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Vitamin D and Prevention of Breast Cancer

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Abstract

Apart from classical actions of vitamin D on bone and mineral metabolism, it exerts diverse protective biological effects against carcinogenesis. Vitamin D may play role in controlling growth of normal breast cells and may help in prevention of growth of malignant mammary cells. Hypovitaminosis D is gaining attention as an emerging risk factor of breast cancer. Some ecological studies suggest association of high levels of sunlight exposure with low prevalence of breast cancer and mortality rates. Hence interest arose among researchers with the hypothesis that high levels of vitamin D might help to reduce the risk of breast cancer. Several mechanisms proposed to link deficiency of vitamin D with breast cancer.

Numerous epidemiological, laboratory and observational studies demonstrated evidence linking higher vitamin D exposures to reduce prevalence of breast cancer. Vitamin D deficiency is potentially modifiable risk factor for breast cancer that can be targeted for prevention of the disease. But its safety, feasibility, effect on biomarkers and long term follow up after supplementation is the chief concerns for its use in chemoprevention of breast cancer. Definite conclusive data from randomized controlled trials about beneficial effect of vitamin D supplementation in prevention of breast cancer is lacking. Serum 25(OH) D is the chief form of circulating vitamin D and most accepted marker of vitamin D status. It is widely used clinical laboratory test to evaluate vitamin D deficiency. In the present review, we attempted to address the issue of vitamin D status as a risk factor for breast cancer and its potential use as chemopreventive therapeutic agent.

Keywords: Vitamin D; Hypovitaminosis D

Introduction

Vitamin D, also known as sunshine vitamin is well recognized as regulator of calcium, phosphorous homeostasis and bone health. But now its emerging role as an anti-neoplastic agent is receiving considerable attention in the clinical research field. It exerts a wide range of immunogenic and antiproliferative activity in the body [1]. Vitamin D deficiency has been found to be associated with occurrence of a variety of cancers like colon, ovary, prostate, multiple myeloma and breast cancer [2]. Breast cancer is the second commonest neoplasm occurring in women and remains major cause of morbidity and mortality. Because of changed lifestyle, incidence of breast cancer is rising strongly in all countries. It includes 1.7 million new cases per year and 25% of all types of cancers [3]. Approximately 12% of the women will have chances to develop breast cancer in their lifetime [4]. It is a heterogeneous multifactorial disease that develops due to complex interplay of several genetic, environmental, reproductive risk factors. Well-established risk factors are menstrual, anthropometric, reproductive, factors as well as use of exogenous estrogen, benign breast disease, positive family history and consumption of alcohol. But these factors cannot explain rising prevalence of breast cancer. With this magnitude of the problem, etiological investigation and identification of additional risk factors and targeting them remains cornerstone in the preventive strategy of breast cancer. Some ecological studies suggest association of high levels of sunlight exposure with low prevalence of breast cancer and mortality rates. Hence interest arose among researchers with the hypothesis that high levels of vitamin D might help to reduce the risk of breast cancer [5].

Prevalence of vitamin D deficiency is rising worldwide in all races even in temperate region. Less exposure to sunlight, use of sunscreens, skin pigmentation, advanced age and inadequate oral intake lead to deficiency of vitamin D [6]. Hypovitaminosis D is emerging as a risk factor for various non-communicable diseases including malignancies. Anticancer properties of vitamin D

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have been well demonstrated in different cells as well as in normal and malignant mammary cells. Several researchers explored association of low levels of vitamin D with the prevalence of breast cancer [7,8]. But the evidence of protective effect of higher levels of vitamin D against breast carcinogenesis remained substantial. Exact mechanism of anticancer action of vitamin D at cellular level is not fully understood. Number of studies investigated hypovitaminosis D as a risk factor for the development of breast cancer, but reported inconclusive data [9,10]. Vitamin D may play role in controlling growth of normal breast cells and may help in prevention of growth of malignant mammary cells. Serum 25(OH)D is the chief form of circulating vitamin D and most accepted marker of vitamin D status. It is widely used clinical laboratory test to evaluate vitamin D deficiency. In the present review, we evaluated the current updates on antineoplastic properties of vitamin D, its association with breast cancer with emphasis on its role in the preventive measures.

