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Role of Vitamin D in Breast Cancer Prevention – A Review

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Abstract

Several recent epidemiological and experimental studies have suggested that decrease vitamin D intake is associated with mammary gland carcinogenesis. Recent studies have begun to evaluate a possible role of increase dietary vitamin D in reducing the risk of breast cancer. Studies show that their anticarcinogenic effect due to their participation in regulating cellular proliferation, terminal differentiation, angiogenesis, and apoptosis in normal and malignant breast cells. Recent studies show that vitamin D Receptor have been found in up to 80% of breast cancers, and human with vitamin D receptor positive tumors had longer disease free survival than those with receptor negative tumors.

Keywords: Vitamin D, Breast cancer, Epidemiology, Risk, Diet.

Introduction

At the right dose vitamin D is important for bone development and bone disease[1-7]. It is newly recognized association of vitamin D with risk of several types of cancer[8-11], especially breast[13] colon [12], ovarian[15], and prostate cancer[16].

Breast cancer is the most commonly diagnosis cancer in the united state and west European countries[17-19]. In term of mortality, breast cancer ranks second only to lung cancer as a cause of death from cancer in U.S. women[20]. Many factors have been related to altered breast cancer risk, including certain menstrual (age at menarche and age at menopause), reproductive (childbearing and lactation) and anthropometric (body mass index and weight gain) factors as well as exogenous estrogen use, endogenous hormone level, family history of breast cancer, ionizing radiation and alcohol consumption[21,22].

This review explores the available literature on vitamin D and breast cancer and defines the current knowledge about the role of vitamin D in breast cancer prevention.

Sources and Metabolism of Vitamin D

Humans get vitamin D from food, such as fish, eggs, fortified dairy products such as milk, butter, cheeses, orange juice, formulas, yogurts etc. and vitamin D containing multivitamins and supplements [23]. Out of this an additional source of vitamin D is sunlight exposure.

The two naturally occurring form of vitamin D are vitamin D_3 (cholecalciferol) which is mainly obtained from animal source and vitamin D2 (ergocalciferol) from plant sources. Vitamin D in the form of D_2 and D_3 is first metabolized to 25(OH) D in the liver and then further metabolized to 1, 25-dihyroxyvitamin D [1, 25(OH) $_2$ D] by 1-α-hydroxylase in the kidneys and other tissues [24]. Both 25(OH) D and 1, 25(OH) $_2$ D can be degraded through the catalysis of vitamin D 24- hydroxylase in various tissue, including the breast. 1, 25-dihyroxyvitamin D is the biologically active form of vitamin D which play important role in breast cancer prevention. Figure 1, shows key processes of vitamin D metabolism.

Epidemiological studies on vitamin D status and breast cancer.

The majority of women who develop breast cancer are of postmenopausal age, and estrogen deficiency and aging are often associated with vitamin D deficiency. However, few epidemiological studies have examined whether dietary intake of vitamin D alters breast cancer incidence in populations [25]. A newly published evaluation of the Nurses' Health Study finds that intakes of dairy products, dairy calcium and total vitamin D (as measured by food-frequency questionnaires) are inversely associated with breast cancer risk in premenopausal but not postmenopausal women. These data are consistent with an earlier study that reports an inverse correlation between intake of dairy products and breast cancer risk. Another recent study includes evaluation of sunlight exposure in addition to vitamin D from diet and supplements in relation to breast cancer risk. In this study, several measures of sunlight exposure and dietary vitamin D intake are associated with a reduced risk of breast cancer; however, the associations are dependent on region of residence. Studies also report links between solar radiation (which induces epidermal synthesis of vitamin D) and breast carcinoma mortality. In two studies in which vitamin D status was measured in relation to breast cancer, low levels of 1,25(OH)$_2$- D_3 were found to be associated with increased breast cancer risk of disease progression.

Vitamin- D3 Receptor as a Target for Breast Cancer Prevention

The Vitamin D-3 receptor (VDR) is a nuclear receptor that modulates gene expression when complexes with its ligand 1-25,-dihydroxycholecalciferol [1,25(OH)$_2$- D_3], which is the biologically active form of vitamin D-3 The cellular effects of VDR signaling include growth arrest, differentiation and/or induction of apoptosis, which indicate that the vitamin D pathway participates in negative-growth regulation. Although

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much attention has been directed in recent years toward the development of synthetic vitamin D analogs as therapeutic agents for a variety of human cancers including those derived from the mammary gland, studies on vitamin D as a chemo preventive agent for breast cancer have been quite limited. The VDR is expressed in normal mammary gland, where it functions to oppose estrogen-driven proliferation and maintain differentiation; this suggests that 1, 25(OH) $_2$-D$_3$ participates in negative-growth regulation of mammary epithelial cells. Furthermore, preclinical studies show that vitamin D compounds can reduce breast cancer development in animals, and human data indicate that both vitamin D status and genetic variations in the VDR may affect breast cancer risk. Collectively, findings from cellular, molecular and population studies suggest that the VDR is a nutritionally modulated growth-regulatory that may represent a molecular target for chemoprevention of breast cancer.

