VOLUME 27 · NUMBER 13 · MAY 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

High Prevalence of Vitamin D Deficiency Despite Supplementation in Premenopausal Women With Breast Cancer Undergoing Adjuvant Chemotherapy

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Submitted August 13, 2008; accepted November 4, 2008; published online ahead of print at www.jco.org on April 6, 2009.

Supported in part by K07 Award No. CA95597 from the National Cancer Institute (D.L.H.); by an Advanced Clinical Research Award in Breast Cancer from the American Society of Clinical Oncology (D.L.H.); by K24 Award No. AR 052665 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (E.S.); and by Novartis Pharmaceuticals Corp.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/09/2713-2151/$20.00

DOI: 10.1200/JCO.2008.19.6162

ABSTRACT

Purpose
Vitamin D deficiency is associated with increased breast cancer risk and decreased breast cancer survival. The purpose of this study was to determine the prevalence of vitamin D deficiency, as measured by serum 25-hydroxyvitamin D (25-OHD), in premenopausal women at initiation of adjuvant chemotherapy for breast cancer and after 1 year of vitamin D supplementation.

Patients and Methods
The study included 103 premenopausal women from the northeastern United States with stages I to III breast cancer who received adjuvant chemotherapy and participated in a 1-year zoledronate intervention trial. All patients were prescribed vitamin D_3 (cholecalciferol) 400 IU and calcium carbonate 1,000 mg daily. At baseline and at 6 and 12 months, bone mineral density (BMD) measurements were obtained and blood was collected and analyzed in batches for serum 25-OHD. Vitamin D deficiency was defined as serum 25-OHD less than 20 ng/mL, insufficiency as 20 to 29 ng/mL, and sufficiency as 30 ng/mL or greater.

Results
At baseline, 74% of women were vitamin D deficient (median, 17 ng/mL). Vitamin D deficiency was slightly less common in white women (66%) compared with black (80%) and Hispanic (84%) women. After vitamin D supplementation for 1 year, less than 15% of white and Hispanic women, and no black women, achieved sufficient 25-OHD levels. Vitamin D levels did not correlate with baseline BMD and were not altered by chemotherapy or bisphosphonate use.

Conclusion
Vitamin D deficiency is highly prevalent in women with breast cancer. The current recommended dietary allowance of vitamin D is too low to increase serum 25-OHD greater than 30 ng/mL. Optimal dosing for bone health and, possibly, improved survival has yet to be determined.

J Clin Oncol 27:2151-2156. © 2009 by American Society of Clinical Oncology

INTRODUCTION

More than 30% to 50% of healthy adults are vitamin D deficient. However, vitamin D deficiency is of particular concern for women with breast cancer.[1-3] In addition to the inverse association identified between serum 25-hydroxyvitamin D (25-OHD) levels and breast cancer development,[4-6] an inverse association between serum 25-OHD levels and risk of breast cancer recurrence and mortality in women diagnosed with breast cancer has been identified in recent prospective studies.[7,8] Vitamin D is also important for bone health, as sufficient levels reduce the risk of hip fracture in women.[9,10] Bone health is a particular concern for survivors of breast cancer, because these women have a 15% higher fracture risk than women without a history of breast cancer.[11] Current breast cancer guidelines encourage daily supplementation with calcium 1,200 mg and vitamin D 400 IU,[12] but the efficacy of this approach is unclear.

Vitamin D is a fat-soluble vitamin that regulates calcium and bone homeostasis. Although modest amounts of vitamin D come from dietary sources, such as fortified dairy products, fatty fish, and supplements, the majority of vitamin D is produced naturally in the body when 7-dehydrocholesterol in the skin is exposed to ultraviolet B (UVB) radiation to produce vitamin D_3 (cholecalciferol). Vitamin D_3 then undergoes two hydroxylation steps, first in the liver to form 25-OHD, the major circulating metabolite, and then in

the kidney to produce 1,25-dihydroxyvitamin D (1,25-$(OH)_2$D), the biologically active form. In addition to its effects on bone and mineral metabolism, 1,25-$(OH)_2$D has pleiotropic anticancer effects, such as inhibition of cell proliferation, promotion of differentiation, and induction of apoptosis in normal and malignant cells.[13-16]