Sources and Metabolism of Vitamin D

Vitamin D is obtained through sunlight exposure, diet and supplements. Foods rich in vitamin D are fish, eggs and fortified dairy products. Cholecalciferol (Vitamin D3) is a naturally occurring form from animal sources while ergocalciferol (vitamin D2) from plant sources. Ultraviolet B (UVB) is needed for photosynthesis of vitamin D in the skin. During exposure to sunlight, UVB photons penetrate into the skin and get absorbed by 7-dehydrocholesterol leading to formation of unstable pro-hormone vitamin D form, which rapidly undergoes rearrangement to form vitamin D3 (cholecalciferol). It circulates in bound form with vitamin D binding protein. When it enters liver, it gets metabolized by vitamin D-25-hydroxylase enzyme (25-OHase) to 25-hydroxyvitaminD (Calcidiol). It is a main storage form in the body and chief form of vitamin D in plasma. Although it is biologically inactive form, it is a precursor for active form of vitamin D. 25(OH) vitamin D undergoes hydroxylation in kidney and other target tissues like breast, colon, prostate by vitamin D-1,25-dihydroxylase to form 1,25 dihydroxyvitamin D that is an active form also called as calcitriol. Its level is regulated homeostatically tightly in a narrow range by renal 1-alpha-hydroxylase [11]. Both 25(OH) D and 1,25(OH)₂D can get degraded by vitamin D 24 hydroxylase in various tissues including breast. So status of vitamin D in circulation depends on its exogenous sources. Methods for estimation of active metabolite of vitamin D are available. But its plasma concentrations are approximately 1000-lower than 25(OH)D level and does not reflect dietary deficiency. Hence serum 25(OH)D, an excellent biological indicator of the availability of vitamin D from oral intake and sunlight exposure is widely used laboratory test in clinical practice. Biological half-life of 25(OH)D is at least 2 months and that of 1,25 (OH)₂D is 4-6 hours [12].

Mechanism of Action of Vitamin D in Breast Cancer Cells

Vitamin D exerts its anti-neoplastic activity by various mechanisms. Its active metabolite form 1,25 (OH)₂ vitamin D binds with nuclear vitamin D receptor (VDR) and further to specific DNA sequences namely vitamin D response elements and modulates expression of specific genes in tissue-specific manner. They encode for proteins required for regulation of cell proliferation, differentiation, apoptosis and angiogenesis. In deficiency of vitamin D, these activities are hampered and enhance cellular growth, neoangiogenesis and carcinogenesis [13]. VDRs, ligand-dependent nuclear transcriptional factor are expressed in almost all tissues including normal as well

as malignant breast cells. Calcitriol has been well recognized as a modulator of cell proliferation and differentiation (cytotoxic and anti-proliferative) in many types of cells including mammary neoplastic cells. But its mechanism of action is still unclear [13]. In animal models, vitamin D has been found to be beneficial to suppress proliferation, tumorigenesis tumor growth. Antiproliferative effect of vitamin D is mediated through VDR, which is a member of nuclear receptor family [14]. Adequate levels of vitamin D are hypothesized to prevent cancer possibly through genomic effects modulated by VDR. Research at molecular level suggests association of increased breast cancer risk with the expression of VDR. VDR genes located on chromosome 12q12-q14 possess more than 470 single-nucleotide polymorphisms. Number of large population based studies examined association between variants of VDR polymorphisms and risk of breast cancer, but with controversial findings [15,16]. Lu D et al observed no significant association of VDR polymorphism with risk of breast cancer in their meta-analysis performed from prospective nested case-control studies [17]. K Townsend et al studied autocrine metabolism of vitamin D in normal and malignant breast tissue by analysis of mRNA expression for 1 alpha-hydroxylase, 24-hydroxylase and VDR. The data indicated upregulation of vitamin D-activating enzyme 1alpha-hydroxylase in breast tumors with dysregulated expression of 24-hydroxylase. This abrogate the effects of local 1,25 (OH)₂D₃ production in tumors by catalyzing catabolism to less active vitamin D metabolites. The enzymes involved in autocrine metabolism of vitamin D in breast tissue may therefore provide important targets for both the prevention and treatment of breast cancer [18].

