

The Role of Vitamin D and its Receptor in Breast Cancer: A Comprehensive Review of the Connection and Potential Implications

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Article History	Abstract
Received: 06 June 2023 Revised: 05 Sept 2023 Accepted: 01 Nov 2023	<i>Vitamin D and its receptor have attracted significant attention due to their potential roles in various biological processes, including breast cancer. Numerous studies, conducted both in vivo and in vitro, have demonstrated that vitamin D and its analogues exert control over diverse cellular mechanisms in both healthy and breast cancer cells. As a steroid hormone, vitamin D requires binding to the vitamin D receptor (VDR), a specific nuclear receptor. The VDR, in conjunction with RXR, forms a heterodimeric complex that binds to the vitamin D response elements (VDREs) on DNA, thereby regulating the transcription of genes responsive to vitamin D. Remarkably, VDR governs the expression of more than 500 genes. Investigations have revealed that vitamin D and its analogues exert regulatory effects on various hormone receptors in breast cancer, influencing treatment response and augmenting cancer cell sensitivity to therapeutic medications. With VDR being expressed in almost all tissues, the significance of vitamin D in cancer biology has been widely acknowledged. Moreover, breast cancer cells themselves express VDR. The identification of the enzyme system responsible for producing 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃) in breast tissue has shed light on the impact of vitamin D on both normal breast tissue and breast cancer cells. Furthermore, evidence indicates that inadequate exposure to solar radiation increases the risk of developing cancer. Given the escalating incidence of breast cancer and the widespread prevalence of vitamin D deficiency, this review aims to comprehensively explore the intricate connection between vitamin D, its receptor, and the likelihood of breast cancer development.</i>
CC License CC-BY-NC-SA 4.0	Keywords: Vitamin D, Vitamin D receptor (VDR), Breast cancer, Hormone receptors, Cancer prevention

1. Introduction

Outline of Vitamin-D and VDR

Since it is produced in the skin under UV radiation, cholecalciferol, the precursor to vitamin D, must be viewed as a prohormone rather than a vitamin [1]. Dietary consumption is among the additional sources. Cholecalciferol is metabolised by 25 hydroxylases in the liver to a more polar hydroxylated form, which was later identified as the main vitamin circulating in the blood as 25 hydroxyCholeCalciferol [2]. Only in the kidney can 1-Alpha Hydroxylase add a second hydroxyl group to create 1,25 dihydroxycholecalciferol, or Vitamin D, that assists in intestinal calcium absorption [3]. Because of its extremely long half-life and high blood concentration, 25-hydroxyvitamin D is regarded as the stable precursor and marker of 1,25- (OH)₂ vitamin D. The form of vitamin D that circulates in the blood is 25-hydroxyvitamin D. [4]. The acceptable range of 25- OH Vitamin D is between 30- 50 ng/ml. An inadequate level of 25-hydroxyvitamin D is in the range of 20 and 31 ng/mL, and a value of less than 20ng/ml is regarded as a deficit [45]. The Vitamin D₃ receptor (VDR), a nuclear receptor belonging to the super family of Ligand-Inducible Transcriptional Regulators, is the site of action of 1,25-dihydroxy Vitamin D. Retinoid X Receptor (RXR) then forms a complex with the active vitamin D-VDR complex. The whole Complex subsequently exerts its

effects by interacting with VitaminD Response Elements (VDREs) found in the promoters of several genes [4]. VDR participates in the post-transcriptional process driven by micro RNAs [12]. The VDR gene, located on chromosome 12q13.11, encodes VDR [13].

