# Vitamin D and Breast Cancer: Latest Evidence and Future Steps

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**ABSTRACT:** Vitamin D (the sunshine vitamin) plays a vital role in calcium homeostasis, skeletal metabolism, and immune, cardiovascular, and reproductive systems' functions. The worldwide prevalence of vitamin D deficiency is approximately 1 billion. Vitamin D deficiency is a serious health problem with numerous health consequences; it is associated with diabetes, rheumatic arthritis, Parkinson, Alzheimer diseases, osteomalacia, osteoporosis, and fractures in adults and cancers. Many reports showed an inverse association between serum vitamin D concentration and incidence of several cancers, including breast, colorectal, kidney, lung, and pancreatic. About 20 different cancers have incidence rates inversely related to solar UV-B doses and serum vitamin D concentration. Considering the rising incidence of breast cancer and high prevalence of vitamin D deficiency, this review aimed to reflect an association between serum vitamin D concentration and breast cancer risk, reveal the link between vitamin D receptor genetic polymorphisms and breast cancer risk, and review the relationship between vitamin D level, breast cancer risk, and prognostic factors such as tumor stage, grade, size, lymph node involvement, and hormone receptor status.

**KEYWORDS:** Vitamin D, breast cancer, vitamin D gene polymorphism

Vitamin D refers to a group of fat-soluble secosteroids that are produced in 2 forms: $D_2$ and $D_3$. The $D_3$ form is produced from 7-dihydroxycholesterol under the skin that is exposed to UV-B light (cholecalciferol) and $D_2$ form originates from dietary sources such as plants and fish (ergocalciferol). Most of the vitamin D (up to 90%) comes from endogenous production under the skin. Both forms undergo hydroxylation in the liver by mitochondrial and microsomal 24-hydroxylase (encoded by CYP24A1) to yield 25-hydroxyvitamin D (25(OH)D) or calcidiol. The 25(OH)D is then transported in the circulation by the vitamin D–binding protein and further metabolized in kidneys to produce 1,25 dihydroxyvitamin D (1,25(OH)2D) (by 1 -hydroxylase that is encoded by CYP27B1) or calcitriol. The half-life of 1,25(OH)2D is only 4 to 6 hours and 1000-fold less than the total 25(OH)D. So, serum vitamin D is usually determined by measuring 25(OH)D biomarker that has a half-life of about 2 to 3 weeks.[1]

Different medical societies' guidelines have different definitions for the cutoff values of vitamin D level. The Institute of Medicine guidelines suggest that individuals are at risk of vitamin D deficiency if 25(OH)D concentration is below 30 nmol/L, inadequacy at serum 25(OH)D concentration between 30 and 50 nmol/L, and individuals are considered sufficient at concentration 50 nmol/L or higher.[2] In contrast, the Endocrine Society guidelines defined that 50 nmol/L is a cutoff value for vitamin D deficiency and the sufficient concentration exceeds 75 nmol/L.[3]

Breast cancer has been considered as the most common type of cancer among the women within 161 countries, and the most common cause for cancer deaths, within 98 countries.[4]

Known and well-established risk factors for breast cancer include age, family history, the density of breast tissue, parity, overweight, alcohol intake, and genetic risk factors such as BRCA mutations.[5] Recently, vitamin D receptor (VDR) genes were reported to increase breast cancer risk.[6] Several molecular breast cancer subtypes have been identified: luminal A and B (accounting for 50%-60% of breast cancer cases), basal-like or triple-negative (10%-20% of breast cancer cases) and human epidermal growth factor receptor 2 (HER2)-enriched (10%-15% of cases).[7] Vitamin D receptor genes operated by vitamin D have important roles in the mammary gland through regulation of calcium transport during lactation, hormone differentiation, and milk production.[8] Many efforts and enormous research have been directed toward identifying vitamin D as a breast cancer risk factor to be targeted for cancer prevention. This is because circulating vitamin D levels (levels ≥45 ng/mL) may protect against breast cancer[9] and because breast cancer chemoprevention drugs that alternate the carcinogenesis process such as estrogen receptor modulators, tamoxifen, raloxifene, and aromatase inhibitor have high toxicities and not effective in the aggressive estrogen receptor–negative (ER–) breast cancers.[10]