Several mechanisms proposed to link deficiency of vitamin D with breast cancer. Malignant cells have decreased intracellular levels of 1 alpha hydroxylase compared to normal cells which decreases synthesis of intracellular calcitriol along with increased breakdown of calcitriol. Hence anticancer activities of vitamin D are hampered. Altered VDR makes them restricted to nucleus resulting in less binding to cytoplasmic calcitriol. Also downregulation of expression of VDR is observed in cancer of colon, breast and lung. One more mechanism likely to link vitamin D and cancer is up-regulation of E-cadherin, a glue like substance by 25(OH)D. It helps to keep cells bound tightly together, and in a well-differentiated state [19]. Qian-Qian Huang et al also reported negligible role of Fok1, Apa1, Cdx2 and Poly-A polymorphisms in breast cancer risk with Bsm1 and Taq1 as possible exceptions in their comparative meta-analysis of crude and adjusted odd ratios [20].

To explain beneficial effect of vitamin D against breast cancer, two distinct pathways have been proposed. One is endocrine pathway in which circulating 1,25 (OH)₂D reaches the breast tissue to exert its anti-carcinogenic effect. Another is autocrine/paracrine metabolic pathway where circulating 25(OH)D reaches mammary tissue and gets catalyzed by 1-alpha-hydroxylase to 1,25 (OH)₂D which bind to VDR and regulate cell proliferation, differentiation and apoptosis [5]. VDRs have been postulated to play significant role to protect from tumor proliferation.

Link between Vitamin D and Breast Cancer

Exact pathogenesis of breast cancer remains unknown. It involves environmental, genetic factors and molecular signaling pathways. In recent few decades, scientific evidence linking vitamin D to breast cancer has grown notably. Geographic variation in the incidence of breast cancer was attributed to the amount of exposure to solar

radiation. Low levels of vitamin D due to poor UVB explain the higher incidence of breast cancer at high altitude due to decreased endogenous synthesis of active vitamin D [8]. Deficiency of vitamin D among breast cancer patients has been reported in various case-control studies [7,9,10]. Hypovitaminosis D is gaining attention as an emerging risk factor of breast cancer. Also its role as prognostic indicator in the management of breast cancer is reported. Some studies linked status of vitamin D levels with recurrence of breast cancer, tumor size and mortality. Maintaining optimal level of vitamin D among patients of breast cancer help in improving survival of the patients.

Sperati F et al investigated role of vitamin D supplementation for prevention of breast cancer in their systematic and meta-analysis. They compared outcome of the randomized controlled trials of administration of vitamin D as single agent or in combination versus placebo or no treatment. They commented that neither vitamin D dosage nor mode of administration affect breast cancer risk significantly. Hence effect of supplementation of vitamin D for prevention of breast cancer remains inconclusive [21]. Similar findings were reported in Mendelian randomisation study [22]. Mohr SB and colleagues analysed data extracted from all case-control and nested case-control studies of serum [25] D and breast cancer risk in their pooled analysis. Their results strongly support inverse association between serum (OH)D and breast cancer risk from four lines of epidemiological studies evidence- geographical variation with latitude and solar UVB radiation, observational studies showing association of vitamin D deficiency with increased risk of breast cancer, studies linking low intake of vitamin D with high risk and basic laboratory studies evaluating in vitro and in vivo mechanisms [19]. Y Kim and Y Je assessed quantitatively the association between vitamin D intake, blood 25(OH)D levels and breast cancer incidence in their systematic review including 30 prospective studies. They also investigated mortality as per levels of blood 25(OH)D among breast cancer. They observed an overall nonsignificant, weak inverse association between vitamin D intake or 25(OH)D levels and risk of breast cancer. However high levels of blood (OH)D were significantly associated with low breast cancer mortality [23]. Imtiaz et al reported deficiency of vitamin D invariably in almost all patients with breast cancer in case-control study [13].

