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Review article

Breast cancer survivors and vitamin D: A review

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Abstract Recent evidence has suggested a role for vitamin D in breast cancer prevention and survival. Studies have reported an inverse relation between vitamin D intake and the risk of breast cancer, improvements in survival after a diagnosis of breast cancer in women with higher levels of vitamin D, and vitamin D insufficiency in up to 75% of women with breast cancer. Preclinical data have indicated that vitamin D affects up to 200 genes that influence cellular proliferation, apoptosis, angiogenesis, terminal differentiation of normal and cancer cells, and macrophage function. Vitamin D receptors have been found in up to 80% of breast cancers, and vitamin D receptor polymorphisms have been associated with differences in survival. Although ongoing studies have investigated a possible link between adequate levels of vitamin D and improved cancer prognosis, breast cancer survivors may derive additional, non–cancer-related benefits from adequate vitamin D levels, including improvements in bone mineral density, quality of life, and mood. Maintaining adequate vitamin D stores is recommended for breast cancer survivors throughout their lifetime.

Keywords: Breast cancer; Cancer survivor; Vitamin D; Vitamin D insufficiency

Introduction

In 2005, the Institute of Medicine urged that cancer survivorship be recognized as a distinct phase of cancer care [1]. Recent evidence has suggested that vitamin D may affect the risk of developing breast cancer, prognosis of breast cancer, and non-cancerous conditions common in breast cancer survivors. General internists are well positioned to review the benefits of adequate levels of vitamin D for overall health of their patients who are breast cancer survivors. 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 survivors.

Vitamin D terminology and metabolism

Vitamin D terminology can be confusing, with overlapping synonyms commonly substituted in the literature. The terminology distinction is important because the forms ingested are not those measured in the body. Table 1 lists selected terms and synonyms used in the description of various compounds referred to broadly as *vitamin D* [2,3]. In general, the letter *D* without a numeral modifier is used when a distinction between the D_2 and D_3 vitamin forms is not necessary. Figure 1 shows key processes in vitamin D metabolism and several sites along that pathway in which conditions can alter its metabolism. In addition to this endocrine pathway, a variety of extrarenal tissues express the 1α-hydroxylase enzyme that converts 25(OH)D to its active metabolite 1,25$(OH)_2$D, suggesting an important role for autocrine/paracrine metabolism in the activity of vitamin D in local tissues [4–6].

Vitamin D and risk of developing breast cancer

Theories about vitamin D and breast cancer have evolved from a growing body of evidence suggesting an inverse

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Table 1
Vitamin D terminology [2,3]

Common term*	Selected synonyms
Vitamin D*	May be inclusive of all forms of vitamin D, including ingestible forms or serum levels
Vitamin D_2*	Ergosterol
Ergocalciferol*	Dihydrotachysterol
	Viosterol
	Calciferol
Vitamin D_3*	Calciol
Cholecalciferol	
25(OH)D*	25-(OH) vitamin D
25-Hydroxyvitamin D	25 (OH) vitamin D
	Calcifediol
	Calcidiol
	25-OH-D, 25-OH-D2, 25-(OH)-D3
	25-Hydroxyergocalciferol
	25-Hydroxy vitamin D
	25-Hydroxycholecalciferol
$1,25(OH)_2D$*	1,25-(OH)2D3 or $1,25\text{-}(OH)_2D_3$[a]
1,25-Dihydroxyvitamin D	1,25-Dihydroxycholecalciferol
Calcitrol	1-α,25-Dihydroxycholecalciferol
	Dihydroxy vitamin D3
	Rocaltrol
	1-α,25-Dihydroxycholecalciferol
	1-α,25-Dihydroxyvitamin D3
	1α,25-Dihydroxyvitamin D

* Term used in the present review.

relation between circulating levels of vitamin D, typically reported as 25(OH)D, and risk of developing breast cancer. The link between vitamin D levels and lower breast cancer risk was initially suggested by investigators reporting a correlation between greater sunlight exposure (higher vitamin D levels) and lower rates of breast cancer [7]. In the 1990s, epidemiologic studies showed a higher incidence of breast cancer and mortality from breast cancer in those living at higher latitudes and in cities with less sunlight because of pollution [7–9]. In 1999, the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study suggested that vitamin D sufficiency and exposure to sunlight decreased the risk of developing breast cancer [10].

Several investigators have built on the environmental data by reporting that higher vitamin D intake and blood levels are inversely associated with incident breast cancer risk [11–15]. One such study of 10 578 premenopausal women and 20 909 postmenopausal women examined the relation between dietary intake of vitamin D and breast cancer occurrence. During an average of 10 y of follow-up, invasive breast cancer was diagnosed in 276 premenopausal and 743 postmenopausal women. There was a moderate association between development of breast cancer in premenopausal women and those with the lowest dietary intake of vitamin D. This was not found in postmenopausal women, although there was a marginally positive association between vitamin D intake and moderately differentiated tumors [14].

Bertone-Johnson et al. [11] used the Nurses' Health Study database to examine the relation between plasma levels of vitamin D and breast cancer risk. They reported that the women in whom breast cancer later developed had lower mean serum 25(OH)D levels than their matched controls. This association was strongest in those 60 y or older. Garland et al. [16,17] reported that individuals with serum 25(OH)D levels of approximately 53 ng/mL had a 50% lower risk of developing breast cancer than those with serum levels lower than 13 ng/mL.

