Vitamin D and Breast Cancer Incidence and Outcome

Rowan T. Chlebowski*

Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, 1124 W. Carson Street, Torrance, CA, 90502

Abstract: Based on preclinical studies and early clinical observations, an association between vitamin D status and breast cancer incidence and outcome has been proposed. Against this background, information on vitamin D and breast cancer was reviewed with focused attention on emerging clinical studies in this area. Prospective cohort studies do not associate 25-hydroxyvitamin D levels with breast cancer incidence. While case-control studies of this question are positive, they may be confounded by reverse causality as 25-hydroxyvitamin D levels are influenced by breast cancer presence and stage. Studies of 25-hydroxyvitamin D and subsequent breast cancer recurrence provide mixed results but strongest associations were seen in analyses uncontrolled for prognostic variables, cancer therapy, BMI and physical activity. The one full-scale randomized, placebo-controlled trial evaluating calcium (1000 mg elemental calcium per day) and vitamin D supplementation (400 IU D₃ per day) with 36,282 participants failed to demonstrate a supplement effect on lowering breast cancer incidence. Breast cancer patients not uncommonly have vitamin D deficiency but limited control populations in available reports preclude precise prevalence estimates. As breast cancer patients are at risk for bone loss and musculoskeletal complaints from cancer or associated therapies, monitoring 25-hydroxyvitamin D levels and vitamin D supplementation in moderate dose (1,000-1,500 IU D₃ per day) can be recommended with expectation of mainly bone benefit. In women with breast cancer, future vitamin D supplementation studies need to be appropriately designed and powered to provide definitive assessments. However, a full-scale randomized trial evaluating the influence of vitamin D supplementation on breast cancer recurrence is likely not feasible.

Keywords: 25-hydroxyvitamin D, Breast cancer, Breast cancer incidence, Breast cancer prevention, Calcium, Case control studies, Cohort studies, Joint symptoms, Meta-analysis, Randomized clinical trials, Total mortality, Vitamin D.

INTRODUCTION

Information on the influence of vitamin D on breast cancer incidence and outcome is complex and controversial. Examination of the same body of clinical evidence has led to a range of conclusions and recommendations regarding public policy and practice in the clinic but also what direction future clinical research activity should take [1-3]. Nonetheless, there is agreement that a solid base of preclinical evidence supports the biological plausibility of a potential role for vitamin D to influence breast cancer [4-6]. A range of developments in the past year have clarified a number of important issues in this area and will be the focus of this presentation.

IDENTIFICATION OF STUDIES

Literature was searched for both observational studies and clinical trials assessing associations among vitamin D intake and 25-hydroxyvitamin D levels with breast cancer incidence and outcome. Factors associated with 25-hydroxyvitamin D levels and vitamin D supplementation studies in breast cancer patients also were a focus. Pubmed and EMBASE databases were searched and symposium proceedings from the American Society of Clinical Oncology, The San Antonio Breast Cancer Symposium, and the European Society of Medical Oncology were reviewed and literature was searched through March 31, 2012. Titles and abstracts were reviewed and full articles were reviewed when relevant.

VITAMIN D INTAKE AND BREAST CANCER INCIDENCE

The association between vitamin D intake from both diet and supplements with breast cancer incidence has been addressed in 11 case-control studies [7-17] with mixed results and some [11, 14-16, 18, 19] find significant associations between higher vitamin D intake and lower breast cancer risk only in premenopausal women. Similarly, cohort studies also provide mixed results, [20-24] precluding definitive conclusions. Taken together, the available observational studies do not provide a compelling or consistent association between vitamin D intake and breast cancer incidence.

SOLAR EXPOSURE AND BREAST INCIDENCE

The relationship between sunlight exposure, UV radiation and breast cancer risk, a topic beyond the scope of the current review, is also controversial with mixed results. While some reviews suggest strong, consistent relationships between higher UV radiation exposure and lower breast cancer risk [26] other recent cohort study reports are negative [21, 22] and problems in using latitude as a proxy for UV radiation have been raised [22]. While a recent report [24] suggested higher dietary and supplement vitamin D intake were associated with lower breast cancer risk only in geographic regions with highest UV radiation exposure, no such effect was seen in the nested case-control study in the Women’s Health Initiative randomized trial [26]. Again, white further studies can be supported, current evidence does not support a compelling association between higher UV radiation exposure and lower breast cancer risk.

