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REVIEW – CANCER RESEARCH

# Influence of vitamin D signaling on hormone receptor status and HER2 expression in breast cancer

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**Abstract**
*Purpose* Breast cancer is a significant global public health issue. It is the leading cause of death among women around the world, with an incidence increasing annually. In recent years, there has been more and more information in the literature regarding a protective role of vitamin D in cancer. Increasingly preclinical and clinical studies suggest that vitamin D optimal levels can reduce the risk of breast cancer development and regulate cancer-related pathways.
*Method* In this review, we focus on the importance of vitamin D in breast cancers, discussing especially the influence of vitamin D signaling on estrogen receptor and human epidermal growth factor receptor 2 (HER2), two major biomarkers of breast cancer today.
*Conclusion* We discuss the possibility of actual and future targeted therapeutic approaches for vitamin D signaling in breast cancer.

**Keywords** Breast cancer · Vitamin D · Vitamin D receptor · Estrogen receptor · HER2

**Abbreviations**

| | |
|---|---|
| AIs | Aromatase inhibitors |
| ARs | Retinoic acid receptors |
| BC | Breast cancer |
| cAMP | Cyclic adenosine monophosphate |
| CRE | cAMP-responsive element |
| CDH1 | Cadherin 1 |
| CDK | Cyclin-dependent kinase |
| COX2 | Cyclooxygenase 2 |
| CTSL | Cathepsin L |
| CYP | Cytochrome P450 |
| CYP27A1 | 25α-Hydroxylase |
| CYP27B1 | 1α-Hydroxylase |
| DBD | DNA-binding domain |
| DFS | Disease-free survival |
| EDF | Endoxifen |
| ER | Estrogen receptor |
| FXRs | Farnesoid X receptors |
| HER2 | Human epidermal growth factor receptor 2 |
| HIF1α | Hypoxia-inducible factor 1α |
| HDT | 4-Hydroxytamoxifen |
| IGF | Insulin-like growth factor |
| IGF1 | Insulin-like growth factor 1 |
| IL-6 | Interleukin-6 |
| LBD | Ligand-binding domain |
| LXRs | Liver X receptors |
| MAPKP5 | Mitogen-activated protein kinase phosphatase 5 |
| MMP1 | Matrix metalloproteinase 1 |
| MMP9 | Matrix metalloproteinase 9 |
| NDT | N-desmethyl tamoxifen |
| NF-κB | Nuclear factor-κB |
| NRs | Nuclear hormone receptors |
| OS | Overall survival |
| PPARs | Peroxisome proliferator-activated receptors |
| PARPi | Inhibitors of poly(ADP-ribose) polymerase |
| PG | Prostaglandin |
| 15-PGDH | 15-Hydroxyprostaglandin dehydrogenase |
| PGE2 | Prostaglandin E2 |
| PR | Progesterone receptor |
| RTKs | Receptor tyrosine kinases |

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| | |
|---|---|
| RXRs | Retinoid X receptors |
| SAM | Selective aromatase modulators |
| STAT3 | Signal transducer and activator of transcription 3 |
| TGF-β | Transforming growth factor-β |
| TNF-α | Tumor necrosis factor-α |
| SERMs | Selective ER modulators |
| SERDs | Selective ER down-regulators |
| SNPs | Germline single nucleotide polymorphisms |
| TAM | Tamoxifen |
| TIMP1 | Tissue inhibitor of metalloproteinases 1 |
| TNBC | Triple-negative breast cancers |
| TRs | Thyroid hormone receptors |
| VDR | Vitamin D receptor |
| VDREs | Vitamin D response elements |
| VEGF | Vascular endothelial growth factor |

## Introduction

Important predictors of disease-free survival (DFS) and overall survival (OS) for breast cancer (BC) are the patient's and tumor's clinicopathological features including tumor size, histological grade, axillary lymph node metastasis and tumor expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) (also known as ErbB2). However, BC is a complex and extremely heterogeneous disease (Cadoo et al. 2013). Even though many therapies for BC including chemotherapy, endocrine therapy, and target therapies have made a significant contribution to the decrease in BC mortality in the past two decades, resistance to treatment such as anti-estrogen agents is a major clinical problem in current BC treatment. For example, about 25% of the patients with ERα-positive tumors receiving 5-year adjuvant tamoxifen therapy develop recurrent disease within 10 years, and 30–40% of the patients in advanced stage with ERα-positive primary tumors do not respond to anti-estrogen therapy (Lundqvist et al. 2014). Therefore, the key point to significantly increase the survival of the BC patients is the development of more specific biomarkers and the identification of new therapeutic targets to overcome the therapy resistance and metastasis process. It has been suggested that ER mutations and the activation of the bidirectional cross talk between the nuclear receptor ERα and tyrosine kinase receptor signaling pathways play an important role in the endocrine resistance (Hart et al. 2015; Jeselsohn et al. 2015; Milani et al. 2014; Montemurro et al. 2013). Consequently, the growth of most anti-estrogen-resistant cells can be stimulated via estrogen-independent mechanisms, such as the activation of the human epidermal growth factor receptor (HER) family, the insulin-like growth factor (IGF), and the nuclear factor-κB (NFκB) signaling (Musgrove and Sutherland 2009; Voudouri et al. 2015). In addition to receptors for classic steroid hormones such as estrogen and progesterone, some nuclear receptors as members of the thyroid–retinoid receptor family of ligand-activated transcription factors also exert profound and complex effects in the etiology of BC (Ditsch et al. 2013; Narvaez et al. 2014). The nuclear vitamin D receptor (VDR), which is found in normal breast tissue and in breast tumors (Welsh 2007a), interacts with its ligand calcitriol, the active form of vitamin D, to modulate the normal mammary epithelial cell genome and subsequent phenotype (Welsh 2011). Based on the literature that will be discussed below, VDR signaling analysis can probably be the basis for optimal vitamin D control and the development of new targeted therapy to escape resistance mechanisms.