In the largest study to date, Chlebowski et al. [18] recently reported the highly anticipated results of the Women's Health Initiative Calcium Plus Vitamin D study, which assessed the incidence of breast cancer as a secondary endpoint in 36 282 postmenopausal women randomly assigned to receive daily doses of 1000 mg of calcium with 400 IU of vitamin D_3 or placebo; participants were followed for an average of 7 y. Participants in both trial protocols were allowed to take vitamin D in addition to that provided in the study. Dietary intake of vitamin D was assessed at baseline and throughout the study for all participants, and 25(OH)D levels were measured at baseline for 2124 participants in a nested case–control group. A higher 25(OH)D level at baseline was associated with lower risk of breast cancer when adjusted for several potential influences, but when also adjusted for body mass index and physical activity, the association disappeared. The incidence of breast cancer was similar in both groups. Although the data do not support a relation between total vitamin D intake, 25(OH)D levels, and breast cancer risk in postmenopausal women, several potential limitations should be noted, including participant compliance with the study medication, the allowance of additional dietary vitamin D supplementation in both groups, and the variability in serum 25(OH)D levels, which can be affected by variable amounts of physical activity, body mass index, sunlight exposure, skin absorption, and genetic factors. The investigators suggested that previous associations between levels of vitamin D and breast cancer may represent confounding factors and not causality; however, the study's limitations make it possible to underestimate the potential effect of vitamin D on breast cancer risk [18,19].

Breast cancer prognosis and vitamin D

Researchers have demonstrated that vitamin D, as activated $1,25(OH)_2D$, influences events at the cellular level that are potentially important in prognosis and survival [20]. The exact role of vitamin D in breast cancer transformation or progression is not known. Activities of $1,25(OH)_2D$ with relevance to cancer include the activation of macrophages and effects on more than 200 genes that influence cellular proliferation, apoptosis, angiogenesis, and terminal differentiation of normal and cancer cells [21,22]. These findings have led to theories regarding the potential impact vitamin D may have in the treatment of breast cancer.

One area of investigation is the influence of vitamin D in the activation of the immune system. Highly activated macrophages have been shown to be tumoricidal and to eradicate cancer cells [23]. Macrophage activation occurs through