25-HYDROXYVITAMIN D LEVELS AND BREAST CANCER INCIDENCE

25-hydroxyvitamin D is a generally accepted marker for vitamin D status [27]. There have been eight nested-case control studies examining the association between baseline 25-hydroxyvitamin D levels and subsequent breast cancer risk. Seven of these studies were nested in cohorts [28-34] and one in a randomized trial [30]. Of these, only the French E3N cohort identified a statistically significant association between lower 25-hydroxyvitamin D levels and higher breast cancer risk [31] (Table 1).

In the Women’s Health Initiative analyses, the initial odds ratio for the association of invasive breast cancer with serum 25-hydroxyvitamin D levels was 1.33 (95% confidence interval [CI]; 1.02-0.72, P-trend = 0.01) [26]. However, when body mass index (BMI) and physical activity were added to the model the
Association was strongly attenuated [26, 35], was no longer significant and approached the null (OR=1.06, 95% CI 0.78-1.43). In addition, the 25-hydroxyvitamin D levels were statistically significantly associated with recreational physical activity and BMI (P<0.001 for both) [26]. As both low physical activity and high BMI are independent, strong predictors of increased breast cancer risk, [34, 35] analyses unable to accurately control for these parameters are subject to confounding. Reliable and comprehensive determination of physical activity levels can be problematic, especially for cohorts who entered patients in earlier times when reasonable assessment methodology was not available.

In the case-control study nested in the randomized National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 primary breast cancer prevention trial, baseline 25-hydroxyvitamin D levels were not associated with subsequent breast cancer risk (OR 1.06, P=0.76) [30]. In addition, these NSABP investigators also conducted a meta-analyses separately evaluating studies of 25-hydroxyvitamin D and breast cancer where blood was collected before diagnosis (cohort studies) and studies where blood was collected after lower breast cancer diagnosis (case-control studies) [30]. Of the six case-control studies, [39-44] all were nominally statistically significant, associating lower 25-hydroxyvitamin D levels with higher breast cancer risk, (OR of 2.49). In contrast, of eight studies with blood collected before diagnosis, only one was statistically significant and the subtotal OR was 1.10. [30]. This observation followed an earlier meta-analysis by Yin and colleagues with a similar observation [44].

As 25-hydroxyvitamin D levels are higher in early compared to later stage breast cancers, [45] the clear dichotomy (interaction P=0.001) [30] in findings between the negative cohort studies and the positive case-control studies suggest reverse causality may explain the low 25-hydroxyvitamin D levels seen in the case-control reports. As more advanced stage [45] and poor prognosis breast cancers [46] have lower 25-hydroxyvitamin D levels, the presence of breast cancer itself, effects of cancer therapy or it’s sequelae could be responsible for the low 25-hydroxyvitamin D levels seen. For example, both chemotherapy use [47] and low physical activity are associated with low 25-hydroxyvitamin D levels and physical activity is commonly decreased for some period following a breast cancer diagnosis, likely related to associated cancer therapies [36, 48].

Taken together, this emerging body of evidence challenges the concept that vitamin D status, as measured by 25-hydroxyvitamin D levels is associated with future breast cancer risk. While other explanations for the available evidence are possible, [49] further studies of this issue must carefully consider the timing of sample collection relative to the breast cancer diagnosis and be able to adjust for BMI and physical activity assessed using state of the art methodology.

Examining the available evidence, other agencies have come to similar conclusions regarding the relationship between vitamin D status and breast cancer incidence risk. The long awaited 2011 update on dietary requirements for calcium and vitamin D from the Institute of Medicine, basing their finding largely on clinical trial evidence, concluded that for cancer the evidence was “inconsistent, inconclusive as to causality and insufficient to inform nutritional requirements” [50, 51]. Most recently, an updated meta-analysis from the US Preventative Services Task Force found no statistically significant dose-response relationship for 25-hydroxyvitamin D levels and breast cancer risk [52].

25-HYDROXYVITAMIN D LEVELS AND BREAST CANCER RECURRENCE

An initial report from Goodwin and colleagues [54] prompted interest in the potential for 25-hydroxyvitamin D levels to influence breast cancer outcome. A cohort of 512 Canadian early stage, resected breast cancer patients had blood samples obtained prior to systemic therapy initiation. After a mean 5.6 years follow-up, those with deficient (<15 nmol/L [6 ng/ml]) compared to sufficient (>72 nmol/L [30 ng/ml]) 25-hydroxyvitamin D levels were at increased risk for distant recurrence risk and death (both, P<0.01) (Table 2). However, the associations were attenuated and became non-significant after multivariate analyses adjusted for traditional prognostic factors [53]. Another Canadian study reported that 25-hydroxyvitamin D levels and recurrence in 667 postmenopausal women with early stage resected breast cancer within the context of a randomized clinical trial. In that setting, where breast cancer therapy was protocol defined, no significant association with event-free survival was seen (P=0.43) [54, 55]. Similarly, in a US population of early stage, resected breast cancer patients entered as a nested case-control study in a randomized nutrition trial within four years from diagnosis, no significant association with breast cancer recurrence or death was seen with baseline 25-hydroxyvitamin D levels [56].

