Breast Cancer RESEARCH

REVIEW

Vitamin D and breast cancer: interpreting current evidence

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Abstract

Preclinical investigations and selected clinical observational studies support an association between higher vitamin D intake and 25-hydroxyvitamin D levels with lower breast cancer risk. However, the recently updated report from the Institute of Medicine concluded that, for cancer and vitamin D, the evidence was 'inconsistent and insufficient to inform nutritional requirements'. Against this background, reports examining vitamin D intake, 25-hydroxyvitamin D levels and breast cancer incidence and outcome were reviewed. Current evidence supports the pursuit of several research questions but not routine 25-hydroxyvitamin D monitoring and vitamin D supplementation to reduce breast cancer incidence or improve breast cancer outcome.

Introduction

The role of vitamin D in relation to breast cancer incidence and outcome is controversial. Evidence from *in vitro* studies [1,2], animal studies [3,4], and selected clinical observational studies [5,6] has generally supported an association between higher vitamin D intakes and levels with lower breast cancer risk, but the results have not been consistent. Nonetheless, intervention strategies based on monitoring of vitamin D status with 25-hydroxyvitamin D (25(OH)D) levels and supplementation with vitamin D have been proposed for implementation in breast cancer clinical practice [6-8].

In contrast are findings from the 2011 report on dietary requirements for calcium and vitamin D from the Institute of Medicine (IOM) [9,10]. For cancer outcomes, the report concluded that 'the evidence was inconsistent, inconclusive as to causality, and insufficient to inform nutritional requirements' [10]. Against this background, current evidence regarding vitamin D and breast cancer was reviewed to inform clinical practice and identify potential research directions.

Identification of studies

A literature search identified observational studies and randomized clinical trials assessing associations among vitamin D intake and/or serum 25(OH)D levels and breast cancer incidence and outcome. We searched the PubMed and EMBASE databases and the American Society of Clinical Oncology and the San Antonio Breast Cancer Symposium proceedings through 31 January 2011 for relevant reports. Search terms included vitamin D, 25-hydroxyvitamin D, 1,25-hydroxyvitamin D, and clinical breast cancer incidence and outcome. The same source literature was searched for review articles addressing optimal and recommended vitamin D intake and 25(OH)D levels and determinants of 25(OH)D levels. Cross-referencing was used to complement relevant report identification. Titles and abstracts were reviewed for relevance. The full text was reviewed for those articles with relevant relationships.

Vitamin D intake and breast cancer incidence

Vitamin D intake (from diet and supplements) and breast cancer incidence have been examined in 10 case–control studies [11-20] and in 10 studies in cohorts with mixed results [5,21-29].

A meta-analyses of five case–control studies reported no overall association between vitamin D intake and breast cancer risk (relative risk = 0.95, 95% confidence interval (CI) = 0.69 to 1.32), but an analysis limited to premenopausal/perimenopausal women demonstrated a significant association (relative risk = 0.83, 95% CI = 0.73 to 0.95) [30]. Other case–control studies identified significant associations in subgroups. In one study, vitamin D exposure mainly early in life (ages 10 to 19, based on outdoor activities) was strongly related to subsequent breast cancer risk (low to high quartile, odds ratio = 0.65, 95% CI = 0.50 to 0.85) [17]. Similar to the studies by Abbas and colleagues [14] and Lin and colleagues [24], two recent studies found significant associations between

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vitamin D exposure and breast cancer incidence only in premenopausal women [18,19].

While a significant inverse association between vitamin D intake and breast cancer risk was seen in a meta-analysis of six of the cohort studies (relative risk = 0.90, 95% CI = 0.83 to 0.98) [30], this analysis did not include two recent, large, well-conducted, completely negative Scandinavian reports or the negative report from a large European cohort [26-28]. In the recent French E3N cohort report, only in regions with the highest ultraviolet solar radiance was high vitamin D intake associated with lower breast cancer risk (hazard ratio (HR) = 0.68, 95% CI = 0.54 to 0.85) [29].

25-Hydroxyvitamin D concentration and breast cancer incidence

Concentration of 25(OH)D is a generally accepted biomarker for determining vitamin D status [31], and studies of 25(OH)D and breast cancer incidence also provide mixed results. Four case–control studies significantly associated lower 25(OH)D levels with higher breast cancer incidence [32-36]. In these studies, however, the 25(OH)D levels were obtained at some interval following breast cancer diagnoses with potential alterations by cancer therapy or its sequellae. For example, women with lower physical activity have lower 25(OH)D levels, and physical activity is consistently decreased for years following a breast cancer diagnosis [37,38]. Positive associations may therefore not be reliable as only one case–control study adjusted for physical activity [33].

