

REVIEW

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Multifaceted Role of Vitamin D in Breast Cancer: A Systematic Review of Genetic and Pathway-Based Mechanisms

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Abstract

Background: Despite advancements in breast cancer (BC) diagnosis and treatment, it continues to be a serious health concern among women due to its high incidence rate. Thus, prevention strategies in BC are essential. Some nutrients such as vitamin D may play a preventive role against BC through different genes which have a vital role in several pathways. These pathways include autophagy, tumorigenesis, apoptosis, immunity, and genome stability. This study aimed to review the role of vitamin D in BC via the network of vitamin D-regulated pathways. **Methods:** This systematic review was conducted following PRISMA guidelines. PubMed, ScienceDirect, and Scopus were searched using a combination of MeSH terms and keywords related to molecular and cellular mechanisms of the effects of vitamin D on breast cancer. A total of 200 articles were initially found, from which 14 relevant studies were selected based on specific inclusion and exclusion criteria. **Results:** Experimental studies have shown possible anti-carcinogenic effects of vitamin D-related genes due to their participation in regulating autophagy, tumorigenesis, apoptosis, immunity, and genome stability in normal and malignant breast cells. Moreover, vitamin D deficiency has the potential to create a supportive environment that promotes proangiogenic processes, tumor cell dissemination, metastasis, and establishment at secondary sites. **Conclusion:** Vitamin D may have systematic roles against BC in humans through various interactions with different genes, which have roles in different and important pathways as underlying mechanisms in the pathophysiology of BC. More broadly, research is also needed to determine the exact protective effect of vitamin D on BC risk.

Keywords: Breast cancer- Vitamin D- pathways- genomics

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Introduction

Cancer is considered as the primary cause of mortality in human. It is known as an essential barrier to increasing life expectancy in all countries. Globally, there are

expected to be 19.3 million new cases of cancer and around 10 million cancer-related deaths in 2020 [1]. Among cancer, breast cancer (BC) is one of the commonest morbidity and mortality cause in women worldwide. BC recently overtook lung cancer as the most commonly

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diagnosed form of cancer, with about 2.3 million new cases in 2020 and it is expected that there would be over 3.2 million new cases year by 2050 [2, 3]. Despite significant recent advancements in early detection and treatment, the incidence rate of BC has been rising in some countries over the past few years [4]. Thus, it appears to be extremely important to develop primary prevention approaches that effectively lower incidence rates of BC. Recently, vitamins such as vitamin D is considered, which might potentially benefit in the prevention of BC via its anticancer properties [5, 6].

The hormone calcitriol or 1,25-dihydroxyvitamin D₃ is derived from vitamin D and affects several functions in human various tissues [7]. In addition to being partially gained from food and supplements, vitamin D can be generated endogenously in the skin by exposure to sunlight. Serum 25-hydroxyvitamin D (25[OH]D) levels < 25 ng/ml are considered to be insufficient levels of vitamin D. Vitamin D insufficiency has been reported as a high prevalence state in many regions. Globally, one billion people are expected to be vitamin D deficient [8]. The well-known functions of vitamin D include regulating bone mineralization and preserving calcium homeostasis [9, 10]. In addition to its benefits for bone health, new studies have looked into its impact in the prevention and treatment of a number of ailments, including cardiovascular disease, autoimmune disorders, as well as cancer [11-13]. According to research in the lab, vitamin D may have strong anti-cancer properties, including anti-inflammatory, anti-invasion, pro-apoptotic, pro-differentiating, and anti-proliferative actions [14-19]. Observational epidemiology researches have demonstrated the associations between decreased risk of BC and increased vitamin D levels, including vitamin D consumption and serum 25(OH) D [20-23]. A recently published meta-analysis of 22 observational studies revealed a strong correlation between a lower risk of BC and higher vitamin D intake [24]. There have been published randomized controlled trials (RCTs) examining the impact of vitamin D on BC; however, the outcomes of these trials did not align with observational studies. A meta-analysis comprising seven RCTs in 2014 found that, while not statistically significant, vitamin D supplementation may be protective against BC [risk ratio (RR) = 0.97, 95% confidence interval (CI): 0.86 to 1.09] [25].

Mechanistically, 1 α ,25(OH)₂D₃ interacts with its receptor named nuclear vitamin D receptor (VDR), then this 1,25(OH)₂D/VDR complex may bind to vitamin D response elements (VDREs) in the promoter region of numerous genes to activate or inhibit transcription. In this way it exerts profound effects on mammary gland physiology and can have a role either in the prevention or onset and development of BC. Numerous 1 α ,25(OH)₂D₃ responsive targets in normal mammary cells and breast malignancies have been identified using genomic profiling. This offering new insights into the molecular mechanisms underlying the regulation of cell cycle, apoptosis, and differentiation by 1 α ,25(OH)₂D₃ and the VDR [26]. In other words, vitamin D via its receptor can influence expression of thousands downstream target genes. Subsequently, each of these genes can play a role

in various pathways. These pathways either can be related to the onset and development of BC or prevention of BC in case of vitamin D deficient and sufficient, respectively [27]. For instance, high expression of KLK6 through vitamin D/VDR in breast cancers has been shown in observational studies to improve survival [28]. Thus, for women with BC, the level of vitamin D may be clinically significant due to its receptor, VDR, which is expressed on the BC cells. Understanding these pathways and interactions can be useful in prevention and treatment of BC. Hence, this study aimed to review the networks of genes and pathways regulated by vitamin D/VDR in the context of BC.

Materials and Methods

For the reporting screening and selection review step, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) suggestion was followed [29] (Figure 1).

Literature search

We conducted a comprehensive literature search using PubMed, ScienceDirect, and Scopus databases. The following MeSH terms and keywords were utilized in various combinations to ensure a thorough search: “Vitamin D”, “cholecalciferol”, “25-Hydroxyvitamin D”, “1,25-Dihydroxyvitamin D₃”, “breast cancer”, “breast neoplasms”, “genomics”, “proteomics”, “metabolomics”, “pathway analysis”, “gene expression”, and “Vitamin D receptor”. Boolean operators (AND, OR) were used to refine the search strategy.

The initial search strategy was as follows: (((“Vitamin D”[MeSH Terms]) OR “cholecalciferol”[All Fields] OR “25-Hydroxyvitamin D”[All Fields] OR “1,25-Dihydroxyvitamin D₃”[All Fields]) AND (“breast neoplasms”[MeSH Terms] OR “breast cancer”[All Fields])) AND (“genomics”[All Fields] OR “proteomics”[All Fields] OR “metabolomics”[All Fields] OR “pathway analysis”[All Fields] OR “gene expression”[All Fields]).

Inclusion and Exclusion Criteria

Papers that satisfied any of the following parameters were considered eligible for this paper:

1. Empirical research studies published in peer-reviewed journals.
2. Studies using different methodologies to investigate the role of vitamin D in breast cancer, including observational studies, experimental lab studies, and epidemiological research.
3. Studies published within the last decade (2013-2023) to ensure the relevance and recency of the data.
4. Studies examining the effects of vitamin D on both normal and malignant breast cells.
5. Studies that evaluate the anti-carcinogenic effects of vitamin D, including its impact on autophagy, tumorigenesis, apoptosis, immunity, and genome stability.
6. Studies assessing the correlation between vitamin D levels (including serum 25-hydroxyvitamin D levels) and breast cancer risk or outcomes.
7. Studies that investigate the mechanistic pathways

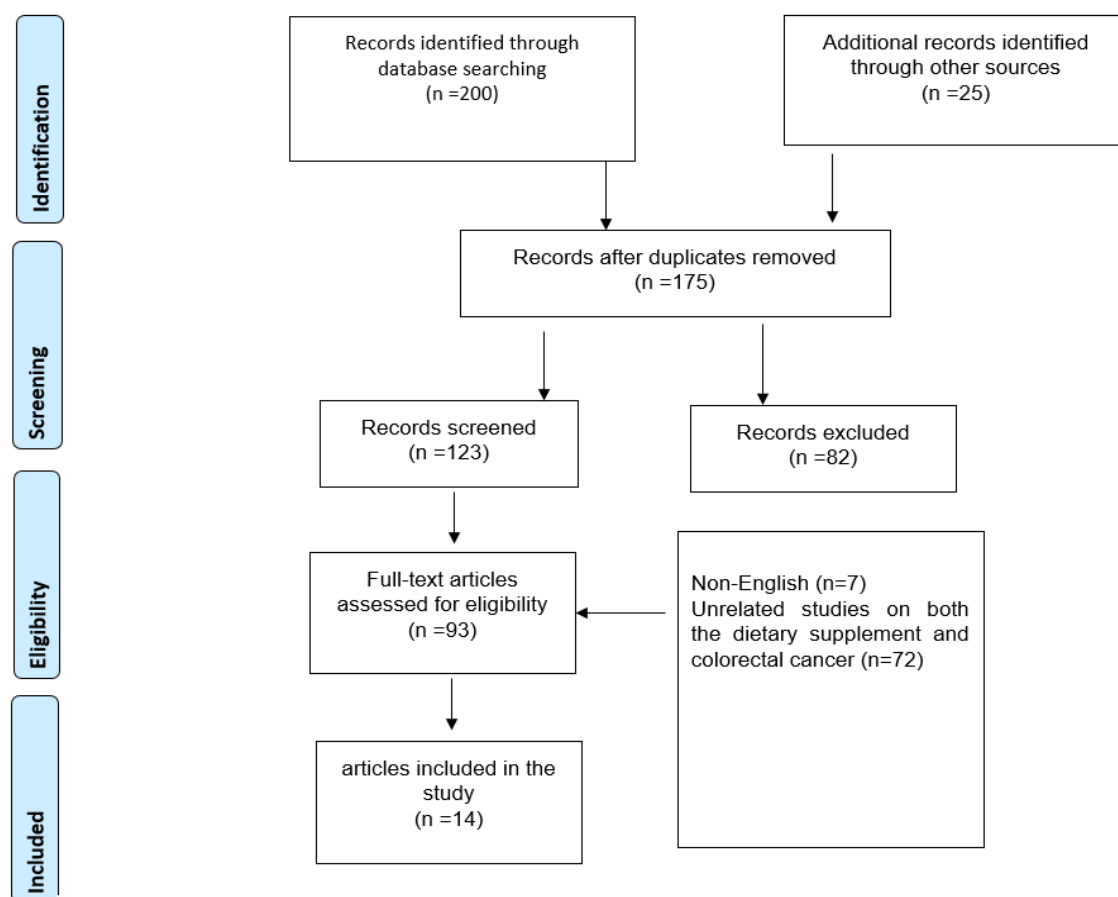


Figure 1. Flow Chart of the Included Studies, Including Identification, Screening, Eligibility and the Final Sample Included.

through which vitamin D influences breast cancer cell biology.

