



Does Vitamin D Prevent Cancer?

D Vitamini Kanseri Önler mi?

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Dear Readers,

The relationship between vitamin D and cancer has been discussed for a long time. Recently, it has become popular again with the increase in its use during the coronavirus disease period and the acceptance of its protective effect from infection. In addition to its different uses, many studies have been conducted on its cancer-protective effect, the need for vitamin D in patients with cancer and the ways of obtaining it. As a surgeon dealing with cancer surgery, I evaluated this patient group with a new perspective as a result of my clinical observations and came to the conclusion that vitamin D levels should definitely be evaluated in these patients.

Vitamin D is a fat-soluble vitamin obtainable from the diet, as well as a seco-steroidal prohormone produced in the skin by ultraviolet B (UVB, 290-320 nm) from sunlight. Vitamin D undergoes two-step processing in the liver and kidney to synthesize calcitriol, a biologically active form that binds to the vitamin D receptor (VDR) to activate its various physiological functions (1,2). There are 2 main isoforms of vitamin D; Vitamins D2 and D3 (3,4). Dietary or skin-derived vitamin D binds to the circulating vitamin D binding protein (VDBP) and is first delivered to the liver. In the liver, vitamin D is metabolized to 25(OH)D (calcidiol) by vitamin D 25-hydroxylase (CYP2R1 and CYP27A1), the major circulating form of vitamin D in serum (5,6).

The classic role of vitamin D is to regulate calcium and phosphate metabolisms, which are essential for bone remodeling. However, extensive studies in recent years have suggested that low sunlight exposure and vitamin D deficiency are also associated with an increased risk of many other non-skeletal diseases such as cancer (7-10).

The first observation of an inverse correlation between sunlight exposure and overall cancer incidence and mortality in North

America was published about 80 years ago (11). Then, in 1980 and 1992, the first epidemiological studies were reported linking low sunlight exposure with a high risk of colon cancer and prostate cancer, respectively. It has been suggested that, rather than exposure to sunlight, vitamin D may protect against the risk of development of colon cancer and prostate cancer (12,13). Since then, many epidemiological studies have supported and expanded the UVB-vitamin D-cancer hypothesis in 18 different cancer types (14). The hypothesis has further been supported by studies showing a direct relationship between vitamin D and cancer risk. Several population-based studies have demonstrated an inverse correlation between serum 25-hydroxyvitamin D (25(OH)D) levels and increased risk of colon (15), breast (16), prostate (17), gastric and other cancers. Therefore, it is stated that vitamin D deficiency may contribute to the development and progression of many types of cancer, and therefore, maintaining adequate serum vitamin D levels may be beneficial for the prevention and treatment of cancer. The clinical use of calcitriol or vitamin D analogues has been investigated, as numerous epidemiological and experimental data have demonstrated the beneficial role of vitamin D in the prevention and treatment of various types of cancer (18).

Anticancer Properties of Vitamin D

Since the beneficial effects of vitamin D in preventing and treating cancer have been observed in epidemiological and preclinical studies, several mechanisms have been proposed to explain its anticancer effects. Data in the literature show that vitamin D can regulate the entire tumorigenesis process, from onset to metastasis and cell-microenvironment interactions (18). These mechanisms include regulation of cell behaviors such as proliferation, differentiation, apoptosis, autophagy and epithelial-mesenchymal transition and modulation of cell-microenvironment interactions such as angiogenesis, antioxidants, inflammation and the immune system.