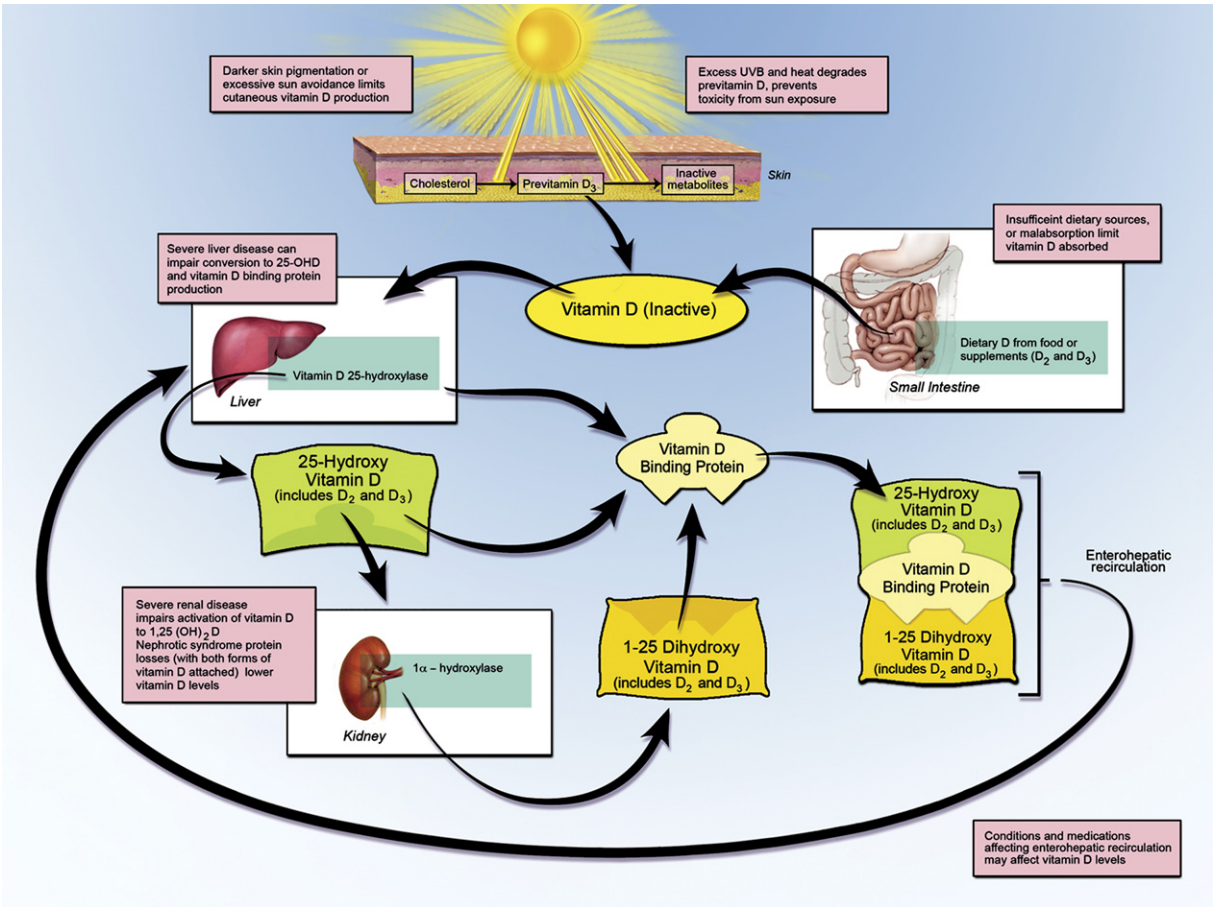

Fig. 1. Metabolism of vitamin D. Exposure to sunlight converts cholesterol in the skin to an inactive form of vitamin D_3. Dietary vitamins D_2 and D_3 are absorbed in the small intestine. Vitamins D_2 and D_3 from both sources are hydroxylated in the liver to circulating 25(OH)D, which is bound to vitamin D–binding protein. In the kidneys, 1α-hydroxylase converts the circulating form to the more active 1,25$(OH)_2$D, which is also bound to vitamin D–binding protein in the circulation. Decreased sunlight absorption and disease states (as indicated) can affect the absorption, activation, metabolism, destruction, or loss of vitamin D at several sites in its metabolic pathway.

inflammation and requires the presence of a vitamin D_3-binding protein (Gc protein), which is a precursor to the principal macrophage-activating factor. Patients with breast cancer have lower levels of this Gc protein, in part because of the increased activity of an enzyme secreted from cancer cells. In 2008, Yamamoto et al. [23] reported the effect of a highly potent macrophage-activating factor (Gc macrophage-activating factor) in 16 patients with metastatic breast cancer. These patients were treated weekly with Gc macrophage-activating factor for up to 5 mo, and their serum levels of Gc protein increased. Among those treated, no recurrences were documented for more than 4 y. These findings suggest that vitamin D may play a critical role in the immune system response to cancer cells.

Other studies have documented that mammary epithelial cell transformation is associated with dysregulation of the normal vitamin D metabolism within the breast [4–6]. Normal breast tissues express several proteins important in local vitamin D activity, including 1α-hydroxylase, an enzyme that creates the metabolically active 1,25$(OH)_2$D, vitamin D receptors (VDRs), and 24-hydroxylase, an enzyme that converts vitamin D into less active metabolites and is generally involved in feedback control [5]. Townsend et al. [6] reported a 27-fold increase in the expression of 1α-hydroxylase in breast tumors compared with non-neoplastic breast tissue, a 7-fold increase in the expression of VDRs, and a 4-fold increase in the expression of 24-hydroxylase. They also found that the increased 24-hydroxylase expression did not correlate with the expression of 1α-hydroxylase and vitamin D receptors in these breast tumors, suggesting an attenuation of the anticancer effect of vitamin D in these tissues.

The role of the VDR in cancer growth is another potential area for targeted therapy. More than 80% of breast tumors have VDRs, which have been postulated to have a protective effect against tumor proliferation [24–26]. Animal studies have shown that VDR deficiency causes increased growth, decreased differentiation, and impaired apoptosis in normal mammary glands with an increase in breast tumor development. In human breast cancer cells, studies have shown that 1,25-$(OH)_2D_3$ upregulates cell-cycle inhibitors, downregulates cell-cycle proliferators, has proapoptotic effects, and changes the underlying cellular phenotype [25]. Colston et al.

[24] demonstrated an increase in disease-free survival in patients with VDR-positive breast cancer versus VDR-negative breast cancer. Lundin et al. [27] described the effect of VDR polymorphisms on breast cancer progression. Patients with breast cancer without a particular VDR polymorphism (*Taq*I) were at increased risk of lymph node metastases, whereas patients who were homozygous for this polymorphism had a trend toward improved survival. Other researchers have shown that patients homozygous for a different VDR polymorphism (*bb BSMI VDR* genotype) are at increased risk of breast cancer compared with those who are heterozygous *Bb* or homozygous for the wild-type *BB* genotype [28]. In 2005, Lowe et al. [28] reported that patients homozygous for the *bb* genotype and with low 25(OH)D levels (<50 nM) had almost seven times the risk of breast cancer as those patients with the *Bb* or *BB* genotype and vitamin D levels higher than 50 nM. In addition, treatment with a potent vitamin D analog prevented skeletal metastases in mice with transplanted human breast cancer cells and induced apoptotic regression [29,30] in others. Roy et al. [26] demonstrated overexpression of VDRs in irradiated and tumorigenic human breast cells compared with normal controls, suggesting that VDR expression may be potentially useful as a marker in the progression of breast carcinogenesis.

A definitive link between serum vitamin D levels and prognosis of (as opposed to risk for) breast cancer has not been demonstrated. However, several observational studies have been published that support a potential relation between higher levels of vitamin D and improved outcomes. Palmieri et al. [31] attempted to clarify the role of vitamin D in breast cancer progression by comparing the levels of serum vitamin D in patients with early breast cancer with the levels in those with advanced breast cancer. In this observational study, they found that the mean concentration of 25(OH)D in those with early-stage breast cancer was higher than in those with advanced or metastatic disease. Investigators in Norway demonstrated a similar correlation between annual ultraviolet exposure and prognosis [32,33]. A correlation among increased skin pigmentation, lower vitamin D levels, and larger breast cancers with increased frequency of nodal involvement has also been reported [34,35].

