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Review

The Significance of Vitamin D Status in Breast Cancer: A State of the Science Review

CEU

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The potential role of vitamin D in the development of breast cancer has been the subject of considerable interest. Laboratory and genetic studies demonstrate promising anticarcinogenic effects of vitamin D. However, inconsistencies persist in results of human studies that have assessed vitamin D supplementation for the prevention of primary and secondary cancers. Despite these discrepancies, screening for vitamin D deficiency and vitamin D supplementation have increased dramatically in the past decade. No official institutional guidelines recommend vitamin D supplementation for cancer prevention, and yet these newly adopted practice norms have outpaced rigorous scientific study. Higher circulating levels of vitamin D [25-hydroxyvitamin D, or 25(OH)D] appear to be associated with reduced risk and improved survivorship of certain malignancies. However, the association has not been found for all cancers. This state of the science review examines the association between vitamin D supplementation, circulating 25(OH)D level, vitamin D receptor polymorphisms, and the risk and mortality of breast cancer. The review addresses the role of supplementation and optimal 25(OH)D levels.
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INTRODUCTION

Vitamin D is a fat-soluble group of secosteroids available through animal-based foods, biosynthesis from ultraviolet B (UVB) radiation in sunlight, and dietary supplementation. The most important compounds for humans in this group are vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol).[1] Actions of the vitamin D group are due to the functions of the active metabolite, calcitriol, which promotes increased intestinal absorption and regulation of serum calcium, magnesium, and phosphate and, in turn, the development and maintenance of bone health.[1] Vitamin D also has multiple other functions and is now recognized more as a prohormone than a vitamin. Similar to the steroid hormones, such as estradiol, calcitriol has the chemical ability to bind with target receptors and may induce a biological response.[2] Vitamin D receptors (VDRs) are present in the nucleus of many tissues in the human body that are not involved in the regulation of calcium and phosphate metabolism, and thus vitamin D has been promoted for use in nonskeletal diseases, such as diabetes and cancer.[2] The purpose of this review is to analyze recent research findings that have examined the association between vitamin D supplementation, circulating serum 25-hydroxyvitamin D [25(OH)D] levels, VDR polymorphisms, and breast cancer risk and mortality. In addition, the current existent guidelines and recommendations for vitamin D replacement in women are reviewed.

To examine the associations between vitamin D, breast cancer risk and mortality, and VDR polymorphisms, a search was conducted in MEDLINE, CINAHL, PubMed, Embase, and the Cochrane Database of Systematic Reviews. The search was supplemented by reference tracking, ancestry approach, and author tracking of selected articles. To be included in the review, articles had to meet the following criteria: written in English; published between January 2010 and November 2018; systematic reviews with or without meta-analyses; and studies that addressed relationships among vitamin D supplementation, vitamin D levels, breast cancer risk and mortality, and VDR polymorphisms. The search terms used were *vitamin D*, *incidence*, *mortality*, *genetics*, *polymorphisms*, and *breast cancer*.

BACKGROUND

In 2011, the Institute of Medicine defined serum concentrations of 25(OH)D less than 20 ng/mL as deficient and recommended supplementation of 600 to 800 international units per day as the recommended dietary allowance (RDA).[3] Clinical experts recommend 25(OH)D levels between 30 ng/mL and 50 ng/mL be maintained for optimal health (Table 1).[4] Up to 80% to 100% of vitamin D intake is absorbed through the skin with conversion of the sterol 7-dehydrocholesterol to vitamin D3 by UVB waves.[5] Thus, the intake of vitamin D in women may vary based on latitude, season, month, weather, skin pigmentation, sunscreen use, and the ozone layer.[6] Natural dietary sources of vitamin D3 may be found in animal-based foods such as fish, meat, eggs, and dairy products. The vitamin D group also includes vitamin D2 that is produced in plants such as fungi and yeasts by UVB exposure. However, meeting the RDA through diet alone may be challenging and influenced by risk factors of clinical significance, as identified by numerous

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Quick Points

- Routine vitamin D screening and supplementation is not currently recommended in the prevention of breast cancer.
- Despite no proven causal association and inconsistent evidence from existing observational studies, screening for vitamin D deficiency and supplementation have increased dramatically in the past decade.
- A more definitive understanding of the complex relationship between 25(OH)D status and breast cancer risk may result from well-designed blinded randomized human trials.
- Vitamin D receptor polymorphisms may affect the risk and mortality of breast cancer. However, the role of vitamin D receptors in the etiology of cancer is still equivocal.
- There may be an association between menopausal status, vitamin D level, and breast cancer risk and mortality.

epidemiologic studies (Table 2).[3,7] Although vitamin D is essential for bone health, deficiency leads to elevated parathyroid hormone, which may lead to hypercalcemia and a variety of symptoms, including fragile bones (osteoporosis), kidney stones, excessive urination, abdominal pain, fatigue, depression, forgetfulness, bone and joint pain, nausea, vomiting, or loss of appetite.[4] In mice, vitamin D deficiency has been shown to promote growth of breast cancer cells.[8]

Vitamin D Metabolism and Physiologic Function

Vitamins D2 and D3 are converted into the hormonally active metabolite, calcitriol, in several steps. Conversion of vitamin D into the active form occurs initially in the liver via cytochrome P450 enzyme, 25-hydroxylase, and the hydroxylation forms 25(OH)D. Another conversion then follows in the kidneys catalyzed by 1 α-hydroxylase to produce the active vitamin D hormone, calcitriol [$1,25(OH)_2D$].[5] Cells with VDRs have the ability to locally convert 25(OH)D to calcitriol and bind with a target receptor to produce a biologic response.[5] Gene transcription, activated by locally available calcitriol at VDRs, controls apoptosis, differentiation, angiogenesis, and cell proliferation (Figure 1).[9] It has been speculated that genetic polymorphic variations of the VDR influence the development of cancer.