Other nonrenal tissues in the body, including the breast, colon, and prostate, have the enzymatic machinery to locally produce 1,25-$(OH)_2$D, the most active vitamin D metabolite.[17-20] These tissues express the vitamin D receptor and 1-α-hydroxylase, the enzyme that converts 25-OHD to 1,25-$(OH)_2$D.[13,17,18] Activated vitamin D binds to the vitamin D receptor to form a nuclear receptor-ligand complex that regulates the expression of up to 200 genes, including *p21, p27, c-fos,* and *c-myc*.[13,21] In preclinical studies, 1,25-$(OH)_2$D inhibited cell proliferation, induced cell differentiation, promoted apoptosis, and decreased angiogenesis.[21,22] In addition, 1,25-$(OH)_2$D has immunomodulatory activity on monocytes and lymphocytes.[23,24]

Risk factors for vitamin D deficiency include older age, darker skin pigmentation, obesity, low dietary intake, and sun avoidance behaviors. As a result, vitamin D deficiency is highly prevalent in the general population, particularly among minorities.[25] Melanin is an effective filter of UVB irradiation, which leads to a higher prevalence of vitamin D deficiency among blacks.[3] Circulating 25-OHD provides an integrated measure of vitamin D from all sources—diet, supplements, and sunlight exposure—and is considered the best indicator of vitamin D body stores.[26-28]

This study was undertaken to determine the prevalence of vitamin D deficiency at diagnosis and during and after adjuvant chemotherapy in premenopausal women with early-stage breast cancer. In addition, we evaluated the effect of standard-dose vitamin D supplementation during this period on serum 25-OHD levels. In this substudy, we hypothesized that standard doses of vitamin D and calcium would not be sufficient to maintain bone density or to raise serum 25-OHD to sufficient levels in premenopausal women undergoing chemotherapy.

PATIENTS AND METHODS

Study Population

Participants were premenopausal women undergoing adjuvant chemotherapy for early-stage breast cancer and participating in a randomized, double-blind, multicenter, phase III trial to compare zoledronic acid 4 mg intravenously every 3 months with placebo for 1 year.[29] Patients were enrolled from March 2002 to June 2006 after surgery but before initiation of chemotherapy. The chemotherapeutic regimens were at the discretion of the treating physician. Exclusion criteria included T score of less than −2.0 at any site, fragility fracture, prior therapy with a bisphosphonate or calcitonin, serum creatinine ≥ 2 mg/dL, or pregnancy. At baseline and at 6 and 12 months, bone mineral density (BMD) measurements were obtained as described,[29] and blood was collected for measurement of serum 25-OHD. On enrollment, data on demographics, reproductive and menstrual history, tobacco exposure, alcohol intake, medications taken, and tumor characteristics were collected. All patients were provided with one tablet of elemental calcium 500 mg (as calcium carbonate) combined with vitamin D_3 200 IU (GlaxoSmithKline, Philadelphia, PA) twice daily (total, elemental calcium 1,000 mg and vitamin D_3 400 IU) for 1 year and were advised to take them. Patients were evaluated every 3 weeks for the first 24 weeks and every 3 months thereafter. At each visit, patients were asked about compliance and were encouraged to take the supplements as recommended. Although all patients reported some use, pill diaries were not a study requirement. The protocol was initially limited to Columbia University Medical Center in New York, NY and then was opened to four additional sites in the northeast United States. The institutional review board of Columbia University Medical Center and the additional sites approved the protocol.

Of the 117 patients who consented to participate, three were ineligible, and 114 were randomly assigned. Of 103 women who were randomly assigned and who completed the baseline, 96 completed the 6-month, and 85 completed the 12-month evaluations.