Many studies examined the association between vitamin D level and breast cancer risk, which generally show an inverse association (Table 1). The meta-analysis conducted by Chen et al[11] revealed that women with the highest quantile of circulating 25(OH)D was associated with a 45% (odds ratio [OR] = 0.55, 95% confidence interval [CI] = 0.38-0.80) decrease in breast cancer risk when compared with those women with the lowest quantile of blood 25(OH)D. Another meta-analysis

**Table 1.** Studies examined the association between vitamin D and breast cancer risk.

| AUTHOR | DESIGN | NUMBER CASE/CONTROL | AIM OF THE STUDY | RESULTS OF THE STUDY |
|---|---|---|---|---|
| Chen et al[11] | Meta-analysis | 11 nested case-control and retrospective and 10 case-control | Association between vitamin D intake, circulating 25(OH)D, and calcium intake in breast cancer risk | The highest quantile of circulating 25(OH)D was found to be associated with a 45% (OR = 0.55, 95% CI = 0.38-0.80) decrease in breast cancer when compared with the lowest quantile |
| Bauer et al[5] | Dose-response meta-analysis | 5206/6450 | Evaluating the association between circulating 25(OH)D and breast cancer risk, stratified by menopause | A step-wise inverse association was observed beyond a threshold of 27 ng/mL, but with flattening of effects above 35 ng/mL, in postmenopausal women |
| Ordóñez-Mena et al[12] | Meta-analysis | | The association of prediagnostic serum 25(OH)D levels with incidence of all cancers | Increased breast cancer risk with higher 25(OH)D concentrations |
| Mohr et al[13] | Pooled analysis | 11 case-controlled studies | Association between 25(OH)D and breast cancer risk | Serum 25(OH)D level of 47 ng/mL was associated with a 50% lower breast cancer risk |
| Stoll et al[14] | Systematic review | 37 studies | Study the relationship between breast cancer and vitamin D, synthesized by skin or brought by food or supplementation | Inverse the relationship between plasma 25(OH)D level, breast cancer risk, and recurrence |
| Shekarriz-Foumani et al[4] | Systematic review | 13 studies | Evaluate the correlation of plasma 25(OH)D deficiency with breast neoplasm risk among women | Vitamin D deficiency has been very prevalent among breast neoplasms, and the risk of breast cancer has increased with low vitamin D levels |
| Bilinski et al[15] | Case-control study | 214/852 | Examine the association between vitamin D status and risk of breast cancer in Australian women | 25(OH)D concentration below 75 nmol/L at diagnosis was associated with a significantly higher risk of breast cancer. Compared with subjects with sufficient 25(OH)D concentration, the odds ratios of breast cancer were 2.3 (95% CI = 1.3-4.3), 2.5 (95% CI = 1.6-3.9) and 2.5 (95% CI = 1.6-3.8) for subjects categorized as severely deficient, deficient, or insufficient vitamin D status, respectively |
| Park et al[16] | Case-control study | 3634/17 133 | Study the association between vitamin D and breast cancer risk among the Asian population. Examined the association between serum 25(OH)D and breast cancer risk stratified by menopausal status and hormone receptor (HR) status of the tumor | Women with vitamin D deficiency had 27% increased the risk for breast cancer compared with women who have sufficient levels of serum 25(OH)D. This association did not significantly vary by menopausal status. HR status has significant inverse association and this association was more pronounced in HR-negative breast cancer, particularly with patients with triple-negative breast cancer |
| Grant[17] | Case-control versus nested case-control studies | 11 studies | Review why case-control studies consistently find inverse correlations between 25(OH)D and breast cancer but not colorectal cancer | 25(OH)D concentration values are only useful for short follow-up times for breast cancer as it develops rapidly |
| Eliassen et al[9] | Nested case-control study | 1506 invasive breast cancer cases | Investigate whether plasma 25(OH)D interacts with breast tumor expression of VDR and its risk of breast cancer in women followed more than 20 y | No overall association was observed between plasma 25(OH)D and breast cancer risk. Women with high plasma 25(OH)D levels in the summer have a reduced breast cancer risk. Plasma 25(OH)D may be inversely associated with risk of tumors expressing high levels of VDR |