VDRs are found throughout the body, including breast tissue, and offer potential antineoplastic protective actions in well-designed laboratory studies.[10–12] Multiple animal and in vitro studies have documented the antineoplastic qualities of vitamin D.[10–12] However, randomized controlled trials (RCTs) in humans and epidemiologic studies that have assessed this relationship have produced inconsistent results.[11] Higher circulating levels of 25(OH)D appear to be associated with reduced risk and improved survivorship of certain malignancies, but this association has not been found for all cancers. Despite these discrepancies, screening for vitamin D deficiency and supplementation have increased dramatically in the past decade. Serum 25(OH)D was the fifth most common laboratory test ordered for Medicare patients in 2014, with a total cost of $323 million.[13] No government or institutional guidelines recommend vitamin D supplementation specifically for cancer prevention, and yet these newly adopted practice norms have outpaced rigorous scientific study.

Table 1. Serum Vitamin D Levels

Category	National Institutes of Health ng/mL	Endocrine Society ng/mL
Deficiency	<12	<20
Insufficiency	12 to <20	21 to 29
Sufficiency	≥20	≥30
Excess	>50	>100[a]

[a] Vitamin D intoxication may occur in serum 25(OH)D levels greater than 150 ng/mL.

Sources: Ross et al; Institute of Medicine;[1] Holick et al; Endocrine Society.[4]

VITAMIN D AND BREAST CANCER RISK

Breast cancer is the most prevalent type of cancer among women. Known risk factors include family history, genetic risk factors such as mutations of the BRCA genes, age, parity, alcohol consumption, obesity, and dense breast tissue.[14] Animal and in vitro investigations have examined the plausible link between VDR genes and breast cancer risk. These studies have found that vitamin D decreases cell proliferation when the VDRs are activated by calcitriol.[5] Additionally, circulating 25(OH)D was also shown to be potentially beneficial because many cell types, including cancer cells, express 1 α-hydroxylase and are thus able to convert 25(OH)D into calcitriol.[9–12]

Table 3 presents a review of the current studies that have assessed the association between vitamin D and breast cancer risk.[11,14-34] This review considers recent meta-analyses, RCTs, Mendelian randomization studies, and prospective and retrospective case-control and cohort studies. The review revealed no standardization across the studies in the reporting of vitamin D levels or doses. For example, some reported vitamin D levels in quartiles; others used different cutoff values. Thus, to provide comparable criteria, the odds ratios (ORs), relative risks (RRs), and/or hazard ratios (HRs) are reported in Tables 3 and 4, and 5 when available.

Early studies identified an association between breast cancer risk and vitamin D levels. For example, a 2010 meta-analysis by Chen et al found that women with the highest quartile levels of 25(OH)D were associated with a 45% lower risk of breast cancer versus women in the lowest quartile (OR, 0.55; 95% CI, 0.38-0.80).[15] Another case-control study by Bilinski et al found that serum 25(OH)D levels less

Table 2. Risk Factors for Vitamin D Deficiency

Risk Factors	Clinical Significance
Antiepileptic medications, corticosteroids, cholestyramine[a]	Drugs interfere with vitamin D metabolism
Liver and kidney disease	Decreased active vitamin D metabolite synthesis
Irritable bowel disease, cystic fibrosis, gastric bypass surgery	Decreased absorption of vitamin D
Obesity	Vitamin D is fat soluble and isolated into adipose tissue, decreased bioavailability
Older age	Decreased ability of skin to convert UVB rays, decreased appetite
Pregnancy	Vitamin D deficiency is more prevalent in pregnancy and lactation
Breastfed infant	Human milk does not have sufficient levels of vitamin D to meet the RDA for infants
Lack of supplemented foods, plant-based diet	Poor nutritional intake
Sunscreen, clothing, decreased outdoor activities, darker skin color, higher latitude, sun avoidance, skin cancer	Reduced sun exposure leads to reduced absorption of UVB rays necessary for vitamin D conversion

Abbreviations: RDA, recommended dietary allowance; UVB, ultraviolet B.
[a]Medications that interfere with vitamin D metabolism include antiseizure medications, corticosteroids, cholestyramine, bisphosphonates, antiretroviral medications, and antituberculosis drugs. Statins and thiazide diuretics increase vitamin D levels.
Sources: Ross et al;[3] National Institutes of Health.[7]

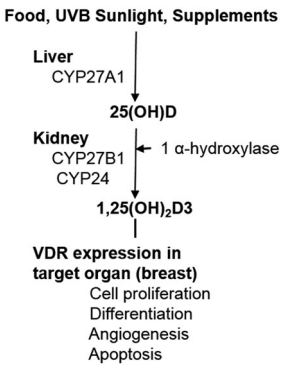

Figure 1. Vitamin D Pathway

Abbreviations: $1,25(OH)_2D3$, 1α,25-dihydroxyvitamin D3 (calcitriol); 25(OH)D, 25-hydroxyvitamin D (calcifediol); CYP24, cytochrome P450 family 24; CYP27A1, cytochrome P450 family 27 subfamily A member 1; CYP27B1, cytochrome P450 family 27 subfamily B member 1; UVB, ultraviolet B; VDR, vitamin D receptor.