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The most important extraskelatal function of vitamin D is its role in the modulation of the immune system (19,20). This includes supporting innate immune system cells such as monocytes, macrophages and dendritic cells in their fight against bacterial infections such as tuberculosis (19). In addition, vitamin D prevents excessive reactions of adaptive immune system cells such as activated T-cells, which can lead to autoimmune diseases such as multiple sclerosis or inflammatory bowel disease (21,22). Vitamin D affects the innate immune system through upregulation of the anti-microbial peptide CAMP (23) or the plasma membrane-associated glycoprotein CD14 (24) that functions as a co-receptor for Toll-like receptors. Vitamin D influences the differentiation, growth, and apoptosis of monocytes, dendritic cells, and different T-cells through regulation of the same set of genes and pathways that drive the growth of cancer cells (25). It suggests that the anti-proliferative effect of vitamin D is related to its role in inducing differentiation and apoptosis of cancer cells and its function in controlling immune cells (26). Furthermore, immune cells are an important component of the supportive microenvironment of tumors. Thus, some of the anti-cancer effects of vitamin D may be based on a modulation of the immune component of the microenvironment that is detrimental to tumor survival (27,28). For example, vitamin D can enhance the antibody-dependent cellular cytotoxicity of macrophages and natural killer cells in the context of cancer treatment with monoclonal antibodies. Importantly, the best anti-cancer effect of vitamin D through modulation of the immune system is primarily the prevention of existing tumors, not the prevention of their formation. Every day, thousands of normal cells in each of us turn into cancer cells, but the vast majority of them are detected at an early stage by cytolytic T-cells and eventually eliminated. In this way, activation of cytolytic T-cells by vitamin D is an effective mechanism in preventing the onset of cancer. A seminal epidemiological report published nearly 40 years ago showed that living at lower latitudes, as well as increased sun exposure, reduced the risk of colorectal cancer, both of which led to higher endogenous vitamin D₃ production (12). It is also known that 1,25(OH)₂D₃ can slow the growth of melanoma cells *in vitro* (29). Both observations prompted the idea that low vitamin D status could be a risk factor for cancer. While studies on vitamin D confirm this concept for colorectal cancer, many *in vitro* studies have concluded that vitamin D will be effective against prostate cancer and breast cancer, as well as lymphoma and leukemia (30).

Although there is a consensus on the cancer-protective effect of vitamin D, there are studies reporting opposing views. Three randomized control studies reported no effect of vitamin D₃ supplementation, while their meta-analysis found that it significantly reduced cancer deaths, but there was no reduction in cancer incidence (31-33). Randomized clinical trials of vitamin D supplementation have inconsistent results. There are also opinions that argue that daily vitamin D and calcium supplementation does not have a protective effect against colorectal, breast and all invasive cancers (31,34). However, a Mendelian randomization study based on 74 single-nucleotide polymorphisms associated with 25(OH)D₃ serum levels showed that vitamin D status was unlikely to be a causal risk factor for most cancers (35). There are also opinions suggesting that the

possible anti-cancer effects of vitamin D₃ are not clear in the whole population. Interestingly, the concept of the personalized vitamin D response index in the smaller vitamin D₃ study conducted in Finland suggests that 1 in 4 people have a low response to vitamin D, meaning that these individuals should increase their daily dose of vitamin D₃ supplementation (36-38). In contrast, those with a high vitamin D response seem to tolerate even a low vitamin D state. Therefore, it is recommended that randomized controlled trials be performed with more parameters, such as body mass index or other markers. In another study, it was reported that a high dosage of 2,000 IU/d of vitamin D together with calcium reduced the incidence of all cancer types in the treatment arm (39,40).

Observational epidemiological studies suggest that low vitamin D status is a risk factor for different types of cancer and that adequate vitamin D₃ supplementation is cancer-preventive.

In conclusion, Vitamin D₃ is a derivative of cholesterol that acts as a direct regulator of the epigenome and transcriptome of a wide variety of human tissues and cell types, including malignant tumor cells, through its 1,25(OH)₂D₃ metabolite and its high-affinity receptor VDR. The pronounced effect of vitamin D on proliferation, differentiation and apoptosis of immune cells also has effects on cancer cells. The growth of malignant tumor cells is controlled directly by the same genes and pathways in immune cells or indirectly by modulated immune cells in their microenvironment. Modulation of the immune system also contributes to the anti-cancer effect of vitamin D. It is generally accepted that the protective effect of vitamin D is also applied to neoplastic diseases such as cancer. First of all, the accepted view is that vitamin D does not act on the control of existing tumors, but on the prevention of their formation. Low vitamin D level is a risk factor for different types of cancer. Therefore, adequate vitamin D₃ supplementation may prevent cancer in patients with low vitamin D levels, especially in patients with risk factors for cancer development. Vitamin D levels should be closely monitored during and after cancer treatment such as surgery, chemotherapy or radiotherapy, and necessary replacements should be made to keep the levels at optimal levels. Another point is that vitamin D levels are mostly low in this patient group, and even if they are normal, they are usually close to the lower limit of normal. In addition to benefiting from sunlight in these patients, giving vitamin D both with diet and as a supplement may contribute to preventing both cancer formation and recurrence after treatment.