Papers were excluded if they met one of the following criteria

Non-peer-reviewed articles, opinion pieces, editorials, and review articles., studies not written in English, unpublished studies, conference abstracts, and thesis documents due to potential issues with peer review and completeness of data, studies that do not directly measure the effects of vitamin D on breast cancer outcomes, studies focusing solely on the basic metabolism of vitamin D without a direct link to cancer outcomes.

Data extraction

Data were systematically extracted from the selected studies by two independent reviewers using a standardized data extraction form to ensure consistency and reduce bias. The form captured relevant information including the first author's name, focus of study, model/method, key findings, implications and notes, aspect related to breast cancer pathophysiology (Table 1). Any discrepancies between the reviewers were resolved through discussion or by consulting a third reviewer if consensus was not achieved. This methodical approach to data extraction aimed to maximize the reliability and validity of the review findings.

Results

Vitamin D/VDR Metabolism and anticancer effects

Vitamin D₃ production initiated around 1.2 billion years ago, when organisms producing cholesterol started to evolve, [30]. On the other hand, vitamin D receptor (VDR) evolved alongside other related members of the nuclear receptor superfamily, farnesoid X receptor (FXR), liver X receptor (LXR) α and β , constitutive androstane receptor (CAR), pregnane X receptor (PXR), and retinoid X receptor (RXR) [31]. In addition, VDR evolved as an endocrine nuclear receptor due to the specialization of its ligand-binding domain for 1,25(OH)₂D₃, approximately 550 million years ago [32, 33]. Furthermore, following its binding to the VDR, 1,25(OH)₂D₃ initiates to function. The VDR then heterodimerizes with RXR, which both are belong to the same superfamily as nuclear receptors [34]. Following VDR-RXR interaction, this complex will go to the nucleus where it will attach to vitamin D response elements (VDREs) in target genes' regulatory regions. This process impacts gene transcription by engaging co-activators and releasing co-repressors [35-37]. VDR is expressed in a wide variety of tissues such as kidney, bone, and intestinal tissue as well as malignant ones [38, 39]. In 1979, the identification of VDR in human cultured breast cancer cells lead to a great interest in a possible link between the vitamin D endocrine system and breast carcinogenesis [40]. In course of further evolution, in patients with benign neoplasms breast cancer, 1,25D

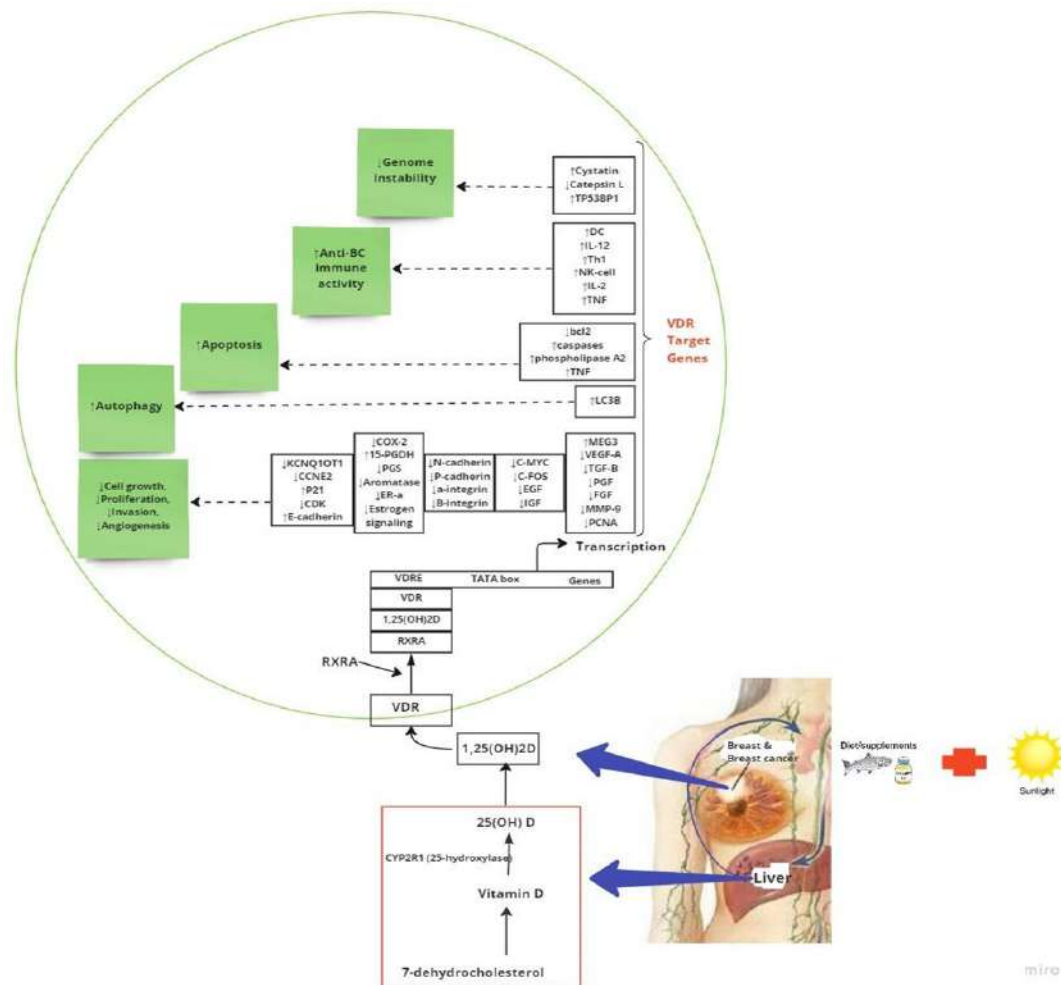


Figure 2. Overall Anti-Cancer Effect of Vitamin D through Pathways Involved in the Regulation of Genome Stability, Immunity, Apoptosis, Autophagy, Proliferation, Cell Growth, Invasion, and Angiogenesis in Breast Cancer.

binding sites were found in their lymph node and breast tissue [41]. Subsequently, expression of VDR mRNA and protein in human breast cancers was validated by cloning the hVDR cDNA and producing anti-VDR monoclonal antibodies [42].

Vitamin D metabolic enzyme CYP27B1 (Cytochrome P450 family 27 subfamily B member 1), a 1 α -hydroxylase and a member of the cytochrome P450 (CYP) superfamily of enzymes with monooxygenase activity, is responsible for converting 25-OHD into the active VDR ligand, 1 α , 25-dihydroxyvitamin D (1,25-D-OHD). The gene that codes for this enzyme is found at locus 12q14.1, which is on the same arm of the human chromosome as VDR. Also, it is located intracellularly in the inner membrane of the mitochondria. CYP27B1 is expressed in normal breast epithelial cells as well as breast cancer cell lines and makes them susceptible to produce VDR ligand [43-46]. Since normal human breast epithelial cells contain both VDR and CYP27B1, they are sensitive to growth inhibition through physiological concentrations of 25 hydroxyvitamin D (25D) [43, 47]. Moreover, cancerous breast cells during in vitro transformation showed the down-regulation of VDR and CYP27B1, which leads to reduction in sensitivity to 25D and 1,25D compared with normal breast epithelial cells [14]. Another

vitamin D metabolic enzyme is CYP24A1 (Cytochrome P450 family 24 subfamily A member 1). This enzyme catabolizes the active ligand 1,25-D-OHD to create the inactive metabolites 1,24,25-trihydroxyvitamin D and 24,25-dihydroxyvitamin D [48]. CYP24A1 similar to CYP27B1 has been detected in normal breast epithelial cells and in breast cancer cell lines. However, cancerous breast cells with up-regulation of CYP24A1 would be less sensitive to 1,25D [48]. Thus, the existence of vitamin D metabolic enzymes adds another layer of complexity to the way vitamin D acts in cancer cells.

According to data from the majority of observational and epidemiological research, serum vitamin D levels and the risk of BC are inversely correlated [49]. In addition, patients with BC have been found to have a high frequency of hypovitaminosis D [50]. A systematic review demonstrated that serum vitamin D can have a preventive impact on BC in premenopausal women [51]. Recently, meta-analysis of observational studies revealed a direct link between low levels of circulating vitamin D and BC [24]. These findings suggested that the availability of 1,25D may have an impact on breast cancer cells' biology. Moreover, it was determined that 1,25D and a range of synthetic VDR agonists exhibited anticancer properties, via regulating apoptosis [52], differentiation [53], and

Table 1. The Overall Anti-Cancer Effects of Vitamin D on Breast Cancer: Studies Summary