Six prospective nested case–control studies, which should provide more reliable findings, have examined 25(OH)D levels and subsequent breast cancer incidence [39-45]. In contrast to case–control studies, only one of these cohort studies that measure 25(OH)D before diagnosis reported a significant association between 25(OH)D levels and breast cancer incidence (Table 1) [45], while one study showed a borderline association [39]. In the positive French E3N cohort, the odds ratio was 0.73 (95% CI = 0.55 to 0.96, P_{trend} = 0.02) and the association was stronger in younger women (age <53 years) [45]. Finally, in a relatively small cohort of female participants in the Third National and Nutritional Examination Survey, no association was seen between 25(OH)D levels and breast cancer mortality [46].

The importance of incorporating physical activity as a covariate is illustrated in findings from the prospective case–control study nested in the Women's Health Initiative (WHI) cohort [42]. In analyses without body mass index and physical activity measures, a statistically significant association was seen between lower 25(OH)D levels and higher breast cancer incidence. The finding was attenuated, however, and became nonsignificant with inclusion of these factors in the analytic model [42].

25-Hydroxyvitamin D concentration in breast cancer patients

Several uncontrolled studies have reported a high frequency of low 25(OH)D levels in breast cancer patients [7,8,47,48]. In one study that identified 74% of breast cancer patients deficient for 25(OH)D (defined as <20 ng/ml or <50 nmol/l), despite a recommendation to take 400 IU vitamin D with calcium daily, few patients (<15%) achieved 25(OH)D levels >30 ng/ml (75 nmol/l) [47]. In a retrospective study of 500 newly diagnosed breast cancer patients, 69% were deficient for 25(OH)D (defined as <32 ng/ml or <80 nmol/l) and were supplemented with 8,000 IU vitamin D_3 daily (from 4,200 IU D_3 capsules). The subsequent 25(OH)D values were increased (19.7 (8.0) ng/ml vs. 37.6 (16.8) ng/ml, respectively; P <0.01) but many remained <32 ng/ml [49].

Based on such findings, some studies have suggested routine monitoring of 25(OH)D and supplemental vitamin D use for those identified at low levels [7,47]. Others note that these uncontrolled observational study reports have not linked 25(OH)D to breast cancer outcomes [50,51]. In addition, the recent IOM report now recommends a lower 25(OH)D level than those used in several of these reports as being sufficient (>20 ng/ml or >50 nmol/l) [9,10].

25-Hydroxyvitamin D levels and breast cancer recurrence

Three studies have examined the association between 25(OH)D levels at diagnosis and subsequent breast cancer outcome (Table 2). Goodwin and colleagues followed a cohort of 522 early-stage breast cancer patients for a mean of 11.6 years [51]. Women were sampled postoperatively before initiation of systemic adjuvant therapy. Those women with deficient 25(OH)D levels (defined as <50 nmol/l or <20 ng/ml), compared with those women with sufficient levels (>72 nmol/l), had a higher risk of distant recurrence (HR = 1.94, 95% CI = 1.16 to 3.25, P <0.01) and of death (HR = 1.73, 95% CI = 1.05 to 2.86, P <0.01). The associations were attenuated, however, and became nonsignificant after multivariate analysis adjusting for traditional prognostic factors [51].

Piura and colleagues examined the same association in 607 postmenopausal women with early-stage, hormone-receptor-positive breast cancer participating in a randomized, controlled adjuvant trial in which all patients received tamoxifen with or without octreotide [52]. In this setting, no association between baseline 25(OH)D levels and relapse-free survival or relapse at any site was seen [52].

Finally, a nested case–control analysis was conducted in the 3,085 early-stage, resected breast cancer patients participating in the Women's Healthy Eating and Living study [53]. Women in this study evaluating a dietary

Table 1. 25-Hydroxyvitamin D and breast cancer incidence: nested case–control studies in cohorts

Cohort	Lead author	Cohort (*n*)	Case patients (*n*)	Control subjects (*n*)	P_{trend} [a]
Cancer Prevention Study II Nutrition Cohort	McCullough	21,965	516	516	0.60
Malmo Diet and Cancer Study	Almquist	53,000	764	764	NS
Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	Freedman	38,660	1,005	1,005	0.81
Women's Health Initiative	Chlebowski	32,826	895	898	0.20
Nurses' Health Study	Bertone-Johnson	32,826	701	724	0.06
French E3N Cohort	Engel	17,391	636	1,272	0.02[b]

[a]P_{trend} for analyses comparing breast cancer incidence in low versus high 25-hydroxyvitamin D groups. [b]Findings driven by results in women <53 years old at sampling.