Published Research Establishes a Correlation Between Vitamin D and The Risk of Breast Cancer

The extra renal locations of 1- Alpha hydroxylase were discovered recently. One of the sites is breast tissue, which has the gene CYP27B1 that codes for an alpha hydroxylase and the enzyme CYP24A1 that catalyses the degradation of vitamin D (1,25 (OH)₂ vitamin D). These genes control the amount of vitamin D in breast tissue and are expressed by immune, stromal, and epithelial cells. The key roles of vitamin D in maintaining the homeostasis of Calcium, Phosphorus, and Magnesium, immune, muscular, and nervous system health, development and remodelling of the mammary gland, control of cell growth, regulation of cell cycle, enhancement of apoptosis, and inhibition of angiogenesis, support the conception that 1,25(OH)₂vitamin D performs a major part in the prevention of tumors[5]. Vitamin D may have an anti-cancer impact because of its crucial function in controlling calcium levels both inside and outside of cells, in the prevention of cell proliferation, apoptosis, plus its immunomodulatory actions. Regulation of GlycogenSynthaseKinase-3 (GSK-3) by vitamin D also lowers the accumulation of cancer cells [6,7,8]. The role that Vitamin D plays in stopping carcinogenesis at different levels is explained by Garland's DINOMIT model of carcinogenesis.

According to this study, vitamin D should be added to the regimen of adjuvant therapy for epithelial malignancies [9]. Large-scale studies have looked at how vitamin D levels are negatively related to the risk of breast cancer in a dose -dependent manner [10]. High vitamin D values are substantially linked with improved carcinoma of the breast survival, according to a meta- analysis on status vitamin D and the incidence of breast cancer or death [23]. Low vitamin D concentrations are strongly associated with increased cancer risk. When compared to healthy controls, the amounts of 25-hydroxyvitamin D are much lower in newly identified cancer of the breast patients, and it was also found that aggressive breast cancer variations have lower amounts of vitamin D in their bodies. When compared with the early stages of cancer of the breast, reduced serum quantities of vitamin D are seen in advanced stages. The same research additionally found that Luminal breast cancer patients had larger amounts of vitamin D than those with nonluminal types. Vitamin D levels are higher in breast cancer patients with oestrogen receptor positivity than in those with oestrogen receptor negativity. Serum vitamin D levels are considerably greater in patients with a good NPI (Nottingham Prognostic Index) prognosis than in patients with an average or poor NPI prognosis group [24].

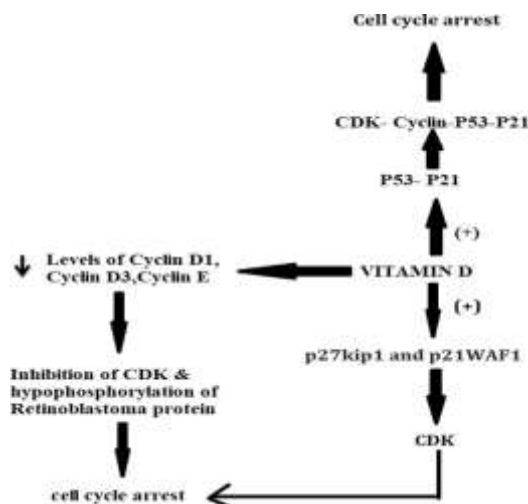


Figure 1: Illustration of the Anti-proliferative action of Vitamin D.

According to a recent study, Luminous cancerous breast cells are affected by vitamin D, but basal-like the breast cancer cells are unaffected in terms of autophagy and antiproliferative activity. The study found that 1,25(OH)₂ vitamin D has an effect upon genes of autophagy in MCF -7 cells and that this modulation is associated with patient survival. With the advancement of breast cancer, vitamin D 1,25 (OH)₂ loses its ability to promote autophagy [25]. According to research on the connection amongst vitamin D status and breast cancer risk in pre- menopausal ladies observed that, women with healthy weights who have reached the brief menopausal stage are more likely to experience breast cancer protection from vitamin D. In addition, Women who consume more above five micrograms per day exhibit protective behaviour [26]. A case- control research conducted at six centers revealed that

consumption of Vitamin D for more than 3.57 micrograms per day has been shown to be protective against carcinoma of the breast and the results were the same across all groups [27]. In both estrogen receptors positive as well as negative breast cancer cells, the 1,25(OH)₂ vitamin D₃ analogue, 22-oxa,1,25(OH)₂ vitamin D₃ demonstrated anti-proliferative and can induce cell differentiation [28].