Within the last year, however, three studies have reported positive associations. In a German population of 1295 breast cancer patients of all stages, after 5.8 years follow-up, those with the lowest (<35 nmol/L [14.0 ng/ml]) vs highest (≥55 nmol/L [22 ng/ml]) 25-hydroxyvitamin D levels had a statistically significantly lower distant disease-free survival and lower overall survival [58] (Table 2). In a relatively small cohort of 251 pre and postmenopausal breast cancer patients of all stages, deaths from breast cancer were significantly lower (HR 0.42, 95% CI 0.21-0.82) in those in the highest quartile (>81 nmol/L [32 ng/ml]) vs lowest

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Lead Author</th>
<th>Cohort (n)</th>
<th>Case Patients</th>
<th>Control Subjects</th>
<th>MR or OR</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer Prevention Study-II Nutrition Cohort</td>
<td>McCullough</td>
<td>21,965</td>
<td>516</td>
<td>516</td>
<td>0.92</td>
<td>0.60</td>
</tr>
<tr>
<td>Malmo Diet and Cancer Study</td>
<td>Almqvist</td>
<td>53,000</td>
<td>764</td>
<td>764</td>
<td>0.96</td>
<td>0.78</td>
</tr>
<tr>
<td>Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial</td>
<td>Freedman</td>
<td>38,660</td>
<td>1005</td>
<td>1005</td>
<td>0.96</td>
<td>0.81</td>
</tr>
<tr>
<td>Women’s Health Initiative</td>
<td>Chlebowski</td>
<td>32,826</td>
<td>895</td>
<td>898</td>
<td>1.06</td>
<td>0.20</td>
</tr>
<tr>
<td>Nurses Health Study</td>
<td>Bertone-Johnson</td>
<td>32,826</td>
<td>701</td>
<td>724</td>
<td>1.37</td>
<td>0.06</td>
</tr>
<tr>
<td>French E3N Cohort</td>
<td>Engel</td>
<td>17,391</td>
<td>636</td>
<td>1272</td>
<td>1.37</td>
<td>0.02</td>
</tr>
<tr>
<td>Nurse’s Health Study II</td>
<td>Eliaxis</td>
<td>29,611</td>
<td>613</td>
<td>1218</td>
<td>1.20</td>
<td>0.32</td>
</tr>
<tr>
<td>NSABP P-1 (randomized)</td>
<td>Amir</td>
<td>19,388</td>
<td>231</td>
<td>856</td>
<td>1.06</td>
<td>0.76</td>
</tr>
</tbody>
</table>
 quartile (< 43 nmol/L [17 ng/ml]) [58]. In a Korean population of 310 early stage breast cancer patients, low 25-hydroxyvitamin D levels determined before definitive surgery were associated with significantly increased recurrence risk (P=0.002) for both luminal A and luminal B subtypes but not HER positive or triple negative tumors [59]. Importantly, the latter three positive studies did not adjust for established prognostic features, cancer therapy, BMI, or physical activity. As a result, their findings are open to some question.

In a provocative report of a case-control study of breast cancer in African American and European American women, 25-hydroxyvitamin D levels were measured and associations between breast cancer risk and single nucleotide polymorphisms (SNPs) in VDR, CYP 24A1 and CYP 27B1 were evaluated by estrogen receptor status [60]. More African Americans had vitamin D deficiency (< 10 ng/ml) than East European Americans with lowest African ancestry. Associations for SNPs differed by race and the authors suggested that such genetic variation could be related to the higher incidence of estrogen receptor negative breast cancers in African Americans. However, most of the associations were not significant after correction for multiple comparisons so validation is needed.

In summary, the results of 25-hydroxyvitamin D association with breast cancer recurrence are inconsistent but the question remains of interest. Future studies must provide multi-variable adjustment to incorporate the known important variables including BMI, physical activity, and breast cancer therapy which can influence both 25-hydroxyvitamin D levels and breast cancer outcome.