## Vitamin D and vitamin D receptor

The most important sources of vitamin D originate from various dietary sources and from cutaneous synthesis with sunlight exposure (Fig. 1). UVB-catalyzed cutaneous reaction contributes approximately to 90% of vitamin $D_3$ production in a vitamin D-sufficient individual (Tian et al. 1993). It then undergoes hydroxylation in the liver to become the circulating prohormone 25-hydroxyvitamin $D_3$ (25OH-D), also called calcidiol, by the 25α-hydroxylase (CYP27A1) and probably also by other enzymes (CYP2R1) (Cheng et al. 2004). 25OH-D is the major circulating form of vitamin D. Its concentration in the serum has served as one of the most reliable biomarkers of vitamin D status (Heaney et al. 2009). Then, conversion of 25-hydroxyvitamin $D_3$ to 1,25-dihydroxyvitamin $D_3$ ($1,25(OH)_2D$) catalyzed by the 1α-hydroxylase (CYP27B1) encoded by the *CYP27B1* gene in humans is accomplished essentially in the kidneys and in other extra-renal sites (Takeyama et al. 1997), such as placenta, breast, ovaries, lung, stomach, and tumor-derived cells as well (Cross 2007; Jones 2007; Liu and Hewison 2012; Radermacher et al. 2006; Zehnder et al. 2001). The $1,25(OH)_2D_3$, also called calcitriol, can then act within the cells where it is produced (in the case of the kidney), or it can be released into the tissue microenvironment and/or the systemic circulation.

As shown in Fig. 2, $1,25(OH)_2D$, or calcitriol, the most active vitamin D metabolite, acts similarly to classical steroid hormones via specific binding to an intracellular receptor VDR, interacting with specific nucleotide sequences (hormone response elements) of target genes and functions via both genomic and non-genomic pathways to regulate around 60 target genes expression and produce a variety of biological effects (Krishnan and Feldman 2011). Classically, the action of calcitriol has been well established as part of the endocrine system that maintains extracellular calcium levels by regulating calcium absorption in the