Proteins Bcl2 and P53, which control apoptosis, are expressed differently with regard to vitamin D and its analogy. They boosted P53 expression while decreasing Bcl2 expression [29]. A population-centered case-control investigation identified a negative correlation between cancer of the breast and 1,25(OH)₂ vitamin D₃ levels. According to the study, early-life nutritional consumption and exposure to sunlight, both lower the possibility of developing breast cancer. In individuals who are at premenopausal stage, there is no conclusive connection between vitamin-D deficiency and breast cancer. This investigation result implies that the need for vitamin D rises during adolescent age, which is also a time of breast development. [30]. Vitamin D concentration in blood is inversely related to circulating tumor cells, which come up with metastatic cascade. Low Vitamin D levels could be an invasive cancer biomarker [31]. MCF10CA1a and MDA-MB cells were treated in an Invitro investigation on the impact of vitamin D in breast-to-bone metastasis, and it was shown that this reduced invasiveness and that the cells lost their ability to survive in the new environment following their invasion of the basement membrane. A crucial point in the metastatic process known as the epithelial mesenchymal transition (EMT) was likewise suppressed by 1,25 (OH)₂ Vitamin D₃. Additionally, vitamin D enhanced E-Cadherin gene expression while decreasing N-Cadherin gene expression, which are EMT indicators [32].

A research investigation found to evaluate the prospective impacts of vitamin D, a group of 512 individuals with initial-stage of breast cancer underwent clinical, pathological, and dietary examination. They found that 24.0% of patients had enough vitamin D (>72 nmol/L), 38.5% had low levels of vitamin D (50-70 nmol/l), and 37.5% turned out to be vitamin D deficient (50 nmol/l). They indicated that women with vitamin D inadequacy experienced distant recurrences following an average follow-up of 11.6 years. From the investigation, it was determined that, a lack of vitamin D may increase a likelihood for developing breast cancer [35]. Population-based research consisting of a cohort of multi-ethnic and multi-centered breast cancer patients observed whether physical exercise, hormones, food habits, and other exposures influence the prognosis and survival rate of cancer of breast and reported that most of the female members of this ethnically diverse population of breast cancer victims had inadequate levels of vitamin D in their serum. This study came to the conclusion that vitamin D insufficiency may be a danger for breast cancer survivors [36].

According to research on vitamin D levels of plasma in early and late stages of breast cancer, individuals with early breast cancer had much higher amounts of the vitamin, whereas those with metastatic breast cancer have dramatically lower levels. Invasive breast cancer in Caucasian women is included in the study. Out of 279 women, 204 had early- stage breast cancer, and the remaining 75 had the illness spread to other organs [37]. a prospective cohort research investigation consisting of 1295 postmenopausal breast cancer patients identified a reverse Correlation among serum 25 (OH) vitamin D and breast cancer death and considerably a higher probability of distant recurrences. Therefore, in postmenopausal individuals with breast cancer, decreased serum Vitamin D levels might be linked to reduced overall survival and diminished chance of cancer-free survival [42]. The prognostic outcomes of vitamin D were measured by a retrospective analysis consisting of 310 cases of breast cancer. Serum Levels of vitamin D have been shown to have a negative correlation with to the prognosis of affected individuals with subtypes of Luminal A and Luminal B. Patients with breast cancer were found to have a higher risk of recurrences than individuals with adequate amounts of vitamin D [43]. An E3N group in France served as the location for a study based on case-control and the research study examined the relationship between blood vitamin D content and the risk of breast cancer. It indicated that the concentration of vitamin D in serum is lower in cases compared to controls; 75% of the women had concentrations of vitamin D below 30 ng/mL, and 37.5 percent reported values under 20 ng/mL. [44]. In a research group of Iraqi women, a retrospective-prospective investigation on the connection between vitamin D and risk of breast cancer have been identified a marginally positive relationship between blood vitamin D and risk. 30 controls and the study comprised 74 cases. [45]. Case-control research at a pair of hospitals in Karachi evaluated the connection between sun exposure, vitamin D supplementation, and serum (25 OH) vitamin D values and breast cancer in 411 incident early-stage breast cancer cases and 784 control subjects. According to this study, patients with blood 25(OH) vitamin D levels more than 30ng/mL had a decreased risk of developing breast cancer than those with levels less than 20ng/mL. The study also found that woman

who supplemented with vitamin D for a period of an year before the registry had substantial breast cancer prevention benefits [48].