Neuhouser et al. [20] used the Health, Eating, Activity, and Lifestyle database to examine the vitamin D status in a multiethnic cohort of breast cancer survivors. After adjusting for multiple factors, these investigators found that women with in situ disease had higher levels of circulating vitamin D than did women with local or regional cancer. They theorized that low circulating levels of vitamin D may have allowed early non-invasive lesions to advance more rapidly. It was also noted that race, body mass index, physical activity level, and the use of tamoxifen were independent contributors to the circulating vitamin D levels. Few women, however, had circulating vitamin D levels that would be considered optimal for health [20,36]. Of the 790 patients included in the analysis, 75% had levels that were considered insufficient. African-American women in the Health, Eating, Activity, and Lifestyle study had the lowest levels of vitamin D and have been reported to have poor rates of breast cancer survival [35]. Crew et al. [37] reported similar findings of a high prevalence of vitamin D deficiency in 103 women with breast cancer, particularly black or Hispanic women.

To date, the serum concentration of vitamin D has not been confirmed as a reliable prognostic indicator for breast cancer.

Non–cancer-related benefits of adequate vitamin D levels

Breast cancer survivors may derive additional, non–cancer-related benefits of adequate vitamin D levels, including improvements in bone mineral density, quality of life, and mood. Breast cancer itself has been associated with an increased risk of fracture [38]. In addition, treatments including cytotoxic chemotherapy, tamoxifen, and aromatase inhibitors have been linked to a decrease in bone mineral density [39–42]. Normalization of serum vitamin D levels may decrease the severity of bone density loss [43].

Vitamin D deficiency has also been associated with other symptoms such as non-specific joint pain, chronic fatigue, and depression. Many of these symptoms are commonly reported in patients on aromatase inhibitor therapy, although the exact cause is unknown. Khan et al. [44] reported improvement in joint pain, mood, fatigue, and vitamin D levels after 12 wk of high-dose oral vitamin D supplementation. Others have shown that supplementation with vitamin D is associated with decreased pain from breast cancer bone metastases and improved quality of life [45].

Psychological well-being, an issue of concern to patients with breast cancer who may have an increased risk of clinical depression, may also be affected by vitamin D levels [46]. The causal relation between depression and vitamin D insufficiency is not clear, because patients with clinical depression may avoid activities normally expected to increase vitamin D levels. However, a large, population-based study in Amsterdam reported lower levels of serum vitamin D in patients with major or minor depression than in normal controls [46]. Although these study subjects were not specifically patients with breast cancer, a similar correlation may exist with breast cancer survivors, many of whom have been shown to be vitamin D deficient [20,37].

Vitamin D, classically associated with calcium metabolism, has been discovered, in recent years, to have functions in many body tissues. Vitamin D sufficiency, typically measured with a 25(OH)D level of 30 ng/mL or higher, has also been associated with improved muscle strength, decreased risk of falls, and lower incidences of heart failure, type 2 diabetes, colorectal cancer, and coronary artery disease [22,47]. Figure 2 demonstrates these and other sites where activated vitamin D has physiologic effects. Given the potential benefits, the high prevalence of vitamin D insufficiency, and the safety of monitored vitamin D supplementation, a ‘‘test-and-treat’’ approach for breast cancer survivors has been recommended [22,48,49].

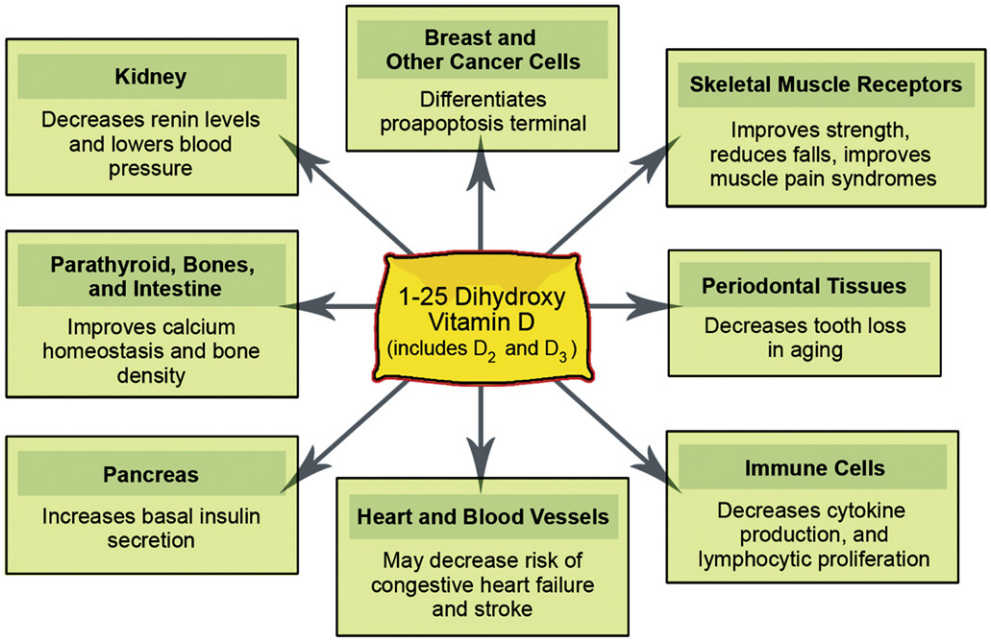

Fig. 2. Cellular effects of $1,25(OH)_2D$. The $1,25(OH)_2D$ has a multitude of effects beyond its well-established role in calcium homeostasis.