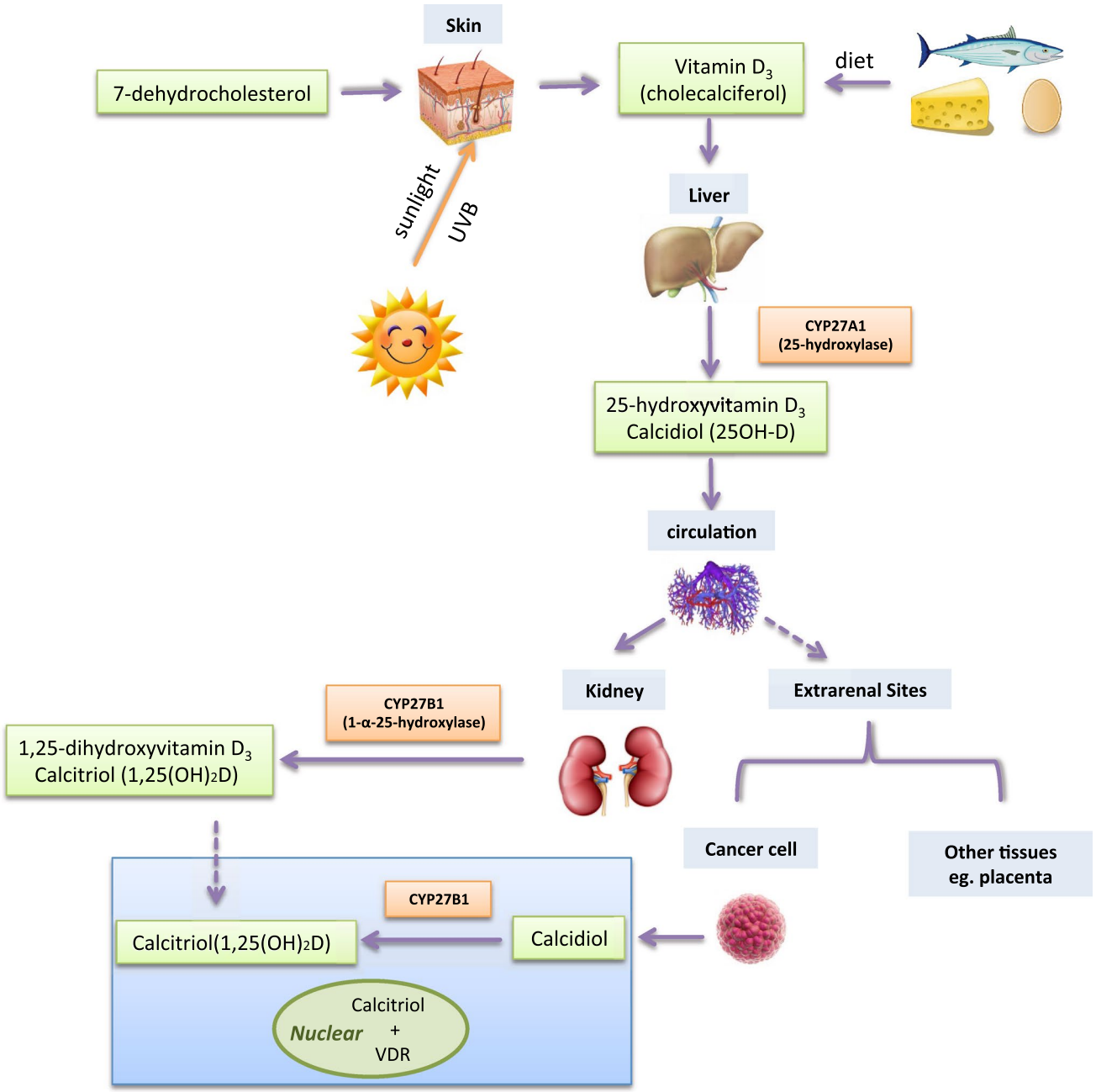


**Fig. 1** Vitamin D metabolism. Vitamin $D_3$ (cholecalciferol) is derived from the diet or synthesized in the skin via the energy of sunlight (ultraviolet B rays) from the precursor 7-dehydrocholesterol. Cholecalciferol is transported to the liver where it is hydroxylated by 25-hydroxylase to form 25-hydroxyvitamin D, also called calcidiol (25OHD), the most abundant and stable vitamin D metabolite. Calcidiol is hydroxylated by 1-α-hydroxylase to 1, 25-dihydroxyvitamin D or calcitriol (1, 25(OH) $_2$D), the most active vitamin D metabolite. The enzyme 1-α-hydroxylase is the cytochrome p450 27B1 (CYP27B1), encoded by the CYP27B1 gene in humans, and is present in the kidneys and in other extrarenal sites including tumors. Calcitriol actions as a steroid hormone are mediated through the vitamin D receptor (VDR), which is a high affinity ligand-activated transcription factor

gut and bone turnover. However, the action of calcitriol is not limited to its endocrine function in bone metabolism. The active metabolite behaves as a hormone and binds to the VDR which is present in nearly all tissues of the human body. In addition, the final enzyme that allows vitamin D activation, the CYP27B1, is present not only in the kidneys but also in many other organs. Both vitamin and enzyme exert their biological effects via paracrine/autocrine actions related to cardiovascular disease, diabetes, cancer, and the immune system (Stocklin and Eggersdorfer 2013).