Numerous studies reported that Plasma vitamin D levels and breast cancer rates have a negative link. Nevertheless, some research revealed a positive correlation between circulating levels of vitamin D and the risk of cancer of breast. In a long-term investigation of the connection between prenatal vitamin D status and breast cancer risk and pregnancy-related breast cancer, it was discovered that vitamin D elevated the risk of pregnancy-associated breast cancers but not the risk of breast cancer during pregnancy [33]. Another randomized double-blind clinical trial on the impact of supplementation of vitamin D in women who are at an increased risk for developing breast cancer before menopause. In this experiment, Two hundred and thirty eight participants were divided into two arms at random, one of which received a 20,000 IU/week vitamin D intervention and measured the density of the breasts at twelve and twenty-four months. After 12 months and 24 months, blood-based biomarkers such Vitamin D, IGF, and IGFBP-3 were also estimated. The study found no discernible differences between the interventional and placebo groups after twelve and twenty-four months of vitamin D treatment. The levels of IGF and IGFBP-3 did not significantly change after 12 and 24 months of vitamin D administration, either. This study thus contradicted previous research that demonstrated the chance of getting breast cancer was found to be negatively correlated with vitamin D intake [34].

A Case-control research in a large population estimated serum 25(OH) Vitamin D and observed that the median value of 25 (OH) Vitamin D in serum of patients is 44.9nmol and for the controls, it is 51.5 nmol, the observations of the study found a considerably inverse link between risk of breast cancer and blood Vitamin D concentration in postmenopausal women. The investigation also looked at vitamin D as a constant variable in the multivariate model and observed that the risk of breast cancer decreased significantly by 0.88 every 10nM increase in 25 OH. serum vitamin D [46]. The impacts of vitamin D in the breast cancer development in pre and post- menopausal women were examined in a large prospective research with 7760 incident instances of metastatic cancer of the breast, but no significant relation among breast cancer risk and vitamin D was identified [47].

Table 1: Research on the connection between vitamin D and breast cancer is summarised

Author	Aim of the study	Type of Study	Result
Alina Vrieling et al [42]	Vitamin D levels in postmenopausal women with breast cancer and survival rate..	1,295 post-menopausal breast cancer patients make up the cohort of this prospective trial.	Vit.D levels were positively connected with a greater chance for mortality (hazard ratio (HR) = 1.08 / 10 nmol/L decrease; 95% confidence interval and markedly correlated with an increased risk in the reappearance of cancer (HR = 1.14 per 10 nmol/L decrease; CI 95%, 1.05 to 1.24). Patients in the lowest tercile of the 25(OH)D (35 nmol/L) exhibited a hazard ratio of 1.55 for overall survival (95% CI, 1.00 to 2.39) and an Long-term disease-free survival rate of 2.09 (95% CI, 1.29 to 3.41).
HeeJeongKim et al [43]	Relationship between deficiency of D vitamin and outcomes in luminal cancer of breast	A Retrospective research on 310 Korean women. 261 patients had invasive breast cancer, while 36 patients out of 310 had in situ ductal carcinoma.	A deficiency in vitamin D has been identified in 75 patients (<20ng/ml), inadequate in 95 patients (20-29ng/ml), and adequate levels (30-150 ng/ml) in 140 patients. Women with low levels of vitamin D had a greater risk of recurrence compared to those with appropriate levels (P = 0.002).
Shirazi L, Almquist M, et al [44]	The connection between blood vit.D levels and the possibility of	nested case-control investigation was conducted in 636 Cases and	In comparison to controls 25.1 ng/mL (SD, 11.0), cases had lower average vitamin D levels. (24.4 ng/mL (SD, 10.9) ; 75% of women exhibited serum Vit.D values under 30 ng/mL and 37.5 % with serum vit.D levels under 20 ng/mL.