**Table 1.** (Continued)

| AUTHOR | DESIGN | NUMBER CASE/CONTROL | AIM OF THE STUDY | RESULTS OF THE STUDY |
|---|---|---|---|---|
| Jamshidinaeini[18] | Case-control | 135/135 | Investigate the relationship between serum concentration and intake of vitamin D and risk of breast cancer | Women in the fourth quartile of serum 25(OH)D level had 3 times lower risk of developing breast cancer compared with those in the first quartile |
| Shaukat et al[19] | Case-control | 42/52 | Determine the association between vitamin D deficiency and breast cancer | Serum vitamin D levels were significantly lower in cases (85.7%) than controls (55.8%). ORs (95% CIs) for breast cancer risk were 7.8 (1.99-30.58) for women with vitamin D concentrations less than 20 ng/mL |
| Bolland et al[20] | Clinical trial | 15 646 | Investigate the effects of the use of personal calcium or vitamin D supplements on the Women's Health Initiative | In 15 646 women (43%) who were not taking personal calcium or vitamin D supplements at randomization, calcium or vitamin D supplements significantly decreased the risk of total, breast, and invasive breast cancers by 14%-20% |
| Neuhouser et al[21] | Clinical trial | Colorectal cancer (310/310) and breast cancer (1080/1080) | Discern whether lifestyle or health-related factors were confounders, effect modifiers, or irrelevant regarding understanding observational associations of serum 25(OH)D with colorectal and breast cancer | In multivariate-adjusted models for colorectal cancer, the association strengthened (OR = 4.45, 95% CI = 1.96-10.10), whereas in multivariate-adjusted breast cancer models, associations were not significant (OR = 1.06, 95% CI = 0.78, 1.43) |
| McDonnell et al[22] | Pooled analysis of randomized trial and prospective cohort study | Lappe cohort (N = 1169), GrassrootsHealth cohort (N = 1135) | Investigate the inverse association between 25(OH)D and cancer risk and identify 25(OH)D response region among women aged 55 years and older | Women with 25(OH)D concentrations ≥40 ng/mL had a 67% lower risk of cancer than women with concentrations <20 ng/mL |
| Grant and Boucher[23] | RCTs | Two vitamin D RCTs | Model is developed for use in designing and analyzing vitamin D RCTs with application to cancer incidence | Improvements to conduct vitamin D RCTs would be to start the trial with a moderate bolus dose to achieve the desired 25(OH)D concentrations and blood spot 25(OH)D assay use in summer and winter annually to monitor seasonal changes in 25(OH)D concentration achievement of desired vitamin D status |
| Lappe et al[24] | Randomized clinical trial | 1156/1147 | Determine whether dietary supplementation with vitamin $D_3$ and calcium reduces the risk of cancer among older women | Healthy postmenopausal women with a mean baseline serum 25(OH)D level of 32.8 ng/mL, supplementation with vitamin $D_3$, and calcium compared with placebo did not result in a significantly lower risk of cancer at 4 y |

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; CI, confidence interval; OR, odds ratio; RCTs, randomized controlled trials; VDR, vitamin D receptor.

of nested case-control studies found a step-wise inverse association beyond a threshold of 27 ng/mL, but with flattening of effects above 35 ng/mL, in postmenopausal women but not in premenopausal.[5] Unexpectedly, the meta-analysis conducted by Ordóñez-Mena et al[12] showed increased breast cancer risk with higher 25(OH)D concentrations. The different finding of this study from the previous other meta-analysis studies may be explained by different settings, different enrolled populations, and differences in the adjusted levels. The study by Ordóñez-Mena et al[12] enrolled cohort data from European population-based cohort studies, whereas the previous studies enrolled

nested case-control studies conducted in the United States with different adjustments for confounders.