than 28 ng/mL were associated with a higher breast cancer risk (OR, 2.5; 95% CI, 1.60-3.90).[19] The inverse relationship of higher circulating 25(OH)D levels and lower breast cancer risk was also noted in white postmenopausal women but not in other ethnic groups residing in low-latitude regions in a case-control study by Kim et al (OR, 0.43; 95% CI, 0.23-0.80).[22] In 2016, Jamshidinaeini et al found women with the highest 25(OH)D quartile to have 3 times lower risk of breast cancer in their case-control study (OR, 0.269; 95% CI, 0.12-0.59).[27] A pooled analysis of 11 case-control studies by Mohr et al concluded that a serum 25(OH)D level higher than 47 ng/mL was associated with a 50% lower risk of cancer.[17]

Mendelian randomization analyses conducted by Dimitrakopoulou et al assessed the associations between circulating 25(OH)D levels and the risk of 7 cancers, including breast cancer. Mendelian randomization is a research method that provides evidence about assumed causal relations between modifiable risk factors and disease, using genetic variants as natural experiments. Using data from large genetic epidemiologic networks, the authors found little evidence for a linear association between vitamin D levels and risk of breast cancer (OR, 1.05; 95% CI, 0.89-1.24).[11] The authors concluded that these results, in combination with the results of other studies, do not support routine vitamin D screening and supplementation as a primary breast cancer prevention strategy.[11] Skaaby et al found similar results in their prospective cohort study of 12,204 Danish women. During the 11-year median follow-up time, the association between vitamin D levels and incidence of breast cancer was not significant (HR, 1.02; 95% CI, 0.96-1.09).[24]

Meta-analyses of observational and case-control studies have demonstrated inconsistent, nonlinear associations between 25(OH)D levels and the risk of developing breast cancer risk (Table 3). The 2011 meta-analysis by Gandini et al identified 6175 cases in 10 studies and noted that a 10 ng/mL increase in serum 25(OH)D level was associated with a lower risk for breast cancer (RR, 0.89; 95% CI, 0.81-0.98).[16] Similarly, the meta-analysis of 8 studies by Shao et al found that higher circulating 25(OH)D levels were associated with a lower risk of breast cancer.[18] However, these studies had limitations because the timing regarding the collection of blood samples before or after breast cancer diagnosis was not taken into consideration.[16,18] Wang et al conducted a meta-analysis of 14 prospective studies and found that serum 25(OH)D levels were inversely associated with breast cancer risk (RR, 0.845; 95% CI, 0.75-0.95) and that every 10 ng/mL increase in serum 25(OH)D concentration was associated with a 3.2% reduction in breast cancer risk.[20] Similarly, Kim et al found that higher serum 25(OH)D levels were associated with lower breast cancer mortality (RR, 0.58; 95% CI, 0.40-0.85) in a meta-analysis of 30 prospective studies of patients with breast cancer. These results suggest that higher vitamin D status is associated with better breast cancer survival.[23] However, the

Table 3. Vitamin D and Breast Cancer Risk

Author, Year	Design and Sample	Outcomes	RR, OR, or HR (95% CI)
Chen et al,[15] 2010	Meta-analysis 7 studies n = 4584 case n = 4941 control	Highest quartile circulating 25(OH)D level is associated with a 45% decrease in BC risk compared with lowest quartile.	OR: 0.55 (0.38-0.80)
Gandini et al,[16] 2011	Meta-analysis Systematic review 10 studies N = 6175	For every 10 ng/mL increase in serum 25(OH)D level, there was an observed decrease in BC risk. Results from only prospective studies did not support this association.	RR: 0.89 (CI, 0.81-0.98)
Mohr et al,[17] 2011	Case-control 11 studies n = 7550 case n = 8790 control	25(OH)D level of 47 ng/mL or higher was associated with 50% lower BC risk. Pooled estimated risk compared highest with lowest quartile. Higher serum 25(OH)D levels reduce BC risk.	OR: 0.61 (0.47-0.80)
Shao et al,[18] 2012	Meta-analysis 8 studies n = 6293 case n = 7282 control	5 of 8 case-control studies showed a statistically significant lower BC risk with higher serum 25(OH)D level. The pooled OR compared the highest quartile serum 25(OH)D level with the lowest quartile.	OR: 0.55 (0.38-0.80)
Bauer et al,[14] 2013	Meta-analysis 9 studies n = 5206 case n = 6450 control	There is an inverse association between serum 25(OH)D level and BC risk in postmenopausal women.	RR: 0.99 (0.97-1.04)
		No association in premenopausal women between low serum 25(OH)D level and BC risk.	RR: 1.01 (0.98-1.04)
		A 5 ng/mL increase in serum 25(OH)D level was associated with a 12% decrease in BC risk in postmenopausal women.	RR: 0.88 (0.79-0.97)
Bilinski and Boyages,[19] 2013	Case-control n = 214 case n = 852 control	Serum 25(OH)D level <28 ng/mL (including insufficient, deficient, and severely deficient levels) at the time of diagnosis was associated higher BC risk.	OR: 2.5 (1.6-3.9)
		Severe deficiency, 25(OH)D level <10 ng/mL, demonstrated greatest BC risk.	OR: 2.3 (1.3-4.3)
		Deficiency, 25(OH)D level between 10 and 20 ng/mL, demonstrated significant BC risk.	OR: 2.5 (1.60-3.90)
		Insufficiency, 25(OH)D level between 20 and 30 ng/mL, was associated with increased BC risk.	OR: 2.5 (1.60-3.80)
Wang et al,[20] 2013	Meta-analysis 14 studies n = 9110 case n = 16,244 control	Serum 25(OH)D levels were inversely significantly associated with BC risk in postmenopausal women. No statistically significant associations were observed in premenopausal women.	RR: 0.84 (0.75-0.95)
Bjelakovic et al,[21] 2014	Systematic review of RCTs 7 studies n = 1918 case n = 24,908 control	Analysis demonstrated 7.7% BC incidence with vitamin D supplementation vs 7.7% BC incidence with placebo; supplementation had no effect on BC risk.	RR: 1.00 (0.94-1.06)

