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Review Articles

Role of Vitamin D in Breast Cancer Prevention and Therapy: Recent Findings

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Abstract

Vitamin D, a fat-soluble vitamin, is produced in the skin exposed to the sunlight or provided by dietary intake. In addition to its role in the regulation of calcium and phosphorus metabolism, vitamin D has been correlated with several ailments such as depression, osteoporosis and cancer. Since vitamin D deficiency has been demonstrated to be linked to higher breast cancer risk, importance has been given to study its possible use in the prevention or even treatment of breast cancer. Herein, we review recent publications studying the vitamin D effects and breast cancer. Role of vitamin D as a preventive agent, its involvement in therapies and the effects of vitamin D supplementation are discussed. Accumulative findings support that vitamin D supplementation might reduce breast cancer risk, enhance effectiveness of chemotherapeutics and improve cancer survival.

***Key words**: vitamin D, breast cancer, chemotherapy, prevention, deficiency.*

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Introduction:

Vitamin D or calciferol is synthesized in the skin after sunlight (ultraviolet B) exposure or provided by dietary sources such as oily fish, egg yolk, some vegetables and mushroom.[1] Both the two forms of vitamin D: ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D3) are biologically inactive. To exert its biological effects, vitamin D is hydroxylated in the liver by the 25-hydroxylase to 25-hydroxyvitamin D. The latter is then hydroxylated in the kidney by the 1α-hydroxylase to form calcitriol, the active form of vitamin D.[2] Calcitriol binds to the vitamin D-binding protein, and regulates the mineral (calcium and phosphate) homeostasis by targeting several tissues such as bone, kidney or intestine.[3]

Vitamin D deficiency affecting about one billion persons around the world, has been correlated to higher risk of several diseases or health problems such as: cardiovascular, erectile dysfunction, cancer,[4] metabolic disorders, diabetes,[5] depression[6] and even death.[7]

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Several studies have shown a marked link between vitamin D deficiency and increased breast cancer risk.[8] A strong association between vitamin D deficiency and enhanced risk of aggressive breast cancer has been demonstrated.[9,10] Furthermore, it seems that early vitamin D supplementation could potentially improve breast cancer survival. [11] Furthermore, calcitriol and its analogs were shown to exhibit promising antibreast cancer activities, both *in vitro* and *in vivo*. In addition, calcitriol has been found to potentiate the effect of several anti-breast cancer drugs.[12] The anticancer effects of calctriol were found to target genomic and/or non-genomic pathways.

Vitamin D deficiency and breast cancer:

The worse survival of breast cancer patients receiving chemotherapy may be attributed partly to the decrease in serum vitamin D levels. Indeed, it has been demonstrated that at the end of chemotherapy, levels of serum vitamin D decreased significantly. Charehbili *et al*. found that neoadjuvant chemotherapy resulted in a significant decrease of vitamin D levels by 16nmol/L. In addition, vitamin deficiency (< 50 nmol/L) occurred in about 56% of breast cancer patients.[13] A high prevalence of vitamin D deficiency has been reported in Chilean breast cancer patients before

endocrine therapy. 70.5% of Chilean breast cancer patients had serum vitamin D concentrations less than 20ng/ml, while 22.5% of them were diagnosed with vitamin D insufficiency (20-29.9ng/ml).[14] Similarly, vitamin D deficiency was reported in 71% of Saudi breast cancer patients. The study supported a significant association between lower vitamin D concentrations (less than 25nmol/L) and higher risk of triple negative breast cancer.[15]

Shirazi *et al*. studied 764 Swedish breast cancer cases and 764 controls with regard to vitamin D status and different prognostic factors. They found that low vitamin D levels were associated to a higher risk of breast cancer and unfavourable prognosis.[16]

Effect of vitamin D supplementation:

Several epidemiologic studies have shown an inverse correlation between higher vitamin D intake (from diet or supplementation) and breast cancer.[17] The protective effect of vitamin D supplementation against breast cancer has been reported.[18] In addition, it has been demonstrated in several clinical studies that vitamin D supplementation enhanced response to anticancer drugs and improved disease free survival.[19] Zeichner *et al*. studied retrospectively the effect of vitamin D supplementation on clinical outcomes in $HER2^+$ nonmetastatic breast cancer breast cancer patients. Vitamin D supplementation resulted in a significant increase in disease-free survival, even after adjusting for tumor size or number of positive metastatic nodes.[20]

Branca *et al*. reported promising positive effects of three weeks pre-surgical vitamin D3 supplementation (10,000 IU/day *per os*) in a patient with recurrent breast cancer.[21]

Breast cancer patients receiving letrozole were supplemented with 2000 and 4000 IU/1000 of Vitamin D3 and calcium for 12 weeks. Vitamin D and Ca supplementation resulted in a significant increase of serum vitamin D, Ca and P, and decreased PTH and ALP levels. Beside the correction of vitamin D deficiency in all treated patients, supplementation decreased the side-effects of letrozole (arthralgia).[22]