Table 2. 25-Hydroxyvitamin D concentration and subsequent breast cancer outcome in patients with resected early-stage disease

			Adjuvant therapy			
Lead author	*n*	Category	Hormonal therapy	Chemotherapy	Mean follow-up (years)	Study outcome
Goodwin	512	Early breast cancer, resected	Tamoxifen per clinical decision	Varies per clinical decision	11.6	Deficient (<50 nmol/l) vs. sufficient (>72 nmol/l) 25(OH)D levels, in multivariant adjusted analyses[a]
		Cohort				Distant recurrence HR = 1.71 95% CI = 1.02 to 2.86[a]
		Premenopausal and postmenopausal				Survival HR = 1.60, 95% CI = 0.96 to 2.64
Piura	622	Early breast cancer, resected	Tamoxifen for 5 years vs. tamoxifen for 5 years + octreotide for 2 years (per protocol)	Varies per clinical decision	7.9	No significant association with event-free survival or relapse-free survival with 25(OH)D level
		Cohort within a randomized clinical trial				
		Postmenopausal				
Jacobs	1,024	Early breast cancer, resected entered within 4 years from diagnosis	Varies per clinical decision	Varies per clinical decision	7.3	No significant association with breast cancer recurrence (local, regional, or distant) or death with 25(OH)D level
		Nested case–control within a randomized clinical trial				
		Premenopausal and postmenopausal				

CI, confidence interval; HR, hazard ratio; 25(OH)D, 25-hydroxyvitamin D. [a]Findings were statistically significant in analyses adjusted for age and tumor stage.

intervention were re-consented within 4 years of early-stage breast cancer diagnosis and were recurrence free at entry. In 512 matched pairs of breast cancer patients who had experienced cancer recurrence and control subjects who were recurrence-free at a comparable follow-up period, no association between 25(OH)D levels at baseline and subsequent breast cancer recurrence was observed. Taken together, these three studies provide mixed findings and no compelling evidence of an association between lower 25(OH)D levels and adverse breast cancer clinical outcome.

The feasibility of conducting a randomized trial of vitamin D supplementation in adjuvant breast cancer has been explored recently. In women with early-stage, resected breast cancer, more than 80% were found to be already using vitamin D supplements at a median daily dose >1,200 IU/day and the median 25(OH)D levels were above 34.3% ng/ml (85.5 nmol/l), exceeding the sufficient level (20 ng/ml or 50 nmol/l). Considering such findings, a phase III trial was not judged to be feasible [54].

Vitamin D and arthralgias in breast cancer patients

Low 25(OH)D levels have been associated with musculoskeletal disorders [55]. More recently, Chlebowski and colleagues found significantly higher joint pain with extremely low 25(OH)D levels (<29 nmol/l or 12 ng/ml)

in 1,993 postmenopausal women [56]. In postmenopausal breast cancer patients, aromatase inhibitors are not uncommonly associated with limiting arthralgias [57], which have been described as greater in those with low 25(OH)D levels [58,59]. Currently, several prospective but nonrandomized trials evaluating higher dose vitamin D regimens have reported less joint pain in women who achieved relatively higher target 25(OH)D levels of 40 ng/ml (100 nmol/l) [59] and 66 ng/ml (218 nmol/l on vitamin D supplementation) [60]. As the recent IOM report has identified concerns about higher clinical risks at 25(OH)D levels >50 ng/ml (125 nmol/l) [9,10] and observations in a breast cancer cohort suggest survival may be optimal for women with 25(OH)D levels <44 ng/ml (110 nmol/l) [51], such high-dose vitamin D strategies require careful clinical trial evaluation before implementation in general practice.

Vitamin D, 25-hydroxyvitamin D levels and mammogram breast density

Reports of associations among vitamin D intake, 25(OH)D levels and mammographic breast density have been mixed. Early reports associated higher vitamin D intake with lower mammographic breast density [61], perhaps especially in premenopausal women [62,63]. A series of more recent studies, however, reports no such association in either premenopausal women [64,65] or postmenopausal women [64-68].