	different subtypes of breast cancer.	1,272 Controls.	
Sascha Abbas et al.[46]	Incidence of post-menopausal cancer of the breast with blood levels of vitamin D	1394 breast cancer samples and 1365 normal samples were used for a large population's case- control research.	A substantially reversed link amongst vitamin D values and the risk of post-menopausal cancer of the breast was found. The higher classes of Vit.D (30-45, 45-60, 60- 75, and 75 nM) had ORs that were, respectively, 0.57 (0.45-0.73), 0.49 (0.38-0.64), 0.43 (0.32-0.57), and 0.31 (0.24-0.42) compared to the lowest category (30 nM) (P trend 0.0001).
D.Minet al.[7]	MiR-302c and miR-520c are downregulated by vitamin D therapy, which makes tumour cells more susceptible to cytotoxicity caused by natural killer cells.	Study of cell lines in	The haematological cancer cell line's sensitivity was boosted by vitamin D treatment. MDA-MB-231 and Kasumi-1 solid tumour cell lines to NK92 cells. After therapy with vitamin D, the activity of miR-302c and miR-520c was increased, the levels of each exhibited a negative correlation with those of the ligands MICA/B and ULBP2 for NKG2D.
Crew KD et al. [8]	Concentration of Vit.D in blood and the possibility of cancer of breast are correlated.	A population-centered case-control research with 1,075 controls and One thousand twenty six incident breast cancer cases. To find the overall pooled odds ratio for the greatest vs. lowest quantile of the vitamin D, information from eleven studies were includes the meta-analysis on the meta-analysis on 30 prospective studies . Among 6092 breast cancer patients, there were 31 867 incidences of breast cancer (n = 24 studies)	The average (SD) blood vitamin D values in the cases and controls, respectively, were 27.1 (13.0) and 29.7 (15.1) ng/mL (P 0.0001). Plasma level of vitamin D was reversely linked to breast cancer risk in a dose- dependent manner (Ptrend = 0.002).
Mohr SB et al.[15]	Cancer of the breast prevention with blood vitamin D: a combined analysis		With a 95% confidence interval of 0.47 to 0.80, the total Peto odds ratio calculated across all 11 studies indicated the highest quantile's risks in comparison to the lowest quantile's to be 0.61. This research lends credence to the idea that elevated serum 25(OH)vit.D Conc. Lowers the risk of cancer of breast. Observational study review revealed a 50% reduction in the incidence of breast cancer with a blood Vit.D concentration of 47ng/ml.
Y Kim and Y Je[23]	Vitamin D intake, serum levels of 25(OH)Vit.D, and the probability of developing or fatality from breast cancer		The pooled relative risks of breast cancer incidence were 0.95 (95% CI: 0.88- 1.01) and 0.92 (95% CI: 0.83-1.02) for the highest vs. lowest intakes of vitamin D and blood 25(OH)D, respectively. Breast cancer and overall mortality rates were significantly lower in patients with high blood 25(OH)D levels (pooled RR=0.61, 95% CI: 0.48- 0.79).

