

# The Challenges of Using Vitamin D in Cancer Prevention and Prognosis

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**P**atients with breast or prostate cancer also suffer from a poor quality of life often related to bone metastases, with low vitamin D, related hypocalcemia and reactive hyperparathyroidism (increase of parathyroid hormone) playing important roles [1]. In the article by Segal and co-authors in this issue of *IMAJ* [1], the use of bisphosphonates – the standard care for preventing skeletal morbidity – is considered mandatory in patients with bone metastases, together with vitamin D replacement therapy.

However, there are several extra-skeletal roles that were recently recognized for vitamin D metabolites and especially calcitriol (1,25(OH)D<sub>3</sub>), also known as the “D hormone,” since the hormonally active metabolite of vitamin D synthesized from cholesterol in an intracrine manner deserves important consideration, particularly in cancer prevention [2].

## EXTRA-MUSCULOSKELETAL EFFECTS OF VITAMIN D

A large amount of experimental data show that calcitriol stimulates apoptosis and differentiation in tumor cells and also inhibits invasion, metastasis and tumor angiogenesis in experimental models of breast cancer? [3] [Figure 1]. In addition, calcitriol also exhibits sev-

eral anti-inflammatory effects, including suppression of prostaglandin action, inhibition of p38 stress kinase signaling, and the subsequent production of pro-inflammatory cytokines and inhibition of NF- $\kappa$ B signaling. On the other hand, several investigational studies suggest that serum 25(OH)D (the early vitamin D metabolite) is inversely associated with the risk of different types of cancer. Furthermore, some studies in cancer patients have revealed an intriguing association between low 25(OH)D levels and poor prognosis [4,5].

## VITAMIN D AND CANCER

A prominent endocrine role for 1,25(OH)D<sub>3</sub> in peripheral estrogen metabolism and related cell proliferative activities was recently discovered. Calcitriol decreases the expression of aromatase, the enzyme that generally catalyzes the peripheral estrogen synthesis from androgens, as well as in cancer tissue, e.g., breast and prostate cancer, where its intracrine synthesis is increased [6] [Figure 1].

Inflammatory cytokines (tumor necrosis factor- $\alpha$ , interleukins 6 and 1) are also strong enhancers of aromatase activity, as observed in chronic inflammatory conditions such as rheumatoid arthritis synovitis [7] [Figure 1].

Calcitriol exerts an inhibitory effect by a direct repression of aromatase transcription via promoter II, as well as an indirect effect due to a reduction in the levels and biological activity of prostaglandins (especially PGE<sub>2</sub>),

PGE<sub>2</sub> = prostaglandin E<sub>2</sub>

which is a major stimulator of aromatase transcription through promoter II [8] [Figure 1].

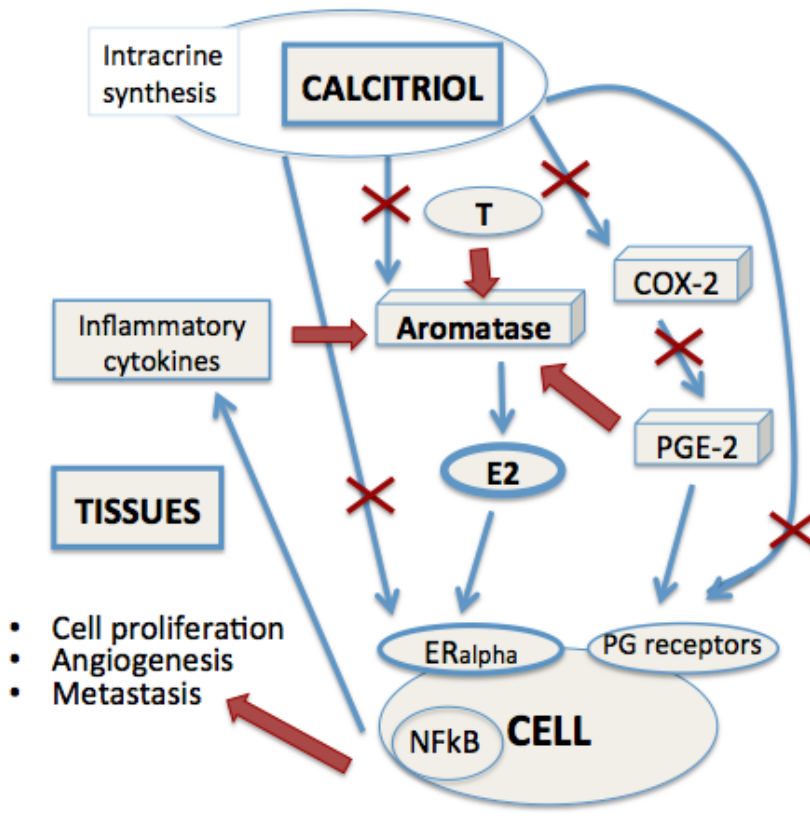
Interestingly, aromatase inhibitors used in breast cancer treatment inhibit the enzymatic activity of aromatase, while calcitriol reduces aromatase expression. Recently, an enhanced growth inhibitory effect from combining calcitriol and aromatase inhibitors in breast cancer cell cultures was revealed [8].

In addition, it was recently shown that calcitriol down-regulates the expression of estrogen receptors and thereby further reduces estrogen signaling in breast cancer cells, including the cell proliferative stimulus provided by estrogens on human cells [9].