(*Continued*)

Table 3. Vitamin D and Breast Cancer Risk

Author, Year	Design and Sample	Outcomes	RR, OR, or HR (95% CI)
Kim et al,[22] 2014	Case-control N = 707	Serum 25(OH)D level was associated with a reduced BC risk among white postmenopausal women, but not in other ethnic groups or in premenopausal women.	OR: 0.43 (0.23-0.80)
Kim and Je,[23] 2014	Meta-analysis 24 studies N = 31,867	The pooled RRs of BC incidence compared the highest vs the lowest serum 25(OH)D level. High serum 25(OH)D level is weakly associated with low BC risk but strongly associated with better BC survival.	RR: 0.92 (0.83-1.02)
Skaaby et al,[24] 2014	Cohort N = 159	No significant association between 25(OH)D level and BC risk.	HR: 1.02 (0.96-1.09)
Park et al,[25] 2015	Case-control n = 3634 case	Inverse relationship exists between serum 25(OH)D level and BC risk.	OR: 1.27 (1.15-1.39)
	n = 17,133 control	Inverse relationship exists between serum 25(OH)D level and BC risk in premenopausal Korean women.	OR: 1.26 (1.09-1.45)
		Inverse relationship exists between serum 25(OH)D level and BC risk in postmenopausal Korean women.	OR: 1.25 (1.10-1.41)
Reimers et al,[26] 2015	Case-control n = 967 case n = 997 control	*Cdx2*, *Bgl1*, and *Taq1* do not show BC risk association. VDR *Bsm1*, *Apa1*, *Fok1*, and Poly (A) gene polymorphisms correlate with increased BC risk.	Pooled OR varied by individual VDR polymorphism
Jamshidinaeini et al,[27] 2016	Case-control n = 135 case n = 135 control	Highest quartile serum 25(OH)D level associated with 3 times lower BC risk compared with lowest quartile.	OR: 0.27 (0.12-0.59)
McDonnell et al,[28] 2016	Pooled analysis n = 1169 Lappe n = 1135 Grassroots	Women with serum 25(OH)D concentrations >40 ng/mL, compared with <20 ng/mL, had 67% lower BC risk.	HR: 0.33 (0.12-0.90)
Ordóñez-Mena et al,[29] 2016	Meta-analysis 3 studies N = 378	Significant BC risk reduction for serum 25(OH)D levels between 30 and 50 ng/mL. BC risk increases with higher serum 25(OH)D.	HR: 0.67 (0.52-0.87)
Shekarriz-Foumani and Khodaie,[30] 2016	Systematic review 13 studies n = 9401 case n = 20,998 control	Inverse association of 25(OH)D level and BC risk. High prevalence of vitamin D deficiency and insufficiency in patients with BC and increased BC risk with serum 25(OH)D deficiency.	Not listed
Dimitrakopoulou et al,[11] 2017	Mendelian randomization N = 15,748	Insignificant evidence for a linear causal association between 25(OH)D level and BC risk.	OR: 1.05 (0.89-1.24)
Lappe et al,[31] 2017	Population RCT n = 1156 vitamin D supplementation n = 1147 placebo	Vitamin D supplementation did not reduce BC risk in postmenopausal women with serum 25(OH)D levels <32.8 ng/mL.	HR: 0.70 (0.47-1.02)

(*Continued*)

Table 3. Vitamin D and Breast Cancer Risk

Author, Year	Design and Sample	Outcomes	RR, OR, or HR (95% CI)
Estébanez et al,[32] 2018	Meta-analysis 68 case-control and cohort studies N = 1,251,934	A protective relationship between high serum 25(OH)D level and BC risk exists in premenopausal women in cohort studies.	OR: 0.85 (0.74-0.98)
		A protective relationship between high serum 25(OH)D level and BC risk exists in premenopausal women in case-control studies.	OR: 0.65 (0.56-0.76)
Machado et al,[33] 2018	Case-control n = 209 case n = 418 control	Postmenopausal women had lower serum 25(OH)D level and more obesity at time of BC diagnosis.	OR: 1.52 (CI,1.04-2.22)
McDonnell et al,[34] 2018	Two RCTs One prospective N = 5038	82% lower BC incidence rate with serum 25(OH)D level ≥60 ng/mL, compared with <20 ng/mL, in postmenopausal women.	Rate ratio: 0.18; $P = .006$

Abbreviations: 25(OH)D, 25-hydroxyvitmain D; BC, breast cancer; HR, hazard ratio; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.

2016 meta-analysis by Ordóñez-Mena et al revealed surprisingly inconsistent results with increased breast cancer risk noted in women with higher 25(OH)D levels.[29] Different findings between the Ordóñez-Mena study and the meta-analyses conducted prior to 2016 may be explained by the different settings and study populations involved. Most of the studies included in the prior meta-analyses were nested case-control studies conducted in the United States, with limited and heterogeneous adjustment for confounders. The large Ordóñez-Mena analysis included cohort data from European older adult populations, excluding premenopausal women, and employed consistent adjustment for the most important confounder variables common to all included studies.[29]