First Author	Study Focus	Model/Method	Key Findings	Implications and Notes	Aspect
Luz E. Tavera-Mendoza (Tavera-Mendoza et al., 2017)	Vitamin D Receptor (VDR) Autophagy and breast cancer	MCF-7 human-like BC-cell models and Mouse models	Vitamin D activates VDR leading to increased autophagy and dietary vitamin D increases autophagy in normal mammary glands	Indicates a preventative role of vitamin D against breast cancer, highlighting its pro-autophagy effects.	pro-Autophagy
Maria Hoyer-Hansen (Hoyer-Hansen et al., 2007)	Investigating the role of calcium in presence of vitamin D in autophagosome formation	MCF-7 cells autophagy assays electron microscopy	Calcium increase triggers autophagosome formation; CaMKK- β and AMPK mediate this process. Bcl-2 in the ER inhibits this process.	Calcium is a crucial regulator of autophagy, activated by vitamin D, underlining its pro-autophagy effects.	pro-Autophagy
Louise Flanagan (Flanagan et al., 2003)	Examining effects of Vitamin D compounds on ER-negative breast cancer	SUM-159PT cell line in vitro assays, mouse xenograft models	Vitamin D compounds particularly EB1089 inhibited growth and invasion, induced apoptosis in SUM-159PT cells and reduced xenograft tumor size.	Vitamin D3 compounds are effective against ER-negative breast cancer, showing potential as a therapeutic agent with anti-tumorigenesis properties.	anti-Tumorigenesis
Natalin Pendas-Franco (Pendas-Franco et al., 2007)	Effect of Vitamin D on breast cancer cells	Human breast cancer cell lines (e.g., MDA-MB-453), microscopy, Western blotting, RT-PCR, flow cytometry, and assays	1,25-dihydroxyvitamin D3 induces significant changes in cell size, morphology, and cytoarchitecture; enhances cell-to-cell adhesion, reduces adhesion to laminin, downregulates myoepithelial markers like N-cadherin and SMA.	Suggests that Vitamin D could be used to manage breast cancer aggressiveness, possibly impacting treatment approaches with anti-tumorigenesis effects.	anti-Tumorigenesis
JoEllen Welsh (Welsh et al., 2002)	Role of the Vitamin D3 receptor (VDR) in controlling growth through its influence on proliferation and apoptosis in mammary glands and breast cancer cells.	Animal Model: VDR knockout (KO) mice, Cell Culture: Breast cancer cell lines and primary cultures from WT and VDR KO mice, Biochemical Assays	VDR KO mice show abnormal mammary gland development with increased growth and delayed involution. VDR is essential for apoptosis induction by 1,25-dihydroxyvitamin D3. Up-regulation of VDR enhances sensitivity to 1,25-dihydroxyvitamin D3, offering a therapeutic avenue.	Emphasizes the critical role of VDR in mammary gland development and its potential as a therapeutic target in breast cancer treatment. Supports the potential of VDR-targeted interventions to manage or treat breast cancer with anti-tumorigenesis effects.	anti-Tumorigenesis
Carmen J. Narvaez (Narvaez et al., 2001)	Roles of 1 α ,25-dihydroxyvitamin D3 and the vitamin D3 receptor (VDR) in growth regulation of mammary epithelial cells.	In Vitro Cell Studies: Breast cancer cell lines like MCF-7, Animal Models: Use of VDR null mice	1 α ,25-dihydroxyvitamin D3 induces cell cycle arrest and apoptosis in breast cancer cells, promotes differentiation in normal mammary epithelial cells, and shows crucial role in mammary gland development.	Indicates that 1 α ,25-dihydroxyvitamin D3 and VDR are integral in controlling mammary cell growth, apoptosis, and differentiation. This has implications for the therapeutic use of Vitamin D3 analogs in breast cancer treatment, potentially leading to preventive strategies against breast cancer development with anti-tumorigenesis effects	anti-Tumorigenesis
K W Colston (Colston, 2002)	Regulation of growth and apoptosis in breast cancer cells by vitamin D and its analogs.	Cell culture using MCF-7, gene expression studies, and molecular biology techniques.	Vitamin D analogs inhibit cell proliferation and enhance apoptosis, affecting ER and other growth factors.	Vitamin D analogs are potential therapeutic agents in breast cancer, with reduced hypercalcemic effects and potential for combination treatments.	Anti-Tumorigenesis
Puneet Dhawan (Dhawan et al., 2009)	Role of 1,25-dihydroxyvitamin D3 in modulating C/EBP β and VDR in breast cancer cells.	Cell culture, protein and gene expression studies on MCF-7 and MDA-MB-231 cells	1,25(OH)2D3 enhances C/EBP β and VDR expression, inhibiting cell proliferation.	C/EBP β and VDR modulation by 1,25(OH)2D3 can be therapeutic targets in breast cancer treatment.	Anti-Tumorigenesis
G. Prianov (Prianov and Colston, 2001)	Interaction of vitamin D analog CB1093 with apoptosis mediators in breast cancer cells.	Cell viability, DNA fragmentation, and cPLA2 activation assays on breast cancer cells	CB1093 enhances TNF α and ceramide-induced cPLA2 activation, reducing cell viability.	Suggests vitamin D analogues can potentiate apoptosis in breast cancer cells through cPLA2 pathway modulation.	Pro-Apoptosis
Dafina Rucker (Rucker et al., 1994)	Effect of 1,25-dihydroxyvitamin D3 on enhancing TNF-induced cytotoxic effects in breast cancer cells.	Cell viability assays in MCF-7 cells and endothelial cells	1,25(OH)2D3 enhances TNF's cytotoxic effect specifically in breast cancer cells, not endothelial cells.	Indicates potential of 1,25(OH)2D3 to increase TNF effectiveness in cancer therapy while minimizing systemic toxicity.	Pro-Apoptosis
Sharon Y. James (James et al., 1996)	Impact of Vitamin D3 and its analogues on apoptosis induction in breast cancer cells.	Cell lines studies with apoptosis assays on MCF-7 cells	Vitamin D3 and EB1089 induce apoptosis, reducing Bcl-2 and increasing p53 and p21 levels.	Supports use of Vitamin D3 and its analogues as therapeutic agents in breast cancer treatment by modulating apoptotic pathways.	Pro-Apoptosis
Wei Zheng (Zheng et al., 2019)	Effects of 1,25-dihydroxy vitamin D3 on breast cancer cell lines through Ras/MEK/ERK pathway modulation.	Cell proliferation, migration, invasion, and apoptosis assays on ER-positive and negative breast cells.	Inhibits cell proliferation, migration, and invasion, especially in ER-negative cells, via the Ras/MEK/ERK pathway.	1,25-(OH)2D3 shows promise as a therapeutic agent for ER-negative and drug-resistant breast cancers by targeting specific molecular pathways.	Pro-Apoptosis
Esma Karkeni (Karkeni et al., 2019)	Effects of vitamin D on breast cancer progression and immune response under different dietary conditions.	Animal models with dietary variations to study tumor growth and immune cell infiltration.	Vitamin D modulates tumor growth and immune response, affected by dietary conditions.	Highlights importance of dietary conditions in vitamin D supplementation for breast cancer treatment, affecting immune modulation and tumor microenvironment.	Immune-modulation
Susana Gonzalo (Gonzalo, 2014)	Role of 1 α ,25-dihydroxyvitamin D3 in DNA repair in TNBC and BRC-A1-deficient breast cancer cells.	Studies on BRC-A1-deficient cells and immunohistochemical analysis of breast tumors for DNA repair proteins.	1 α ,25(OH)2D3 enhances stability of 53BP1, improving DNA repair and reducing tumor cell proliferation in TNBC.	Proposes a new therapeutic strategy enhancing DNA repair protein stability in TNBC, which could help manage treatment resistance and improve outcomes.	Genome-instability

cell cycle arrest [54] in VDR positive breast cancer cells and in some animal tumor models [55-57]. Inhibition of epithelial mesenchymal transition (EMT) [58, 59], metastasis [60-62], energy metabolism [62-67], and invasion [56], as well as activation of autophagy [68-72] are the other essential identified regulated pathways by 1,25D in several systems of breast cancer models. It is yet unclear what precise pathways and processes connect the 1,25D VDR complex to the biological effects that have been identified. Hence, some important pathways related to the general anticancer effect of vitamin D in context of BC are described below (Figure 2).

Vitamin D and pro-Autophagy

Autophagy (macro-autophagy) or “self-eating” refers to a highly conserved lysosomal mechanism whereby a cell undergoes the breakdown and elimination of aged, impaired, or anomalous proteins and other constituents inside its cytoplasm [73]. Numerous stress signals, such as protein aggregation, malnutrition, oxidative damage, hypoxia, and endoplasmic reticulum (ER) stress, can cause autophagy [74]. The physiological consequences of autophagy exhibit variability and might potentially play a dual role in cancer progression. It can either suppress or promoting tumor growth, depending on different contexts and stages of cancer development [75, 76]. However, autophagy typically defends against damage and the onset of cancer in healthy tissue [76].

Autophagy is activated by vitamin D, which functions as a protective mechanism that inhibits oxidative stress and apoptosis. Following UV light exposure, vitamin D causes keratinocytes to enter into autophagic state in order to store energy and block the AKT/GSK3/mTOR pathway. Additionally, vitamin D stimulates the production of reactive oxygen species (ROS) by activating the PINK1/PARKIN-dependent mitophagy process. This promotes post-UV DNA repair and inhibits oxidative DNA damage [77]. Modulation of autophagy by 1,25(OH)2D3 has been indicated in a variety of cells [78]. For instance, vitamin D induces pro-survival autophagy in endothelial cells through the up-regulation of Beclin-1 and the inactivation of the ERK1.2-AKT pathway [79]. Furthermore, it has been shown that vitamin D has a role in regulating the MEK/ERK and PTEN/PI3K/AKT/mTOR signaling pathways. Hence can promoting the activation of autophagy in hepatocytes. It has been found that inhibiting these signaling pathways reduces the beneficial impact of vitamin D in mitigating hepatic injury [80]. Also, to prevent myocardial hypertrophy, vitamin D regulates autophagy in cardiomyocytes by inhibiting the β -catenin/TCF4/GSK-3 β and mTOR signaling pathways [81]. Vitamin D activates autophagy via the AMPK/mTOR signaling pathway in chondrocyte cells to inhibit inflammation associated with osteoarthritis [82]. In terms of BC, it should be noted that, when breast cancer progresses, losses of induced autophagy profile in mammary gland tissue has been shown. Mechanistically, MAP1LC3B (LC3B), a crucial gene in the autophagic process, was constitutively inhibited by VDR in luminal BC cells. Treatment with 1,25(OH)2D3, however, slightly lead to LC3B gene over-expression [71]. In MCF7

cells, 1,25(OH)2D3 also induces autophagy through activating calcium/calmodulin-dependent protein kinase 2 (CAMKK2) and 5'AMP-activated protein kinase (AMPK), both of which mediate calcium-induced autophagy [83]. Moreover, ATG12, BCL2, ESR1, PIK3C3, and PRKAG2 have been reported as differentially expressed autophagy-related genes in human datasets contain ER+ breast cancer patients. These genes probably function as important signaling nodes in the autophagy pathways that vitamin D targets in breast tumors [68].

Vitamin D and anti-Tumorigenesis

Anti-invasion and anti-metastasis: Numerous investigations have demonstrated that calcitriol (1,25-dihydroxyvitamin D3), a hormonally active metabolite of vitamin D, can prevent ER-negative BC cells from spreading and invading both in vitro and in vivo [56, 84]. This inhibition effect occurs through induction of the expression of E-cadherin in certain BC cells lacking the ER by CDH1-promoter demethylation, which is inversely associated with invasion and metastasis [85]. The increased expression of PA inhibitor1 (PAI1) and MMP inhibitor 1, as well as decreased activities of matrix metalloproteinases (MMPs), urokinase-type plasminogen activators (uPA), and tissue-type plasminogen activators (TPA) are the other mechanisms explaining calcitriol's suppressive effects on invasion and metastasis [17]. Furthermore, inhibition of N-cadherin expression by 1,25(OH)2D3 in many human BC cell lines, which belongs to the cadherin superfamily, has been found to be related to the suppressive effects of 1,25(OH)2D3 on invasion and metastasis [86]. Notably, invasive tumor cells display a high level of the mesenchymal marker N-cadherin [87]. N-cadherin can bind smooth muscle, neuronal, endothelial, and stromal fibroblast cells. Consequently, N-cadherin may facilitate perineural and stromal invasion [88]. Furthermore, it's been documented that 1,25(OH)2D3 can suppress the expression of a number of myoepithelial markers, including b4-integrin, a6-integrin, and P-cadherin [86]. P-cadherin expression has been shown to be associated with poor prognosis, higher proliferation, lymph node metastasis, and high histological grade in estrogen or progesterone receptors negative BC cells [89, 90]. Recent evidence suggests that a6b4 and a6b1 integrins are essential for BC cell survival and development through increased vascular endothelial growth factor transcription and translation [91]. Thus, the inhibition of a6 and b4-integrins might potentially impede the process of malignant transformation.