Besides its effect against breast cancer progression, and its role in enhancing effectiveness of chemotherapeutic agents, vitamin D supplementation is recommended to reduce the negative recurrence of anti-breast cancer standard therapies on bone density and to prevent risks of fractures both in premenopausal and postmenopausal women.[23]

In recent years, accumulative findings support that vitamin D supplementation could be a safe and economic alternative to improve breast cancer prognosis and outcome.[24]

Vitamin D as a chemotherapeutic agent:

As majority of triple negative breast cancers and about 90% of breast tumours express vitamin D receptor, the latter became one of the favourite targets of anti-breast cancer therapy. Triple negative breast cancer cells were inhibited by vitamin D_3. Inhibition of cell growth was accompanied by induction of apoptosis and accumulation of cells in G1 and G0/G1phase. Furthermore, vitamin D3 was able to inhibit the growth of breast cancer stem cells.[25]

The alkynylphosphonate analogue of calcitriol EM1 has displayed important anticancer activity against breast cancer cells.[26] The analog showed promising anti-metastatic effects in a murine model of breast cancer.[27]

Calcitriol and its analogs, calcipotriol and EB1089 inhibited the growth of SUM-229PE and SKBR3 breast cancer cells. Furthermore, when combined with gefitinib, calcitriol and its analogs induced apoptosis of breast cancer cells, arrested their cell cycle at G2/M phase and inhibited the MAPK signalling pathway.[28] Vitamin D3 combined with metformin was able to exhibit antitumor effects against MDA-MB-231 breast cancer cells by targeting m-TOR signalling pathway.[29]

Vitamin D was also studied for its anti-metastatic actions. Both vitamin D and its less calcemic analog MART-10 have been shown to inhibit the invasion and migration of MCF-7 cells. The anti-migration and invasion ability of vitamin D and MART-10 were confirmed by the increase of E-cadherin protein expression and down regulation of the epithelial–mesenchymal transition (EMT)-related transcription factors such as Snail, Slug, and Twist.[30] Vitamin D and MART-10 induced apoptosis of ER+ MCF-7 breast cancer cells and overexpression of pro-apoptotic proteins Bcl and Bax.[31]

Therapeutic effects of vitamin D are mediated through the binding of the active hormone to the vitamin D receptor which results in modulation of several genes and molecules pathways.[32,33] Activation of the vitamin D receptor by p38 and c-Jun NH_2-terminal kinases cooperation has been demonstrated to be responsible of the cytotoxic activity of vitamin D against breast cancer cells.[34] Similarly, Bi *et al.* found that anticancer activity of calcitriol against colorectal cancer cells was attributed to the interaction of JNK1 with the vitamin D receptor.[35]

Vitamin D appears to target CCN genes modulation in breast cancer cells, through a cell-specific context or by interfering with other signalling molecules such as oestrogen.[36] Vitamin D was shown to induce inhibitory effect against triple negative breast cancer cells by targeting thirty-five genes. Vitamin D treatment resulted in the down regulation of four genes involved in metastases formation (Plau, Hbegf, Postn and Has2).[37]

Recently, Sheng *et al*. identified 523 genes regulated by vitamin D in human breast cancer explants. They reported

that vitamin D up-regulated tumour suppressor genes such as CLMN, SERPINB1, EFTUD1and KLK6.[38]

Vitamin D as a preventive agent:

The preventive effect of vitamin D may be explained by its inhibitory effect against the tumor-initiating cells. Breast tumor-initiating cells thought to be responsible of drug-resistance, metastases and disease relapse became important targets of new anticancer therapy researches.[39] *In vivo* inhibitory effects of dietary vitamin D and calcitriol against mouse breast tumor-initiating cells were recently demonstrated. It has been suggested that the inhibitory effects of calcitriol may be mediated through inhibition of Wnt/â-catenin pathway.[40] As administration of vitamin D results in hypercalcemia limiting its clinical usefulness, novel vitamin D analogs were developed to exert better anticancer actions with reduced. Gemini vitamin D analog BXL0124 has been demonstrated to exhibit promising anti-breast cancer effects.[41,42] BXL0124 was found to inhibit the Notch signalling pathway in $CD44^{+}/CD24^{-/low}$ cancer stem cells by targeting its ligands through a HES1 dependent manner.[43] Both vitamin D and its analog BXL0124 were reported to be able to suppress the growth of breast cancer stem cells, without inducing apoptosis. Indeed, vitamin D and BXL0124 significantly altered their mammosphere forming efficiency and mammosphere phenotype. Vitamin D and BXL0124 resulted in a marked decrease of levels of markers of stem cell maintenance and stem cell signalling molecules (CD44, CD49f, c-Notch1and pNFkB).[44]

Conclusion:

Although inconsistence still remains among literature regarding the positive effects against breast cancer, accumulative findings support the inverse correlation between higher vitamin D intake and breast cancer risk. Furthermore, both vitamin D and its analogues have been shown to induce apoptosis and cell cycle arrest of several breast cancer cells lines. Similarly, vitamin D could be a promising anti-metastatic agent. Discussed literature supports the fact that vitamin D supplementation might reduce breast cancer risk, enhance effectiveness of chemotherapeutics and improve cancer prognosis and outcome.

Conflict of interest: None.

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