		or 870 fatalities (n = 6 studies).	
Arunkumar Karthikayan et al.[24]	Invasive breast cancer variants are associated with poor prognostic factors in breast carcinoma patients and low serum vitamin D concentrations.	a case-control study with 78 matched healthy controls and 78 cancerous breast patients, with respect to co- morbidities, weight, age, parity, height, and menopausal state.	Cases had considerably lower mean blood vitamin D levels than controls (p = 0.0001). When compared to the opposing groups, patients with higher tumour grades, nonluminal breast cancers, and ER negative breast cancers all had considerably lower vitamin D levels.
–ShuanMeet Leeet al.[26]	Vitamin D's impact on breast cancer risk in subtropical Taiwanese premenopausal women of normal weight.	By the interview date and menopausal status, 200 new cases of breast cancer patients from Taipei Hospital were compared to 200 controls.	Vitamin D consumption and breast cancer risk were shown to be significantly correlated (P = 0.02) in premenopausal women. vitamin D consumption was negatively related with the development of breast cancer in patients with a BMI of less than 24 kg/m(2) (P for trend = 0.002), and a threshold impact was noticed (Q2- Q4 vs. Q1: OR, 0.46; 95% CI, 0.23-0.90).
M Rossi et al [27]	Risk of Cancer of the Breast and D- vitamin Intake: A Case- Control Research in Italy.	The research comprised 2569 breast cancer patients. who had undergone histological confirmation and 2588 hospital controls.	The combined OR was 0.79 (95% CI 0.70-0.90) when the respondents in the three consumption deciles with the greatest consumption levels were compared to those in the lowest deciles. It was discovered that vitamin D intake above 143 IU has a preventative impact for breast cancer. Across strata of menopausal state, the inverse relationship was constant..
JA Knight et al. [30]	Vitamin D and breast cancer: Possibly related	a population- centered case- control investigation with 1,135 controls and 972 cases of women who developed invasive breast cancer incidentally.	In people aged 10 to 19 who engaged in more outdoor activities, their risk of developing breast cancer was lower (e.g., OR, 0.65; 95% CI, 0.50- 0.85; P for trend = 0.0006). use of fish liver oil (OR, 0.76; 95% CI, 0.62-0.92) and increased consumption of milk (OR, 0.62; 95% CI, 0.45- 0.86 for a weekly average of at least 10 glasses compared to none; P for trend = 0.0004) were also associated with a lower risk. Ages 20 to 29 had weaker evidence of correlations, while ages 45 to 54 had none.
Michal Megoet al [31]	circulating tumour cells and vitamin D in early breast cancer	24 healthy donors and 91 patients with non-metastatic breast cancer ,participated in this case–control research.	A combined analysis revealed that CTC-negative The greatest survival rates were seen in those with vitamin D levels above the average level (HR = 0.18, 95% CI 0.05-0.63, p = 0.004). Patients who have vitamin D levels above the normal range survive longer overall. (hazard ratio (HR) = 0.36, 95% CI 0.16- 0.80, p = 0.017).
TomaszWil manskiet al[32]	MCF10CA1a and MDA- MB-231 cells have less	In vitro research on MCF10CA1a and MDA-MB- 231	Using the rMET model, breast-to-bone metastases of MCF10CA1a and MDA- MB-231 cells was reduced by 10% and was prevented by 70% and

	ability to proliferate in the presence of vit.D.	epithelial cells of breast tissue.	21%, respectively, by vitamin D treatment of the cells.
Calypse B AgborSanga yaet al[33]	Prospective study on vitamin D levels in the blood during pregnancy and the risk of cancer of breast	A case-control research. 100 case samples and 100 matched controls. Additionally investigated was the Pregnancy-related cancer of the breast risk (PABC; 111 cases & controls). Double-blind, randomised, placebo-controlled trial 208 women were included, 103 of whom received the intervention. The baseline 25(OH)D for 33% of the population was 20 ng/mL, and 78% had an elevated baseline mammographic density. The median age was 44.6 years.	In the first and second pregnancy samples, No connection could be made between the serum 25- OHD level and the risk of breast cancer (OR=1.4, 95%CI 0.6-3.4; OR=1.4, 95%CI 0.7-2.8, respectively), but it was linked to a higher chance of PABC (OR=2.7, 95%CI 1.04-6.7).
Katherine D Crew et al[34]	Research on the Supplementati on of vit.D in Premenopausa l Women who are at a Higher Risk for Cancer of Breast .		Mammographic density changes were negligibly different and minor. At 12 months and 24 months following vitamin D administration (20,000 IU/week), there was no appreciable drop in blood IGF-1 and IGFBP-3 levels.
Pamela J.Goodwin et al.[35]	Results of serum vitamin D levels in predicting prognosis during the early breast cancer	a prospective analysis of 512 women with the initial stages of cancer of the breast.	When compared to women with acceptable ranges of vit.D, the women with inadequate amounts were at a greater risk of mortality and distant recurrence (hazard ratio [HR] = 1.94; 95% CI, 1.16 to 3.25) respectively. Poor results for breast cancer may be linked to vitamin D deficiency.
Angel Arnaout et al[49]	Evaluation of the impact of large doses of vitamin D3 on the growth and apoptosis of breast tumours.	83 incident breast cancer patients participated in a randomised, phase 2, double-blinded experiment; the average drug intake period was 19 days..	On tumour growth or apoptosis, there were no appreciable differences between the control and vitamin D arms.