Randomized trials of calcium and vitamin D supplementation and breast cancer incidence

The WHI randomized 36,282 postmenopausal women to placebo or supplementation with calcium (1,000 mg/day) plus vitamin D_3 (400 IU/day), with hip fracture as the primary outcome and colorectal cancer and breast cancer as secondary outcomes [69,70]. After 7 years of intervention, there was no difference in invasive breast cancer incidence (528 vs. 546 breast cancers, respectively; HR = 0.96, 95% CI = 0.85 to 1.09) between the randomization groups. In subgroup analyses, women in the highest vitamin D intake quintile at entry (≥600 IU/day) actually had a higher breast cancer incidence with supplemental vitamin D use (HR = 1.34, 95% CI = 1.01 to 1.78) [42]. In the case–control analyses nested in this trial, the mean 25(OH)D level was 50 ± 21 nmol/l among the 895 participants who subsequently were diagnosed with breast cancer, with a closely comparable level of 52 ± 21 nmol/l in the 898 matched controls who did not develop breast cancer [42].

One other clinical trial has evaluated calcium plus vitamin D influence on cancer risk in a smaller study using a larger vitamin D dose. In 1,179 postmenopausal women randomized to placebo, to calcium alone (1,400 to 1,500 mg/day) or to calcium plus 1,100 IU vitamin D_3/day in a 1:2:2 ratio [71], there were fewer total cancers in the calcium plus vitamin D supplement compared with the placebo group (2.9% vs. 6.9%, P <0.05). This finding was based on the distribution of a total of 33 cancer cases but, as only 13 breast cancers were diagnosed, meaningful interpretation regarding breast cancer influence is precluded.

Randomized clinical trials of vitamin D and total mortality in general populations

Vitamin D supplementation has been evaluated in a number of full-scale randomized, clinical trials, with or without calcium, mostly with fracture as the major endpoint. These trials have generally reported few details of clinical outcomes other than fractures or provided systematic evaluation of causes of death. Interest in the potential benefit of vitamin D supplementation on a range of clinical outcomes and overall health, however, prompted interest in examining mortality in these randomized trials.

A meta-analysis of nine larger trials (all entering >582 participants) incorporating 57,311 participants (including 36,282 from the WHI trial [72]) identified 4,777 deaths during a median 5.7 years of follow-up [73]. The trial size-adjusted mean vitamin D_3 dose was a relatively modest 528 IU/day. Total mortality was 8% lower in the vitamin D supplement group, a finding of borderline significance (HR = 0.92, 95% CI = 0.86 to 0.99, P <0.05) (Figure 1) [73]. A subsequent analysis suggested lower mortality when vitamin D was given with calcium supplementation [74]. These results should not be simply extrapolated to a 'more is better' concept since an observational study has suggested a U-shaped curve with lowest mortality risk at moderate 25(OH)D levels and increased mortality risk at both low and high levels of 25(OH)D [75].

Further attempts to clarify this potential survival influence of supplemental vitamin D in a conventional dose should be pursued with additional follow-up of existing conventional dose trials. In addition, there is an ongoing full-scale randomized trial evaluating supplemental vitamin D in a higher daily dose (2,000 IU D_3) plus omega 3 fatty acids (1,000 mg/day) versus placebo in a large population of about 20,000 otherwise healthy men and women [76]. This trial has begun but results are not expected for several years. Additionally, the Vitamin D and Longevity trial is examining an intermittent high-dose vitamin D regimen in the United Kingdom [77].

Supplemental vitamin D adverse effects

While vitamin D is relatively safe, a review of randomized or quasi-randomized trials found adverse effects of hypercalcemia, gastrointestinal symptoms and renal disease significantly increased by vitamin D administration in