Vitamin D testing and treatment

Measurement of vitamin D stores is more accurate than reliance on dietary or sun-exposure history in the assessment of breast cancer survivors [50]. Living in a sun-rich climate does not ensure sufficient vitamin D levels, and environmental effects such as heavy clothing can contribute to insufficiency [51]. Few foods in nature contain vitamin D (salmon, mackerel, tuna fish, sardines, egg, beef liver); therefore, many foods are fortified with it (milk, margarine, cereals, orange juice) [52,53]. Serum 25(OH)D measurement is the most accurate determination of vitamin D levels for most patients. The half-life of 25(OH)D, the body's major reservoir of vitamin D, is 2 to 3 wk. The half-life of $1,25(OH)_2D$, the active form of vitamin D, is approximately 6 to 8 h. The $1,25(OH)_2D$ levels are labile and less accurate than those of 25(OH)D for overall vitamin D status [21,54]. Many laboratories will report total 25(OH)D levels as a combination of $25(OH)D_2$ and $25(OH)D_3$. Vitamin D_3 is manufactured in the skin and absorbed from dietary sources. Vitamin D_2 is exclusively derived from ingestion [55]. This distinction is useful, because a patient taking supplemental oral ergocalciferol (vitamin D_2) who has normal total 25(OH)D levels with low $25(OH)D_2$ levels is nearly entirely dependent on skin production of $25(OH)D_3$ and is not absorbing the oral supplement [54].

Reference ranges for vitamin D vary by laboratory and the form of vitamin D measured. The generally accepted low-normal value for 25(OH)D of 25 ng/mL was established as the lowest level that prevented development of secondary hyperparathyroidism. The generally accepted high-normal value of 80 ng/mL is derived from the lowest credibly reported case of vitamin D toxicity. Most patients with symptomatic vitamin D toxicity have values higher than 150 ng/mL [19,48]. Table 2 provides current recommendations for vitamin D status that have been correlated with specific health outcomes [36,52,56]. Several recent studies reviewing non–cancer-related benefits relative to vitamin D levels have suggested that 25(OH)D concentrations of 30 ng/mL or higher indicate vitamin D sufficiency [22,36]. However, a single measurement represents only one time point, and repeated measurements are recommended to reflect long-term vitamin D status [57].

Table 2
Vitamin D levels in adults and established health benefits

Vitamin D	Established clinical benefit	Serum level	Other potential benefits
Total 25(OH)D	Bone mineral density	Recommended ≥30 ng/mL	Tuberculosis
	Dental health		Diabetes mellitus
	Lower extremity strength and function	Optimal 36–40 ng/mL	Multiple sclerosis
	Risk of falls		Hypertension
	Risk of fractures		Rickets
	Colorectal cancer		Osteomalacia
			Other cancers

Data are from Grant and Holick [52], Vieth et al. [56], and Bischoff-Ferrari et al. [36].

Guidelines for oral vitamin D supplementation vary widely, likely related to difficulty accounting for sunlight's contribution to serum levels. The most widely recognized guidelines are those of the National Academy of Sciences Institute of Medicine Food and Nutrition Board [55]. This board has not established a recommended dietary allowance for vitamin D. Their recommended average intake for vitamin D (as vitamin D_3 or cholecalciferol) for women aged 19 to 30 y is 5 μg or 200 IU/d, for ages 51 to 70 y 10 μg or 400 IU/d, and for women older than 70 y 15 μg or 600 IU/d. These doses assume individuals have limited sun exposure. Doses in excess of the board's tolerable upper intake level of 2000 IU/d may temporarily be required to raise 25(OH)D levels to the targeted range. The board emphasizes that the upper intake level is not a ''toxic'' dose but represents the maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. These recommendations were published 12 y ago and are in the process of being updated. The Institute of Medicine is meeting in 2009 to review and update data on the dietary reference intakes for vitamin D [58].

For patients with vitamin D deficiency, supplemental ''booster'' doses of oral ergocalciferol (vitamin D_2), 50 000 IU weekly over 4 to 8 wk, are recommended for patients with normal absorption from the gastrointestinal tract [22]. The 25(OH)D levels should be assessed at monthly to quarterly intervals until the target level is achieved. Maintenance doses of oral vitamin D_2 or D_3, 400 to 800 IU/d, can then be started to maintain 25(OH)D levels in the desired range (30–50 ng/mL) [22]. Holick [22] provided a comprehensive overview of vitamin D supplementation in normal and specific populations (obesity, interfering medications, chronic kidney disease, and nephrotic syndrome).

Vitamin D toxicity is exceedingly rare in adults [59,60]. Most clinical findings are referable to concurrent hypercalcemia: anorexia, nausea, vomiting, renal insufficiency, fatigue, and headache. Joint pain and nephrocalcinosis have been reported less often. Initial management focuses on hydration and diuresis. The 25(OH)D levels can guide therapy, but initial strategies must often be used before the levels are known. Because of the long half-life of 25(OH)D, monitoring and clinical management of toxicity must continue until symptoms and values normalize. For patients with elevated vitamin D levels, sun avoidance and a diet low in vitamin D are helpful. In severe, persistent cases, cholestyramine has been used to interrupt enterohepatic recirculation of vitamin D and hasten decline in blood levels, but this agent is not considered a standard of care [59,60].

