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Anticancer Effect of Vitamin D

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Abstract:

Epidemiological studies indicate that vitamin D insufficiency could have an etiological role in various human cancers. Preclinical research indicates that the active metabolite of vitamin D, $1\alpha,25(\text{OH})_2\text{D}_3$, also known as calcitriol, or vitamin D analogues might have potential as anticancer agents because their administration has antiproliferative effects, can activate apoptotic pathways and inhibit angiogenesis. In addition, $1\alpha,25(\text{OH})_2\text{D}_3$ potentiates the anticancer effects of many cytotoxic and antiproliferative anticancer agents.

Introduction:

Vitamin D is a fat-soluble vitamin that is naturally present in very few foods, added to others, and available as a dietary supplement. It is also produced endogenously when ultraviolet rays from sunlight strike the skin and trigger vitamin D synthesis. Vitamin D obtained from sun exposure, food, and supplements is biologically inert and must undergo two hydroxylations in the body for activation. The first occurs in the liver and converts vitamin D to 25-hydroxyvitamin D [25(OH)D], also known as calcidiol. The second occurs primarily in the kidney and forms the physiologically active 1,25-dihydroxyvitamin D [$1,25(\text{OH})_2\text{D}$], also known as calcitriol. Vitamin D promotes calcium absorption in the gut and maintains adequate serum calcium and phosphate concentrations to enable normal mineralization of bone and to prevent hypocalcemic tetany. It is also needed for bone growth and bone remodeling by osteoblasts and osteoclasts. Without sufficient vitamin D, bones can become thin, brittle, or misshapen. Vitamin D sufficiency prevents rickets in children and osteomalacia in adults. Together with calcium, vitamin D also helps protect older adults from osteoporosis. Vitamin D has other roles in the body, including modulation of cell growth, neuromuscular and immune function, and reduction of inflammation. Many genes encoding proteins that regulate cell proliferation, differentiation, and apoptosis are modulated in part by vitamin D. Many cells have vitamin D receptors, and some convert 25(OH)D to $1,25(\text{OH})_2\text{D}$.

Table : Serum 25-Hydroxyvitamin D [25(OH)D] Concentrations and Health*

nmol/L**	ng/mL*	Health status
<30	<12	Associated with vitamin D deficiency, leading to rickets in infants and children and osteomalacia in adults
30 to <50	12 to <20	Generally considered inadequate for bone and overall health in healthy individuals
≥50	≥20	Generally considered adequate for bone and overall health in healthy individuals
>125	>50	Emerging evidence links potential adverse effects to such high levels, particularly >150 nmol/L (>60 ng/mL)

* Serum concentrations of 25(OH)D are reported in both nanomoles per liter (nmol/L) and nanograms per milliliter (ng/mL). 1 nmol/L = 0.4 ng/mL . ⁽¹⁾

Discussion:

The discussion will be based on three studies that were taken randomly from different sources. 1_The first study proved that ; Presence of vitamin D receptors in noncalcemic tissues and subsequent identification of its involvement in growth factor(s)-mediated cellular function suggested its probable beneficial role in genesis, progression and survival of cancerous

growths. Data collected from both *in vitro* and *in vivo* studies are highly optimistic regarding its potential in prevention and regression of colorectal, prostate and breast cancers. The vitamin has been found to interfere with the transduction pathways of various growth factor(s)-activated receptors (receptor tyrosine kinases) thereby modulating transcription and alteration of genomic functions resulting in inhibition of cell proliferation and angiogenesis and facilitation of cell differentiation and apoptosis. It also increases the level of an endogenous protein - cystatin D, which possesses antitumor and antimetastatic property, by facilitation of the expression of the gene coding for it. Though not as a primary anticancer agent, this vitamin may be used for the prevention of cancer and included as an adjuvant in combination chemotherapy for the treatment of cancer.⁽²⁾

