Optimizing Vitamin D Concentrations for Breast Cancer Risk Reduction

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Abbreviations: 25(OH)D = 25-hydroxyvitamin D, ER = estrogen receptor, IOM = Institute of Medicine, VDR = vitamin D receptor.

Vitamin D is a fat-soluble essential precursor to an active hormonal form that is an important regulator of numerous health conditions. Vitamin D is present naturally or is added to many foods, and is commonly taken as a dietary supplement. Vitamin D is converted to the active 25-hydroxyvitamin D form, or 25(OH)D, in the liver, and it is the form usually detected in serum as an indicator of vitamin D concentration. 25(OH)D is then converted in the kidney to the biologically active form 25-dihydroxyvitamin D (calcitriol). Food contains the vitamin D3 form, which is metabolized to 25(OH)D3. Vitamin D is also converted to the active form via sunlight exposure of unprotected skin to ultraviolet B radiation from the cutaneous 7-dehydrocholesterol to previtamin D3, which is then metabolized to vitamin D3. Calcitriol binds to the nuclear vitamin D receptor (VDR). The association of calcitriol to its receptor initiates normal transcription and leads to optimal gene expression.

The importance of vitamin D in bone health has been recognized for decades. Vitamin D is responsible for increased absorption of calcium and phosphorus required for maintenance of normal bone mineralization. Adequate plasma concentrations between 30 and 60 ng/mL also contribute to improvements in other health conditions such as hypertension, cardiovascular disease, diabetes, autoimmune disease, and cancer.[16] Although it is expected that through food intake and sun exposure most individuals would have sufficient concentrations for health maintenance, it has been clear in recent years that many are vitamin D deficient.[8] A deficiency state has been correlated with poor bone health as well as an increased risk of cancer and other chronic illnesses.

The vitamin's role in cancer has been reported in both preclinical and epidemiologic studies. Published studies suggest that adequate vitamin D concentrations are associated with reduced incidence of several cancers including colorectal and breast cancer, and may contribute to high rates of aggressive prostate cancer.[1,4,5,17] Several potential mechanisms have been proposed to explain the role of vitamin D in reducing breast cancer risk. Vitamin D induces differentiation, regulates proliferation and apoptosis, but inhibits angiogenesis, invasion and metastases, induces differentiation of immune cells in the tumor microenvironment, and produces antiinflammatory effects.[7,14] Epidemiologic studies suggest that adequate vitamin D concentrations can exert a beneficial effect reducing both breast cancer development and progression. Low vitamin D concentrations have been significantly correlated with poor tumor characteristics such as large tumor size and high grade.[9,11] Vitamin D may also have a role in the treatment of breast cancer, likely in combination with other standard and novel therapies. For example, in hormone receptor-positive breast cancer, vitamin D inhibits estrogen synthesis and signaling, down regulates the estrogen receptor (ER), regulates aromatase, and may provide therapeutic benefit when combined with aromatase inhibitors.[14] Finally, vitamin D may ameliorate side effects associated with agents commonly used to treat breast cancer or to prevent a recurrence, such as aromatase inhibitor-induced musculoskeletal pain.[13,15] Vitamin D and calcium are recommended to women taking aromatase inhibitors to maintain bone health.[10]

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In the current issue of *Medicine,* Bauer and colleagues[3] report results from a quantitative nonlinear dose-response meta-analysis of prospective studies that evaluated the association between circulating 25(OH)D and breast cancer risk, stratified by menopausal status.[3] Since prior prospective study results have been inconsistent, the authors hypothesized that differences in menopausal status and a nonlinear dose-response may have accounted in part for the discrepancy. Most previous reports have not evaluated nonlinear dose-response relations.

The authors conducted a systematic search of MEDLINE and EMBASE for studies published from 1966 through May 2011. They also attempted to identify unpublished cohorts. They identified 9 prospective studies with 11 datasets that assessed circulating 25(OH)D concentrations and incident breast cancers. The dataset included 5206 cases and 6450 control cases. The data were pooled (but not at the individual level) using dose-response random-effects meta-regression models, while nonlinear effects, spline models were optimized for thresholds. Overall, the investigators reported a borderline association between circulating 25(OH)D and breast cancer risk (RR per 5 ng/mL = 0.99; 95% confidence interval [CI], 0.97–1.00). The association was observed in postmenopausal but not in premenopausal women. They also report that the association in the lowest (<27 ng/mL) or highest range (≥35 ng/mL) of 25(OH)D concentrations was flat. The risk decreased in the 27–35 ng/mL concentration range in the postmenopausal women group such that a 5 ng/mL increase in 25(OH)D was associated with a 12% lower risk of breast cancer (RR = 0.88 per 5 ng/mL; 95% CI, 0.79–0.97).

The authors demonstrate the feasibility of determining an optimal range of plasma vitamin D concentrations for breast cancer risk reduction in postmenopausal women using a novel approach and define a range between 27 and 35 ng/mL. Moreover, there may be a threshold that is associated with reduced incidence. This result can now be validated in studies incorporating individual level data.