The randomized trials of vitamin D supplementation have further confounded this area of inquiry. Bjelakovic et al included 18 RCTs and found a 7.7% incidence in any type of cancer among people receiving vitamin D supplementation versus a 7.6% incidence of any type of cancers in the control group (RR, 1.00; 95% CI, 0.94-1.06).[21] Interestingly, although no firm evidence was found that vitamin D supplementation decreased or increased cancer occurrence in elderly women, these RCTs revealed that vitamin D combined with calcium increased the incidence of nephrolithiasis (RR, 1.17; 95% CI, 1.03-1.34).[21] The RCT by Lappe et al randomly assigned 2303 postmenopausal women to receive vitamin D and calcium or placebo for 4 years with follow-up visits every 6 months. At 4 years, 5.58% of the women in the placebo group and 3.89% of the women in the vitamin D supplementation group were diagnosed with any type of cancer.[31] Thus, vitamin D supplementation was not associated with reduced cancer risk (HH, 0.70; 95% CI, 0.47-1.02).[31] The authors noted that the lack of association may be the result of higher serum baseline levels of 25(OH)D in the study participants compared with the general US population.[31] The most recent pooled analysis of 2 RCTs and one prospective study by McDonnell et al found that higher 25(OH)D concentrations were associated with a dose-response decrease in breast cancer risk. The authors noted that serum vitamin D concentrations 60 ng/mL or higher were the most protective and that concentrations below 20 ng/mL had the highest risk for breast cancer.[34] At this time, prospective epidemiologic evidence of an association between serum 25(OH)D levels and breast cancer risk remains inconclusive, and vitamin D supplementation studies have not shown that supplementation decreases the risk.

VITAMIN D AND BREAST CANCER MORTALITY

Table 4 presents a current literature review on the association between vitamin D and breast cancer mortality.[35–44] This review evaluated recent meta-analyses, prospective cohort studies, and case-control studies from 2014 to 2018. The case-control study by Shirazi et al found that women with low serum 25(OH)D levels had more unfavorable breast cancer prognosis defined according to tumor type, size, lymph node involvement, historical grade, estrogen receptor status, and progesterone receptor status.[39] Mohr et al conducted a meta-analysis of 5 studies published in 2014 that assessed the relationship between vitamin D levels at the time of breast cancer diagnosis and case fatality rates. Overall, these studies found women with higher vitamin D levels were more likely to have a better prognosis when women in the highest serum 25(OH)D concentration category were compared with women in the lowest serum 25(OH)D concentration category (HR, 0.56; 95% CI, 0.4-0.7).[36] It is important to note, however, that one of the 5 studies included in this meta-analysis had results that were not statistically significant and that one demonstrated higher 25(OH)D concentration was associated with lower case fatality in an age adjusted analysis, but not in a multivariate analysis.[36]

The large meta-analysis by Kim et al of 30 studies revealed that among 6092 patients with breast cancer, high blood 25(OH)D levels were significantly associated with lower breast cancer mortality (RR, 0.58; 95% CI, 0.40-0.85) and overall mortality (RR, 0.61; 95% CI, 0.48-0.79).[23] These authors concluded that high vitamin D status is weakly associated with low breast cancer risk but strongly associated with better breast cancer survival. This conclusion was further supported by the meta-analysis of 5 studies by Maalmi et al. Their

Table 4. Vitamin D and Breast Cancer Mortality

Author, Year	Design and Sample	Outcomes	RR, OR, or HR (95% CI)
Kim and Je,[27] 2014	Meta-analysis 6 studies N = 6092	High serum 25(OH)D level is strongly associated with better BC survival.	RR: 0.58 (0.40-0.85)
Maalmi et al,[35] 2014	Meta-analysis 5 studies N = 4413	Higher serum 25(OH)D levels (>30 ng/mL) significantly reduced BC mortality.	HR: 0.58 (0.38-0.84)
Mohr et al,[36] 2014	Meta-analysis 5 studies N = 471	There is a significant reduction in BC mortality with increasing 25(OH)D level.	OR: 0.56 (0.40-0.70)
Jeffreys et al,[37] 2015	Meta-analysis N = 11,112	This study addresses issues of confounding and reverse causality. Supplementation had little effect on BC survival in postmenopausal women.	HR: 0.78 (0.70-0.88)
de Sousa Almeida-Filho et al,[38] 2016	Cross-sectional N = 192	Insufficient (20-29 ng/mL) and deficient (<20 ng/mL) serum 25(OH)D levels are associated with high grade tumors and metastatic BC.	
		All patients with triple-negative BC were deficient in 25(OH)D.	
		There is an association of estrogen receptor-negative BC and vitamin D insufficiency.	OR: 3.77 (1.76-8.09)
		There is an association between estrogen receptor-negative BC and vitamin D deficiency.	OR: 3.99 (1.83-8.68)
		There is an association between positive axillary lymph nodes and vitamin D insufficiency.	OR: 1.59 (1.03-2.33)
		There is an association between positive axillary lymph nodes and vitamin D deficiency.	OR: 1.58 (1.02-2.92)
Shirazi et al,[39] 2016	Case-control n = 764 cases n = 17,035 control	The lowest risk of aggressive BC occurs with intermediate 25(OH)D levels; aggressive BC risk with unfavorable prognosis is associated with high and low levels.	OR: 0.77 (0.59-1.00)
Vaughan-Shaw et al,[40] 2017	Meta-analysis Systematic review 15 studies N = 44,165	Higher serum 25(OH)D level is associated with better BC survival. *BSM1* rs1544410 variant improved BC survival.	HR: 0.75 (0.56-0.95)
Yao et al,[41] 2017	Case-cohort Pathways N = 1666	Compared with the lowest tertile, women with the highest tertile serum 25(OH)D levels had superior survival. There is an inverse association with low 25(OH)D level, disease progression, and death. Serum 25(OH)D was lower in women with advanced-stage tumors and lowest in premenopausal women with triple-negative BC.	HR: 0.72 (0.54-0.98)
Madden et al,[42] 2018	Cohort N = 2581	Vitamin D supplementation after BC diagnosis is linked with decreased BC mortality by 20%-49%, with better survival if initiated within 6 months.	HR: 0.80 (0.64-0.99)
Viala et al,[43] 2018	Retrospective N = 327	Women with serum 25(OH)D levels <20 ng/mL were unable to reach pCR in BC with NAC. Hormone receptor-positive, human epidermal growth factor-negative, and triple-negative BCs were associated with low serum 25(OH)D levels.	OR: 0.43 (0.43-0.80)