References

1. Zhang R, Naughton DP. Vitamin D in health and disease: current perspectives. *Nutr J* 2010;9:65.
2. Bouillon R, Carmeliet G, Verlinden L, van Etten E, Verstuyf A, Luderer HF, et al. Vitamin D and human health: lessons from vitamin D receptor null mice. *Endocr Rev* 2008;29:726-76.
3. Heaney RP. Vitamin D in health and disease. *Clin J Am Soc Nephrol* 2008;3:1535-41.
4. Jäpelt RB, Jakobsen J. Vitamin D in plants: a review of occurrence, analysis, and biosynthesis. *Front Plant Sci* 2013;4:136.
5. Jones G, Prosser DE, Kaufmann M. Cytochrome P450-mediated metabolism of vitamin D. *J Lipid Res* 2014;55:13-31.

6. Schuster I. Cytochromes P450 are essential players in the vitamin D signaling system. *Biochim Biophys Acta* 2011;1814:186-99.
7. Bikle DD. Extraskelatal actions of vitamin D. *Ann N Y Acad Sci* 2016;1376:29-52.
8. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr* 2004;80:1678S-88S.
9. Wang H, Chen W, Li D, Yin X, Zhang X, Olsen N, et al. Vitamin D and Chronic Diseases. *Aging Dis* 2017;8:346-53.
10. Feldman D, Krishnan AV, Swami S, Giovannucci E, Feldman BJ. The role of vitamin D in reducing cancer risk and progression. *Nat Rev Cancer* 2014;14:342-57.
11. Bertino JR. Landmark Study: The Relation of Solar Radiation to Cancer Mortality in North America. *Cancer Res* 2016;76:185.
12. Garland CF, Garland FC. Do sunlight and vitamin D reduce the likelihood of colon cancer? *Int J Epidemiol* 1980;9:227-31.
13. Hanchette CL, Schwartz GG. Geographic patterns of prostate cancer mortality. Evidence for a protective effect of ultraviolet radiation. *Cancer* 1992;70:2861-9.
14. Grant WB, Mohr SB. Ecological studies of ultraviolet B, vitamin D and cancer since 2000. *Ann Epidemiol* 2009;19:446-54.
15. Garland CF, Comstock GW, Garland FC, Helsing KJ, Shaw EK, Gorham ED. Serum 25-hydroxyvitamin D and colon cancer: eight-year prospective study. *Lancet* 1989;2:1176-8.
16. Engel P, Fagherazzi G, Boutten A, Dupré T, Mesrine S, Boutron-Ruault MC, et al. Serum 25(OH) vitamin D and risk of breast cancer: a nested case-control study from the French E3N cohort. *Cancer Epidemiol Biomarkers Prev* 2010;19:2341-50.
17. Tretli S, Hernes E, Berg JP, Hestvik UE, Robsahm TE. Association between serum 25(OH)D and death from prostate cancer. *Br J Cancer* 2009;100:450-4.
18. Giammanco M, Di Majo D, La Guardia M, Aiello S, Crescimanno M, Flandina C, et al. Vitamin D in cancer chemoprevention. *Pharm Biol* 2015;53:1399-434.
19. Chun RF, Liu PT, Modlin RL, Adams JS, Hewison M. Impact of vitamin D on immune function: lessons learned from genome-wide analysis. *Front Physiol* 2014;5:151.
20. Medrano M, Carrillo-Cruz E, Montero I, Perez-Simon JA. Vitamin D: Effect on Haematopoiesis and Immune System and Clinical Applications. *Int J Mol Sci* 2018;19:2663.
21. Dankers W, Colin EM, van Hamburg JP, Lubberts E. Vitamin D in Autoimmunity: Molecular Mechanisms and Therapeutic Potential. *Front Immunol* 2017;7:697.
22. Lu M, McComish BJ, Burdon KP, Taylor BV, Körner H. The Association Between Vitamin D and Multiple Sclerosis Risk: 1,25(OH)2D3 Induces Super-Enhancers Bound by VDR. *Front Immunol* 2019;10:488.