Measurement of Plasma 25-OHD

Serum samples were stored in aliquots at −80°C until measurement. Samples were analyzed by radioimmunoassay (RIA) as previously described (Diasorin, Stillwater, MN).[30] Interassay precision at 15 ng/mL was 14%.

Statistical Methods

Descriptive analyses are presented for the demographic and clinical characteristics. The distribution of serum 25-OHD levels was categorized as deficient (< 20 ng/mL), insufficient (20 to 29 ng/mL), and sufficient (≥ 30 ng/mL). Researchers have suggested two distinct minimum serum concentrations of 25-OHD for vitamin D sufficiency, greater than 20 ng/mL and greater than 30 ng/mL.[31] Deficiency was additionally categorized as less than 12 ng/mL to describe vitamin D inadequacy (ie, severe deficiency). Differences between women with and without vitamin D deficiency with respect to demographic and clinical characteristics were examined with χ^2 tests. Pearson correlations were used to assess the association between change in vitamin D level and change in BMD during the year, and independent *t* tests calculated to estimate treatment group differences in vitamin D levels at 6 and 12 months. All statistical analyses were conducted with SAS (version 9.1; SAS Institute, Cary, NC).

RESULTS

Baseline characteristics of the participants are listed in Table 1. The median age was 43 years (range, 27 to 54 years). The population was racially and ethnically diverse and was comprised of 51% non-Hispanic white, 34% Hispanic, 12% non-Hispanic black, and 3% Asian. All women received four to eight cycles of chemotherapy and approximately two thirds received adjuvant hormonal therapy. Approximately one third of the women reported vitamin D supplement use before enrollment.

The median serum 25-OHD at baseline and at 6 and 12 months were 17 ng/mL (range, 3 to 42 ng/mL), 18 ng/mL (range, 9 to 38 ng/mL), and 19 ng/mL (range, 7 to 38 ng/mL), respectively. At baseline, 74% of participants were vitamin D deficient; this rate decreased to 65% and 60% at 6 and 12 months, respectively (Fig 1). The percentage of patients with vitamin D inadequacy (ie, 25-OHD < 12 ng/mL) was 12% at baseline and was 7% at 6 and 12 months. Only 6% of patients had sufficient (ie, ≥ 30 ng/mL) levels of serum 25-OHD at baseline, and 11% had sufficient levels after 1 year of vitamin D supplementation. Mean serum parathyroid hormone levels at baseline and at 6 and 12 months were 24, 27, and 27 pg/mL, respectively. Mean serum 25-OHD levels did not differ significantly between the placebo and bisphosphonate-treated groups (18 *v* 17 ng/mL, 19 *v* 19 ng/mL, and 19 *v* 21 ng/mL at baseline, 6 months, and 12 months, respectively; $P > .05$). Similarly, there were no significant between-group differences at any of these time points. Baseline serum 25-OHD concentration was not significantly associated with age, ethnicity, body mass index (BMI), and season of blood draw in our study population (data not shown).

Vitamin D deficiency was slightly less common among white women (66%) compared with black (80%) and Hispanic (84%) women (Fig 2). After vitamin D supplementation for 1 year, the

Table 1. Baseline Patient Characteristics

Characteristic	No.	%
Age, years		
Median	43	
Range	27-54	
Ethnicity		
White	53	51
Hispanic	35	34
Black	12	12
Asian	3	3
BMI, kg/m^2		
Median	25	
Range	18-44	
Stage		
I	32	34
II	57	60
III	6	6
Hormone receptor status		
Positive	67	65
Negative	36	35
No. of chemotherapy cycles		
4*	17	17
6-8†	86	83
Hormonal therapy		
None	36	35
Tamoxifen	48	47
Aromatase inhibitor	19	18
Prior vitamin D supplementation	34	33
Serum 25-OHD, ng/mL		
Median	17	
Range	3-42	