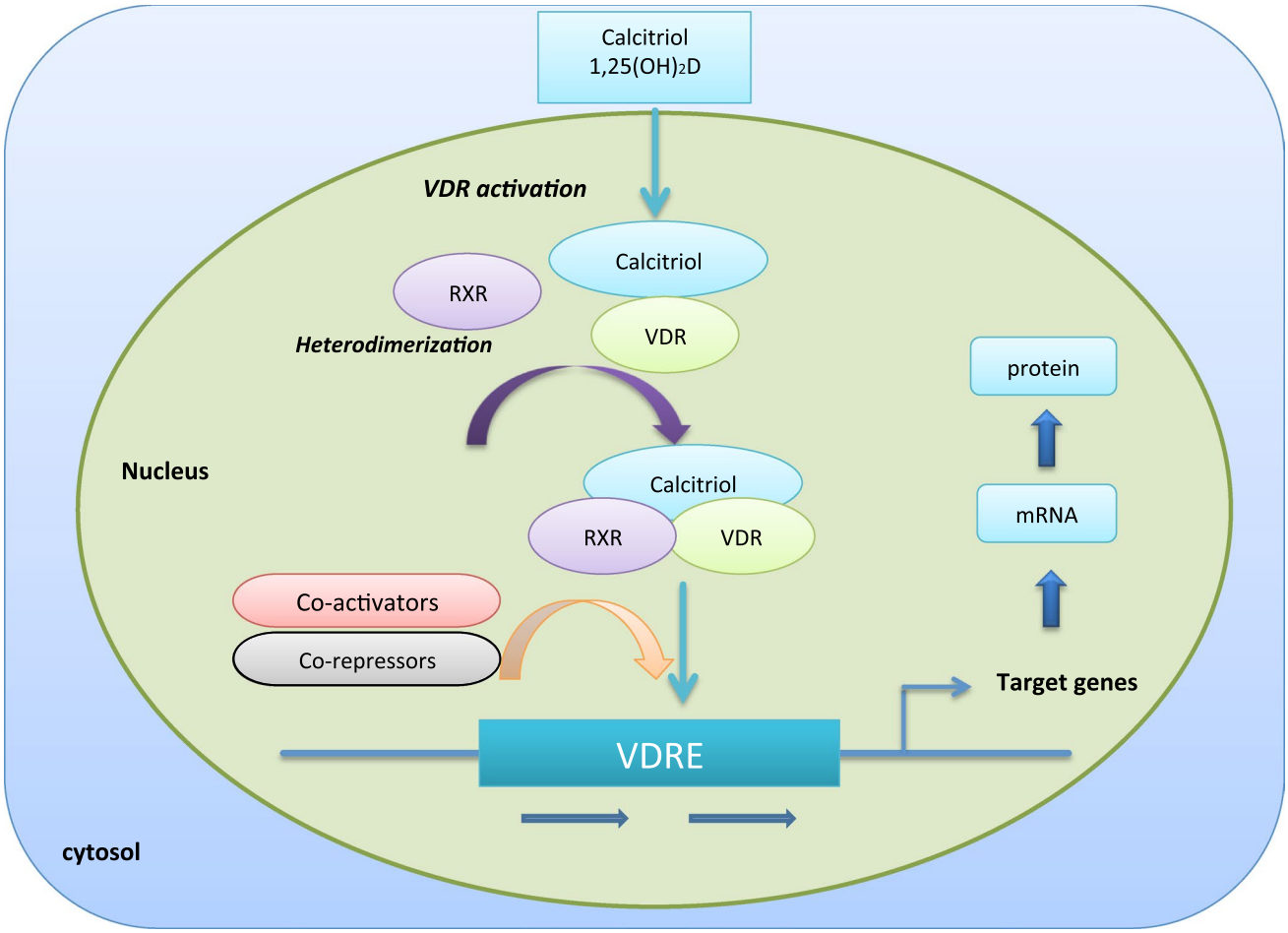


**Fig. 2** Mechanism of VDR action at target cells. Intracellular calcitriol binds to the VDR, thereby causing its dimerization with the retinoid X receptor (RXR). The ligand-bound VDR–RXR complex binds to structurally distinct vitamin D response elements (VDREs) in multiple, widely spaced vitamin D-responsive regions, and this causes a change in the recruitment of co-activators or co-repressors, which leads to positive or negative transcriptional regulation of gene expression

The human VDR (hVDR) gene is localized in chromosome 12q12–14 (Fig. 3) and consists of multiple promoter regions (A–C) followed by the coding region spanning exons 2 through 9 (Khan et al. 2014; Zella et al. 2007). The hVDR (containing 427 amino acids) is a 48-kDa protein with a short N-terminal extension, a DNA-binding domain (DBD) including two zinc finger motifs, each of which contains a single zinc atom in a tetrahedral arrangement with four invariant cysteine residues (DeLuca 2008), a hinge region which allows conformational flexibility, a ligand-binding domain (LBD) that binds $1,25(OH)_2D$, and an AF-2 domain for transcriptional cofactors to bind to (Christakos et al. 2016; Rochel et al. 2000; Welsh 2007b). VDR belongs to the nuclear hormone receptors (NRs) family. The NRs, active as homodimers, have been classified as type 1 NRs, whereas the VDR that bind as heterodimers with another NR, the retinoic X receptor, are known as type 2 NRs (Yen 2015). The type 1 NRs include the estrogen, androgen, progesterone, and mineralocorticoid receptors, and the type 2 NRs include VDR, retinoic acid receptors (RARs), retinoid X receptors (RXRs), thyroid hormone receptors (TRs), peroxisome proliferator-activated receptors (PPARs), liver X receptors (LXRs), and farnesoid X receptor (FXR). RXR plays a pivotal role in mediating the functions of these receptors by acting as their obligate partner. Ligand-bound VDR-calcitriol heterodimerizes with its cognate co-receptor RXR to control expression of genes involved in different functions. Recently, the structure of the ligand-bound VDR–RXR DNA complex was characterized using cryo-electron microscopy (Orlov et al. 2012), suggesting cooperative and allosteric effects between the LBD and the DBD in VDR-mediated regulation of gene expression. The RXR–VDR heterodimer, in contrast to other members of the type 2 NR subfamily, is non-permissive when RXR does not bind its cognate ligand, and its role in VDR-mediated transactivation by liganded