23. Gombart AF. The vitamin D-antimicrobial peptide pathway and its role in protection against infection. *Future Microbiol* 2009;4:1151-65.
24. Zanoni I, Granucci F. Role of CD14 in host protection against infections and in metabolism regulation. *Front Cell Infect Microbiol* 2013;3:32.
25. Sever R, Brugge JS. Signal transduction in cancer. *Cold Spring Harb Perspect Med* 2015;5:a006098.
26. Balomenos D, Martín-Caballero J, García MI, Prieto I, Flores JM, Serrano M, et al. The cell cycle inhibitor p21 controls T-cell proliferation and sex-linked lupus development. *Nat Med* 2000;6:171-6.
27. Sherman MH, Yu RT, Engle DD, Ding N, Atkins AR, Tiriaci H, et al. Vitamin D receptor-mediated stromal reprogramming suppresses pancreatitis and enhances pancreatic cancer therapy. *Cell* 2014;159:80-93.
28. Wu X, Hu W, Lu L, Zhao Y, Zhou Y, Xiao Z, et al. Repurposing vitamin D for treatment of human malignancies via targeting tumor microenvironment. *Acta Pharm Sin B* 2019;9:203-19.
29. Colston K, Colston MJ, Feldman D. 1,25-dihydroxyvitamin D3 and malignant melanoma: the presence of receptors and inhibition of cell growth in culture. *Endocrinology* 1981;108:1083-6.
30. Markotic A, Langer S, Kelava T, Vucic K, Turcic P, Tokic T, et al. Higher Post-Operative Serum Vitamin D Level is Associated with Better Survival Outcome in Colorectal Cancer Patients. *Nutr Cancer* 2019;71:1078-85.
31. Wactawski-Wende J, Kotchen JM, Anderson GL, Assaf AR, Brunner RL, O'Sullivan MJ, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med* 2006;354:684-96.
32. Avenell A, MacLennan GS, Jenkinson DJ, McPherson GC, McDonald AM, Pant PR, et al. Long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of vitamin D(3) and/or calcium (RECORD trial). *J Clin Endocrinol Metab* 2012;97:614-22.
33. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *BMJ* 2003;326:469.
34. Chlebowski RT, Johnson KC, Kooperberg C, Pettinger M, Wactawski-Wende J, Rohan T, et al. Calcium plus vitamin D supplementation and the risk of breast cancer. *J Natl Cancer Inst* 2008;100:1581-91.
35. Ong JS, Dixon-Suen SC, Han X, An J; Esophageal Cancer Consortium; 23 and Me Research Team, et al. A comprehensive re-assessment of the association between vitamin D and cancer susceptibility using Mendelian randomization. *Nat Commun* 2021;12:246.
36. Vukić M, Neme A, Seuter S, Saksa N, de Mello VD, Nurmi T, et al. Relevance of vitamin D receptor target genes for monitoring the vitamin D responsiveness of primary human cells. *PLoS One* 2015;10:e0124339.
37. Seuter S, Virtanen JK, Nurmi T, Pihlajamäki J, Mursu J, Voutilainen S, et al. Molecular evaluation of vitamin D responsiveness of healthy young adults. *J Steroid Biochem Mol Biol* 2017;174:314-21.
38. Carlberg C, Haq A. The concept of the personal vitamin D response index. *J Steroid Biochem Mol Biol* 2018;175:12-7.
39. Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr* 2007;85:1586-91.
40. Lappe J, Watson P, Travers-Gustafson D, Recker R, Garland C, Gorham E, et al. Effect of Vitamin D and Calcium Supplementation on Cancer Incidence in Older Women: A Randomized Clinical Trial. *JAMA* 2017;317:1234-43.