Abbreviations: BMI, body mass index; 25-OHD, 25-hydroxyvitamin D.
*Four cycles of doxorubicin/cyclophosphamide or paclitaxel.
†Six to eight cycles of doxorubicin/cyclophosphamide/paclitaxel, cyclophosphamide/doxorubicin/fluorouracil; or cyclophosphamide/methotrexate/fluorouracil.

proportion of breast cancer patients with vitamin D deficiency decreased slightly. However, less than 15% of whites and Hispanics, and no blacks, achieved sufficient levels of serum 25-OHD (ie, ≥ 30 ng/mL) with supplementation. According to the inclusion criteria, all women had a BMD T score of greater than −2.0; however, 90% had T scores greater than −1.0. Vitamin D levels did not correlate with BMD measurements.

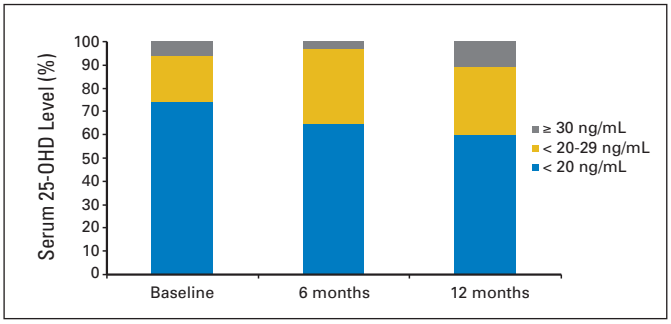

Fig 1. Distribution of serum 25-hydroxyvitamin D (25-OHD) levels over time with vitamin D supplementation for 1 year.

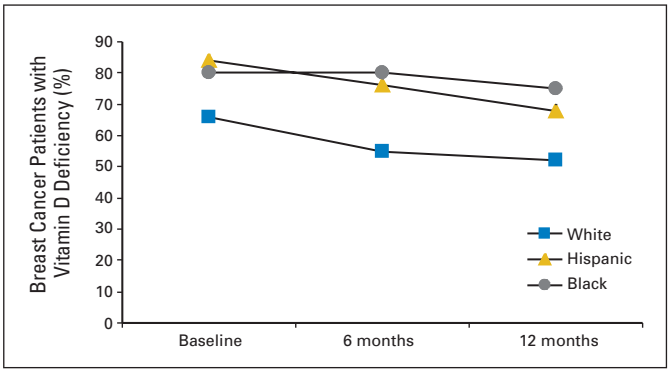

Fig 2. Prevalence of vitamin D deficiency (defined as serum 25-hydroxyvitamin D < 20 ng/mL) over time with vitamin D supplementation for 1 year, stratified by ethnicity.

DISCUSSION

In a cohort of premenopausal women with newly diagnosed, early-stage breast cancer, we found a high prevalence of vitamin D deficiency (greater than 70%), particularly among black and Hispanic women. After 1 year of supplementation with vitamin D_3 400 IU daily, which is twice the dietary reference intake for premenopausal women, only a small percentage (< 15%) of whites and Hispanics, and no blacks, achieved sufficient levels of 25-OHD.

Greater than 30% of healthy adults are vitamin D deficient.[1-3] Similar prevalence rates have been reported among women with breast cancer.[8,32,33] In a cohort of 1,026 predominantly white women with newly diagnosed breast cancer from Long Island, NY, our group found that 33% had vitamin D deficiency (ie, < 20 ng/mL), and an additional 27% had insufficient levels (ie, 20 to 29 ng/mL[33a]). We report a much higher prevalence of vitamin D deficiency in this study population, perhaps because of the higher proportion of black and Hispanic women in our cohort. Melanin is extremely efficient at absorption of UVB radiation; as a result, increased skin pigmentation markedly reduces vitamin D photosynthesis.[34] In addition, after a breast cancer diagnosis, dietary and behavioral changes, such as decreased dietary intake of vitamin D or sunlight exposure, may occur, which may alter circulating 25-OHD levels. A limitation of this study is the lack of information on sunlight exposure and dietary intake of vitamin D.