Patterns of VDR expression in breast cancer cells

The mammary gland's ductal and lobular epithelial cells express VDR. During adolescence, pregnancy, and breastfeeding, VDR and its hormone are crucial for the development of breast tissue[16]. In a study, the expression of VDR was seen in lesions that were benign, carcinoma of the ducts in situ, and advanced ductal carcinoma in addition to normal breast tissue. This study found that VDR expression is 100% in normal glands, 93.5% in benign lesions, in carcinoma in situ it is 47.3% and it is 56.2% in invasive lesions, with a statistically significant difference between normal, benign, in situ carcinoma, and invasive carcinomas[17]. Recent research on the expression of VDR in the nucleus, nuclear membrane, cytoplasm, and cell membrane of cancer cells revealed a statistically significant correlation between VDR negative and a number of tumour features linked to a poor prognosis. Additionally, it was noted that mastectomies were performed on VDR-negative cancers more frequently than VDR-positive cancers. A highly significant connection was identified between nuclear VDR positivity and a reduced risk of breast cancer death in breast cancers with luminal B-like molecular subtype, according to the expression of VDR about breast cancer mortality stratified by molecular subtypes [18]. Numerous tissue and cell types have shown to contain VDR, and well-differentiated cells showed the highest levels of VDR-mRNA expression. All cell lines have a sizable amount of VDR-mRNA. The significance of VDR expression for anti-proliferative activity was demonstrated by the considerable growth inhibition of MCF-7 and T47 D cells with intermediate VDR levels compared to MDA-MB-231 cells with low levels of VDR [14].

The role of VDR in adipose tissue

In an animal study, VDR- flox mice and fabp4 cre mice were crossed to produce CVF mice with adipose-specific VDR deletion. These mice showed high growth rates, increased visceral fat mass, and a substantial rise in epithelial density and the growth of the mammary gland, all of which support the antiproliferative effect of VDR on the mammary epithelium [19].

Risk of breast cancer and VDR expression

The connection between VDR expression and the survival rates of breast cancer patients was examined in a cohort study on breast cancer patients. Based on the Immuno Reactivity Score (IRS), progression-free survival, the overall survival rate, and expression of VDR in each of the three groups, the results were dichotomized into three groups. Patients with high IRS showed significantly greater progression-free survival and overall survival as contrasted with those with positive IRS for expression of VDR. [20]. By using RT-PCR, Michael Friedrich et al. examined the RNA-level VDR expression in breast cancer and discovered statistically significant protein-level VDR. When compared to normal breast tissue, carcinoma of the breast patients has higher protein levels of VDR expression. However, there is no distinction at the mRNA level between soft tissue in the breast and cancer of the breast in the face of VDR [21]. Silencing vitamin D receptors is linked to greater levels of autophagy, according to a new MCF-7 cell study.

After the addition of 1,25(OH)₂ vitamin D, this effect remained unchanged [25]. In three separate tissues—normal breast tissue, cancerous breast tissue, and healthy tissue next to cancer tissue—Kathryn Mc Carthy et al. quantified the expression of VDR mRNA. They noticed that breast cancer tissue has a stronger increase of VDR mRNA than the breast tissue that is normal and healthy tissue next to cancerous tumour. These values' biological significance is still being researched [22]. In order to determine the function of VDR in the origin of carcinoma of the breast, a population- centered case-control investigation on a sizable group consisting of 1631 cases was conducted. The study was conducted in Caucasian and African-American survivors of breast cancer among the age cohort between 35 and 64 and investigated the connection between VDR gene variation and the probability of getting breast cancer. According to the study, postmenopausal Caucasian carriers of the Bsml bb genotype had a much greater chance of developing breast cancer. The bb genotype of Bsml did not appear to be associated in any way that was meaningful with African American women. The poly(A)genotype and breast cancer risk were also found to have no discernible association in neither the Caucasian nor the African American populations. In the study, different reactions were discovered [38].