2_The second study proved that is : Some of the common mechanisms underlying anticancer effects of calcitriol include antiproliferative effects by calcitriol inhibiting the mitogenic signaling by growth factors, such as IGF-1, by increasing the expression of IGF-1 binding protein, epidermal growth factor, and an increase in growth inhibitors such as TGF- β . Calcitriol increases the expression of cyclin-dependent kinase (CDK) inhibitors p21 and p27, decreasing CDK activity and arresting the cell cycle. Calcitriol induces apoptosis by activating of intrinsic pathways of apoptosis through suppression of apoptosis-specific genes such as BCL-2. Calcitriol induces cell-specific pro-differentiation mechanisms such as regulation of β catenin, JUN N-terminal kinase, and NF κ B signaling pathways. Calcitriol inhibits angiogenesis by suppression of the expression of vascular endothelial growth factor (VEGF) through transcriptional repression of hypoxia-inducible factor 1 alpha and IL-8 in an NF- κ B-dependent manner. VDR null mice have increased expression of pro-angiogenic factors such as HIF1 α , VEGF, angiopoietin 1, and platelet-derived growth factor (PDGF) in tumors. Calcitriol has a direct antiproliferative action on tumor-derived endothelial cells.⁽³⁾

3_Third study : Laboratory and animal evidence as well as epidemiologic data suggest that vitamin D status could affect cancer risk. Strong biological and mechanistic bases indicate that vitamin D plays a role in the prevention of colon, prostate, and breast cancers. Emerging epidemiologic data suggest that vitamin D may have a protective effect against colon cancer, but the data are not as strong for a protective effect against prostate and breast cancer, and are variable for cancers at other sites . Studies do not consistently show a protective or no effect, however. One study of Finnish smokers, for example, found that subjects in the highest quintile of baseline vitamin D status had a threefold higher risk of developing pancreatic cancer. A recent review found an increased risk of pancreatic cancer associated with high levels of serum 25(OH)D (≥ 100 nmol/L or ≥ 40 ng/mL) .Vitamin D emerged as a protective factor in a prospective, cross-sectional study of 3,121 adults aged ≥ 50 years (96% men) who underwent a colonoscopy. The study found that 10% had at least one advanced cancerous lesion. Those with the highest vitamin D intakes (>645 IU/day) had a significantly lower risk of these lesions . However, the Women's Health Initiative, in which 36,282 postmenopausal women of various races and ethnicities were randomly assigned to receive 400 IU vitamin D plus 1,000 mg calcium daily or a placebo, found no significant differences between the groups in the incidence of colorectal cancers over 7 years . More recently, a clinical trial focused on bone health in 1,179 postmenopausal women residing in rural Nebraska found that subjects supplemented

daily with calcium (1,400–1,500 mg) and vitamin D₃ (1,100 IU) had a significantly lower incidence of cancer over 4 years compared with women taking a placebo . The small number of cancers (50) precludes generalizing about a protective effect from either or both nutrients or for cancers at different sites. This caution is supported by an analysis of 16,618 participants in NHANES III (1988–1994), in which total cancer mortality was found to be unrelated to baseline vitamin D status . However, colorectal cancer mortality was inversely related to serum 25(OH)D concentrations. A large observational study with participants from 10 western European countries also found a strong inverse association between prediagnostic 25(OH)D concentrations and risk of colorectal cancer .⁽¹⁾

Conclusion:

Vitamin D deficiency appears to predispose individuals to increased risk of developing a number of cancers. Compelling epidemiological and experimental evidence supports a role for vitamin D in cancer prevention and treatment in many types of cancers. Preclinical studies show that 1,25D₃, the active metabolite of vitamin D, and its analogs have antitumor effects in vitro and in vivo through multiple mechanisms including the induction of cell cycle arrest, apoptosis, differentiation and the suppression of inflammation, angiogenesis, invasion, and metastasis. 1,25D₃ also potentiates the effect of chemotherapeutic agents and other agents in the combination treatment .

References:

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