Anti-angiogenesis

Angiogenesis is the normal physiological process that is essential for the growth and development of new blood vessels (neovascularization). It is a well-known fact that, neovascularization plays a key role in the transport of oxygen and nutrients [92]. It is necessary to maintain the angiogenic shift the equilibrium between pro- and anti-angiogenic factors for newly created blood vessels to mature and stabilize. This equilibrium is lost during the angiogenesis of tumors, which results in changed vascular properties and, ultimately, tumor growth,

multiplication, differentiation, and metastasis [93]. There are several molecular players in tumor angiogenesis, such as vascular endothelial growth factor A (*VEGFA*), transforming growth factor- β 1 (*TGF- β 1*), placental growth factor (*PGF*), basic fibroblast growth factor (*bFGF*), and matrix metalloproteinases (*MMPs*) [94]. Importantly, the process of neovascularization with pro-angiogenic factors (*VEGFA*, *TGF- β 1*, *PGF*, *bFGF*, and *MMPs*) is concurrent with the growth and progression of breast cancer. Recent evidence suggests that in BC cells vitamin D can lead to down-regulation of *VEGFA*, *TGF- β 1*, *PGF*, *bFGF*, and *MMP-9* through induce expression of maternally expressed gene 3 (*MEG3*) [95]. *MEG3*, is a long non-coding RNA (lncRNA) that is vital to numerous biological processes. *MEG3* is an imprinted gene that is 35 kb in length and has 10 exons. Through post-translational modifications, translation, transcription, and epigenetic effects, *MEG3* may affect specific and targeted gene activity. The role of *MEG3* in a variety of tumor types has been extensively studied and its impact on BC has only recently identified [96]. Furthermore, the effects of *MEG3* on the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathway in BC cells has been determined [97]. PCNA [98], *MMP-9* [99] and *VEGFA* [100] are downstream targets of PI3K/AKT signaling that promote mammary cancer proliferation, metastasis, and angiogenesis [101]. Thus, the aberrantly activated AKT signaling pathway stimulates cell proliferation and tumor angiogenesis, which are essential to the progression of BC [102]. Recent study related to the effect of *MEG3* on AKT signaling pathway has been reported that over-expressed *MEG3* can has a suppressive effect on cell growth, invasion, and angiogenesis. This effect was attributed to the down-regulation of PCNA, *MMP-9*, and *VEGFA* expression by over-expressed *MEG3* [95]. Thus, anti-angiogenesis property of vitamin D through *MEG3*/AKT can be considered.

Anti-proliferation

There are a large number of published studies that describe the inhibition effect of vitamin D, calcitriol, on human BC cell line growth and proliferation [103, 104]. ER-positive BC cell lines are reported to be more susceptible than ER-negative cell lines to the growth-inhibitory effects of calcitriol [105]. Cell cycle arrest in the G0/G1 phase of the cell cycle in ER-positive cells is an essential factor for growth-inhibitory effects of calcitriol. In this context, calcitriol can lead to up-regulation of cyclin-dependent kinase inhibitors (p21 Waf/Cip1), down-regulation of cyclin-dependent kinase activity, and dephosphorylation of the retinoblastoma protein [106, 107]. Moreover, calcitriol and its analogs have been found to have inhibitory effects on the growth and proliferation of BC cells through the regulation of oncogenes, specifically c-myc and c-fos. Additionally, these compounds modulate the activities of various growth factors, including insulin-like growth factor-I (IGF-I), epidermal growth factor (EGF), and transforming growth factor (TGF) [103, 108]. Furthermore, another mechanism which contributed to the antiproliferative effects of 1,25(OH)₂D₃ is induction of CCAAT enhancer-

binding protein α (C/EBP α) expression, a member of the C/EBP family of transcription factors, which is a potent enhancer of VDR transcription in MCF-7 breast cancer cells [109].

Vitamin D and pro-Apoptosis

In BC cells, vitamin D triggers morphological and biochemical alterations linked to apoptosis, such as DNA breakage and chromatin condensation, as well as the generation of reactive oxygen species, disruption of mitochondria, and release of cytochrome C [110-112]. 1,25(OH)₂D₃ can either decreases the expression of bcl-2 and bcl-XL, as anti-apoptotic factors or increases the bax, bak as pro-apoptotic factors. This action of 1,25(OH)₂D₃ leads cells toward death rather than survival [113]. Furthermore, through the activation of caspases, calcitriol may enhance the death of some BC cells caused by tumor necrosis factor (TNF) [114, 115] and phospholipase A2 [108]. Moreover, it has been reported that following 48 hours of exposure to 100 nM 1,25(OH)₂D₃, MCF-7 cells display the distinguishing characteristics of apoptosis, including chromatin and cytoplasmic condensation, pyknotic nuclei, and reorganized nuclear matrix proteins [52, 110]. Another mechanism by which vitamin D can induce apoptosis is its inhibition effect on anti-apoptotic signaling pathway, RAS/MEK/ERK [36]. Following 1,25(OH)₂D₃ treatment, RAS expression and MEK and ERK1/2 phosphorylation were reduced in BC cells [116].

Vitamin D and immune modulating

Recently vitamin D has been demonstrated as immune-modulating substance, which is involved in a number of illnesses, including autoimmune disorders. The mechanism via which vitamin D exerts its immune-modulating effects, is related to the interaction between vitamin D and its receptor, VDR. VDR has transcriptional effects and is expressed on different cell types, particularly immune system cells [117]. Thus, vitamin D is considered as regulator of certain immune cells and immune system. For instance, vitamin D inhibits the overreaction of activated T cells and other adaptive immune system cells that may result in autoimmune diseases such as multiple sclerosis and inflammatory bowel disease [118]. Based on the evidence, three sets of VDR target genes (i) acute response to infection, (ii) infection in general, and (iii) autoimmune can be formed based on their roles: CAMP, ACVRL1, CEBPB, FN1, MAPK13, NINJ1, LILRB4, LRRC25, SEMA6B, THBD, THEMIS2, and TREM1. Using these target genes of VDR, vitamin D can impact on the innate and adaptive immunity [119]. It should be noted that, stimulation of the innate and suppression of the adaptive immune system by vitamin D lead to its anti-inflammatory effects [36]. Since Virchow first proposed in 1863 that unresolved inflammation can be the cause of cancer development, the role of inflammation in cancer progression is considered [120]. One of the defense mechanisms of the adaptive immune system against intracellular infections, such as cancer cells is related to the cytotoxic (CD8⁺) T lymphocytes. It has been noted that, tumor-infiltrating CD8⁺ lymphocytes (TILs) have been shown to exhibit anti-tumor actions that are

triggered by several pathways [121]. These anti-tumor actions related to the high tumor infiltration of TILs has been associated to a better prognosis in TNBC and HER2-enriched BC [122-124]. In a recent experiment murine E0771 (ER β +, PR+, HER2+) BC cells as a mouse model [125] were injected in the mammary fat pad to assess the impact of vitamin D3 supplementation (cholecalciferol, 40 IU/day) on CD8+ T cell infiltration [126]. According to their experiments, supplementing with vitamin D3 increased the number and activity of CD8+ T cells within the tumor while limiting the growth of the tumor. On the other hand, under situations with high dietary fat after supplementing vitamin D3, tumor development was increased and CD8+ T cell infiltration was decreased. Thus, low- and high-dietary fat conditions can lead to the different response to vitamin D3 supplementation. This influence can be related to the obese mice adipocytes expressing Cyp27a1, which led to reduced systemic levels of 25(OH)D3 as well as CD8+ T cell infiltration. According to these data, dietary intake can influence the effect of vitamin D3 supplementation on cytotoxic T cells activities and tumor growth and infiltration [126]. Furthermore, the gene *CD14* which is associated with innate immunity is regulated by 1,25 vitamin D in human mammary epithelial cells [127]. Thus, vitamin D signaling can trigger innate immunity in mammary tissue.

Vitamin D and Genome instability

Multiple studies have shown that individuals diagnosed with triple-negative breast cancer (TNBC) have the most deficient levels of vitamin D compared to other types of BC. This observation suggests that vitamin D may potentially provide a protective effect against the development of TNBC [128]. TNBC is an aggressive and therapy-resistant form of BC, which its treatment has some challenges [129]. Gonzalo et al. [134] has been showed that TNBC tumors exhibit a deficiency in lamin proteins. This deficiency has been found to contribute to genomic instability through the degradation of the TP53BP1 protein by cathepsin L, as well as the inhibition of RAD51. Consequently, these molecular events lead to abnormal repair of DNA double-strand breaks through either non-homologous end joining (NHEJ) or homologous recombination repair (HRR) mechanisms [130]. Importantly, vitamin D has been reported to has the potential to stimulate a cystatin that inhibits cathepsin L and TP53BP1 proteolytic degradation; thus, it induces NHEJ and, hence, the stability of the genome [128, 131]. Moreover, despite the sensitivity of TNBC and BRCA1-deficient cells to the inhibitors of poly (ADP-ribose) polymerase (PARPi), a significant fraction of these cancers acquire resistance [132]. The resistance of BRCA1-deficient cells and tumors to PARPi has been demonstrated to be influenced by the loss of the DNA repair protein 53BP1. Thus, it is possible to restore the sensitivity of these highly malignant tumors to PARPi and other genotoxic agents by raising the concentration of 53BP1. It should be mentioned that vitamin D has the ability to stabilize tumor cells' 53BP1 levels [133]. BRCA1-deficient breast tumor cells degrade 53BP1 via cathepsin L to maintain genome stability and proliferation

[119]. Nevertheless, 1 α ,25(OH)2D3 therapy may increase genomic instability in response to radiation or PARPi and reduce proliferation by maintaining 53BP1 levels [134].