Conclusions

Researchers have demonstrated that vitamin D influences events at the cellular level that are important in cancer prognosis and survival. Although observational studies have suggested an inverse relation between vitamin D and breast cancer risk and between vitamin D and survival, little is known about the impact of appropriate vitamin D levels and supplementation on the prognosis in women with breast cancer. If vitamin D is to be considered in the therapeutic arsenal in the fight against breast cancer, it needs to be linked to improved survival. Prospective clinical studies are needed to establish this relation, and many are currently ongoing. The preliminary findings in this area appear promising.

One consistent finding in all the population studies included in this review was an extremely high prevalence of vitamin D deficiency. Low levels of vitamin D may exacerbate complications of breast cancer therapy such as bone loss, depression, and fatigue. Women with an increased risk for or a recent diagnosis of breast cancer and breast cancer survivors should have vitamin D levels monitored and supplemented. The goal of therapy is to maintain a serum 25(OH)D level of 30 to 50 ng/mL. Maintaining the serum level at lower than 80 ng/mL poses minimal risk of toxicity, regardless of vitamin D intake. The method of replacement should be based on the individual's behavior and needs. Patients who spend most of their day in environments of high-intensity sunlight require less dietary supplementation. Maintenance of adequate vitamin D stores should be continued throughout the lifetime of breast cancer survivors.

Additional material: Search strategy

The Ovid MEDLINE database (1966 to August 2008) was searched using the Medical Subject Heading (MeSH) *breast neoplasms* combined with the MeSH *vitamin D* or the text words *vitamin D*. To further narrow the search, the keywords *survivor or survivorship or recurrence or mortality* plus the MeSH *prognosis* or the keywords *prognostic or prognosis* were included. The search was then limited to English-language references and human subjects. This yielded 53 relevant references. The reference lists from those articles were examined, and relevant articles were used. Additional studies were identified through a search of the abstracts published for the 2007 and 2008 American Society of Clinical Oncology annual meetings and breast cancer symposia and the San Antonio Breast Cancer Symposia using the search terms *vitamin D* and *breast cancer*. Abstracts from these meetings were included if they were the only known reference to the clinical trial or research mentioned.

For articles on vitamin D in general, the Ovid MEDLINE database (1966 to August 2008) was searched using the heading *vitamin D* and limited to recent review articles in English. Articles on vitamin D in the MicroMedex and the *Williams Textbook of Endocrinology* were selected and reviewed. Reference lists were reviewed for other relevant articles. The search for *vitamin D* on the Mayo Clinic's online reference for medical professionals at http://www.mayoclinic.org/medicalprofs/ provided links to the *Endocrinology Update* issue referenced. The US National Library Medicine's ChemIDPlus Database was searched for references to vitamin D and its analogs, synonyms, and structures.