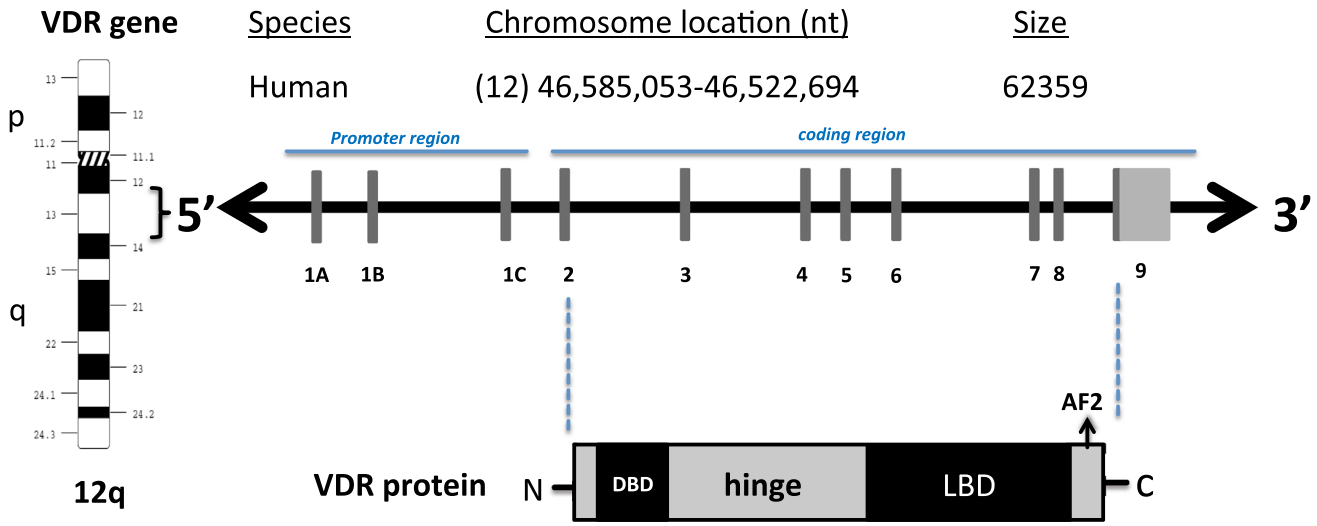


**Fig. 3** Human VDR gene structure and VDR protein. The VDR gene is evolutionarily conserved among fish, birds, and mammals. The human VDR gene is localized on chromosomes 12, which is composed of multiple promoter regions (A–C) and eight coding exons. The two core functional domains of the VDR are the highly conserved NH2-terminal DNA-binding domain (DBD) and the more variable COOH-terminal ligand-binding domain (LBD). The DBD is a cysteine-rich zinc finger region, and the LBD is composed of at least 12 α-helices (H1-H12; the ligand-dependent activation function (AF2) corresponds to H12 and 3 β-sheets (S1-3)). The DBD and the LBD are connected through a hinge region

RXR–VDR has not been fully characterized. However, the scope of calcitriol and VDR biology has expanded to include a wide range of physiological cellular responses (Bettoun et al. 2003; Carson et al. 2014).

## Vitamin D signaling and breast cancer

The ligand-bound VDR–RXR complex binds to vitamin D response elements (VDREs) in multiple regulatory regions inducing positive or negative transcriptional regulation of gene expression. These target genes are involved in diverse molecular pathways, thereby resulting in a wide range of calcitriol-mediated anticancer actions via autocrine and paracrine including anti-proliferation, anti-inflammation, induction of apoptosis, stimulation of differentiation, inhibition of invasion, metastasis and angiogenesis on various malignant cells (Christakos et al. 2016; Diaz et al. 2015; Feldman et al. 2014) (Fig. 4). While the small intestines, bones, and kidneys are the primary organs responsive to calcitriol due to their central role in calcium homeostasis, VDR has been shown to be present in other tissues and organs (Colston 2008), including mammary cells (Diaz et al. 2015).

Although epidemiological and early clinical trials are inconsistent, recent meta-analyses of all relevant, published epidemiological data support the concept that optimal vitamin D status has a protective effect against development of BC (Chen et al. 2010). For instance, large epidemiologic studies have demonstrated that vitamin D deficiency is associated with more aggressive tumors, increased rates of BC recurrence, and a decrease in cancer-specific OS (Abbas et al. 2008; Bertone-Johnson et al. 2005; Lowe et al. 2005). It has been postulated that more than 220,000 new cases of breast and colorectal cancers would be prevented annually worldwide simply by raising serum 25OH-D concentrations to approximately 40–60 ng/mL (Garland et al. 2009). Studies in VDR knockout mice provide evidence that vitamin D signaling through the VDR opposes estrogen-driven proliferation of mammary epithelial cells and maintains normal differentiation (Welsh et al. 2003). Kim et al. (2011) later reported that serum 25OH-D levels were related to BC survival, particularly in the luminal subtype. In our clinic, we analyzed the relationship between VDR expression and survival in 82 BC patients, the result of which indicates high VDR expression in breast tumors is associated with better survival (Ditsch et al. 2012). Meanwhile, a meta-analyses of 8 studies including 5691 BC patients support that there is an association of low levels of vitamin D with increased risk of recurrence and death in early stage BC patients (Rose et al. 2013). Meanwhile, the other four meta-analyses identified a significant inverse relationship between the circulating concentrations of vitamin D and BC (Chen et al. 2013; Gandini et al. 2011; Kim and Je 2014; Yin et al. 2010). Given calcitriol exerts its anticancer activity by binding to VDR, VDR gene polymorphism should be associated with BC risk. As discussed above, many population-based reports conclude that BC risk was associated with specific vitamin D-related germline single nucleotide polymorphisms (SNPs) (e.g.,