Discussion

In conclusion, several reports have shown that vitamin D can acts as protective factor against breast cancer by its interaction with vitamin D receptor, VDR, which is exists on several cellular surface including mammary glands. Vitamin D/VDR complex then move to the nucleus and impact on various target genes transcription and/or translation. Each of the VDR target genes play a role in important pathways related to the pathophysiology of breast cancer. Hence, this study has reviewed the influence of vitamin D on autophagy, invasion and metastasis, angiogenesis, proliferation, immunity, and genome stability, which highlight the general anti-cancer effect of vitamin D in breast cancer. These findings suggest that in general vitamin D/VDR complex expression can influence on breast cancer progression, and may be applied as anti-tumor substance in alongside currently available cancer treatments like chemotherapy. In contrast to observational studies, which found the protective role of vitamin D on breast cancer development, however, no clearly evidence of exact association/causality was detected in terms of the vitamin D protective effect on breast cancer risk by genome wide association study (GWAS) and mendelian randomization (MR) analysis [135] or randomized controlled trials (RCT) [6]. Therefore, further investigation and experimentation regarding the protective role of vitamin D on breast cancer progression is strongly recommended. The results of these interventional studies will extend our knowledge related to the possible application of vitamin D in both the prevention and treatment of breast cancer.

Author Contribution Statement

SD, SA, AM, AS, GHAT, SMP, ZS, ZM, MT, KHAM, HM, MKM, MA, GHAT and MGH designed the study and were involved in the data collection, analysis, and drafting of the manuscript. MV, ASHK, SKH, SMP and SD were involved in the design of the study, analysis of the data, and critical review the manuscript. All authors read and approved the final manuscript.

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Ethics approval

This study has been assessed and approved by the local ethics review boards at Shahid Beheshti University Medical Sciences, Tehran, Iran (IR.SBMU.nnftri. Rec.1403.009).

Availability of data and material

The data underlying this article will be shared on reasonable request to the corresponding author

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Competing interests

The authors stated no competing interests.

References

- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-49. <https://doi.org/10.3322/caac.21660>.
- Łukasiewicz S, Czezelewski M, Forma A, Baj J, Sitarz R, Stanisławek A. Breast cancer—epidemiology, risk factors, classification, prognostic markers, and current treatment strategies—an updated review. *Cancers*. 2021;13(17):4287. <https://doi.org/10.3390/cancers13174287>.
- Hortobagyi GN, de la Garza Salazar J, Pritchard K, Amadori D, Haidinger R, Hudis CA, et al. The global breast cancer burden: Variations in epidemiology and survival. *Clin Breast Cancer*. 2005;6(5):391-401. <https://doi.org/10.3816/cbc.2005.n.043>.
- Barrios CH, Reinert T, Werutsky G. Global breast cancer research: Moving forward. *Am Soc Clin Oncol Educ Book*. 2018;38:441-50. https://doi.org/10.1200/edbk_209183.
- Grant WB. Review of recent advances in understanding the role of vitamin d in reducing cancer risk: Breast, colorectal, prostate, and overall cancer. *Anticancer Res*. 2020;40(1):491-9. <https://doi.org/10.21873/anticancer.13977>.
- Li Z, Wu L, Zhang J, Huang X, Thabane L, Li G. Effect of vitamin d supplementation on risk of breast cancer: A systematic review and meta-analysis of randomized controlled trials. *Front Nutr*. 2021;8:655727. <https://doi.org/10.3389/fnut.2021.655727>.
- Feldman D, Krishnan AV, Swami S, Giovannucci E, Feldman BJ. The role of vitamin d in reducing cancer risk and progression. *Nat Rev Cancer*. 2014;14(5):342-57. <https://doi.org/10.1038/nrc3691>.
- Holick MF. The vitamin d deficiency pandemic: Approaches for diagnosis, treatment and prevention. *Rev Endocr Metab Disord*. 2017;18(2):153-65. <https://doi.org/10.1007/s11154-017-9424-1>.
- Bhamb N, Kanim L, Maldonado R, Svet M, Metzger M. Effect of modulating dietary vitamin d on the general bone health of rats during posterolateral spinal fusion. *J Orthop Res*. 2018;36(5):1435-43. <https://doi.org/10.1002/jor.23832>.
- Anderson PH, Atkins GJ, Turner AG, Kogawa M, Findlay DM, Morris HA. Vitamin d metabolism within bone cells: Effects on bone structure and strength. *Mol Cell Endocrinol*. 2011;347(1-2):42-7. <https://doi.org/10.1016/j.mce.2011.05.024>.
- Schwartz GG, Skinner HG. Vitamin d status and cancer: New insights. *Curr Opin Clin Nutr Metab Care*. 2007;10(1):6-11. <https://doi.org/10.1097/MCO.0b013e328011aa60>.
- Pilz S, Verheyen N, Gröbler MR, Tomaschitz A, März W. Vitamin d and cardiovascular disease prevention. *Nat Rev Cardiol*. 2016;13(7):404-17. <https://doi.org/10.1038/nrcardio.2016.73>.
- Altieri B, Muscogiuri G, Barrea L, Mathieu C, Vallone CV, Mascitelli L, et al. Does vitamin d play a role in autoimmune endocrine disorders? A proof of concept. *Rev Endocr Metab Disord*. 2017;18(3):335-46. <https://doi.org/10.1007/s11154-016-9405-9>.
- Kemmis CM, Welsh J. Mammary epithelial cell transformation is associated with deregulation of the vitamin d pathway. *J Cell Biochem*. 2008;105(4):980-8. <https://doi.org/10.1002/jcb.21896>.
- Swami S, Krishnan AV, Feldman D. 1alpha,25-dihydroxyvitamin d3 down-regulates estrogen receptor abundance and suppresses estrogen actions in mcf-7 human breast cancer cells. *Clin Cancer Res*. 2000;6(8):3371-9.
- Shaukat N, Jaleel F, Moosa FA, Qureshi NA. Association between vitamin d deficiency and breast cancer. *Pak J Med Sci*. 2017;33(3):645-9. <https://doi.org/10.12669/pjms.333.11753>.
- Koli K, Keski-Oja J. 1alpha,25-dihydroxyvitamin d3 and its analogues down-regulate cell invasion-associated proteases in cultured malignant cells. *Cell Growth Differ*. 2000;11(4):221-9.
- Chung I, Han G, Seshadri M, Gillard BM, Yu WD, Foster BA, et al. Role of vitamin d receptor in the antiproliferative effects of calcitriol in tumor-derived endothelial cells and tumor angiogenesis in vivo. *Cancer Res*. 2009;69(3):967-75. <https://doi.org/10.1158/0008-5472.Can-08-2307>.
- Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *nature*. 2008;454(7203):436-44. <https://doi.org/10.1038/nature07205>.
- Knight JA, Lesosky M, Barnett H, Raboud JM, Vieth R. Vitamin d and reduced risk of breast cancer: A population-based case-control study. *Cancer Epidemiol Biomarkers Prev*. 2007;16(3):422-9. <https://doi.org/10.1158/1055-9965.Epi-06-0865>.
- Shin MH, Holmes MD, Hankinson SE, Wu K, Colditz GA, Willett WC. Intake of dairy products, calcium, and vitamin d and risk of breast cancer. *J Natl Cancer Inst*. 2002;94(17):1301-11. <https://doi.org/10.1093/jnci/94.17.1301>.
- O'Brien KM, Sandler DP, Taylor JA, Weinberg CR. Serum vitamin d and risk of breast cancer within five years. *Environ Health Perspect*. 2017;125(7):077004. <https://doi.org/10.1289/ehp943>.
- Bidgoli SA, Azarshab H. Role of vitamin d deficiency and lack of sun exposure in the incidence of premenopausal breast cancer: A case control study in sabzevar, iran. *Asian Pac J Cancer Prev*. 2014;15(8):3391-6. <https://doi.org/10.7314/apjcp.2014.15.8.3391>.
- Hossain S, Beydoun MA, Beydoun HA, Chen X, Zonderman AB, Wood RJ. Vitamin d and breast cancer: A systematic review and meta-analysis of observational studies. *Clin Nutr ESPEN*. 2019;30:170-84. <https://doi.org/10.1016/j.clnesp.2018.12.085>.
- Cardoso AT, Nanji L, Costa J, Vaz-Carneiro A. [analysis of the cochrane review: Vitamin d supplementation for prevention of cancer in adults. *Cochrane database syst rev*. 2014, 6: Cd007469]. *Acta Med Port*. 2014;27(4):411-3.
- Narvaez CJ, Matthews D, LaPorta E, Simmons KM, Beaudin S, Welsh J. The impact of vitamin d in breast cancer: Genomics, pathways, metabolism. *Front physiol*. 2014;5:213. <https://doi.org/10.3389/fphys.2014.00213>.
- Welsh J. Vitamin d and breast cancer: Mechanistic update. *J Bone Miner Res*. 2021;5(12):e10582. <https://doi.org/10.1002/jbm4.10582>.
- Sheng L, Anderson PH, Turner AG, Pishas KI, Dhatrik DJ, Gill PG, et al. Identification of vitamin d3 target genes in human breast cancer tissue. *J Steroid Biochem Mol Biol*. 2016;164:90-7. <https://doi.org/10.1016/j.jsbmb.2015.10.012>.

29. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group* t. Preferred reporting items for systematic reviews and meta-analyses: The prisma statement. *Ann Intern Med*. 2009;151(4):264-9. <https://doi.org/10.7326/0003-4819-151-4-200908180-00135>.
30. Seb  -Pedr  s A, Degnan BM, Ruiz-Trillo I. The origin of metazoa: A unicellular perspective. *Nat Rev Genet*. 2017;18(8):498-512. <https://doi.org/10.1038/nrg.2017.21>.
31. Krasowski MD, Ni A, Hagey LR, Ekins S. Evolution of promiscuous nuclear hormone receptors: Lxr, fxr, vdr, pxxr, and car. *Mol Cell Endocrinol*. 2011;334(1-2):39-48. <https://doi.org/10.1016/j.mce.2010.06.016>.
32. Whitfield GK, Dang HT, Schluter SF, Bernstein RM, Bunag T, Manz  n LA, et al. Cloning of a functional vitamin d receptor from the lamprey (*petromyzon marinus*), an ancient vertebrate lacking a calcified skeleton and teeth. *Endocrinology*. 2003;144(6):2704-16. <https://doi.org/10.1210/en.2002-221101>.
33. Carlberg C, Velleuer E. Vitamin d and the risk for cancer: A molecular analysis. *Biochem Pharmacol*. 2022;196:114735. <https://doi.org/10.1016/j.bcp.2021.114735>.
34. Peehl DM, Feldman D. Interaction of nuclear receptor ligands with the vitamin d signaling pathway in prostate cancer. *J Steroid Biochem Mol Biol*. 2004;92(4):307-15. <https://doi.org/10.1016/j.jsbmb.2004.10.006>.
35. Leyssens C, Verlinden L, Verstuyf A. Antineoplastic effects of 1, 25 (oh) 2d3 and its analogs in breast, prostate and colorectal cancer. *Endocr Relat Cancer*. 2013;20(2):R31-R47. <https://doi.org/10.1530/ERC-12-0381>.
36. Christakos S, Dhawan P, Verstuyf A, Verlinden L, Carmeliet G. Vitamin d: Metabolism, molecular mechanism of action, and pleiotropic effects. *Physiological reviews*. 2016;96(1):365-408. <https://doi.org/10.1152/physrev.00014.2015>.
37. Jeon S-M, Shin E-A. Exploring vitamin d metabolism and function in cancer. *Exp Mol Med*. 2018;50(4):1-14. <https://doi.org/10.1038/s12276-018-0038-9>.
38. Welsh J. Vitamin d and breast cancer: Past and present. *J Steroid Biochem Mol Biol*. 2018;177:15-20. <https://doi.org/10.1016/j.jsbmb.2017.07.025>.
39. Vanhevel J, Verlinden L, Doms S, Wildiers H, Verstuyf A. The role of vitamin d in breast cancer risk and progression. *Endocr Relat Cancer*. 2022;29(2):R33-R55. <https://doi.org/10.1530/ERC-21-0182>.
40. Eisman J, MacIntyre I, Martin T, Moseley J. 1, 25-dihydroxyvitamin-d receptor in breast cancer cells. *Lancet*. 1979;314(8156-8157):1335-6. [https://doi.org/10.1016/s0140-6736\(79\)92816-2](https://doi.org/10.1016/s0140-6736(79)92816-2).
41. Eisman J, Macintyre I, Martin T, Frampton R, King R. Normal and malignant breast tissue is a target organ for 1, 25-(oh) 2 vitamin d3. *Clin Endocrinol*. 1980;13(3):267-72. <https://doi.org/10.1111/j.1365-2265.1980.tb01053.x>.
42. Voutsadakis IA. Vitamin d receptor (vdr) and metabolizing enzymes cyp27b1 and cyp24a1 in breast cancer. *Mol Biol Rep*. 2020;47(12):9821-30. <https://doi.org/10.1007/s11033-020-05780-1>.
43. Kemmis CM, Salvador SM, Smith KM, Welsh J. Human mammary epithelial cells express cyp27b1 and are growth inhibited by 25-hydroxyvitamin d-3, the major circulating form of vitamin d-3. *J Nutr*. 2006;136(4):887-92. <https://doi.org/10.1093/jn/136.4.887>.
44. Milani C, Welsh J, Katayama M, Lyra E, Maciel M, Brentani M, et al. Human breast tumor slices: A model for identification of vitamin d regulated genes in the tumor microenvironment. *J Steroid Biochem Mol Biol*. 2010;121(1-2):151-5. <https://doi.org/10.1016/j.jsbmb.2010.03.051>.
45. Townsend K, Banwell CM, Guy M, Colston KW, Mansi JL, Stewart PM, et al. Autocrine metabolism of vitamin d in normal and malignant breast tissue. *Clin Cancer Res*. 2005;11(9):3579-86. <https://doi.org/10.1158/1078-0432.CCR-04-2359>.
46. Adams JS, Rafison B, Witzel S, Reyes RE, Shieh A, Chun R, et al. Regulation of the extrarenal cyp27b1-hydroxylase. *J Steroid Biochem Mol Biol*. 2014;144:22-7. <https://doi.org/10.1016/j.jsbmb.2013.12.009>.
47. Rowling MJ, Kemmis CM, Taff  ny DA, Welsh J. Megalin-mediated endocytosis of vitamin d binding protein correlates with 25-hydroxycholecalciferol actions in human mammary cells. *J Nutr*. 2006;136(11):2754-9. <https://doi.org/10.1093/jn/136.11.2754>.
48. Welsh J. Function of the vitamin d endocrine system in mammary gland and breast cancer. *Mol Cell Endocrinol*. 2017;453:88-95. <https://doi.org/10.1016/j.mce.2017.04.026>.
49. Atoum M, Alzoughool F. Vitamin d and breast cancer: Latest evidence and future steps. *Breast Cancer*. 2017;11:1178223417749816. <https://doi.org/10.1177/1178223417749816>.
50. Pazdiora P, Svobodova S, Fuchsova R, KU  CERA R, Prazakova M, Vrzalova J, et al. Vitamin d in colorectal, breast, prostate and lung cancer: A pilot study. *Anticancer Res*. 2011;31(10):3619-21.
51. Est  banez N, G  mez-Acebo I, Palazuelos C, Llorca J, Dierssen-Sotos T. Vitamin d exposure and risk of breast cancer: A meta-analysis. *Sci Rep*. 2018;8(1):9039. <https://doi.org/10.1038/s41598-018-27297-1>.
52. Welsh J. Induction of apoptosis in breast cancer cells in response to vitamin d and antiestrogens. *Biochem Cell Biol*. 1994;72(11-12):537-45. <https://doi.org/10.1139/o94-072>.
53. Mathiasen IS, Colston KW, Binderup L. Eb 1089, a novel vitamin d analogue, has strong antiproliferative and differentiation inducing effects on cancer cells. *J Steroid Biochem Mol Biol*. 1993;46(3):365-71. [https://doi.org/10.1016/0960-0760\(93\)90226-m](https://doi.org/10.1016/0960-0760(93)90226-m).
54. Bower M, Stein R, Hedley A, Coombes R, Colston K, Gazet J-C, et al. Topical calcipotriol treatment in advanced breast cancer. *Lancet*. 1991;337(8743):701-2. [https://doi.org/10.1016/0140-6736\(91\)90280-3](https://doi.org/10.1016/0140-6736(91)90280-3).
55. VanWeelden K, Flanagan L, Binderup L, Tenniswood M, Welsh J. Apoptotic regression of mcf-7 xenografts in nude mice treated with the vitamin d3 analog, eb1089. *Endocrinology*. 1998;139(4):2102-10. <https://doi.org/10.1210/endo.139.4.5892>.
56. Flanagan L, Packman K, Juba B, O'Neill S, Tenniswood M, Welsh J. Efficacy of vitamin d compounds to modulate estrogen receptor negative breast cancer growth and invasion. *J Steroid Biochem Mol Biol*. 2003;84(2-3):181-92. [https://doi.org/10.1016/s0960-0760\(03\)00028-1](https://doi.org/10.1016/s0960-0760(03)00028-1).
57. Colston KW, Mackay AG, James SY, Binderup L, Chander S, Coombes RC. Eb1089: A new vitamin d analogue that inhibits the growth of breast cancer cells in vivo and in vitro. *Biochem Pharmacol*. 1992;44(12):2273-80. [https://doi.org/10.1016/0006-2952\(92\)90669-a](https://doi.org/10.1016/0006-2952(92)90669-a).
58. Li J, Luco A-L, Camirand A, St-Arnaud R, Kremer R. Vitamin d regulates cxcl12/cxcr4 and epithelial-to-mesenchymal transition in a model of breast cancer metastasis to lung. *Endocrinology*. 2021;162(7):bqab049. <https://doi.org/10.1210/endo/bqab049>.
59. Narvaez CJ, LaPorta E, Robilotto S, Liang J, Welsh J. Inhibition of has2 and hyaluronic acid production by 1, 25-dihydroxyvitamin d3 in breast cancer. *Oncotarget*. 2020;11(30):2889. <https://doi.org/10.18632/oncotarget.27587>.
60. Horas K, Zheng Y, Fong-Yee C, Macfarlane E, Manibo J, Chen Y, et al. Loss of the vitamin d receptor in human breast cancer cells promotes epithelial to mesenchymal