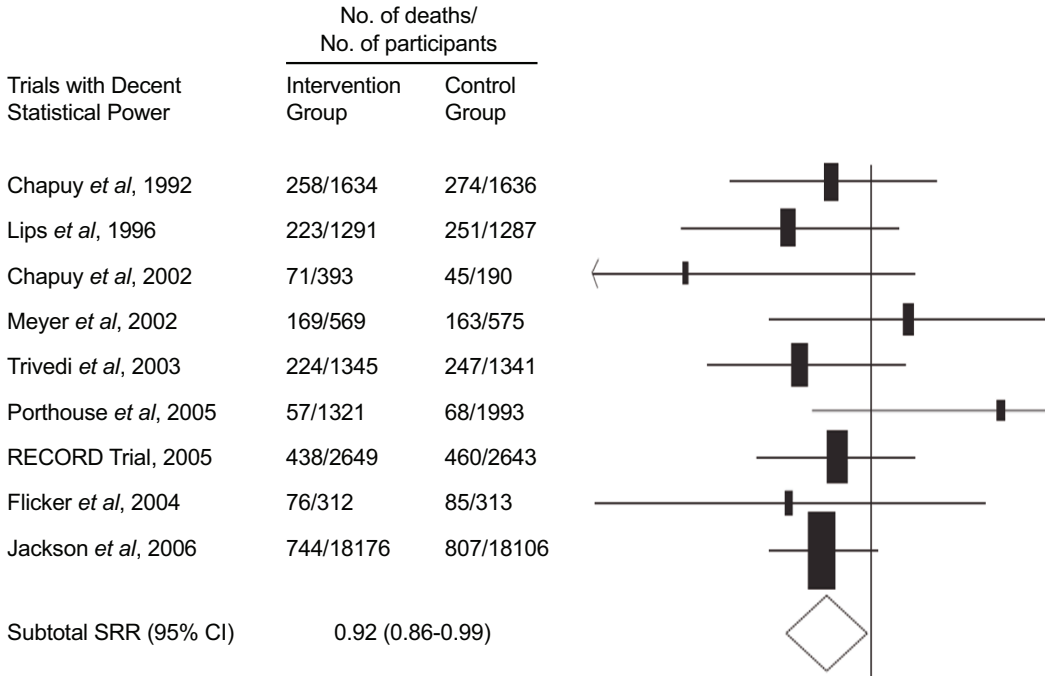

Figure 1. Vitamin D and total mortality in a meta-analysis of randomized controlled trials. Meta-analysis of randomized, controlled trials evaluating supplementation with vitamin D alone or in combination with calcium compared with placebo or no intervention on total mortality. The size of the box indicates the number of deaths, and the horizontal lines indicate the 95% confidence interval (CI). Adapted with permission from Autier and Gandini [73]. RR, relative risk.

conventional dosage (<1,000 IU/day) [43], the latter being of importance given the prevalence of renal deficiency in breast cancer patients [78]. While several pilot studies of short-term, parental high-dose vitamin D on safety have been reported [60,79], the side efforts of high-dose regimens for long duration use are unknown. Finally, the IOM report has identified safety concerns potentially associated with 25(OH)D levels >50 ng/ml (>125 nmol/l) [9,10].

Factors influencing 25-hydroxyvitamin D levels, vitamin D and breast cancer

It is not commonly recognized that factors other than sunlight exposure and vitamin D intake (both dietary and supplement) make a substantial contribution to 25(OH)D levels. In a pooling cohort consortium with 4,723 samples from 10 cohorts, statistically significant positive correlates of 25(OH)D included male sex, summer sample, physical activity and multivitamin use. Significant negative correlates were body mass index, winter and spring samples, diabetes, sedentary behavior, smoking and Black race/ethnicity [80]. The findings of relatively low 25(OH)D levels in Black women compared with White women have led to speculation regarding the potential role of low 25(OH)D contributing to the observed ethnic disparity in breast cancer outcome [81,82].

In randomized trials, an inconsistent relation has been observed between total vitamin D intake (diet plus supplement) and subsequent 25(OH)D levels [83]. In the WHI cohort, when 25(OH)D levels were compared with total vitamin D intake (dietary and supplement) [42], the difference in median vitamin D intake comparing low (deficient, 24 nmol/l) with high (optimal, 82 nmol/l) quintiles was only 238 IU daily, about one-half of the usual multivitamin tablet. In addition, only 3% of those in the highest quintile had vitamin D intakes >1,000 IU/day (Figure 2). Compared with vitamin D intake, stronger associations with 25(OH)D were seen for body mass index and physical activity with leaner, more physically active women having significantly higher levels (P <0.0001) [42]. Failure to control for these two factors could thus potentially confound observational studies of 25(OH)D and breast cancer.