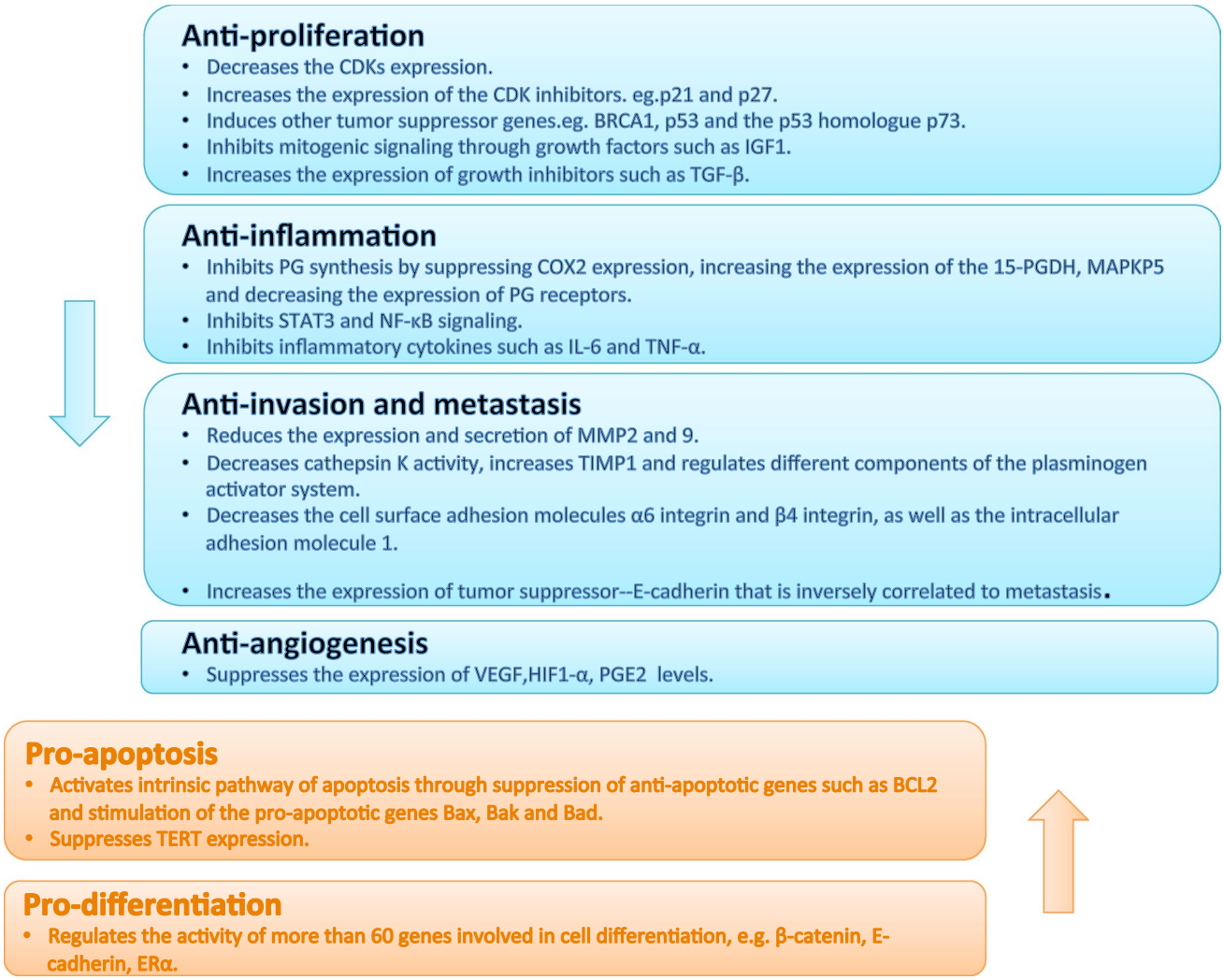


**Fig. 4** Anticancer effect of calcitriol. The actions of up-regulating or down-regulating different molecular targets result in a wide range of calcitriol-mediated anticancer actions, as summarized in this figure

Cdx-2, FokI, BsmI, ApaI, and TaqI), supporting the biological plausibility of a relationship between vitamin D and BC risk (Mun et al. 2015; Nemenqani et al. 2015; Reimers et al. 2015; Zhang and Song 2014). Since different subtypes exhibit distinct patterns of disease progression, it is likely that VDR expression or function, and thus sensitivity to changes in vitamin D status, may be subtype specific, yet this has not rigorously been explored. For the purpose of this review, we will focus from a new angle on the influence of vitamin D signaling on the 3 broad phenotypes of BC commonly used in clinical practice: estrogen receptor (ER) positive, human epidermal growth factor receptor 2 (HER2) positive, and triple negative (TNBC, characterized by lack of expression of ER, PR, and HER2). Clearly, specific distinct signaling pathways can inhibit BC growth through calcitriol.