### CAUTION AND VITAMIN D SUPPLEMENTATION AND BREAST CANCER INCIDENCE IN RANDOMIZED TRIALS

In the only full scale study which has been conducted, the Women’s Health Initiative investigators randomly assigned 36,282 postmenopausal women to 1,000 mg elemental calcium with 400 IU of vitamin D3 daily or placebo in a trial where hip fracture was the primary outcome [61] and colorectal cancer [62] and invasive breast cancer were the secondary outcomes [26]. The incidence of invasive breast cancer was closely comparable in the two randomization groups (528 vs 546 breast cancers, respectively) (HR 0.79, 95% CI 0.65-0.97). However, there were more breast cancers in the supplement group than in the placebo group for those in the highest quartile of total vitamin D intake at baseline (HR 1.34, 95% CI 1.01-1.78) (P interaction = 0.003) [26]. As about 60% of participants took over 80% of their study pills, adherence is a study limitation and also that 25-hydroxyvitamin D levels, while in women taking personal calcium and vitamin D supplements, the additional protocol calcium and vitamin D supplementation did not alter cancer risk. Based on these findings, Bolland and colleagues suggested that there was a low threshold for calcium or vitamin D for breast cancer benefit that was exceeded by the non-protocol use of such supplements [63].

Against this background, Bolland and colleagues [63] performed additional analyses of the same data using a limited-access dataset obtained from the National Heart Lung and Blood Institute. In analyses similar to those published in the original WHI report, [26] calcium and vitamin D supplement use was examined in the 15,646 women who were not taking personal calcium or vitamin D supplement at randomization. In that setting, randomization to the calcium and vitamin D supplement group was associated with a significantly lower risk of invasive breast cancers while in women taking personal calcium and vitamin D supplements, the additional protocol calcium and vitamin D supplementation did not alter cancer risk. Based on these findings, Bolland and colleagues suggested that there was a low threshold for calcium or vitamin D for breast cancer benefit that was exceeded by the non-protocol use of such supplements [63].

In a Letter to the Editor in response, we suggested caution in reinterpreting the Women’s Health Initiative calcium and vitamin D trial breast cancer results [64]. We indicated that we had originally reported similar findings but did not emphasize them because other
results were not consistent with an hypothesis that achieving a low threshold for supplemental calcium and vitamin D was sufficient to result in a breast cancer reduction. On the basis of such a hypothesis, women with the lowest baseline 25-hydroxyvitamin D levels would have the greatest breast cancer reduction with randomization to the supplement group. However, no such effect was seen. Also a low threshold hypothesis would predict that women not taking personal supplements and randomized to the placebo group would have a high breast cancer incidence since all others in the WHI trial would be above the presumptive vitamin D threshold and have a lower incidence. Again, no such effect was seen. In summary, the WHI published data are inconsistent with a low threshold effect resulting in breast cancer risk reduction for relatively low dose vitamin D supplementation with calcium.

Some have questioned the adequacy of the WHI vitamin D$_3$ dose of 400 IU per day. The dosage reflected the then current recommendations from the Institutes of Medicine [65]. However, as use of non-protocol vitamin D supplementation was permitted, total vitamin D intake incorporating diet plus non-protocol supplement plus protocol supplement was 773 IU (mean) per day in the supplement group compared to 367 IU (mean) per day in the placebo group, both after two years [26]. Based on a comprehensive analyses of a dose response randomized trial, it has recently been concluded that a vitamin D$_3$ total dosage of 600 IU per day would “meet the nutritional requirements of nearly all (97.5%) healthy persons” [66]. Thus, the WHI trial of calcium and vitamin D supplementation evaluated the influence of the currently recommended vitamin D intake.

Calcium plus vitamin D influence on cancer incidence has been evaluated in one other randomized clinical trial using a larger vitamin D dose but in a smaller study population. A total of 1,179 postmenopausal women were randomized to placebo, calcium alone (1,400-1,500 mg/d) or calcium plus 1,100 IU vitamin D$_3$ in a 1:2:2 ratio [67]. Of the 50 cancer cases seen, there were fewer cancers in the supplement compared to placebo group (2.9% vs 6.9%, P<0.05) but only 13 breast cancers were including precluding reliable interpretation.

25-HYDROXYVITAMIN D LEVELS IN BREAST CANCER PATIENTS

While studies consistently report a high prevalence of relatively low 25-hydroxyvitamin D levels in breast cancer patients, [68, 69] Cescon and colleagues [70] addressed the feasibility of conducting a randomized trial evaluating the influence of vitamin D on recurrence risk in early stage breast cancer patients. They examined 25-hydroxyvitamin D levels and vitamin D supplement use in a recently diagnosed cohort of breast cancer patients from Los Angeles and Toronto identified between March 2009 and January 2010 identified within two years of diagnosis.