The inverse association between vitamin D level and breast cancer risk was also shown in pooled and review studies. Mohr et al[13] reported in their pooled analysis of 11 case-control studies that individuals in the highest quintile versus the lowest quintile of 25(OH)D concentrations had a reduction in breast cancer risk, in which serum 25(OH)D level of 47 ng/mL was associated with a 50% lower risk of breast cancer. Similar inverse association was also reported by Stoll et al[14] in their systematic review of 37 studies. They suggested that elevated

serum 25(OH)D through the sun exposure and dietary intake more than 400 IU per day vitamin D supplementation decreased breast cancer risk and recurrence. Similar findings were also reported by Shekarriz-Foumani et al[4] in their systematic review who reviewed 13 studies and found that serum 25(OH)D deficiency has been very prevalent among breast cancer neoplasms.

For breast cancer–controlled studies, case-control studies consistently find an inverse correlation between 25(OH)D and breast cancer risk.[15,16] Bilinski et al[15] showed that 25(OH)D concentration below 75 nmol/L at diagnosis was associated with a significantly higher risk of breast cancer. Compared with subjects with sufficient 25(OH)D concentration, the ORs of breast cancer were 2.3 (95% CI = 1.3-4.3), 2.5 (95% CI = 1.6-3.9), and 2.5 (95% CI = 1.6-3.8) for subjects categorized as severely deficient, deficient, or insufficient vitamin D status, respectively.[15] Other studies have found similar reduction in the risk for breast cancer. Park et al[16] found that serum 25(OH)D less than 20 ng/mL was associated with 27% increased risk of breast cancer. Similar results have been reported by Colagar et al,[25] Bertrand et al,[26] Reimers et al,[27] and Kim et al.[28] The prevalence of vitamin D deficiency in breast cancer population has ranged from 23% to 95.6%.[4] Jamshidinaeini et al[18] found that women in the fourth quartile of serum 25(OH)D level had 3 times lower risk of developing breast cancer compared with those in the first quartile. Inverse association was only seen in premenopausal women (OR = 0.25; 95% CI = 0.094-0.687). They also found that dietary intake of vitamin D was inversely associated with breast cancer risk (OR fourth quartile versus first quartile = 0.39; 95% CI = 0.196-0.784), and this inverse association remained significant after adjusting for the confounding factors.[18] Similar results were reported by Shaukat et al[19] who studied 42 newly diagnosed breast cancer cases and 52 controls. They found that serum vitamin D levels were significantly lower in cases (85.7%) compared with controls (55.8%). The unadjusted and adjusted ORs for breast cancer in cases and controls showed a statistically significantly increased risk of breast cancer. After adjustment for age, parity, body mass index, sun exposure, economic status, and education status, the OR (95% CI) for breast cancer risk was 7.8 (1.99-30.58) for women with vitamin D concentrations less than 20 ng/mL.[19] To support the robust nature of breast cancer case-control studies, Grant shows that results of 11 studies from 7 countries align in a robust power-law fit to the OR versus mean 25(OH)D concentrations. He showed that 25(OH)D concentration values are only useful for short follow-up times for breast cancer as it develops rapidly.[17]

Although most case-controlled studies, meta-analysis, and pooled reviews found that 25(OH)D concentration was inversely related to breast cancer risk, only a few randomized controlled trials (RCTs) of vitamin D support this finding. Bolland et al[20] in their study of the Women's Health Initiative randomized trial showed that among 15 646 women (43%) who were not taking personal calcium or vitamin D supplements at randomization, coadministered calcium and vitamin D significantly decreased the risk of total breast and invasive breast cancers by 14% to 20%. In contrast, Neuhouser et al[21] in another Women's Health Initiative randomized trial did not find an association between vitamin D and breast cancer risk, in their multivariate-adjusted breast cancer models, and the associations were not significant (OR = 1.06; 95% CI = 0.78-1.43).

McDonnell et al[22] in their pooled analysis of the randomized trial and prospective cohort study (Table 1) support this inverse association between 25(OH)D concentration and risk of breast cancer and highlighted the importance of cancer prevention by achieving 25(OH)D substantially above 20 ng/mL. They reported that women with 25(OH)D concentration more than 20 ng/mL had 67% lower risk of any invasive cancer compared with serum 25(OH)D less than 20 ng/mL.[22] Lappe et al[24] found in a randomized clinical trial among healthy postmenopausal women with a mean baseline serum 25(OH)D level of 32.8 ng/mL, supplementation with vitamin $D_3$, and calcium compared with placebo did not result in a significantly lower risk of cancer at 4 years. The reason for lack of support between 25(OH)D levels and breast cancer risk in most RCTs is the poor design of some RCTs. Most vitamin D RCTs to date have considered the vitamin D dose, rather than initial, final, or changes in serum 25(OH)D concentrations. So a recent study by Grant and Boucher[23] developed a model for use in designing and analyzing vitamin D RCTs with application to cancer incidence. Model input variables are vitamin D dose, baseline and achieved 25(OH)D concentrations, known rates of cancer for the population, and numbers of participants for the treatment. This model may improve vitamin D RCT.