Abbreviations: 25(OH)D, 25-hydroxyvitmain D; BC, breast cancer; HR, hazard ratio; NAC, neoadjuvant chemotherapy; OR, odds ratio; pCR, pathological complete response; RR, relative risk; VDR, vitamin D receptor.

Table 5. Vitamin D Receptor Polymorphism Studies

Author, Year	Design and Sample	Result
Lopes et al,[47] 2010	Case-control n = 189 case n = 379 control	Deregulation of the VDR polymorphism *CYP27B1* and *CYP24A1* pathways in BC favor tumor progression. Tumor cells cannot synthesize active vitamin D and can degrade it more quickly.
Dorjgochoo et al,[48] 2011	Case-control N = 5242	559 SNPs in 12 vitamin D-related genes were studied. 6 genes showed minimal associations, and 6 genes were insignificant for association in BC risk.
Fuhrman et al,[49] 2013	Case-control n = 484 case n = 845 control	*CYP24A1* SNPs *rs34043203* and *rs2762934* show inverse association with BC risk (OR,1.35; 95% CI, 1.09-1.67). *Bsm1* VDRP has inverse association with BC risk (OR,0.82; 95% CI, 0.70-0.97). No significant association between *Fok1* and BC risk.
Perna et al,[50] 2013	Cohort analysis 2 studies N = 498	There is a significant association between the VDR polymorphism *rs731236* rare homozygous genotype and BC mortality.
Gnagnarella et al,[51] 2014	Meta-analysis 14 studies n = 11,480 case n = 16,082 control	Considering VDRP Fok1 and BC risk, ff vs FF has an OR of 1.05 (95% CI, 0.90-1.22), and Ff vs FF has an OR of 1.03 (95% CI, 0.95-1.12). The f allele is associated with a high risk for cancers, especially in white people.
Raimondi et al,[52] 2014	Meta-analysis 73 studies n = 45,218 case n = 52,057 control	Considering VDRP Bsm1 and BC risk, Bb has an OR of 0.94 (95%CI, 0.90–0.99), and BB has an OR of 0.83 (95% CI, 0.89-0.98). There is 6%-7% reduction of all cancer risk with Bb and BB alleles compared with bb.
Clendenen et al,[53] 2015	Case-control n = 734 case n = 1435 control	There is no association between serum 25(OH)D level and RXRA gene with BC risk.
Mondul et al,[54] 2015	Case-control 6 studies n = 9456 case n = 10,816 control	OR, 0.56 (95% CI, 0.32–0.97). The possible association of DHCR7 with ER-negative disease should be examined further. There is no association between 4 SNPs (GC, CYP24A1, CYP2R1, and DHCR7) and BC risk.
Reimers et al,[20] 2015	Case-control n = 967 case n = 997 control	Cdx2, Bgl1, and Taq1 VDRPs do not show association with BC. VDRP Bsm1, Apa1, Fok1, and Poly (A) gene polymorphisms may increase BC risk.
Li et al,[55] 2016	Meta-analysis n = 9264 case n = 12,516 control	There is no overall significant BC risk associated heterozygous *Fok1* among premenopausal women, whereas overall significant BC risk was associated with the homozygous model.
Lu et al,[46] 2016	Meta-analysis 8 studies n = 14,082 case n = 18,455 control	There is no significant association between *Fok1*, *Bsm1*, *Taq1*, and *Apa1* VDR polymorphisms and BC risk.
Serrano et al,[56] 2016	Meta-analysis 22 studies n = 35,525 case n = 38,675 control	VDRP Cdx2 gg genotype was associated with a 12% increased risk of all cancers. There was no significant association Taq1 and Apa1 variant genotypes and BC risk.
Dimitrakopoulou et al,[11] 2017	Mendelian randomization n = 15,748 case n = 18,084 control	This study did not prove linear causal association between VDR polymorphisms *s2282679*, *rs10741657*, *rs12785878*, and *rs6013897* and BC risk.

(*Continued*)

Table 5. Vitamin D Receptor Polymorphism Studies

Author, Year	Design and Sample	Result
Iqbal and Khan,[57] 2017	Systematic review Meta-analysis 34 studies n = 26,372 case n = 32,883 control	VDR polymorphisms *Bsm1*, *Apa1*, *poly(A)*, and *Fok1* were associated with BC risk. VDR polymorphisms *Bgl1*, *Cdx2*, and *Taq1* did not show any association with BC risk.
Laczmanski et al,[58] 2017	Meta-analysis n = 1739 case n = 2975 control	Considering VDR Fok1 polymorphism and cancer genesis: F variant reduced the risk of cancer by 4%, especially in female sex-associated cancer (OR, 0.96; 95% CI, 0.93–0.99). Fok1 was not associated with BC.
Chiang et al,[59] 2018	Western blot, migration and invasion assays, enzyme-linked immunosorbent assay, immunofluorescent stain	MART-10, a $1\alpha,25(OH)_2D^3$ analog, potently repressed metastasis of estrogen receptor-positive BC cells with VEGF-A overexpression.
O'Brien et al,[10] 2018	Case-cohort n = 1070 case n = 1277 control	DNA methylation of CpGs in vitamin D-related genes may interact with serum 25(OH)D level to affect BC risk.