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References

[1] Hewitt M, Greenfield S, Stovall E, editors. From cancer patient to cancer survivor: lost in transition. Washington, DC: National Academies Press; 2006.
[2] Vitamin D. ChemIDPlus advanced. Bethesda, MD: National Library of Medicine; 2008.
[3] Dial J, Sandoval M, Reid S, Vitamin D. Micromedex Healthcare Series. Colorado: Thomson Reuters (Healthcare) Inc.; 2000.
[4] Kemmis CM, Welsh J. Mammary epithelial cell transformation is associated with deregulation of the vitamin D pathway. J Cell Biochem 2008;105:980–8.
[5] Townsend K, Evans KN, Campbell MJ, Colston KW, Adams JS, Hewison M. Biological actions of extra-renal 25-hydroxyvitamin D-1 α-hydroxylase and implications for chemoprevention and treatment. J Steroid Biochem Mol Biol 2005;97:103–9.
[6] Townsend K, Banwell CM, Guy M, Colston KW, Mansi JL, Stewart PM, et al. Autocrine metabolism of vitamin D in normal and malignant breast tissue. Clin Cancer Res 2005;11:3579–86.
[7] Gorham ED, Garland FC, Garland CF. Sunlight and breast cancer incidence in the USSR. Int J Epidemiol 1990;19:820–4.
[8] Garland FC, Garland CF, Gorham ED, Young JF. Geographic variation in breast cancer mortality in the United States: a hypothesis involving exposure to solar radiation. Prev Med 1990;19:614–22.
[9] Gorham ED, Garland CF, Garland FC. Acid haze air pollution and breast and colon cancer mortality in 20 Canadian cities. Can J Public Health 1989;80:96–100.
[10] John EM, Schwartz GG, Dreon DM, Koo J. National Health and Nutrition Examination Survey. Vitamin D and breast cancer risk: the NHANES I Epidemiologic follow-up study, 1971–1975 to 1992. Cancer Epidemiol Biomarkers Prev 1999;8:399–406.
[11] Bertone-Johnson ER, Chen WY, Holick MF, Hollis BW, Colditz GA, Willett WC, et al. Plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D and risk of breast cancer. Cancer Epidemiol Biomarkers Prev 2005;14:1991–7.
[12] Cui Y, Rohan TE. Vitamin D, calcium, and breast cancer risk: a review. Cancer Epidemiol Biomarkers Prev 2006;15:1427–37.
[13] Knight JA, Lesosky M, Barnett H, Raboud JM, Vieth R. Vitamin D and reduced risk of breast cancer: a population-based case–control study. Cancer Epidemiol Biomarkers Prev 2007;16:422–9.
[14] Lin J, Manson JE, Lee IM, Cook NR, Buring JE, Zhang SM. Intakes of calcium and vitamin D and breast cancer risk in women. Arch Intern Med 2007;28:1050–9.
[15] McCullough ML, Rodriguez C, Diver WR, Feigelson HS, Stevens VL, Thun MJ, et al. Dairy, calcium, and vitamin D intake and postmenopausal breast cancer risk in the Cancer Prevention Study II Nutrition Cohort. Cancer Epidemiol Biomarkers Prev 2005;14:2898–904.
[16] Garland CF, Grant WB, Mohr SB, Gorham ED, Garland FC. What is the dose–response relationship between vitamin D and cancer risk? Nutr Rev 2007;65(8 pt 2):S91–5.
[17] Garland CF, Gorham ED, Mohr SB, Grant WB, Giovannucci EL, Lipkin M, et al. Vitamin D and prevention of breast cancer: pooled analysis. J Steroid Biochem Mol Biol 2007;103:708–11.
[18] Chlebowski RT, Johnson KC, Kooperberg C, Pettinger M, Wactawski-Wende J, Rohan T, et al., Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of breast cancer. J Natl Cancer Inst 2008;100:1581–91.
[19] Speers C, Brown P. Breast cancer prevention using calcium and vitamin D: a bright future? J Natl Cancer Inst 2008;100:1562–4.
[20] Neuhouser ML, Sorensen B, Hollis BW, Ambs A, Ulrich CM, McTiernan A, et al. Vitamin D insufficiency in a multiethnic cohort of breast cancer survivors. Am J Clin Nutr 2008;88:133–9.
[21] Bringhurst FR, Demay MB, Kronenberg HM. Hormones and disorders of mineral metabolism. In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR, editors. Williams textbook of endocrinology. 11th ed. Philadelphia: Saunders Elsevier; 2008, p. 1203–68.
[22] Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266–81.
[23] Yamamoto N, Suyama H, Yamamoto N, Ushijima N. Immunotherapy of metastatic breast cancer patients with vitamin D-binding protein-derived macrophage activating factor (GcMAF). Int J Cancer 2008; 122:461–7.
[24] Colston KW, Berger U, Coombes RC. Possible role for vitamin D in controlling breast cancer cell proliferation. Lancet 1989;1:188–91.
[25] Pendas-Franco N, Gonzalez-Sancho JM, Suarez Y, Aguilera O, Steinmeyer A, Gamallo C, et al. Vitamin D regulates the phenotype of human breast cancer cells. Differentiation 2007;75:193–207.
[26] Roy D, Calaf G, Hei TK. Role of vitamin D receptor gene in radiation-induced neoplastic transformation of human breast epithelial cell. Steroids 2003;68:621–7.
[27] Lundin AC, Soderkvist P, Eriksson B, Bergman-Jungestrom M, Wingren S. South-East Sweden Breast Cancer Group. Association of breast cancer progression with a vitamin D receptor gene polymorphism. Cancer Res 1999;59:2332–4.
[28] Lowe LC, Guy M, Mansi JL, Peckitt C, Bliss J, Wilson RG, et al. Plasma 25-hydroxy vitamin D concentrations, vitamin D receptor genotypes and breast cancer risk in a UK Caucasian population. Eur J Cancer 2005;41:1164–9.
[29] El Abdaimi K, Dion N, Papavasiliou V, Cardinal PE, Binderup L, Goltzman D, et al. The vitamin D analogue EB 1089 prevents skeletal metastasis and prolongs survival time in nude mice transplanted with human breast cancer cells. Cancer Res 2000;60:4412–8.
[30] VanWeelden K, Flanagan L, Binderup L, Tenniswood M, Welsh J. Apoptotic regression of MCF-7 xenografts in nude mice treated with the vitamin D3 analog, EB1089. Endocrinology 1998;139:2102–10.
[31] Palmieri C, MacGregor T, Girgis S, Vigushin D. Serum 25-hydroxyvitamin D levels in early and advanced breast cancer. J Clin Pathol 2006; 59:1334–6.
[32] Porojnicu AC, Lagunova Z, Robsahm TE, Berg JP, Dahlback A, Moan J. Changes in risk of death from breast cancer with season and latitude: sun exposure and breast cancer survival in Norway. Breast Cancer Res Treat 2007;102:323–8.
[33] Robsahm TE, Tretli S, Dahlback A, Moan J. Vitamin D3 from sunlight may improve the prognosis of breast-, colon- and prostate cancer (Norway). Cancer Causes Control 2004;15:149–58.
[34] Elledge RM, Clark GM, Chamness GC, Osborne CK. Tumor biologic factors and breast cancer prognosis among white, Hispanic, and black women in the United States. J Natl Cancer Inst 1994;86:705–12.
[35] Li CI, Malone KE, Daling JR. Differences in breast cancer stage, treatment, and survival by race and ethnicity. Arch Intern Med 2003; 163:49–56.
[36] Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr 2006;84:18–28 (errata Am J Clin Nutr 2006;84:1253 and 2007;86:809).
[37] Crew KD, Shane E, Cremers S, McMahon DJ, Irani D, Sierra A, et al. High prevalence of vitamin D deficiency in a multi-ethnic cohort of premenopausal breast cancer patients. J Clin Oncol 2008;26(15S). abstract 9583.
[38] Kanis JA, McCloskey EV, Powles T, Paterson AH, Ashley S, Spector T. A high incidence of vertebral fracture in women with breast cancer. Br J Cancer 1999;79:1179–81.
[39] Eastell R, Hannon RA, Cuzick J, Dowsett M, Clack G, Adams JE, ATAC Trialists' Group. Effect of an aromatase inhibitor on bmd and bone turnover markers: 2-year results of the Anastrozole, Tamoxifen,