The author’s pre-specified feasibility criteria for conducting a vitamin D versus placebo randomized clinical trial were that > 50% of patients would have 1) deficient or insufficient vitamin D levels, 2) were taking < 1,000 IU vitamin D supplement per day and 3) were willing to participate in such a study. Of the 173 eligible patients, 84% were using vitamin D supplements with median dose per day of about 1300 IU. The rates of deficiency, insufficiency and adequacy of hydroxyvitamin D levels were about 4%, 22% and 74% respectively. The relatively high proportion of vitamin D supplement use suggest patients and/or clinicians have largely recognized the issue of vitamin D deficiency in the breast cancer setting. As only under 13% of study population met the pre-specified feasibility criteria, it appears that, at least in large urban centers in the North America, a randomized trial addressing the issue of vitamin D deficiency influence on breast cancer recurrence may not be practical.

VITAMIN D SUPPLEMENTATION AND 25-HYDROXYVITAMIN D LEVELS

The recent update of the Institute of Medicine report on calcium and vitamin D requirements with a recommendation based primarily on bone health outcomes as related to 25-hydroxyvitamin D levels concluded that levels of at least 50 nmol/L (20 ng/ml) would meet the needs of at least 97.5% of the population. In addition, the committee concluded that there was no compelling evidence that 25-hydroxyvitamin D levels above this were associated with greater benefit for bone health or other outcomes [50, 51].

The Institute of Medicine reports emphasis the randomized clinical trial evidence. Some have taken exception to the Institute of Medicine findings [71, 72] and give more weight to evidence from ecological and case-control reports. Readers are invited to review those publications and make their own judgments.

The first comprehensive evaluation of dose-response evaluation to vitamin D supplementation in healthy postmenopausal women provides a framework for consideration of dosage in breast cancer patients. The Vitamin D Supplementation in Older Subjects (VIDOS) placebo-controlled, clinical trial randomized postmenopausal white women with vitamin D insufficiency (25-hydroxyvitamin D level ≤ 50 nmol/L [20 ng/ml]) and adequate calcium intake to placebo or vitamin D$_3$ doses ranging from 400-4,800 IU per day [66]. Based on results, a 600 IU dose was modeled to achieve a 25-hydroxyvitamin D level > 50 nmol/L [20 ng/ml], a level judged sufficient by the Institute of Medicine to meet vitamin D requirements [51]. Somewhat higher dosage was required for women with BMI > 25 kg/m$^2$.

While others report no increased risk of hypercalcemia with usual vitamin dose [73] in this study, some concern was raised regarding high dosages of vitamin D since between 3-9% of participants had hypercalcemia and 12-33% had hypercalcuria, [66], with hypercalcuria related to renal stone risk [74]. In addition, a recent comprehensive review of conventional dose vitamin D (< 1000 IU per day) studies found hypercalcemia, gastroenteritis symptoms and renal disease significantly increased [75]. In the WHI clinical trial, renal stones were significantly increased with the 400 IU per day dose, an increase of 68 cases over placebo in 18,176 treated women [61]. It is unclear how these comprehensive findings in healthy postmenopausal women relate to vitamin D dosage in breast cancer patients with vitamin D deficiency.

VITAMIN D SUPPLEMENTATION IN BREAST CANCER PATIENTS

In breast cancer patients, a series of uncontrolled studies have reported a relatively high frequency of low 25-hydroxyvitamin D levels [68, 69] but several of these reports based findings on criteria for sufficient levels of 25-hydroxyvitamin D substantially higher (75 nmol/L [30 ng/ml]) [68] and 80 nmol/L [32 ng/ml] [69] than the 50 nmol/L [20 ng/ml] level recommended by the Institute of Medicine [51]. Nonetheless, a substantial number of breast cancer patients have lower 25-hydroxyvitamin D levels then currently recommended. The absence of appropriate control populations make estimation of the actual prevalence of 25-hydroxyvitamin D deficiency in women with breast cancer relative to women without cancer but having similar age and characteristics difficult to determine. In one report, using a convenience control population, a higher prevalence of vitamin D insufficiency was seen in the controls compared to breast cancer patients who had completed cancer treatment [76].