As expected, vitamin D levels did not correlate with BMD measurements, because the overwhelming majority of patients had normal bone densities at baseline, and because BMD is influenced by changes to the hormonal milieu that result from chemotherapy-induced ovarian dysfunction. A notable change in 25-OHD concentration after chemotherapy was not observed in two studies.[35,36] The modest increase in serum 25-OHD that we observed with supplementation was consistent with what would be expected at this dose level,[37] which suggests that chemotherapy did not significantly alter serum 25-OHD levels.

Vitamin D increases dietary calcium absorption by 30% to 40% and is directly related to BMD.[9,37] Vitamin D deficiency is often associated with increases in serum parathyroid hormone, which can result in increased osteoclast-mediated bone resorption.[38] Vitamin D supplementation is associated with decreased falls in the

elderly because of increased muscle strength[39] and with decreased risk of hip fracture in postmenopausal women, although these results are controversial.[9,10] Premenopausal women diagnosed with breast cancer have higher-than-average rates of bone loss and fracture as they age, which results in a lifetime risk of vertebral fractures nearly five times that of the general population.[40] Although bisphosphonates prevent bone loss during chemotherapy, the best time to initiate bisphosphonate therapy is uncertain. Moreover, although current guidelines recommend supplementation with calcium and vitamin D,[12,29] neither the optimal dose to recommend nor the effect of supplementation with the commonly available dose of vitamin D 400 IU per day have been prospectively evaluated. Our results indicate clearly that vitamin D 400 IU per day has minimal efficacy in correcting this widespread problem.

In the United States, cancer mortality for several cancers, including breast, colon, and prostate, shows a latitudinal gradient, as mortality rates increase among individuals who reside at higher latitudes.[8,41-46] In 1990, Garland et al[47] reported an inverse association between total average annual sunlight energy that strikes the ground and age-adjusted breast cancer mortality in the United States. Studies from Norway demonstrated that prognosis was better for cancers diagnosed in the summer season (which corresponds to maximal 25-OHD levels) compared with winter months.[48-50] Evidence suggests that high levels of vitamin D at the time of diagnosis and, thus, during cancer treatment may improve prognosis for breast, colon, and prostate cancer.[49]

Recent prospective cohort studies have associated higher circulating 25-OHD levels with improved survival for non–small-cell lung cancer,[51] colorectal cancer,[52,53] and breast cancer.[8,53] On the basis of a single measurement of serum 25-OHD up to 12 years before cancer death, data from the third National Health and Nutrition Examination Survey demonstrated significant inverse correlations for breast and colorectal cancer but not for all-cancer mortality.[53] The risk of breast cancer mortality was lower among individuals with serum 25-OHD between 50 and 80 nmol/L (ie, 20 to 32 ng/mL) compared with less than 50 nmol/L (ie, $<$ 20 ng/mL; odds ratio, 0.28; 95% CI, 0.08 to 0.93). However, because of small numbers, the trend was not statistically significant.[53] In a prospective cohort study of 512 women with early-stage breast cancer diagnosed in 1989 to 1995, 25-OHD was measured in archived blood specimens that were obtained at diagnosis.[8] Mean plasma 25-OHD was 23 ng/mL, and 37.5% of patients were vitamin D deficient (ie, $<$ 20 ng/mL). Compared with women who had sufficient levels of 25-OHD (ie, $\geq$ 30 ng/mL), distant-disease–free survival and overall survival were significantly worse in women with vitamin D deficiency (distant-disease–free survival: hazard ratio, 1.94; 95% CI, 1.16 to 3.34; and overall survival: hazard ratio, 1.73; 95% CI, 1.05 to 2.86).[8]

African Americans diagnosed with breast cancer generally have poorer survival rates compared with whites, even after adjustment for stage of disease, level of treatment received, and other prognostic factors. Possible explanations for the ethnic disparities in breast cancer clinical outcomes include differences in tumor biology and access to care. In general, African Americans have 25% to 50% lower circulating vitamin D levels compared with whites. Data from the third National Health and Nutrition Examination Survey showed that mean serum 25-OHD levels among white, Hispanic, and black women were 76.0 nmol/L (ie, 30 ng/mL), 56.7 nmol/L (ie, 23 ng/mL), and 45.3 nmol/L (ie, 18 ng/mL), respectively ($P < .0001$).[25] Lower breast cancer survival rates among blacks may be partially explained by lower serum 25-OHD.[54] This may represent a potentially modifiable risk factor that may alter breast cancer prognosis among black and Hispanic women.