Mechanism Through Which Vitamin D Prevent Breast Cancer

Biologically active form of vitamin D is 1, 25(OH) $_2$D, that exert its effects through binding to nuclear vitamin D receptor (VDR) and further binding to specific DNA sequences that influence cellular proliferation, apoptosis, angiogenesis, and terminal differentiation of normal and cancer cells[26,27].

Two distinct pathways of vitamin D biosynthesis and action have been proposed in mammary carcinogenesis, one involving 1, 25(OH) $_2$D and other involving 25(OH) D[28,29]

. In the endocrine pathway, circulating 1, 25(OH) $_2$D reaches the breast tissue to exert its anticarcinogenic effect. The other pathway is the autocrine/paracrine pathway, in which circulating 25(OH) D reaches the breast tissue and is further catalyzed to 1, 25(OH) $_2$D by the 1-α-hydroxylase in the breasts. The locally produced 1, 25(OH) $_2$D may bind to VDR and therefore regulating cell proliferation, differentiation, and apoptosis.

VDR Polymorphisms and Breast Cancer Risk.

It is increasingly apparent that genetic variability can influence individual responsiveness to dietary or pharmaceutical interventions. There is considerable interest in the genetically determined differences in the VDR signaling pathway in relation to disease susceptibility. A number of common allelic variants (or polymorphisms) in the human VDR gene were identified and these were extensively studied with respect to risk for a variety of diseases including breast cancer. The best-studied VDR polymorphisms include a start codon polymorphism (*Fok*I) in exon 2, *Bsm*I and *Apa*I polymorphisms in an intronic region between exons VIII and IX, a *Taq*I variant in exon IX and a singlet (A) repeat in exon IX. Seven published reports examine the relationship between one or more VDR polymorphisms and breast cancer incidence or progression. Six of these studies identify specific alleles of the VDR that correlate with breast cancer incidence and/or metastasis, whereas one study fails to detect a significant correlation.

Although these findings are certainly intriguing, the underlying basis for an association between VDR polymorphisms and breast cancer susceptibility is currently unclear. Three of the VDR polymorphisms that are linked to breast cancer susceptibility (BSMI, *Apa*I or *TAq*I variants) do not alter the amount, structure or function of the VDR protein produced. There is evidence, however, that two of these polymorphisms [the VDR start codon polymorphism defined by fokI and the singlet (A) repeat in exon IX] have functional significance. The FokI site dictates which of two potential translation initiation sites is used. Individuals that lack the FokI restriction site initiate translation at the first site and express the full-length VDR, which consists of 427 amino acids. In contrast, individuals with the FokI restriction site use a second ATG site and generate a VDR protein of 424 amino acids. Although no significant differences in ligand affinity, DNA binding or transactivation activity are found between these two VDR forms when studied independently, when the VDR start codon polymorphism is considered simultaneously with the singlet (A) repeat in exon IX, differences in VDR function are detected in vitro In transient transfection assays with a vitamin D-responsive reporter gene, the shorter VDR variant is shown to interact more strongly with transcription factor IIB and display higher potency than the longer VDR variant. These data support the concept that functionally relevant polymorphisms in the VDR exist, and further studies are required to determine whether the VDR genotype interacts with other risk factors for breast. In this review, we highlight epidemiological, clinical, cellular and molecular research studies that address the role of vitamin D and its receptor in the normal mammary gland and in breast cancer. Although these studies provide considerable evidence that 1, 25(OH) $_2$-D$_3$ and the VDR play a role in mammary gland biology that might affect susceptibility to transformation, numerous outstanding research issues remain to be addressed. Studies to define the downstream targets of VDR in the normal mammary gland that participate in reducing susceptibility to breast cancer are essential. Of particular interest is whether critical windows of development exist during which intervention with vitamin D-based preventive strategies are most effective. Gene-profiling studies using the VDR-KO mouse model will likely prove useful in addressing this issue.

Investigations into how the transformation process affects the vitamin D-signaling pathway also are needed. Date from mammary cell lines suggest that oncogenic transformation with or ras inhibits VDR signaling and induces resistance to the growth-inhibitory effects of 1, 25(OH) $_2$- D$_{3,}$ but additional research is needed to determine whether these interactions are relevant to human breast cancer. Date presented in Figure 3 suggest that transformation might be associated with deregulation of 1, 25(OH) $_2$- D$_3$ metabolism in mammary cells (either loss of vitamin D 1-hydroxylase activity and/or enhancement of 24-hydroxylase activity). In support of this concept, the vitamin D 24-hydroxylase gene recently was shown as amplified in human breast cancer Additional studies are necessary to determine actual enzyme activities as a function of neoplastic progression in mammary cells and to assess whether the vitamin D hydroxylase are useful targets for breast cancer prevention or therapy.