The influence of vitamin D supplementation on 25-hydroxyvitamin D levels in breast cancer patients have been reported from retrospective observational studies and studies using both randomized and non-randomized designs (Table 3). Crew and...
Table 3. Effects of Vitamin D Supplementation on 25-Hydroxyvitamin D Levels and Musculoskeletal Symptoms in Breast Cancer Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Author</th>
<th>N</th>
<th>Design</th>
<th>Population</th>
<th>Intervention:</th>
<th>Outcome:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aromatase Inhibitor-Induced Musculoskeletal Symptom (AIMISS) Study</td>
<td>Rastelli</td>
<td>60</td>
<td>Randomized, double-blind, placebo controlled</td>
<td>Breast cancer patients with AIMISS</td>
<td>50,000 vitamin D capsules/wk for 8-16 weeks, then monthly for 4 months</td>
<td>Statistically significant reduction in AIMISS with vitamin D</td>
</tr>
<tr>
<td></td>
<td>Amir</td>
<td>40</td>
<td>Prospective, single-center, single arm phase II study</td>
<td>Breast cancer patients with bone metastases receiving bisphosphonate</td>
<td>10,000 IU vitamin D&lt;sub&gt;2&lt;/sub&gt; po qwk x 4 months</td>
<td>No significant palliative effect on bone pain</td>
</tr>
<tr>
<td>B-ABLE Aromatase Inhibitor Bone Loss</td>
<td>Prieto-Alshamba</td>
<td>222</td>
<td>Prospective cohort</td>
<td>Breast cancer patients initiating aromatase inhibitor therapy, ineligible for bisphosphonate</td>
<td>Calcium (1 g) plus vitamin D&lt;sub&gt;2&lt;/sub&gt; (800 IU) per day and 16,000 IU q2wk of 25OH D&lt;sub&gt;3&lt;/sub&gt; x 30 ng/ml x 3 months</td>
<td>Higher 25-hydroxyvitamin D protected against bone loss (P=0.0001) and those with levels ≥ 40 ng/ml had less loss (P=0.005).</td>
</tr>
<tr>
<td>Columbia University</td>
<td>Crew</td>
<td>103</td>
<td>Single arm study</td>
<td>Stage I-III breast cancer participating in zoledronic intervention trial after chemotherapy</td>
<td>All prescribed calcium carbonate 1000 mg/d and vitamin D&lt;sub&gt;2&lt;/sub&gt; 400 IU/d</td>
<td>25-hydroxyvitamin D median level of 17 ng/ml at baseline increased to 19 ng/ml at 12 months</td>
</tr>
<tr>
<td></td>
<td>Khan</td>
<td>60</td>
<td>Single arm study</td>
<td>Breast cancer patients beginning letrozole began</td>
<td>A standard dose calcium and vitamin D&lt;sub&gt;2&lt;/sub&gt; x 4 weeks, if 25-hydroxyvitamin D&lt;sub&gt;3&lt;/sub&gt; &lt; 40 ng/ml begun on D&lt;sub&gt;3&lt;/sub&gt; 50,000 IU/qwk x 12</td>
<td>25-hydroxyvitamin D levels &gt; 40 ng/ml in all 41; those with levels &gt; 66 ng/ml (median) had less disability from joint pain (52 vs 19%; P=0.026)</td>
</tr>
<tr>
<td>University of Kansas</td>
<td>Peppone</td>
<td>224</td>
<td>Retrospective study</td>
<td>224 breast cancer patients Stage O-III</td>
<td>Vitamin D supplement based on baseline 25-hydroxyvitamin D levels either non, 1000 IU/d, or high dose ≥ 50,000 IU/d</td>
<td>Only high dose significantly increased 25-hydroxyvitamin D levels</td>
</tr>
</tbody>
</table>

VITAMIN D AND JOINT AND BONE PAIN IN BREAST CANCER PATIENTS

While some studies have associated low 25-hydroxyvitamin D levels with exacerbation of joint symptoms, [27, 80] in a subset of 1911 participants in the WHI randomized clinical trial, calcium (1,000 mg) and vitamin D<sub>2</sub> (400 IU) supplementation daily did not influence joint pain or swelling when compared to placebo [80]. Aromatase inhibitor use, which profoundly lowers estrogen levels, is not uncommonly increases musculoskeletal symptoms [81] and an interaction between aromatase inhibitor associated musculoskeletal complaints and low 25-hydroxyvitamin D levels has been proposed [82]. However, no such association was seen in subgroup analyses in the large Arimidex, Tamoxifen Alone or Together (ATAC) Trial [83].