This is one of the first studies to examine the effects of standard-dose vitamin D supplementation on serum 25-OHD levels in breast cancer patients. We observed that cholecalciferol 400 IU daily for 1 year raised serum 25-OHD levels only modestly, by less than 3 ng/mL. At this dose of vitamin D, the proportion of breast cancer patients with vitamin D deficiency did not change appreciably, particularly among blacks and Hispanics. In the United States, the recommended dietary allowance of vitamin D is 200, 400, and 600 IU daily for adults less than 50 years old, aged 50 to 70 years, and aged greater than 70 years of age, respectively.[55] The 2005 Dietary Guidelines for Americans recommend that groups at high risk for vitamin D deficiency, including older adults, people with dark skin, and those exposed to insufficient UV radiation, should consume vitamin D 1,000 IU daily.[56] However, these recommendations had not been widely adopted during the time of enrollment for this study.

Oral daily intake of vitamin D 1,000 IU can increase serum 25-OHD levels by about 10 ng/mL; however, variability in response may be due to other factors, such as sunlight exposure, BMI, and dietary intake.[37] Our analysis did not account for dietary intake or UV radiation. However, all patients resided in the northeast United States for the duration of the study. Given the high prevalence of vitamin D deficiency in the general population and among breast cancer patients, women may have to consume vitamin D up to 3,000 IU daily to increase serum 25-OHD to sufficient levels (ie, $\geq$ 30 ng/mL), which exceeds the National Academy of Sciences upper limit of 2,000 IU/d.[56] Although circulating 25-OHD levels of 32 ng/mL are associated with normal mineral metabolism, data from observational studies suggest that optimal levels for breast cancer prevention exceed 40 to 50 ng/mL.[5] Potential toxic effects of vitamin D, such as hypercalcemia, hypercalciuria, bone demineralization, or nephrocalcinosis, are rare and generally only occur when serum 25-OHD levels exceed 150 ng/mL.[57]

Our study has several strengths, including the relatively large, ethnically diverse patient population and the serial measurements of vitamin D status by an assay that takes into account both exogenous sources and endogenous production. In addition, the vitamin D assay used had high precision. Patients undergoing chemotherapy may have been less adherent to the recommendations to take supplements, as nausea may have interfered. Although we encouraged patients at each visit to take the supplements, we did not perform pill counts or administer pill diaries. In addition, lack of adherence may have influenced the minimal effect of supplementation. Despite the large proportion of minorities in our study population, the number of women in each ethnic group was small, which limited our ability to control for other factors that influence circulating vitamin D levels, such as age, BMI, and season of blood draw.

In summary, although the RDA of vitamin D in premenopausal women is only 200 IU daily, our study suggests that a dose of 400 IU daily is inadequate in breast cancer patients, even to maintain skeletal

health,[58] and is probably too low for meaningful anticancer effects. In the time since the upper safety limit of 2,000 IU daily of vitamin D was set in 1997, accumulating evidence in trials of healthy adults suggests that doses well above those currently recommended are safe.[59] However, controversy in this field remains. Although the efficacy of vitamin D supplementation for reducing breast cancer mortality is still uncertain, it may be prudent to follow serum levels of 25-OHD and replete to sufficient levels in premenopausal women with breast cancer to improve bone health for this large and growing population of breast cancer survivors.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Katherine D. Crew, Elizabeth Shane, Donald J. McMahon, Dawn L. Hershman
Financial support: Dawn L. Hershman
Administrative support: Dinaz Irani
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