In the WHI cohort, a multivariant predictive model could account for only 21% of the differences in 25(OH)D levels between individuals in a random sample of 3,055 postmenopausal women [84]. This finding is consistent with other reports in which a substantial proportion of 25(OH)D difference between individuals is probably genetically determined [85,86]. The largely unexplained factors influencing differences in 25(OH)D levels between individuals complicate understanding of associations with

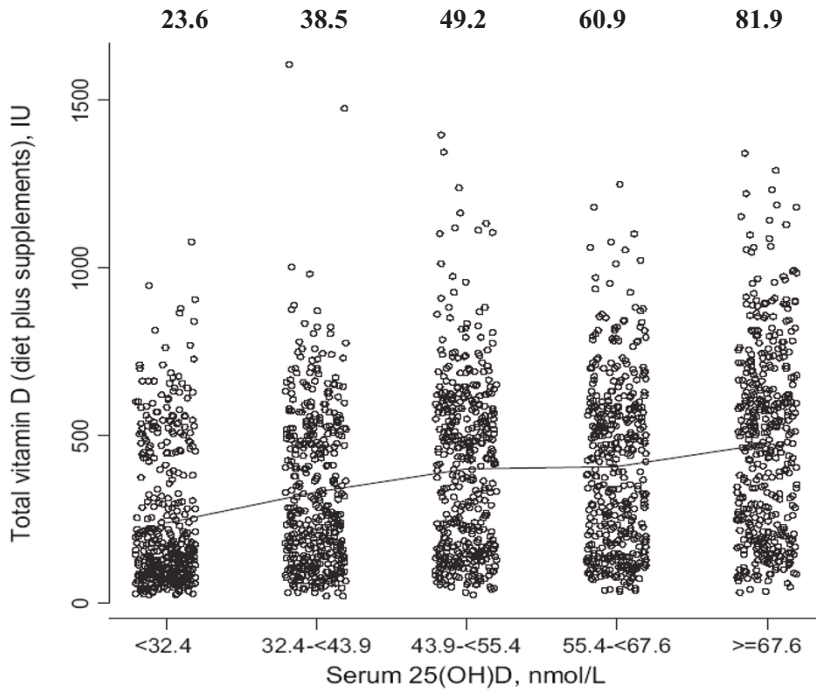

Figure 2. Total vitamin D intake and serum 25-hydroxyvitamin D by quintile. Individual total vitamin D intake (diet plus supplementation) and serum 25-hydroxyvitamin D (25(OH)D) levels at baseline. Serum 25(OH)D levels from 1,067 women identified as control subjects from a nested case–control study performed in the Women's Health Initiative trial evaluating calcium and vitamin D. Daily intakes of dietary and supplemental vitamin D were determined from self-report. The range of vitamin D intakes substantially overlaps in each 25(OH)D quintile. Line segments connect the mean vitamin D intake level in each quintile, which was 23.6, 38.5, 49.2, 60.9, and 81.9 nmol/l, respectively. Adapted with permission from Chlebowski and colleagues [42].

disease states and development of rationale therapeutic strategies.

Conclusions

The recent IOM report on calcium and vitamin D requirements provides an authoritative base for consideration of vitamin D and breast cancer issues. For vitamin D, the IOM recommendations are based primarily on bone health outcomes. The total recommended daily vitamin D intake for women <71 years old is 600 IU/day. For those 71 years or older, an intake of 800 IU/day – corresponding to a serum 25(OH)D level of 20 ng/ml (50 nmol/l) – is recommended. These levels and cutoff points are lower than proposed by some in the current literature but the IOM committee did not judge higher level recommendations to be justified by available evidence [9,10].Randomized clinical trial evidence indicates that vitamin D supplementation (at a dose of about 400 to 800 IU/day), together with supplemental calcium, results in a modest decrease in fracture risk for women at higher fracture risk [87]. As many breast cancer patients are at fracture risk based on age and effects of cancer therapy (such as oophorectomy, chemotherapy-associated amenorrhea, and aromatase inhibitors), use of vitamin D supplements (400 to 800 IU/day) plus calcium in those at increased fracture risk can be recommended. For early-stage breast cancer patients, suggestions regarding routine monitoring of 25(OH)D levels and vitamin D supplementation to some target level are inferential and based on mixed observational study results.

Current evidence is sufficient to support further study of factors influencing 25(OH)D levels, associations between 25(OH)D levels and breast cancer in premenopausal and Black women, moderate dose (≤2,000 IU D_3/day) supplemental vitamin D use and breast cancer incidence, and observational studies evaluating whether a threshold higher 25(OH)D level is associated with adverse clinical outcome in women with breast cancer. Before routine clinical application of any strategies targeting vitamin D status for breast cancer prevention or therapy are undertaken, the limitations of the current evidence should be considered.

Abbreviations

CI, confidence interval; HR, hazard ratio; 25(OH)D, 25-hydroxyvitamin D; IOM, Institute of Medicine; WHI, Women's Health Initiative.

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Competing interests
The author declares that he has no competing interests.

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