- cell transition and skeletal colonization. *J Bone Miner Res.* 2019;34(9):1721-32. <https://doi.org/10.1002/jbmr.3744>.
61. Liu X, Bi L, Wang Q, Wen M, Li C, Ren Y, et al. Mir-1204 targets vdr to promotes epithelial-mesenchymal transition and metastasis in breast cancer. *Oncogene.* 2018;37(25):3426-39. <https://doi.org/10.1038/s41388-018-0215-2>.
 62. Wilmanski T, Barnard A, Parikh MR, Kirshner J, Buhman K, Burgess J, et al. 1 α , 25-dihydroxyvitamin d inhibits the metastatic capability of mcf10ca1a and mda-mb-231 cells in an in vitro model of breast to bone metastasis. *Nutr Cancer* 2016;68(7):1202-9. <https://doi.org/10.1080/01635581.2016.1213868>.
 63. Narvaez C, Grebenc D, Balinthe S, Welsh J. Vitamin d regulation of has2, hyaluronan synthesis and metabolism in triple negative breast cancer cells. *J Steroid Biochem Mol Biol.* 2020;201:105688. <https://doi.org/10.1016/j.jsbmb.2020.105688>.
 64. Beaudin S, Welsh J. 1, 25-dihydroxyvitamin d regulation of glutamine synthetase and glutamine metabolism in human mammary epithelial cells. *Endocrinology.* 2017;158(12):4174-88. <https://doi.org/10.1210/en.2017-00238>.
 65. Sheeley MP, Andolino C, Kiesel VA, Teegarden D. Vitamin d regulation of energy metabolism in cancer. *Br J Pharmacol.* 2022;179(12):2890-905. <https://doi.org/10.1111/bph.15424>.
 66. Wilmanski T, Zhou X, Zheng W, Shinde A, Donkin SS, Wendt M, et al. Inhibition of pyruvate carboxylase by 1 α , 25-dihydroxyvitamin d promotes oxidative stress in early breast cancer progression. *Cancer Lett.* 2017;411:171-81. <https://doi.org/10.1016/j.canlet.2017.09.045>.
 67. Wilmanski T, Buhman K, Donkin SS, Burgess JR, Teegarden D. 1 α , 25-dihydroxyvitamin d inhibits de novo fatty acid synthesis and lipid accumulation in metastatic breast cancer cells through down-regulation of pyruvate carboxylase. *J Nutr Biochem.* 2017;40:194-200. <https://doi.org/10.1016/j.jnutbio.2016.11.006>.
 68. Li Y, Cook KL, Yu W, Jin L, Bouker KB, Clarke R, et al. Inhibition of antiestrogen-promoted pro-survival autophagy and tamoxifen resistance in breast cancer through vitamin d receptor. *Nutrients.* 2021;13(5):1715. <https://doi.org/10.3390/nu13051715>.
 69. Lin J, Chen X, Sun M, Qu X, Wang Y, Li C, et al. Upregulation of microRNA-181a-5p increases the sensitivity of hs578t breast cancer cells to cisplatin by inducing vitamin d receptor-mediated cell autophagy. *Oncol Lett.* 2021;21(4):1-. <https://doi.org/10.3892/ol.2021.12508>.
 70. Guizzardi S, Picotto G, Rodriguez V, Welsh J, Narvaez C, Bohl L, et al. Combined treatment of menadione and calcitriol increases the antiproliferative effect by promoting oxidative/nitrosative stress, mitochondrial dysfunction, and autophagy in breast cancer mcf-7 cells. *Can J Physiol Pharmacol.* 2020;98(8):548-56. <https://doi.org/10.1139/cjpp-2019-0585>.
 71. Tavera-Mendoza LE, Westerling T, Libby E, Marusyk A, Cato L, Cassani R, et al. Vitamin d receptor regulates autophagy in the normal mammary gland and in luminal breast cancer cells. *Proc Natl Acad Sci U S A.* 2017;114(11):E2186-E94. <https://doi.org/10.1073/pnas.1615015114>.
 72. Bristol ML, Di X, Beckman MJ, Wilson EN, Henderson SC, Maiti A, et al. Dual functions of autophagy in the response of breast tumor cells to radiation: Cytoprotective autophagy with radiation alone and cytotoxic autophagy in radiosensitization by vitamin d3. *Autophagy.* 2012;8(5):739-53. <https://doi.org/10.4161/auto.19313>.
 73. White E. Deconvoluting the context-dependent role for autophagy in cancer. *Nat Rev Cancer.* 2012;12(6):401-10. <https://doi.org/10.1038/nrc3262>.
 74. Nishimura T, Tamura N, Kono N, Shimanaka Y, Arai H, Yamamoto H, et al. Autophagosome formation is initiated at phosphatidylinositol synthase-enriched subdomains. *EMBO J.* 2017;36(12):1719-35. <https://doi.org/10.15252/embj.201695189>.
 75. Li X, He S, Ma B. Autophagy and autophagy-related proteins in cancer. *Mol Cancer.* 2020;19(1):12. <https://doi.org/10.1186/s12943-020-1138-4>.
 76. Mathew R, White E. Autophagy in tumorigenesis and energy metabolism: Friend by day, foe by night. *Curr Opin Genet Dev.* 2011;21(1):113-9. <https://doi.org/10.1016/j.gde.2010.12.008>.
 77. Rybchyn MS, De Silva WGM, Sequeira VB, McCarthy BY, Dilley AV, Dixon KM, et al. Enhanced repair of uv-induced DNA damage by 1, 25-dihydroxyvitamin d3 in skin is linked to pathways that control cellular energy. *J Invest Dermatol.* 2018;138(5):1146-56. <https://doi.org/10.1016/j.jid.2017.11.037>.
 78. Mathew R, White E. Autophagy, stress, and cancer metabolism: what doesn't kill you makes you stronger. In: *Cold Spring Harbor symposia on quantitative biology.* 2011: Cold Spring Harbor Laboratory Press; 2011: 389-396.
 79. Uberti F, Lattuada D, Morsanuto V, Nava U, Bolis G, Vacca G, et al. Vitamin d protects human endothelial cells from oxidative stress through the autophagic and survival pathways. *J Clin Endocrinol Metab.* 2014;99(4):1367-74. <https://doi.org/10.1210/jc.2013-2103>.
 80. Yang J, Chen Q, Tian S, Song S, Liu F, Wang Q, et al. The role of 1, 25-dihydroxyvitamin d3 in mouse liver ischemia reperfusion injury: Regulation of autophagy through activation of mek/erk signaling and pten/pi3k/akt/mTORC1 signaling. *Am J Transl Res.* 2015;7(12):2630.
 81. Wei H, Qu H, Wang H, Ji B, Ding Y, Liu D, et al. 1, 25-dihydroxyvitamin-d3 prevents the development of diabetic cardiomyopathy in type 1 diabetic rats by enhancing autophagy via inhibiting the β -catenin/tcf4/gsk-3 β /mTOR pathway. *J Steroid Biochem Mol Biol.* 2017;168:71-90. <https://doi.org/10.1016/j.jsbmb.2017.02.007>.
 82. Kong C, Wang C, Shi Y, Yan L, Xu J, Qi W. Active vitamin d activates chondrocyte autophagy to reduce osteoarthritis via mediating the AMPK-mTOR signaling pathway. *Biochem Cell Biol.* 2020;98(3):434-42. <https://doi.org/10.1139/bcb-2019-0333>.
 83. Hoyer-Hansen M, Bastholm L, Szyniarowski P, Campanella M, Szabadkai G, Farkas T, et al. Control of macroautophagy by calcium, calmodulin-dependent kinase kinase- β , and bcl-2. *Mol Cell.* 2007;25(2):193-205. <https://doi.org/10.1016/j.molcel.2006.12.009>.
 84. Verma A, Cohen DJ, Schwartz N, Muktipaty C, Koblinski JE, Boyan BD, et al. 24r, 25-dihydroxyvitamin d3 regulates breast cancer cells in vitro and in vivo. *BBA General Subjects.* 2019;1863(10):1498-512. <https://doi.org/10.1016/j.bbagen.2019.05.013>.
 85. Lopes N, Carvalho J, Duraes C, Sousa B, Gomes M, Costa JL, et al. 1 α , 25-dihydroxyvitamin d3 induces de novo e-cadherin expression in triple-negative breast cancer cells by cdh1-promoter demethylation. *Anticancer Res.* 2012;32(1):249-57.
 86. Pendás-Franco N, González-Sancho JM, Suárez Y, Aguilera O, Steinmeyer A, Gamallo C, et al. Vitamin d regulates the phenotype of human breast cancer cells. *Differentiation.* 2007;75(3):193-207. <https://doi.org/10.1111/j.1432-0436.2006.00131.x>.
 87. Seidel B, Braeg S, Adler G, Wedlich D, Menke A. E- and n-cadherin differ with respect to their associated p120ctn isoforms and their ability to suppress invasive growth in