Vitamin D deficiency increased the risk for breast cancer among both pre- and postmenopausal women. Bidgoli et al[29] have studied serum 25(OH)D levels in Iran among newly diagnosed premenopausal women with breast cancer and showed more than 50% of analyzed individuals had very severe or severe vitamin D deficiency. The 25-hydroxyvitamin D deficiency caused 7.5-fold greater risk among postmenopausal breast cancer women compared with control.[28] Likewise, 25(OH)D levels more than 38.0 ng/mL and regular vitamin D supplementation were associated with lower breast cancer among postmenopausal women.[30]

It is very important to conduct vitamin D RCTs, and according to the model by Grant and Boucher,[23] that would start the trial with a moderate bolus dose to achieve the desired 25(OH)D concentrations among both pre- and postmenopausal women, and blood spot 25(OH)D assay use in summer and winter annually to monitor seasonal and long-term changes in 25(OH)D concentration and compliance, and to allow dosage adjustment for achievement of desired vitamin D status. The results of these trials are a key prevention tool for primary prevention of cancer rather than expanding early detection or improving treatment.

Low levels of vitamin D were recorded among patients with breast cancer compared with healthy controls.[31] Moreover, low vitamin D levels were common at breast cancer diagnosis and were associated with a poor prognosis; about 94% women with vitamin D level less than 20 ng/mL develop metastases and 73% die of the advanced disease.[32] The 25(OH)D levels are significantly higher in patients with early-stage breast cancer compared with those with locally advanced or metastatic disease.[33] The relationship between vitamin, breast cancer, and prognostic factors such as tumor stage, grade, size, lymph node involvement, and hormone receptors status is contradictory. The 25-hydroxyvitamin D level had a significant inverse association with metastatic breast cancer.[34] Low vitamin D levels were associated with advanced stages of the disease, tumor size, and grade in postmenopausal patients,[34] as well as in premenopausal women with triple-negative cancer.[35] Insufficient and deficient 25(OH)D levels had a higher proportion of tumors with locally advanced and metastatic disease, more positive lymph node, a lower proportion of ER-positive, progesterone receptor–positive tumors, and higher Ki-67.[36] Normal vitamin D patients had a higher frequency of luminal A (47.7%) and luminal B (32.2%) tumors when compared with patients with vitamin D insufficiency or deficiency.[36] Similar results were reported by a South Korean study, which showed a significant association between low levels of 25(OH)D and poor outcome in breast cancer and triple-negative tumors.[37] By contrast, no relationship between serum vitamin D levels and any of the tumor prognostic features was shown by the study conducted by Imtiaz et al.[38] This inconsistency among different studies may be related to differences in sample sizes and limitations of demographic data related to ethnicity and lifestyle. The menopausal status may be another factor associating with vitamin D status and VDR polymorphism must also be considered. In addition, modifying effects of environmental factors, such as dietary factors, candidate gene variants of other genes of vitamin D pathways, such as vitamin D–binding proteins, and enzymes that involve in the activation and degradation of vitamin D, such as CYP2R1, CYP27A1, CYP27B1, and CYP24A1, must also be considered.

Vitamin D exerts its effects via VDR, which is found in breast epithelial cells. Vitamin D receptor was first identified in a breast cancer cell line in 1979 and later identified in human breast tumor tissues.[39] It has an intracellular hormone receptor that binds to 1,25(OH)2D and interacts with VDR response elements of target genes. Vitamin D regulates the transcription of more than 60 genes that are responsible for antiproliferative, prodifferentiating, antimetastatic, and proapoptotic effects on cells.[8,13] Decreased serum vitamin D levels result in enriched cellular growth, neoangiogenesis, and cancer development, and VDR knockout mice showed higher rates of preneoplastic mammary lesions.[40] A recent study[7] suggests that a potential mechanism underlying the link between vitamin D levels and breast cancer is by regulating autophagy within both normal mammary epithelial cells and luminal breast cancer cells. This may pinpoint the role of vitamin D and its receptor in modulating autophagy and highlight the potential of using vitamin D as a cancer-preventive agent.