Alone or in Combination (ATAC) trial (18233230). J Bone Miner Res 2006;21:1215–23.
[40] Perez EA, Weilbaecher K. Aromatase inhibitors and bone loss. Oncology (Williston Park) 2006;20:1029–39.
[41] Powles TJ, Hickish T, Kanis JA, Tidy A, Ashley S. Effect of tamoxifen on bone mineral density measured by dual-energy x-ray absorptiometry in healthy premenopausal and postmenopausal women. J Clin Oncol 1996;14:78–84.
[42] Lonning PE, Geisler J, Krag E, Lokkevik E, Risberg T, Hagen AI, et al. Vitamin D deficiency: a threat to bone health in breast cancer patients during adjuvant treatment with aromatase inhibitors. J Clin Oncol 2006;24(18S). abstract 554.
[43] Cauley JA, Lacroix AZ, Wu L, Horwitz M, Danielson ME, Bauer DC, et al. Serum 25-hydroxyvitamin D concentrations and risk for hip fractures. Ann Intern Med 2008;149:242–50.
[44] Khan QJ, Reddy PS, Kimler BF, Sharma P, Baxa S, O'dea AP, et al. Effect of high-dose vitamin D on joint pain and fatigue from adjuvant letrozole. J Clin Oncol 2008;26(15S). abstract 9618.
[45] Simmons C, Ooi W, Dranitsaris G, Cole DE, Vieth R, Oldfield M, et al. Phase II study of vitamin D (10,000 IU daily) supplementation in bisphosphonate-treated breast cancer patients with bone metastases (abstract 176). Presented at the 2008 Breast Cancer Symposium; Washington, DC; September 5–7, 2008.
[46] Hoogendijk WJ, Lips P, Dik MG, Deeg DJ, Beekman AT, Penninx BW. Depression is associated with decreased 25-hydroxyvitamin D and increased parathyroid hormone levels in older adults. Arch Gen Psychiatry 2008;65:508–12.
[47] Michos ED, Melamed ML. Vitamin D and cardiovascular disease risk. Curr Opin Clin Nutr Metab Care 2008;11:7–12.
[48] Hampton T. Breast cancer prevention strategies explored. JAMA 2006; 295:2128–9.
[49] Holick MF. High prevalence of vitamin D inadequacy and implications for health. Mayo Clin Proc 2006;81:353–73.
[50] Trang HM, Cole DE, Rubin LA, Pierratos A, Siu S, Vieth R. Evidence that vitamin D3 increases serum 25-hydroxyvitamin D more efficiently than does vitamin D2. Am J Clin Nutr 1998;68:854–8.
[51] Binkley N, Novotny R, Krueger D, Kawahara T, Daida YG, Lensmeyer G, et al. Low vitamin D status despite abundant sun exposure. J Clin Endocrinol Metab 2007;92:2130–5.
[52] Grant WB, Holick MF. Benefits and requirements of vitamin D for optimal health: a review. Altern Med Rev 2005;10:94–111.
[53] US Department of Agriculture. Nutrient database. Available at: http://www.nal.usda.gov/fnic/foodcomp/search/. Accessed July 18 2009.
[54] Vitamin D deficiency: a new understanding. Mayo Clin Endocrinol Update 2006;1:4–5.
[55] Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Vitamin D: DRI dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington, DC: National Academies Press; 1997. p. 250–87.
[56] Vieth R, Bischoff-Ferrari H, Boucher BJ, Dawson-Hughes B, Garland CF, Heaney RP, et al. The urgent need to recommend an intake of vitamin D that is effective. Am J Clin Nutr 2007; 85:649–50.
[57] Tangpricha V, Pearce EN, Chen TC, Holick MF. Vitamin D insufficiency among free-living healthy young adults. Am J Med 2002; 112:659–62.
[58] Institute of Medicine. Available at: http://www.iom.edu/?ID=61770. Accessed July 18, 2009.
[59] Vitamin D. HazardText. Thomson Healthcare; 2008. Available at: http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/F13564/DUPLICATIONSHIELDSYNC/4F8418/ND_PG/PRIH/ND_B/HCS/SBK/2/ND_P/Main/PFPUI/U41ex6J2SRDVeI/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/46/ContentSetId/54/SearchTerm/vitamin/SearchOption/BeginWith. Accessed October 12, 2008.
[60] Vitamin D. Poisindex managements. Thomson Healthcare; 2008. Available at: http://www.thomsonhc.com/hcs/librarian/ND_T/HCS/ND_PR/Main/CS/F13564/DUPLICATIONSHIELDSYNC/4F8418/ND_PG/PRIH/ND_B/HCS/SBK/5/ND_P/Main/PFPUI/U41ex6J2SRErId/PFActionId/hcs.common.RetrieveDocumentCommon/DocId/46/ContentSetId/51/SearchTerm/vitamin%20d%20/SearchOption/BeginWith. Accessed October 12, 2008.