VDR was discovered to be expressed in breast cancer in a sizable population-centered cohort study involving 1114 female patients. ImmunoReactiveScore was used to categorise VDR expression into two categories: moderate and strong expressions. The study found that, rather than affecting breast cancer survival rates, the expression of VDR was inversely connected with the features of invasive breast cancer. Additionally, The research discovered that in patients older than 50, an expression of Ki67 was inversely associated to the expression of VDR [39]. According to a survey of a small number of cancers of the breast patients, The occurrence of vitamin D receptors was not correlated

with other prognostic factors including oestrogen receptors, tumour T-stage, etc. Additionally, the VDR Status hasn't shown any portable changes in survival or invasion-free survival rates [41].

Table 1: Investigations of the relationship between VDR and breast cancer

Author	Aim of the study	Type of Study	Results
Nair Lopes et al[17]	changes in pathways of metabolism and vit.D signalling in the development of cancer of breast	172 out of 306 cases of invasive tumours were studied in a cohort. Out of 131 instances of in situ tumours, 62 (47.3%) had VDR staining.	VDR was expressed often (93.5%) in benign lesions while it was expressed less frequently (56.2%) in invasive tumours. Additionally, there was a direct correlation between VDR expression and oestrogen receptor positive in breast tumours
Linnea Huss et al [18]	Breast cancer patient survival is correlated with the presence of vitamin D receptors in invasive breast tumours.	Over 700 primary, invasive breast tumours from the Malmö Diet and Cancer analysis underwent immunohistochemistry staining for VDR as part of a prospective cohort analysis.	Numerous tumour characteristics linked to poor prognosis were shown to be statistically considerably correlated with VDR negative, including big tumour size ($p = 0.002$) and higher Nottingham grade ($p 0.001$).
Mathew DG et al.[19]	Adipose-specific VDR deletion modifies body fat and boosts mammary epithelial density.	An animal study (mice models).	- Increased body weight as a consequence to a fatty diet was caused by adipose-specific the VDR gene deletion. - The abdominal fat from mice lacking the adipose-specific VDR gene showed higher Ucp1 expression. - Adipose-specific Vdr deletion increased the ductal proliferation of the breast tissue.
Nina Ditsch et al.[19]	The Relationship Between Overall Survival rate in breast Cancer and VDR Expression	A cohort study on 82 breast cancer patients	VDR demonstrated a negative correlation with both involvement of lymph nodes and size of tumour (Spearman ρ [SR] = 0.411, $p0.01$). According to the findings of this study's bivariate correlation analysis, the expression of VDR is negatively related to tumour size and involvement of lymph nodes. Additionally, in univariate analysis, VDR expression was a variable having prognostic significance. Individuals with elevated VDR-IRS had an improved prognosis compared to individuals with a low IRS.
Kathryn MC Carthy et al[22]	manifestation of VDR mRNA and the Expression 25-OHvitamin D-1-hydroxylase in	Case-control research Following benign breast surgery, 18 samples of normal breast tissue from healthy individuals	The median VDR mRNA expression in T samples (3.3 106; $p=0.002$) were substantially higher than those in AN (1.65 106; $p=0.002$) and NN samples.

healthy breast tissue and breast cancer (NN) and 30 samples of adjacent normal breast tissue (AN) and tumour (T) were studied.

4. Conclusion

According to numerous studies, vitamin D and its analogues had cancer-preventing impacts on cancer cell growth, death, and inflammation. Breast cancer progression is influenced by vitamin D in terms of metastasis, epithelial-mesenchymal transformation, and cancer recurrence. All of these investigations, both in vivo and in vitro, illustrate the significance of vit.D and the development of vitamin D receptors that Vitamin D intake and risk of breast cancer have an antagonistic relationship. But, other randomised clinical trials do not find proof for the protective role of vit.D in reducing the risk and progression of Breast cancer. In order to confirm the extent to which Vitamin D or its analogues work and the current cancer therapies to treat various forms of Breast cancer, substantial research is required.

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Conflict of interest

The Authors declare that they have no potential conflicts of interest concerning the Authorship and publication of the article.

Authors' contribution

Kuppusamy Baskaran, the corresponding author, assigned the duties to each author, gave his suggestions, and assisted in collecting the data. Vemuri Helena collected the data from the published literature and edited the final version of the manuscript. Arumugam Suresh and Natarajan Muninathan suggested collecting the data and drafting the manuscript.

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