## Vitamin D signaling in ER-positive breast cancers

The role of estrogen in breast carcinogenesis and cancer progression has been already clearly established as early as in 1896 since Beatson's (1896) first clinical observation of the anti-tumor effect of ovariectomy in a BC patient. The effects of estrogen on proliferation are mainly mediated by their interaction with the estrogen receptor (ER). Estrogens drive the proliferation of mammary epithelial cells and therefore promote the growth of ER-positive BC. At the gene expression level, ER-positive BC mainly composes luminal A and luminal B subtypes. Approximately 75% of BCs express nuclear staining of ER and 55% of PR (Anderson et al. 2002; Nadji et al. 2005). PR positivity can be considered as a surrogate for ER positivity due to the expression of the PR requiring functioning ER (Cadoo et al.

2013). Some epidemiologic studies have suggested that intake of vitamin D reduced risk of ER-positive BC (Blackmore et al. 2008; Kawase et al. 2010; McCullough et al. 2005; Rollison et al. 2012) while vitamin D deficiency is associated with poor outcomes in luminal type BC patients (Kim et al. 2011). Notably, ER-positive cells tend to express higher levels of VDR than ER-negative cells (Buras et al. 1994). Therefore, calcitriol mediates actions that are especially effective in ER-positive BC.

### Calcitriol suppresses the expression of aromatase, reducing estrogen synthesis, via direct and indirect pathways

Aromatase, encoded by the *CYP19A1* gene, is the enzyme that catalyzes estrogen synthesis from androgenic precursors. It is mainly expressed in the ovaries of premenopausal women, and therefore, inhibition of aromatase is now one of the key strategies in BC treatment. Circulating estrogen levels from the ovaries dramatically decline after menopause but estrogen is still synthesized within extragonadal organs particularly in adipose tissue including breast, bone, and brain (Lumachi et al. 2015). Adipose tissue is the major site of estrogen biosynthesis in postmenopausal women, with the local production of estrogen in breast adipose tissue implicated in the development of BC and aromatase expression being higher in human BC than in normal breast tissue (Chen 1998). In human adipose tissue, aromatase is primarily expressed in the mesenchymal stromal cells and is a marker of the undifferentiated pre-adipocyte phenotype (Rubin et al. 2000). In a vitamin D-relevant study (Krishnan et al. 2010a, b), authors demonstrated new mechanisms by which calcitriol can suppress the expression of aromatase, thereby reducing estrogen synthesis via direct and indirect pathways. Firstly, calcitriol significantly decreases aromatase expression in both ER-positive (MCF-7, ZR-75-1, and T47-D) and ER-negative (MDA-MB-231) human BC cell lines and reduces total aromatase mRNA levels and aromatase enzymatic activity, in a cell model of pre-adipocyte. Then, the authors showed that aromatase expression decreases after calcitriol administration to nude mice carrying MCF-7 xenografts, as well as in the mammary adipose tissue surrounding the xenograft tumors. Interestingly, this calcitriol inhibition of aromatase expression is tissue selective, as the authors described a parallel significant increase of the aromatase mRNA level in human osteosarcoma cells, confirming earlier reports of calcitriol-mediated up-regulation of aromatase in osteoblasts (Enjuanes et al. 2003; Tanaka et al. 1996; Yanase et al. 2003). Besides, a modest increase in aromatase mRNA was observed in human ovarian cancer cells after calcitriol treatment, whereas in mice bearing MCF-7 xenografts, calcitriol administration did not alter ovarian aromatase mRNA. Previously, Kinuta et al. (2000) reported that VDR null mutant mice have a decreased aromatase activity in the ovary, testis, and epididymis. Using different promoters distributed over a regulatory region upstream of the CYP19A1 gene, the expression of CYP19A1 was shown to be regulated in a tissue-selective manner (Bulun and Simpson 2008). The promoters that drive CYP19A1 gene expression may differ between tissues, but also between normal and cancer tissues. For example, aromatase transcription switches from promoter I.4 of CYP19A1 in normal breast adipose tissue to predominantly promoter I.3 and promoter II both in the tumor epithelial cells and in the surrounding breast adipose fibroblasts (BAFs) (Bulun et al. 2009; Krishnan et al. 2010a, b; Simpson et al. 2002; Zhou and Chen 1999). Aromatase promoter I.3/II is a cyclic adenosine monophosphate (cAMP)-responsive promoter, with a cAMP-responsive element (CRE) that overlaps the proximal VDRE (Krishnan et al. 2010b; Zhou and Chen 1999). It is possible that the occupancy of the VDRE by a VDR-RXR heterodimer may competitively inhibit the positive regulator CRE-binding protein-1 from binding to the CRE, leading to a decrease in aromatase transcription. The promoter-reporter assay and ChIP analysis performed by Krishnan et al. support this hypothesis and concluded that calcitriol directly represses aromatase transcription in the promoter II of CYP19A1 in BC cells, through 2 putative VDREs: a distal VDRE (at −373 to −358 bp) and a proximal VDRE (at −299 to −284 bp) (promoter II transcriptional start site as −1), identified in this promoter. Therefore, the tissue-specific regulation of aromatase expression by calcitriol in BC could be explained by either the differential use of aromatase promoters induced by calcitriol treatment of the different cell types, and/or by the differences in factors such as the various co-modulators recruited by calcitriol-bound VDR to the aromatase promoter.