Other studies have evaluated the influence of vitamin D supplementation on clinical endpoints in breast cancer patients. In a single arm study of 40 breast cancer patients receiving bisphosphonate who had bone metastases, vitamin D<sub>2</sub> (10,000 IU) and calcium (1,000 mg) daily were provided for four months but no significant improvement in global pain scale was seen [84]. Sixty postmenopausal breast cancer patients beginning aromatase inhibitors with baseline 25-hydroxyvitamin D levels < 40 ng/ml [10 nmol/L] received 50,000 IU D<sub>3</sub> supplementation weekly for 12 weeks. The intervention increased 25-hydroxyvitamin D levels and women with levels > 66 ng/ml [16 nmol/L] reported “no disability from joint pain” less commonly than did women with lower levels [85]. In a similar population of 60 postmenopausal breast cancer patients who were on aromatase inhibitors, using a double-blind, placebo-controlled randomized phase II study design, supplementation with higher dose vitamin D<sub>2</sub> 50,000 IU capsules weekly for either 8 or 16 weeks and then monthly to complete five months was compared to placebo. While musculoskeletal pain was initially improved in the supplementation groups, the effect was subsequently attenuated [86].

In a larger study, vitamin D threshold to prevent both aromatase-inhibitor arthralgia [87] and bone loss [88] was examined in 223 women who were ineligible for bisphosphonate. All received calcium (1 g) and oral vitamin D<sub>2</sub> 800 IU daily plus 16,000 IU every 2 weeks for baseline 25-hydroxyvitamin D < 30 ng/ml [7.5 nmol/L]. Those who reached levels ≥ 40 ng/ml [10 nmol/L] had significantly attenuated joint pain (P=0.02) [87] reduced bone loss (P=0.005) [87] compared to those with 25-hydroxyvitamin D levels < 30 ng/ml [7.5 nmol/L]. The absence of bone targeted intervention like bisphosphonates complicates interpretation.

colleagues noted that, with 400 IU vitamin D<sub>2</sub> with calcium per day in their clinic population, < 15% achieved 25-hydroxyvitamin D levels > 75 nmol/L [30 ng/ml] [68]. In a retrospective study of newly diagnosed breast cancer patients, administration of vitamin D<sub>3</sub> 8,000 IU daily increased mean 25-hydroxyvitamin D levels from 19.7 [49 nmol/L] to 37.6 [94 nmol/L], respectively, P<0.01 but many remained below 32 ng/ml [80 nmol/L] [77]. In a retrospective study of 224 early stage breast cancer patients, vitamin D supplementation was based on baseline 25-hydroxyvitamin D levels: ≥ 32 ng/ml, no supplement; 25-31 ng/ml, 1,000 IU per day; < 24 ng/ml, 60,000 IU per week; < 15 ng/ml, 100,000 IU per week. After 8-16 weeks, weekly high dose supplementation significantly increased 25-hydroxyvitamin D levels while daily 1,000 IU dose supplementation did not [78]. This study was performed as a component of usual clinical care and was not randomized, controlled or blinded and the 1,000 IU dose was recommended but not prescribed. Taken together, the data suggest, but do not currently conclusively support, an hypothesis that higher vitamin D dosage may be needed in early stage breast cancer patients with low 25-hydroxyvitamin D levels.
Taken together, the findings are suggestive of potential joint symptom benefit with higher dose vitamin D use but larger studies with clear hypothesis and study designs are needed to confirm an association between some target 25-hydroxyvitamin D level and aromatase inhibitor-associated joint pain.

**FACTORS INFLUENCING 25-HYDROXYVITAMIN D LEVELS**

Interpretation of associations between 25-hydroxyvitamin D levels and clinical outcome are not straight forward since several factors such as BMI and physical activity are associated not only with 25-hydroxyvitamin D levels but also clinical outcomes of interest such as breast cancer. In addition, a substantial proportion of the difference in 25-hydroxyvitamin D levels between individuals is currently not understood.

In a cohort consortium of 4,723 pooled samples, statistically significant positive correlates of 25-hydroxyvitamin D level included male sex, summer sample, physical activity and multivitamin use. Significant negative correlates included BMI, winter and spring samples, diabetes, sedentary behavior, smoking, and Black race/ethnicity [89]. Considering the differences in 25-hydroxyvitamin D levels between individuals, in 3,055 postmenopausal women participating in the WHI clinical trial, a multi-variate predictive model could account for only 21% of the differences [90]. This finding suggests, as has other reports, [91, 92] that a large portion of differences in 25-hydroxyvitamin D seen between individuals are likely genetically determined. Such findings raise legitimate questions regarding an expectation that strategies involving high dose vitamin D supplementation to increase 25-hydroxyvitamin D levels will, in fact, impact target diseases of interest.