Vitamin D in Chemoprevention of Breast Cancer

Chemoprevention is the process of alteration of carcinogenesis by drug intervention among high risk individuals. In case of breast cancer, tamoxifens, raloxifens, SERMs, aromatase inhibitors have been tried as chemopreventive agents. But they are not accepted due to compliance and potential adverse events. Vitamin D deficiency is potentially modifiable risk factor for breast cancer that can be targeted for prevention of the disease. But its safety, feasibility, effect on biomarkers and long term follow up after supplementation is the chief concerns for its use in chemoprevention of breast cancer. Vitamin D₃ is more efficient than vitamin D₂ in increasing 25(OH)D levels which is a precursor of calcitriol [24]. Vitamin D can be obtained from foods or supplements, but endogenous synthesis of vitamin D is an important source. Importance of exposure to sunlight has been highlighted in the cancer prevention guidelines. According to the country, region and season, time and type of sun exposure for cancer prevention must be studied. Sunlight is the most cost effective, feasible, efficient and easily available source of vitamin D than any

dietary sources and supplementation. Data from multi-level model reported that dietary intake of vitamin D has no impact on serum 25(OH)D levels in comparison to sunlight exposure [25]. Garland CF et al carried out pooled analysis to assess the dose-response relation between serum 25(OH)D levels and risk of breast cancer. According to their analysis, individuals with 25(OH)D levels more than 52ng/ml had 50% lower risk to have breast cancer. This serum level corresponds to daily intake of 4000IU. Serum 25(OH)D level raises by 10ng per 1000IU intake. Intake of 2000 IU/day of Vitamin D₃ and, when possible, moderate exposure to sunlight approximately 12 minutes per day, could raise serum 25(OH)D to 52 ng/ml, a level associated with 50% reduction in incidence of breast cancer, according to observational studies. Serum 25(OH)D levels mainly depend upon sun exposure [26].

Numerous ecologic, laboratory and observational studies demonstrated evidence linking higher vitamin D exposures to reduce prevalence of breast cancer. But protective effect of vitamin D supplementation against breast cancer risk remains contradictory because of certain gaps in the research. It has been proposed that supplementation of vitamin D 4000IU/day will be beneficial and safe as a primary prevention strategy [27]. Several studies in the literature documented association of vitamin D with breast cancer risk and survival. But relatively less is known about dose regimens, response and overall benefits of supplementation of vitamin D. Definite conclusive data from randomized controlled trials about beneficial effect of vitamin D supplementation in prevention of breast cancer is lacking [28]. Women's Health Initiative failed to support protective role of vitamin D over a period of seven years for breast cancer [29]. Long-term duration of follow up is another important issue to assess role of vitamin D in the prevention of breast cancer.

Potential Adverse Effects of Vitamin D

Potential benefits of supplementation of vitamin D for prevention of breast cancer among high-risk individuals must be weighed against possible adverse effects. Relatively vitamin D is a safe drug if administered in conventional dosage. Some of reported adverse events are hypercalcemia, gastrointestinal symptoms and renal stones, bone demineralization. Being a fat-soluble vitamin, excess supplementation of vitamin D leads to hypovitaminosis. Unpredictable relation between intake of vitamin D and its blood levels make difficulty in standardizing dose of vitamin D. Specific cut-off points to define protective role of vitamin D are controversial. But most of the authorities suggest levels of 25(OH)D more than 30ng/ml as sufficient and more than 150ng/ml potentially toxic level [30,31].

Supplementation of vitamin D can cause vitamin D toxicity easily because difference between appropriate and toxic intake is fairly small. Hence dose adequacy represents very critical issue for supplementation of vitamin D. One should weigh the potential benefits of vitamin D that could reduce breast cancer risk versus the possibility of toxicity of vitamin D. Vitamin D intake at dose of 2000-4000IU per day with target of 45ng/ml serum (OH)D will help in prevention of breast cancer.

Conclusion

Apart from classical actions of vitamin D on bone and mineral metabolism, it exerts diverse protective biological effects against carcinogenesis. Evidence from epidemiological, case-control, observational and laboratory studies support anti-neoplastic role of vitamin D. Clinical research suggests link between vitamin D and

breast cancer. But results of randomized controlled trials and clinical observational studies are inconclusive to support protective role of supplementation of vitamin D in the prevention of breast cancer. Estimation of concentration of 25(OH)D in serum is a commonly accepted biomarker for assessment of vitamin D status. Intervention strategies for monitoring of vitamin D status by serum 25(OH)D levels and supplementation with vitamin D to reduce incidence of breast cancer need to be studied in future.

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