Thus, these impressive new achievements suggest that the inhibition of estrogen synthesis and signaling by 1,25(OH)D<sub>3</sub> and its anti-inflammatory actions might play an important role in the use of calcitriol for the prevention and/or treatment of breast cancer at least [10].

Clinically, the consequences of low serum 25(OH)D levels seem to support the vitamin D protective role in cancer. 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% lower risk of breast cancer than those with levels of 13 ng/ml [11]. In addition, a large 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 [12].

**Figure 1.** Calcitriol decreases the expression of aromatase (the enzyme that converts androgenic precursors to estrogens) in both normal (mainly postmenopausal) and cancer peripheral tissues. Calcitriol interacts directly through the transcriptional repression of the aromatase promoter II and indirectly through the reduction (inhibiting cyclooxygenase-2) of levels of prostaglandin E2 (PGE2), a major stimulator of aromatase transcription via promoter II. Calcitriol down-regulates the expression of PG receptors, which are essential for PG cell signaling (proliferation, angiogenesis, and other procarcinogenic pathways). Calcitriol also down-regulates estrogen receptor alpha (ERalpha) levels by the direct transcriptional repression of the ERalpha promoter. T = testosterone, NFkB = nuclear factor kinase-intracellular signaling



Interestingly, one 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 [13]. After 4 years of treatment, the supplemented group showed a 60% lower risk of developing cancer than the placebo group [13]. However, in another randomized trial, the Women's Health Initiative, no effect of calcium and 400 IU vitamin D/day was found on the incidence of breast cancer, probably because the dose

was inadequate to efficiently raise the 25(OH)D blood levels [14].

#### WHAT ABOUT AROMATASE, CALCITRIOL AND PROSTATE CANCER?

It is now evident that prostate is an estrogen target tissue, and estrogens directly and indirectly affect growth and differentiation of prostate. The precise role of endogenous and exogenous estrogens in directly affecting prostate growth and differentiation in the context of benign prostate hypertrophy is complex and might also include local

genotoxic effects from estrogens [15]. However, estrogens and selective estrogen receptor modulators (SERMs) have been shown respectively to promote or inhibit prostate proliferation, signifying potential roles in BPH [16]. Therefore, since serum testosterone levels in men drop by about 35%–40% between the ages of 21 and 85, while estradiol levels remain constant or increase, this changing androgen:estrogen (testosterone:estrogens) ratio under the aromatase effect has been implicated in the development of both BPH and malignant prostate disease [17,18].

Recently, estrogenic effects due to the influence of aromatase were found in the development of colon and rectal cancer, confirming that estrogen may at least influence the risk through an inflammation-related mechanism [19]. Once again, vitamin D and its analogs are described as potent inhibitors of colorectal cancer growth and metastasis. Recent studies have defined relationships between the  $\beta$ -catenin-TCF pathway (a known contributor to colorectal cancer progression) and the vitamin D receptor pathway, explicating the underlying mechanisms [20]. In addition, vitamin D also regulates the innate immune response, and as such influences susceptibility to inflammatory bowel disease, a predisposing factor in colorectal cancer [19].

#### CONCLUSIONS

Vitamin D deficiency in cancer patients must be recognized and treated in time, together with bisphosphonates to reduce musculoskeletal implications (metastases) and symptoms; however, other more fundamental consequences related to calcitriol deficiency seem connected to its cancer preventive effects [1].

Finally, calcitriol and its analogs should be further evaluated in clinical trials in patients with early or precancerous disease. In the case of established

BPH = benign prostate hypertrophy

cancer, it is reasonable to consider that combination therapy will be required and that vitamin D, calcitriol, or an analog added to other effective therapies will likely increase the benefit of the standard therapy and perhaps reduce some of the side effects.

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**Capsule**

**HVEM signaling at mucosal barriers provides host defense against pathogenic bacteria**

The herpes virus entry mediator (HVEM), a member of the tumor-necrosis factor receptor family, has diverse functions, augmenting or inhibiting the immune response. HVEM was recently reported as a colitis risk locus in patients, and in a mouse model of colitis the authors demonstrated an anti-inflammatory role for HVEM, but its mechanism of action in the mucosal immune system was unknown. Shui et al. report an important role for epithelial HVEM in innate mucosal defense against pathogenic bacteria. HVEM enhances immune responses by NF-κB-inducing kinase-dependent Stat3 activation, which promotes the epithelial expression of genes important for immunity. During intestinal *Citrobacter rodentium* infection, a mouse model for enteropathogenic *Escherichia coli* infection, Hvem-/- mice showed decreased

Stat3 activation, impaired responses in the colon, higher bacterial burdens and increased mortality. We identified the immunoglobulin superfamily molecule CD160, expressed predominantly by innate-like intraepithelial lymphocytes, as the ligand engaging epithelial HVEM for host protection. Likewise, in pulmonary *Streptococcus pneumoniae* infection HVEM is also required for host defense. These results pinpoint HVEM as an important orchestrator of mucosal immunity, integrating signals from innate lymphocytes to induce optimal epithelial Stat3 activation, which indicates that targeting HVEM with agonists could improve host defense.

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Eitan Israeli

**The world is in greater peril from those who tolerate or encourage evil than from those who actually commit it**

Albert Einstein (1879-1955), German-born theoretical physicist and Nobel laureate who developed the general theory of relativity, effecting a revolution in physics. Einstein is often regarded as the father of modern physics and the most influential physicist of the 20th century