Perhaps most important are translational studies to examine whether dietary vitamin D affects breast cancer development and how vitamin D interacts with hormonal factors such as estrogens, phytoestrogens and selective estrogen-

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response modifiers like tamoxifen. Large-scale intervention studies such as the Women's Health Initiative, which is examining the effects of calcium and vitamin D supplementation on cancer, osteoporosis and heart disease in post-menopausal women, offer the best approach toward addressing this important issue. Until more definitive answers are available, all women should be particularly attentive to their calcium and vitamin D intake to ensure that recommended daily allowances are met. This is particularly important because estrogen deficiency and aging are commonly associated with marginal vitamin D status.

Conclusion

Collectively, the studies described in this and other recent reviews provide convincing evidence that vitamin D and its receptor represent targets for breast cancer prevention and therapy. Because the ligand for the VDR can be derived from dietary sources, we propose that this receptor represents a nutritionally modulated growth- regulatory gene in the mammary gland. Implications of this concept are that specific dietary guidelines for breast cancer prevention might ultimately be developed for the general population, breast cancer patients or individuals with specific VDR polymorphisms. Furthermore, this concept implies that synthetic vitamin D analogs designed to trigger specific effects in the mammary gland might be effective in the prevention of human breast cancer.

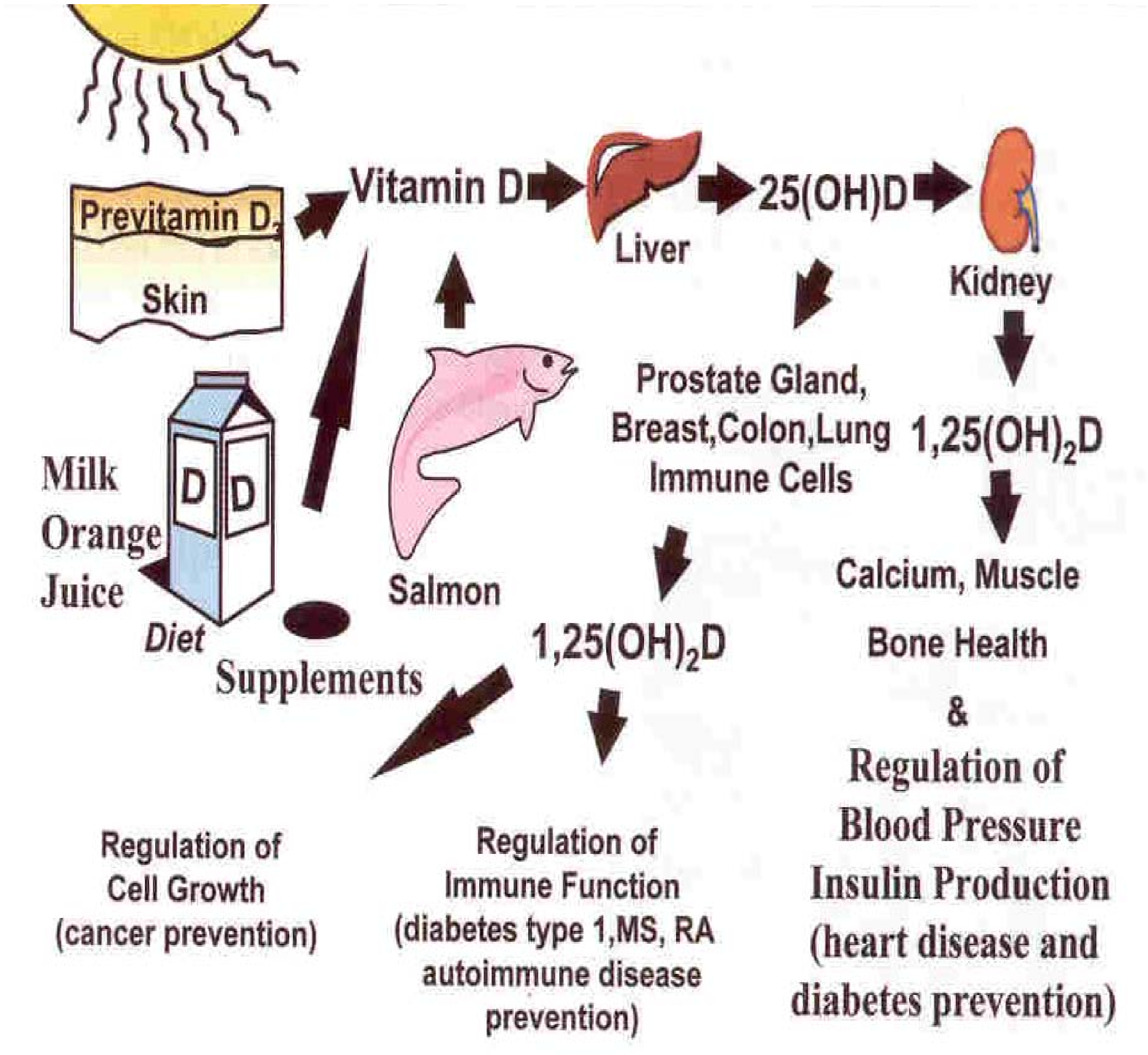

Figure 1, key process of vitamin D metabolism

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