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BC, breast cancer; ER, estrogen receptor; OR, odds ratio; SNP, single-nucleotide polymorphism; VDR, vitamin D receptor; VEGF-A, vascular endothelial growth factor-A.

study included 4431 patients with breast cancer and compared mortality across 2 to 5 categories of 25(OH)D levels. For patients with breast cancer, the pooled analysis compared highest with lowest 25(OH)D categories for overall mortality (HR, 0.62; 95% CI, 0.49-0.78) and breast cancer-specific mortality (HR, 0.58, 95% CI, 0.38-0.84).[35] Conversely, the large 2015 meta-analysis by Jeffreys et al found no association between vitamin D supplementation and breast cancer survival in postmenopausal women.[37] The authors posit that previous observational studies' finding of better survival among women prescribed vitamin D supplementation may have been subject to confounding by indication.

The large prospective cohort study of 1666 breast cancer survivors by Yao et al completed enrollment in 2013, and the follow-up is ongoing. After adjustment for clinical prognostic factors, this study found that women with the highest 25(OH)D levels had greater overall survival when compared with women with the lowest 25(OH)D levels (HR, 0.72; 95% CI, 0.54-0.98).[41] The authors concluded that low serum 25(OH)D levels were independently associated with poorer survival, advanced stage, and recurrence in women with breast cancer. Additionally, low 25(OH)D levels were also associated with prognostic characteristics including the triple-negative breast cancer subtype.[41] Triple-negative breast cancer is a heterogeneous subgroup of tumors accounting for 15% to 20% of all breast cancers. Triple-negative breast cancer is defined by the absence of expression of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2. The triple-negative subtype is a more aggressive cancer with worse disease-specific outcomes than other breast cancer subtypes because of distinct molecular subtypes that respond differently to chemotherapy and targeted agents.[44] The studies by de Sousa Almeida-Filho et al in 2016 and Viala et al in 2018 found that vitamin D deficiency and insufficiency in women were significantly associated with triple-negative breast cancer (Table 4).[38,43] Furthermore, Viala et al hypothesized that vitamin D deficiency may clinically affect tumor treatment response given the VDR role in proliferation, apoptosis, and angiogenesis.[43]

The 2018 study by Madden et al of a large national breast cancer cohort in Ireland found a highly positive reduction in mortality if vitamin D supplementation was initiated after breast cancer diagnosis.[42] These authors found a 20% to 49% reduction in breast cancer-specific mortality in women who took supplemental vitamin D compared with women who did not use supplements (HR, 0.80; 95% CI, 0.64-0.99), and the reduction was higher (HR, 0.51; 95% CI, 0.34-0.74) if vitamin D supplementation was initiated within 6 months after the breast cancer diagnosis.[42]

Although some of the associations noted in the studies summarized in Table 4 are null or weak, none of the studies indicated poorer survival with higher 25(OH)D concentrations. Thus, current evidence suggests vitamin D may be useful as a nontoxic and inexpensive agent to improve survival in women with breast cancer. These findings support the need for more RCTs to investigate the effect of vitamin D on breast cancer survival. Grant and Boucher created a modeling proposal from which many current RCTs are being designed and conducted.[45] A more definitive understanding of the complex relationship between 25(OH)D status and breast cancer may result from well-designed and blinded randomized human trials.

VITAMIN D POLYMORPHISMS AND BREAST CANCER

Several studies have revealed an association between cancer risk and vitamin D-related genetic variants with respect to the VDR polymorphisms *Fok*I, *Bsm*I, *Taq*I, *Apa*I, and *Cdx*2. These 5 polymorphisms were found to have functional effects on receptor affinity for vitamin D and may affect the risk of breast cancer.[46] However, the evidence from multiple

studies, including meta-analyses, Mendelian randomization, case-control and systematic reviews, that have found an inverse association between VDR polymorphisms and breast cancer risk is inconsistent (Table 5).[10,11,20,23,46–59] For example, the 2016 meta-analysis of 8 studies by Lu et al did not reveal any significant association between *Fok*I, *Bsm*I, *Taq*I, and *Apa*I VDR polymorphisms and risk of breast cancer.[46] However, the systematic meta-analysis by Iqbal et al found that VDR polymorphisms *Fok*I, *Bsm*I, and *Apa*I were associated with breast cancer, whereas *Taq*I and *Cdx*2 were not associated with breast cancer.[57] Another large meta-analysis from 135 different populations conducted by Laczmanski et al found only *Fok*I to be associated with breast cancer risk (OR, 0.96; 95% CI, 0.93-0.99).[58] Moreover, Dimitrakopoulou et al and Reimers et al found little evidence for a linear causal relationship between the VDR polymorphisms and breast cancer.[11,26] Increased VDR expression appears inversely related to more aggressive tumor characteristics, including hormonal receptor negative, estrogen receptor negative, human epidermal growth factor 2 negative, and larger tumor size.[40] Additionally, the association between VDR polymorphisms, breast cancer risk, and mortality may vary with race, menopausal status, and ethnicity.[22,55]

In summary, the role of VDRs in the etiology of breast cancer is equivocal at this time. Genetic variation in the vitamin D pathway should be considered when designing potential intervention strategies with vitamin D supplementation. Review findings suggest the need for further study of VDR polymorphisms to improve our knowledge of the vitamin D pathway. Better understanding of VDR polymorphisms could provide additional evidence for a potential protective therapeutic role against breast cancer incidence.[60] VDR polymorphisms might also serve as predictors for diagnosis, occurrence, prognosis, and mortality.[61]