**VITAMIN D SUPPLEMENTATION AND TOTAL MORALITY IN RANDOMIZED TRIALS**

Based on the potential influence of low vitamin D status on common life-threatening conditions, meta-analyses have examined risk of death from any cause in participants evaluating vitamin D supplementation (ergocalciferol [vitamin D$_2$] or cholecalciferol [vitamin D$_3$]). In a Cochrane Database Systematic Review, Bjelakovic and colleagues [93] identified 50 randomized trials with 94,148 participants (including 36,282 from the WHI trial) [94]. Vitamin D$_3$ was associated with a modest but statistically significant decrease in all cause mortality in studies described as including “predominately elderly women” [93]. Autier and Gandini [95] included a meta-analyses of nine larger trials (all entering > 582 participants) with a total of 57,311 randomized with 5.7 years median follow-up. An 8% lower total mortality was seen in the vitamin D supplement group (P<0.05) with the average vitamin D dosage of 528 IU per day. Finally, Zittermann and colleagues [96] in another meta-analysis for found lowest mortality 25-hydroxyvitamin D levels from 30 to 35 ng/ml (7.5-8.7 nmoL/L).

These results are of interest and will be pursued in an ongoing full-scale randomized trial evaluating supplemental vitamin D$_3$ 2,000 IU per day plus omega 3 fatty acids (1.00 mg/day) vs placebo in 20,000 otherwise healthy men and women [97] and a similar study is ongoing in the United Kingdom [98]. While awaiting results from such efforts, caution is indicated as reliable information on long term safety of vitamin D supplementation is unclear with a solitary, unconfounded analysis suggesting a U shaped curve for lower mortality at moderate 25-hydroxyvitamin D levels and higher mortality at both high and low 25-hydroxyvitamin D levels [99].

**RECOMMENDATIONS FOR THE CLINIC**

Randomized clinical trial evidence indicates that vitamin D supplementation (in dose of about 400-800 IU per day), together with calcium decreases fracture risk in women at higher fracture risk. As many early stage breast cancer patients are at fracture risk based on age and effects of cancer therapy (such as oophorectomy, chemotherapy associated amenorhea, and aromatase inhibitor use), monitoring of 25-hydroxyvitamin D levels and use of vitamin D$_3$ supplementation (1,000-1,500 IU per day) plus calcium following clinical recommendations [100] in those at fracture risk can be endorsed. Current evidence does not support use of high dose vitamin D supplementation to some target level above 50 nmoL/L [20 ng/ml] with an expectation of reducing breast cancer recurrence risk or symptoms.

**CONCLUSIONS**

In summary, prospective cohort studies do not associate high 25-hydroxyvitamin D levels with low breast cancer incidence. The universally positive case-control studies of the same question may well be confounded by reverse causality as the presence of breast cancer or sequelae of associated therapy lower 25-hydroxyvitamin D levels. Studies of 25-hydroxyvitamin D and subsequent breast cancer recurrence provide mixed results with strongest associations of low 25-hydroxyvitamin D levels with high risk of recurrence seen with analyses uncontrolled for prognostic variables, cancer therapy, BMI and physical activity. BMI and physical activity, associated with both 25-hydroxyvitamin D levels and breast cancer risk, if not carefully controlled, are potential confounders of observational study reports. The prevalence of relatively low vitamin D levels seems somewhat greater in early stage breast cancer patients but adequate control population information is lacking. The only full-scale randomized clinical trial, conducted in the Women’s Health Initiative, did not demonstrate a lower breast cancer incidence in postmenopausal women randomized to 1,000 mg of calcium and 400 IU vitamin D$_3$, daily. Influence of higher dose vitamin D on secondary endpoints in breast cancer patients has been evaluated predominately in relatively small studies using randomized as well as non-randomized study designs precluding definitive conclusions. Stronger evidence regarding vitamin D and 25-hydroxyvitamin D associations with other clinical endpoints including overall mortality warrant further evaluation. Breast cancer patients with early stage disease are at risk for bone loss, so monitoring of 25-hydroxyvitamin D and appropriate vitamin D supplement use seems reasonable. Current evidence does not support use of high dose vitamin D regimens in anticipation of benefit for breast cancer recurrence or breast cancer survival.

**CONFLICT OF INTEREST**

The author confirms that this article content has no conflict of interest.

**ACKNOWLEDGEMENTS**

The described studies in the Women’s Health Initiative were supported by the National Heart, Lung and Blood Institute, U.S. Department of Health and Human Services.

**REFERENCES**


Carcinogenesis, **2008**, *29*(1), 93-99.


Vitamin D and Breast Cancer