The meta-analysis is associated with several strengths including predefined study selection criteria, a thorough review of all references from retrieved articles, the use of a standardized protocol to extract data, and direct contact with relevant investigators for additional data. Group discussion and review were used to resolve discrepancies. Assumptions were conservative such that when relative risk (RR) estimates were reported for more than 1 set of adjustments, the most adjusted estimate was selected. Importantly, the authors focused on 1 outcome, breast cancer risk.

The meta-analysis is also associated with several limitations. First, the analysis was not based on individual level data, thus not allowing for standardization of cutpoints across studies, uniform assessment of the potential confounders, or examination of the effects of different assays and batches. Second, the authors were not able to obtain individual data from 1 large trial, which may have influenced the reported estimates. Third, data regarding dietary vitamin intake or sun exposure were not available and are likely to have varied by study. Finally, the authors were unable to examine the association between circulating 25(OH)D concentrations and breast cancer subtype. Given that a reduction in breast cancer risk was observed only in postmenopausal women, it is possible that a benefit is limited to reduction in ER-positive tumors, which the majority of postmenopausal women are likely to develop. This may also explain the lack of association in premenopausal women, given the higher proportion of ER-negative tumors seen in this group.

Another recent meta-analysis provides complementary results. Hong and colleagues[12] assessed a dose-response relationship by restricted cubic spline model and multivariate random effect. The authors included data from 10 publications including 14,450 breast cancer cases regarding dietary calcium intake, data from 13 publications including 20,343 breast cancer cases for dietary vitamin D intake, and data from 12 publications including 8716 breast cancer cases for serum vitamin D concentrations. The authors observed a linear relationship between calcium intake and breast cancer risk, while a nonlinear relationship was found for vitamin D intake and for serum vitamin D concentrations and breast cancer risk.

Together, the dose-response meta-analyses by Bauer et al[3] and by Hong et al[12] suggest that there is a threshold effect between plasma vitamin D concentrations and breast cancer risk. The Bauer study[3] provides important information supporting maintenance concentrations of vitamin D, ideally 27–35 ng/mL, to optimize breast cancer risk reduction. Statistical approaches such as the authors have used to more precisely define the relationship between plasma concentrations and risk reduction, thereby identifying an effective range of circulating vitamin D concentrations, is an important step toward a more personalized approach to breast cancer risk reduction and prevention. Similarly, Hong and colleagues[12] reported that women with dietary calcium intake of about 600 mg/d, dietary vitamin D intake of about 400 IU/d, and serum vitamin D concentrations of approximately 30 ng/mL were at the lowest risk of breast cancer.

Although existing data do not provide conclusive evidence that vitamin D deficiency is associated with an increased risk of breast cancer in all women, the bone health benefits and protection from chronic disease associated with adequate concentration of vitamin D are equally important. Individuals should be encouraged to practice a lifestyle that helps increase vitamin D concentrations, such as maintaining ideal body weight, smoking cessation, and increasing physical activity. At the same time, supplementation is readily available and should be considered in all adults to achieve an adequate concentration. Indeed, given the emerging interest in vitamin D's role in maintenance of several health conditions, the Institute of Medicine (IOM) convened a meeting to evaluate high-quality evidence. The IOM panel issued a consensus report[2] stating that the evidence supporting the role of vitamin D and calcium in bone health continued to be strong, and the recommended dietary allowance (RDA) for an average adult is 600–800 IU/d of vitamin D and 1000–1200 mg/d of calcium. However, the evidence supporting the role of high levels of vitamin D in bone and other health conditions was not conclusive. Members of the United States Preventive Services Task Force concluded that combined vitamin D (300–1100 IU/d) and calcium supplementation (500–1200 mg/d), but not vitamin D supplementation alone, can reduce fracture risk in older adults. Direct evidence was not available to provide recommendations for vitamin D supplementation to improve cancer-related outcomes or prevent specific cancers.

Future studies should not only address the role of vitamin D in reducing risk of breast cancer or improving outcomes of those diagnosed with the disease, but also evaluate predictive biomarkers of vitamin D response that can be used to monitor effectiveness of interventions. For example, alterations in VDR expression may explain in part differential outcomes among populations or individuals. Studies should explore associations between single nucleotide polymorphisms (SNPs) and risk. Indeed, in 1 study certain homozygous VDR polymorphisms were present in high frequency in elevated-risk women.[6] Altered metabolism or catabolism of vitamin D may also vary. Cross-talk among VDR and other hormone receptors may also lead to differential outcomes. Finally, additional studies are required in premenopausal women and in racially diverse populations.

In summary, measurement of plasma concentrations should be used to ensure that a dose of vitamin D of 30–60 ng/mL is

maintained through lifestyle modifications and dietary supplementation to preserve bone health as we await validation studies assessing the role of the vitamin in breast cancer risk. A large pooled analysis that includes prospective observational studies conducted worldwide and includes centralized vitamin D measures when possible is in progress and may provide additional information on some of these outcomes. Future studies should evaluate the role of vitamin D deficiency not only for breast cancer risk by subtype but also with regard to time of diagnosis, and as a determinant of breast cancer prognosis and treatment response.

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