The VDR gene lies on the long arm of chromosome 12 (12q12-14), with more than 200 single-nucleotide polymorphisms verified in it.[41] The most common studied allelic variants within VDR were as follows: FokI (T/C) in exon II, BsmI (A/G) and ApaI (C/A) between exon VII and IX, TaqI (T/C) variant in exon IX,[42] and poly(A).[43] Reports show which of these polymorphisms associated with breast cancer are inconsistent (Table 2). Iqbal and Khan[6] in their systematic meta-analysis showed that VDR gene polymorphisms, Bsm1, Apa1, poly(A), Fok1, and Apa1, were associated with the breast cancer, whereas Cdx2, Bgl1, and Taq1 polymorphisms did not show any association. In another meta-analysis conducted by Laczmanski et al[44] for 125 951 persons from 135 populations, Fok1 VDR polymorphism was associated with increased breast cancer risk (OR = 0.96; 95% CI = 0.93-0.99. Another meta-analysis of 8 studies did not show any significant association between Fok1, Bsm1, Taq1, Apa1, VDR polymorphism, and breast cancer risk (Table 2).[45] The VDR polymorphism case-control studies (Table 2) showed different associations between different VDR polymorphisms and breast cancer risk among different populations: ApaI and TaqI confer high breast cancer susceptibility among Egyptian women,[46] Taq1 among Jordanian women,[47] Bsma1 among Pakistani women,[48] and poly(A) microsatellite among Iranian women.[25] BsmI but not Fok1 was associated with the risk of breast cancer among Iranian women.[49] However, Shaikh et al[50] in their mini review compare the impact of VDR gene polymorphisms, Fok1, Bsm1, Taq1, Apa1, and poly(A), on the development of breast cancer and showed inconsistent results, with no conclusive statements about the significance of the VDR genotype on breast carcinoma development (Table 2).

## Conclusions

This review shows that most of the vitamin D studies support the inverse association between vitamin D level and breast cancer risk, and retrospective and prospective epidemiologic studies revealed that vitamin D deficiency is associated with increased breast cancer risk. Nonetheless, there is an urgent need for better designed and randomized clinical trials that will address the association of vitamin D level with breast cancer risk, breast cancer development, recurrence, and survival at different breast cancer stages. These trials can be developed according to the model by Grant and Boucher[23] for designing and analyzing vitamin D RCT with application to cancer incidence. Input variables will be vitamin D dose, baseline and achieved 25(OH)D concentrations, known rates of cancer for the population, and numbers of participants for the treatment. These studies should be applied to different population ethnicities, for pre- and postmenopausal women, with VDR