IMPLICATIONS FOR PRACTICE

When caring for women at high risk for breast cancer, currently diagnosed with breast cancer, or at risk for vitamin D deficiency, clinicians should be aware of current guidelines. Risk factors for vitamin D deficiency include pregnancy breastfeeding, dark skin, obesity, digestive disease, and absorption problems (eg, bariatric surgery or malabsorption disorders), kidney disease, special diets, lack of exposure to UVB from sunlight, and regular use of some medications (Table 2). The US Preventive Services Task Force found insufficient evidence that vitamin D supplementation prevents cancer in community-dwelling adults but does recommend screening for deficiency persons who have risk factors. However, the American Society for Clinical Pathology recommends against routine screening for vitamin D deficiency for the general population.[62]

Menopausal status may influence the relationship between vitamin D and breast cancer risk and mortality. Understanding the current evidence may help clinicians discern which patients to screen for vitamin D deficiency or insufficiency. Multiple well-conducted studies conclude that there is a significant inverse relationship between vitamin D status and breast cancer risk in postmenopausal women.[14,20,22,25,33,34] This association is not consistently found in premenopausal women.[14,20,22] However, the recent well-conducted meta-analysis by Estébanez et al did associate vitamin D sufficiency with decreased breast cancer risk in premenopausal women.[32] Bauer et al asserted that a 5 ng/mL increase in serum 25(OH)D level was associated with a 12% decrease in breast cancer risk in postmenopausal women, but no association was found in premenopausal women.[14] Kim et al found that higher serum vitamin D levels were associated with decreased breast cancer risk in white postmenopausal women, but not in premenopausal women or women from other ethnic groups.[22] Conversely, Park et al showed that an inverse relationship exists between serum 25(OH)D level and breast cancer risk in both pre- and postmenopausal Korean women.[25] The evidence supports routine screening for vitamin D insufficiency and deficiency in postmenopausal women. There was no reviewed evidence that supported vitamin D supplementation as means to decease breast cancer risk or mortality regardless of menopausal status.[31,37]

The current dietary recommendations of vitamin D for women aged older than 18 years is 600 to 800 international units of vitamin D3 daily.[63] Vitamin D toxicity may occur with over-supplementation. Key diagnostic findings include serum 25(OH)D levels higher than 150 ng/mL and elevated calcium levels. Vitamin D toxicity may lead to hypercalcemia and potential kidney damage. Signs and symptoms of hypercalcemia can include nausea, vomiting, constipation, loss of appetite, polyuria, polydipsia, nephrolithiasis, pruritus, muscle weakness, cardiac dysrhythmias, hyperthermia, and hypertension. Physical examination may reveal lethargy, abdominal pain, bone or muscle pain, skin excoriations, and weight loss in women with vitamin D intoxication. Current scientific consensus recommends using serum 25(OH)D testing to standardize results and improve comparability of data, accuracy of testing, and assessment of individuals' vitamin D status.[64,65]

Patients are increasingly requesting vitamin D testing at routine office visits. As this review demonstrates, testing is only recommended for persons with known risk factors. However, vitamin D is a popular topic in the mainstream media, and its reputation has outpaced current scientific evidence. If a person is using vitamin D supplements, assessment of dosing and symptoms of toxicity is necessary at each visit. Clinicians can help patients comprehend the adverse effects of vitamin D toxicity and provide safe recommendations for dietary intake and supplementation. Likewise, clinicians should monitor 25(OH)D levels to screen for toxicity in patients' self-administering megadoses of over-the-counter vitamin D.

CONCLUSION

This review found that multiple vitamin D studies support the inverse association between vitamin D level and breast cancer risk and mortality. Currently, screening for vitamin D deficiency and supplementation with vitamin D are not recommended strategies for primary cancer prevention.[11] Critical gaps in the supporting evidence include lack of data from well-designed randomized controlled clinical trials, although many current trials are being conducted. Optimal tailored screening and treatment recommendations to mitigate breast

cancer risk and poor prognosis may be developed from the findings of current trials. However, clinical trials designed to show that vitamin D reduces cancer risk have been modeled after pharmaceutical trials, which can prove a causative linear dose response.[42] Unfortunately, that methodology is not valid for vitamin D studies because people obtain vitamin D not only from supplements but also from UVB exposure and diet.

Vitamin D supplements are generally safe, inexpensive, and widely available over the counter. The Institute of Medicine supports a role for vitamin D in skeletal health. Breast cancer is extremely costly; in 2010 the national burden was $16.5 billion.[66] McDonnell et al assert that if women could increase their serum 25(OH)D levels from the current national average of 30 ng/mL[67] to 55 ng/mL, then theoretically more than $6 billion of annual cost could be eliminated.[34] Despite a plausible role of vitamin D in the prevention of breast cancer, this assertion is not validated by the extant evidence. Vitamin D supplementation could potentially be prescribed for prevention of primary and recurrent breast cancer if the ongoing and future human trials successfully identify causative protective actions, but research gaps and discrepancies must first be addressed. The current evidence is insufficient, inconclusive, and contradictory for extraskeletal benefits from vitamin D supplementation, including breast cancer prevention and survival.[1,49,50] The US Preventive Services Task Force found no evidence of benefit from vitamin supplementation for the prevention of breast cancer, and its findings are again reflected in the results of this review.[68,69] Claims of health benefits of vitamin D are ahead of the evidence. Vitamin D deficiency may not be the cause of breast cancer but possibly the consequence of the disease.[70]

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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