- pancreatic cancer cells. *Oncogene*. 2004;23(32):5532-42. <https://doi.org/10.1038/sj.onc.1207718>.
88. De Wever O, Mareel M. Role of tissue stroma in cancer cell invasion. *J Pathol*. 2003;200(4):429-47. <https://doi.org/10.1002/path.1398>.
89. Kovacs A, Dhillon J, Walker R. Expression of p-cadherin, but not e-cadherin or n-cadherin, relates to pathological and functional differentiation of breast carcinomas. *Mol Pathol*. 2003;56(6):318. <https://doi.org/10.1136/mp.56.6.318>.
90. Paredes J, Albergaria A, Oliveira JoT, Jerónimo C, Milanezi F, Schmitt FC. P-cadherin overexpression is an indicator of clinical outcome in invasive breast carcinomas and is associated with cdh3 promoter hypomethylation. *Clin Cancer Res*. 2005;11(16):5869-77. <https://doi.org/10.1158/1078-0432.CCR-05-0059>.
91. Chung J, Mercurio AM. Contributions of the $\alpha 6$ integrins to breast carcinoma survival and progression. *Mol Cells*. 2004;17(2):203-9.
92. Badodekar N, Sharma A, Patil V, Telang G, Sharma R, Patil S, et al. Angiogenesis induction in breast cancer: A paracrine paradigm. *Cell Biochem Funct*. 2021;39(7):860-73. <https://doi.org/10.1002/cbf.3663>.
93. Papetti M, Herman IM. Mechanisms of normal and tumor-derived angiogenesis. *Am J Physiol Cell Physiol*. 2002;282(5):C947-C70. <https://doi.org/10.1152/ajpcell.00389.2001>.
94. Relf M, LeJeune S, Scott PA, Fox S, Smith K, Leek R, et al. Expression of the angiogenic factors vascular endothelial cell growth factor, acidic and basic fibroblast growth factor, tumor growth factor β -1, platelet-derived endothelial cell growth factor, placenta growth factor, and pleiotrophin in human primary breast cancer and its relation to angiogenesis. *Cancer Res*. 1997;57(5):963-9.
95. Zhang C-y, Yu M-s, Li X, Zhang Z, Han C-r, Yan B. Overexpression of long non-coding rna meg3 suppresses breast cancer cell proliferation, invasion, and angiogenesis through akt pathway. *Tumor Biol*. 2017;39(6):1010428317701311. <https://doi.org/10.1177/1010428317701311>.
96. Hussain MS, Majami AA, Ali H, Kumar G, Almalki WH, Alzarea SI, et al. The complex role of meg3: An emerging long non-coding rna in breast cancer. *Pathol Res Pract*. 2023;154850. <https://doi.org/10.1016/j.prp.2023.154850>.
97. Zhu M, Wang X, Gu Y, Wang F, Li L, Qiu X. Meg3 overexpression inhibits the tumorigenesis of breast cancer by downregulating mir-21 through the pi3k/akt pathway. *Arch Biochem Biophys*. 2019;661:22-30. <https://doi.org/10.1016/j.abb.2018.10.021>.
98. Rössig L, Jadidi AS, Urbich C, Badorff C, Zeiher AM, Dimmeler S. Akt-dependent phosphorylation of p21cip1 regulates pcna binding and proliferation of endothelial cells. *Mol Cell Biol* 2001. <https://doi.org/10.1128/MCB.21.16.5644-5657.2001>.
99. Adams LS, Phung S, Yee N, Seeram NP, Li L, Chen S. Blueberry phytochemicals inhibit growth and metastatic potential of mda-mb-231 breast cancer cells through modulation of the phosphatidylinositol 3-kinase pathway. *Cancer Res*. 2010;70(9):3594-605. <https://doi.org/10.1158/0008-5472.CAN-09-3565>.
100. Tang Y, Nakada MT, Rafferty P, Laroia J, McCabe FL, Millar H, et al. Regulation of vascular endothelial growth factor expression by emmprin via the pi3k-akt signaling pathway. *Mol Cancer Res*. 2006;4(6):371-7. <https://doi.org/10.1158/1541-7786.MCR-06-0042>.
101. Atif F, Yousuf S, Stein DG. Anti-tumor effects of progesterone in human glioblastoma multiforme: Role of pi3k/akt/mtor signaling. *J Steroid Biochem Mol Biol*. 2015;146:62-73. <https://doi.org/10.1016/j.jsbmb.2014.04.007>.
102. Liu W, Bagaitkar J, Watabe K. Roles of akt signal in breast cancer. *Front Biosci*. 2007;12(4011):9. <https://doi.org/10.2741/2367>.
103. Krishnan AV, Swami S, Feldman D. Vitamin d and breast cancer: Inhibition of estrogen synthesis and signaling. *J Steroid Biochem Mol Biol*. 2010;121(1-2):343-8. <https://doi.org/10.1016/j.jsbmb.2010.02.009>.
104. Welsh J, Wietzke JA, Zinser GM, Smyczek S, Romu S, Tribble E, et al. Impact of the vitamin d3 receptor on growth-regulatory pathways in mammary gland and breast cancer. *J Steroid Biochem Mol Biol*. 2002;83(1-5):85-92. [https://doi.org/10.1016/s0960-0760\(02\)00277-7](https://doi.org/10.1016/s0960-0760(02)00277-7).
105. Narvaez CJ, Zinser G, Welsh J. Functions of 1 α , 25-dihydroxyvitamin d3 in mammary gland: From normal development to breast cancer. *Steroids*. 2001;66(3-5):301-8. [https://doi.org/10.1016/s0039-128x\(00\)00202-6](https://doi.org/10.1016/s0039-128x(00)00202-6).
106. Fan FS, Yu WC. 1, 25-dihydroxyvitamin d3 suppresses cell growth, DNA synthesis, and phosphorylation of retinoblastoma protein in a breast cancer cell line. *Cancer investig*. 1995;13(3):280-6. <https://doi.org/10.3109/07357909509094463>.
107. Simboli-Campbell M, Narvaez CJ, VanWeelden K, Tenniswood M, Welsh J. Comparative effects of 1, 25 (oh) 2 d3 and eb1089 on cell cycle kinetics and apoptosis in mcf-7 breast cancer cells. *Breast Cancer Res Treat*. 1997;42(1):31-41. <https://doi.org/10.1023/a:1005772432465>.
108. Colston K. Mechanisms implicated in the growth regulatory effects of vitamin d in breast cancer. *Endocr Relat Cancer*. 2002;9(1):45-59. <https://doi.org/10.1677/erc.0.0090045>.
109. Dhawan P, Weider R, Christakos S. Ccaat enhancer-binding protein α is a molecular target of 1, 25-dihydroxyvitamin d3 in mcf-7 breast cancer cells. *J Biol Chem*. 2009;284(5):3086-95. <https://doi.org/10.1074/jbc.M803602200>.
110. James SY, Mackay AG, Colston KW. Effects of 1, 25 dihydroxyvitamin d3 and its analogues on induction of apoptosis in breast cancer cells. *J Steroid Biochem Mol Biol*. 1996;58(4):395-401. [https://doi.org/10.1016/0960-0760\(96\)00048-9](https://doi.org/10.1016/0960-0760(96)00048-9).
111. Simboli-Campbell M, Narvaez CJ, Tenniswood M, Welsh J. 1, 25-dihydroxyvitamin d3 induces morphological and biochemical markers of apoptosis in mcf-7 breast cancer cells. *J Steroid Biochem Mol Biol*. 1996;58(4):367-76.
112. Narvaez CJ, Welsh J. Role of mitochondria and caspases in vitamin d-mediated apoptosis of mcf-7 breast cancer cells. *J Biol Chem*. 2001;276(12):9101-7. <https://doi.org/10.1074/jbc.M006876200>.
113. Krishnan AV, Feldman D. Mechanisms of the anti-cancer and anti-inflammatory actions of vitamin d. *Annu Rev Pharmacol Toxicol*. 2011;51:311-36. <https://doi.org/10.1146/annurev-pharmtox-010510-100611>.
114. Pirianov G, Colston K. Interactions of vitamin d analogue cb1093, tnfa and ceramide on breast cancer cell apoptosis. *Mol Cell Endocrinol* 2001;172(1-2):69-78. [https://doi.org/10.1016/s0303-7207\(00\)00380-4](https://doi.org/10.1016/s0303-7207(00)00380-4).
115. Rucker D, Ravid A, Liberman UA, Garach-Jehoshua O, Koren R. 1, 25-dihydroxyvitamin d3 potentiates the cytotoxic effect of tnf on human breast cancer cells. *Mol Cell Endocrinol* 1994;106(1-2):157-62. [https://doi.org/10.1016/0303-7207\(94\)90198-8](https://doi.org/10.1016/0303-7207(94)90198-8).
116. Zheng W, Cao L, Ouyang L, Zhang Q, Duan B, Zhou W, et al. Anticancer activity of 1, 25-(oh) 2d3 against human breast cancer cell lines by targeting ras/meek/erk pathway. *Onco Targets Ther*. 2019;721-32. <https://doi.org/10.2147/OTT.S190432>.
117. Pandolfi F, Franza L, Mandolini C, Conti P. Immune modulation by vitamin d: Special emphasis on its role in prevention and treatment of cancer. *Clin Ther*. 2017;39(5):884-

93. <https://doi.org/10.1016/j.clinthera.2017.03.012>.
118. Grotsky DA, Gonzalez-Suarez I, Novell A, Neumann MA, Yaddanapudi SC, Croke M, et al. Bca1 loss activates cathepsin L-mediated degradation of 53bp1 in breast cancer cells. *J Cell Biol*. 2013;200(2):187-202. <https://doi.org/10.1083/jcb.201204053>.
119. Koivisto O, Hanel A, Carlberg C. Key vitamin d target genes with functions in the immune system. *Nutrients*. 2020;12(4):1140. <https://doi.org/10.3390/nu12041140>.
120. Balkwill F, Mantovani A. Inflammation and cancer: Back to virchow? *Lancet*. 2001;357(9255):539-45. [https://doi.org/10.1016/S0140-6736\(00\)04046-0](https://doi.org/10.1016/S0140-6736(00)04046-0).
121. Martínez-Lostao L, Anel A, Pardo J. How do cytotoxic lymphocytes kill cancer cells? *Clin Cancer Res*. 2015;21(22):5047-56. <https://doi.org/10.1158/1078-0432.CCR-15-0685>.
122. Kurozumi S, Matsumoto H, Kurosumi M, Inoue K, Fujii T, Horiguchi J, et al. Prognostic significance of tumour-infiltrating lymphocytes for oestrogen receptor-negative breast cancer without lymph node metastasis. *Oncol Lett*. 2019;17(3):2647-56. <https://doi.org/10.3892/ol.2019.9938>.
123. Gao Z-h, Li C-x, Liu M, Jiang J-y. Predictive and prognostic role of tumour-infiltrating lymphocytes in breast cancer patients with different molecular subtypes: A meta-analysis. *BMC cancer*. 2020;20:1-14. <https://doi.org/10.1186/s12885-020-07654-y>.
124. Oshi M, Asaoka M, Tokumaru Y, Yan L, Matsuyama R, Ishikawa T, et al. Cd8 t cell score as a prognostic biomarker for triple negative breast cancer. *Int J Mol Sci*. 2020;21(18):6968. <https://doi.org/10.3390/ijms21186968>.
125. Le Naour A, Koffi Y, Diab M, Le Guennec D, Rougé S, Aldekwer S, et al. Eo771, the first luminal b mammary cancer cell line from c57bl/6 mice. *Cancer Cell Int*. 2020;20:1-13. <https://doi.org/10.1186/s12935-020-01418-1>.
126. Karkeni E, Morin SO, Bou Tayeh B, Goubard A, Josselin E, Castellano R, et al. Vitamin d controls tumor growth and cd8+ t cell infiltration in breast cancer. *Front Immunol*. 2019;10:1307. <https://doi.org/10.3389/fimmu.2019.01307>.
127. Thakur A, Kondadasula SV, Ji K, Schalk DL, Bliemeister E, Ung J, et al. Anti-tumor and immune modulating activity of t cell induced tumor-targeting effectors (tite). *Cancer Immunol Immunother*. 2021;70:633-56. <https://doi.org/10.1007/s00262-020-02692-8>.
128. Blasiak J, Pawlowska E, Chojnacki J, Szczepanska J, Fila M, Chojnacki C. Vitamin d in triple-negative and bca1-deficient breast cancer—implications for pathogenesis and therapy. *Int J Mol Sci*. 2020;21(10):3670. <https://doi.org/10.3390/ijms21103670>.
129. Al-Mahmood S, Sapiezynski J, Garbuzenko OB, Minko T. Metastatic and triple-negative breast cancer: Challenges and treatment options. *Drug Deliv Transl Res*. 2018;8(5):1483-507. <https://doi.org/10.1007/s13346-018-0551-3>.
130. Lees-Miller S, Meek K. Repair of DNA double strand breaks by non-homologous end joining. *Biochimie*. 2003;85(11):1161-73. <https://doi.org/10.1016/j.biochi.2003.10.011>.
131. Bhargava R, Onyango DO, Stark JM. Regulation of single-strand annealing and its role in genome maintenance. *Trends Genet*. 2016;32(9):566-75. <https://doi.org/10.1016/j.tig.2016.06.007>.
132. Wooten J, Mavingire N, Damar K, Loaiza-Perez A, Brantley E. Triumphs and challenges in exploiting poly (adp-ribose) polymerase inhibition to combat triple-negative breast cancer. *J Cell Physiol*. 2023;238(8):1625-40. <https://doi.org/10.1002/jcp.31015>.
133. Gonzalez-Suarez I, Redwood AB, Grotsky DA, Neumann MA, Cheng EHY, Stewart CL, et al. A new pathway that regulates 53bp1 stability implicates cathepsin l and vitamin d in DNA repair. *EMBO J*. 2011;30(16):3383-96. <https://doi.org/10.1038/emboj.2011.225>.
134. Gonzalo S. Novel roles of 1α, 25 (oh) 2d3 on DNA repair provide new strategies for breast cancer treatment. *J Steroid Biochem Mol Biol*. 2014;144:59-64. <https://doi.org/10.1016/j.jsbmb.2013.09.009>.
135. Jiang X, Dimou NL, Al-Dabhani K, Lewis SJ, Martin RM, Haycock PC, et al. Circulating vitamin d concentrations and risk of breast and prostate cancer: A mendelian randomization study. *Int J Epidemiol*. 2019;48(5):1416-24. <https://doi.org/10.1093/ije/dyy284>.



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