**Table 2.** Vitamin D studies and polymorphism in breast cancer.

| STUDY (YEAR) | STUDY TYPE | POLYMORPHISM | POPULATION | CASE/CONTROL | OR (95% CI) | RESULTS |
|---|---|---|---|---|---|---|
| Iqbal and Khan (2017)[6] | Systemic review and meta-analysis | Cdx2, Fok1, Bsm1, Apa1, Bgl1, Taq1, and poly(A) | Asian, white, African American, Hispanic, European, Japanese, Hawaiian, Polish, German, French Canadian, Swedish, Turkish | 34 studies (26, 372/32, 883) | Bsm1 bb versus BB; SOR = 1.18, 95% CI = 1.054-1.322 Apa1 aa versus AA; SOR = 1.18, 95% CI = 0.87-1.59 Poly(A) LL versus SS; SOR = 1.41, 95% CI = 1.06-1.88 Fok1 ff + Ff versus FF; SOR = 1.25, 95% CI = 0.896-1.759 Apa1 aa + Aa versus AA; SOR = 1.13, 95% CI = 0.95-1.35 Poly(A) LL + LS versus SS; SOR = 1.19, 95% CI = 1.00-1.43 Poly(A) L versus S; SOR = 1.18, 95% CI = 1.03-1.35) | VDR gene polymorphisms: Bsm1, Apa1, poly(A), Fok1, Apa1 were associated with the breast cancer, whereas Cdx2, Bgl1, and Taq1 do not show any association with breast cancer |
| Laczmanski et al (2017)[44] | A meta-analysis | FokI | | 125951 persons from 135 populations | Fok1 associated with increased breast cancer risk (OR=0.96, 95% CI=0.93-0.99) | F variant reduces the risk of cancer by 4%, irrespective of the location of the cancer |
| Lu et al (2016)[45] | Meta-analysis | Fok1, Bsm1, Taq1, Apa1 | Asian, white, African American, Hispanic Hawaiian | 8 studies | There were no association between Fok1 gene allele contrast f versus F (OR=0.859; 95% CI=0.685-1.079) | The estimated VDR polymorphism showed no significant association between Fok1, Bsm1, Taq1, Apa1 polymorphism, and breast cancer risk |
| El-Shorbagy (2017)[46] | Case-control | Taq1, Apa1, Bsm1 | Egyptian | 100/50 | TC in Taq1 and TG in Apa1 showed an increased risk of breast cancer (OR=3.71, 95% CI=1.04-13.28 and OR=7.05, 95% CI=2.02-24, respectively) | ApaI and TaqI confer high breast cancer susceptibility, in Egyptians women |
| Atoum et al (2017)[47] | Case-control | Taq1 | Jordanians | 122/100 | TaqI TT, Tt, and tt genotype frequencies were 41%, 46%, and 13% for breast cancer compared with 42%, 50%, and 8% for control | Statistical difference was found between different VDR TaqI genotypes and circulating levels of 25(OH)D among Jordanian women with breast cancer |
| Rashid et al (2015)[48] | Hospital-based case-control study | Bsma1 and Fok1 | Pakistan | 463/1012 | b allele of the BsmI was associated with an increased breast cancer risk (OR=1.28, 95% CI=1.09-1.49) | BsmI but not Fok1 polymorphism in the VDR gene was associated with an increased breast cancer risk in Pakistani women negative for BRCA1/2 germline mutations |

**Table 2.** (Continued)

| STUDY (YEAR) | STUDY TYPE | POLYMORPHISM | POPULATION | CASE/CONTROL | OR (95% CI) | RESULTS |
|---|---|---|---|---|---|---|
| Colagar et al (2015)[25] | Case-control | | Iranian | 134/127 | L allele frequency was significantly higher in patients with cancer than in controls (OR = 1.73, CI = 1.16-2.57) | VDR gene polymorphism in the poly(A) microsatellite is associated with 25(OH)D levels and that can affect the breast cancer risk |
| Shahabi et al (2017)[49] | Cohort | FokI, BsmI | Iranian | 203/214 | An association between the bb and Bb genotypes of the BsmI and the increased risk of breast cancer (OR = 1.74, CI = 1.06-2.87 and OR = 2.08, CI = 1.31-3.29, respectively) | BsmI but not Fok1 was associated with the risk of breast cancer in Iranian women |
| Shaikh et al (2016)[50] | Mini review | Fok1, Bsm1, Taq1, Apa1, poly(A) | Asian, white, African American, Hispanic, non-Hispanic, German, Turkish, Spanish, Indian, Australian, Taiwanese, Chinese, Latinas, Mixed, Finnish | 23 studies | — | No conclusive statements could be presented about the significance of the VDR genotype Fok1, Bsm1, Taq1, Apa1, and poly(A) on breast cancer development |

Abbreviations: CI, confidence interval; OR, odds ratio; VDR, vitamin D receptor.

polymorphism screening. The lifestyle, dietary factors, and gene variants of other genes that influence vitamin D pathways, such as vitamin D–binding proteins, and the enzymes that involve in vitamin D activation, such as CYP2R1, CYP27A1, CYP27B1, and CYP24A1, should also be taken into account.

## Author Contributions
MA: collecting data, drafting the article, critical revision of the article.
FA: collecting data, revision of the article.

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