Vitamin D_3 is synthesized from 7-dehydrocholesterol in the skin by exposure to ultraviolet light (200nm–300nm) from the sun. Alternatively, vitamin D, in the form of vitamin D_2 (from plants) or vitamin D_3 (from animals), can be derived from dietary sources. Dietary vitamin D is fat soluble and is absorbed in the small intestine incorporated into chylomicrons. Dietary vitamin D travels to the liver, bound to vitamin D–binding protein and in continued association with chylomicrons and lipoproteins, where it and endogenously synthesized vitamin D3 are metabolized.[15,16] The hepatic enzyme 25–hydroxylase places a hydroxyl group in the 25 position of the vitamin D molecule, resulting in the formation of 25-hydroxyvitamin D or (calcidiol). The association of oral vitamin D with chylomicrons and lipoproteins allows more rapid hepatic delivery when compared with endogenously synthesized or parenterally administered hormone, which circulates exclusively on vitamin D-binding protein. This difference results in a rapid but less sustained increase in plasma 25-hydroxyvitamin D (25OHD) levels obtained with oral as opposed to parenteral administration or endogenous synthesis.[17] Biological activation of vitamin D involves firstly 25-hydroxylation, followed by 1α-hydroxylation to synthesize 1,25D. the synthesis of 25 hydroxyvitamin D (25D) by the liver is constitutive, and the synthesis of 1,25D by the renal 25-hydroxyvitamin D-1α-hydroxylase enzyme, (CYP27B1) is tightly regulated.[18] A third vitamin D metabolising enzyme, the 25-hydroxyvitamin D-24α-hydroxylase (CYP24) converts 25D to 24,25 dihydroxyvitamin D (24,25D) or 1,25D to 1,24,25 trihydroxyvitamin D (1,24,25D), which is the first step of the C-24 oxidation pathway. It catabolize vitamin D metabolites to the water soluble calcitroic acid for rapid excretion by the kidney. This enzyme appears to be co-expressed in tissues with VDR which elicits the action of 1,25D. Thus the biological activity of vitamin D is determined by the combination of the level of VDR expression and the activities of the CYP27B1 and CYP24 metabolizing enzymes.[19]

Measuring Vitamin D Levels

Clinical requirements for measuring plasma 25-OH D levels include assessing vitamin D status and monitoring vitamin D supplementation. A number of radioimmunoassays are used in routine laboratories as well as an automated system that utilizes competitive-protein binding technology.[20] Monitoring vitamin D supplementation is somewhat difficult for the clinical laboratory. In many countries,

the major supplement available is ergocalciferol or vitamin D_2 which is derived from plants. Mammals produce cholecalciferol or vitamin D_3. As such it is considered that there are no known differences with regard to biological activity between the two forms of vitamin D, however the routine assays do not measure them identically.[21] Most of the current assays are standardized to measure $25OHD_3$ and Thus an important lacuna in development in 25OHD assay technology is the availability of assays that can measure $25OHD_2$ and $25OHD_3$ equally. Various studies have proved that an estimated steady state input of vitamin D_3 required to maintain plasma 25OHD levels is 0.7 nmol/L/μg vitamin D_3 per day.[22]

Vitamin D and Cancer

In December, 2008, the World Health Organization, through its International Agency for Research in Cancer (IARC) published a major review of cancer and vitamin D[23] one of the important vitamin D activities is the regulation of cell growth and differentiation. The addition of $1,25(OH)_2D$ to culture media for cancer cell lines produced a strong inhibition of growth. Initially studies were performed in breast cancer and other solid tumor cells lines.[24] and further studies now include the human prostate cancer cell lines as well as normal prostate epithelial tissue and primary prostate cancer cell cultures. The prostate functions as a vitamin D-target organ in that normal epithelial cells express the VDR and display regulation of numerous genes by $1,25(OH)_2D$. complementary DNA microarray analysis of primary human prostatic epithelial cells has revealed that $1,25(OH)_2D$ up-regulates at least 38 genes and down-regulates nine.[25] The highest induction of expression was the gene for the vitamin D catabolic enzyme CYP24. Some of these genes modulate the mitogen-activated kinase (MAPK) pathways associated with growth factor signally while others induce apoptosis or reduce cell cycling activity necessary for cell division and replication.

A study of the effect of $1,25(OH)_2D$ on growth of a number of human prostate cancer cell lines indicated varied responses to $1,25(OH)_2D$ with the LNCaP line being most sensitive while the DU145 cell line was unresponsive.[26] Further studies on the expression of the genes that determine vitamin D activity in these cell lines as well as normal prostate epithelial cells and benign prostate hyperplastic cells indicate a gradation of decreasing CYP27B1 activity as prostate epithelial cells move from normal epithelium with the highest activity through benign prostate hyperplastic epithelium with moderate activity to cancer cells with markedly repressed activity Neither the expression of VDR or CYP24 demonstrates such a relationship with the development of cancer. Also of interest here that when the DU145 cancer cell, which is unresponsive to $1,25(OH)_2D$ is treated with an inhibitor of CYP24 activity, the growth inhibition by $1,25(OH)_2D$ is demonstrated.[27] Another immunohisto-chemical study of a human prostate cancer series indicated that the CYP27B1 protein was present in a significant number of these specimens. Their data suggest that the increased expression of CYP24 or some inactivation of the CYP27B1 enzyme may be important mechanisms for reducing $1,25(OH)_2D$ activity in many clinical prostate cancers.[28]

These findings all suggest that modulation of vitamin D activity through disruption of vitamin D metabolism within cells may play a permissive role in the development of cancer. There is considerable epidemiological evidence that either

decreased sunlight exposure or decreased vitamin D status is associated with increased risk of many cancers. Therefore, a low vitamin D status is confirmed to increase the risk of cancers, the maintenance of an adequate vitamin D status and assessment of vitamin D levels are very simple procedures that could be adopted at the population level. Thus clinical laboratory vitamin D testing would further be Useful. Also, a public health policy is required for the identification of the level of vitamin D required to reduce the risk of cancer.[29]

Role in Cancer Prevention

Supplemental vitamin D intake can address the high prevalence of vitamin D deficiency. Strong evidence indicates that intake or synthesis of vitamin D is associated with reduced incidence and death rates of colon, breast, prostate, and ovarian cancers. More than 1000 laboratory and epidemiological studies have been published citing the relationship between vitamin D and its metabolites and cancer. Long-term studies have demonstrated the efficacy of moderate intake of vitamin D in reducing cancer risk.it therefore becomes imperative for the public health and medical communities to adopt use of vitamin D for cancer prevention.[30]

Conclusion

Understanding of the physiology and pathology of vitamin D is currently increasing at a rapid rate. The realization that vitamin D can act in a paracrine and autocrine manner in addition to its well-described endocrine action has led to significant prospects for the development of new perceptive of the requirement for an adequate vitamin D status for optimal health. A relatively simple and cheap practice of maintaining an adequate vitamin D status can be of immense use to provide health benefits in a number of areas, the time should not be far, when research will determine whether a low vitamin D status influences the development of cancer, whether it increases the absolute risk of cancer or whether it modulates the growth or invasiveness of cancers. Clinical laboratory professionals need to strive to improve the precision and accuracy of current 25OHD assays in clinical use. This work necessitates the collaboration between the profession and apparatus and reagent manufacturers.

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