Furthermore, Lundqvist et al. (2013) showed that EB1089, a vitamin D analogue with less pronounced hypercalcemic effect, is able to decrease the aromatase gene expression and enzyme activity, as well as inhibits aromatase-dependent cell growth. The molecular mechanism for this effect of EB1089 was investigated and found to be mediated by VDR, vitamin D receptor interacting repressor (VDIR), and Williams syndrome transcription factor (WSTF). The data generated by ChIP and Re-ChIP assays revealed that EB1089 leads to an altered binding of nuclear receptors/co-modulators to the CYP19A1 gene promoter, where VDR is recruited to the promoter, while WSTF is dissociated and therefore decreases the gene expression. These results also support the hypothesis that WSTF might act as an activator of CYP19A1 gene expression. This publication reported a new mechanism with the

regulation of the aromatase expression via an interaction between the CYP19A1 promoter and the co-modulators WSTF and VDIR.

Above all, the repression of aromatase transcription via CYP19A1 promoter through VDREs identified in the promoter is a direct pathway to reduce estrogen synthesis.

Meanwhile, Krishnan's study also proved indirect effect decreasing aromatase transcription by reducing the levels of prostaglandins (PGs), which are known stimulators of aromatase transcription in BC cells (Krishnan et al. 2010b). PGs secreted by BC cells or other infiltrating inflammatory cells at the tumor sites stimulate local estrogen synthesis within the breast and thus promote cancer cell proliferation by autocrine/paracrine actions. Cyclooxygenase-2 (COX-2) is the key enzyme required to convert arachidonic acid (AA) to PGs and 15-hydroxyprostaglandin dehydrogenase (15-PGDH) initiates PGs inactivation (Brodie et al. 2001; Brueggemeier et al. 1999; Davies et al. 2002; Davies 2003). The authors showed that calcitriol reduces the levels of biologically active PGs in BC cells by decreasing COX-2 and increasing 15-PGDH expression (Krishnan et al. 2010a, 2012). However, the mechanism for vitamin D-mediated suppression of gene expression by VDR remains unclear. It should be pointed out that PGs are pro-inflammatory molecules that play an important role in the development and progression of BC (Krishnan and Feldman 2011; Thill et al. 2015). An elevated expression of COX-2 in BC is associated with larger tumor size, high histological grade, and poor prognosis (Ristimaki et al. 2002; Harris et al. 2014). In both ER-positive and ER-negative human BC cells, calcitriol can then decrease the expression of COX-2 and increases that of 15-PGDH, thereby limiting the synthesis and biological actions of pro-inflammatory PGs.

### Calcitriol also down-regulates ERα expression

Downstream the aromatase, ERα is the other key protein for the proliferative response to estrogens, implicated in promoting growth and survival of breast epithelial cells (Chan et al. 2015). Earlier literatures (James et al. 1994; Simboli-Campbell et al. 1997; Stoica et al. 1999; Swami et al. 2000) have revealed that calcitriol down-regulates ERα expression in BC cells. Stoica et al. (1999) and Swami et al. (2000) both showed that the negative regulation of ER expression by calcitriol occurred at the transcriptional level and this transcriptional repression is probably directly mediated through the binding of the VDR to one or more negative VDREs (nVDREs) present in the ER promoter. The study (Swami et al. 2013) analyzed the functional activities of 2 nVDREs sites within the ~3.5 kb promoter region of the ERα gene and demonstrated presence of these 2 potential nVDREs. One of these sites, the proximal nVDRE identified previously by Stoica et al. (1999), is an imperfect palindromic sequence located at −94 to −70 bp of the ER gene with reference to the P1 start site, the major start site in ER BC cells (deConinck et al. 1995). The other putative nVDRE was newly identified at −2488 to −2473 bp (distal nVDRE). In this study, transactivation analysis revealed that both nVDREs functioned to mediate calcitriol transrepression. Using an electrophoretic mobility shift assay (EMSA), VDR showed strong binding to both nVDREs in the presence of calcitriol, and ChIP experiment demonstrated the recruitment of the VDR to the distal nVDRE site. In conclusion, the ER promoter region was characterized as containing 2 negative VDREs that act in concert to bind to the VDR and both nVDREs are required for the maximal inhibition of ER expression by calcitriol.

Consequently, by both actions, reducing estrogen synthesis and down-regulating ERα levels, calcitriol attenuates the stimulus of estrogen on BC cells, leading to significant inhibition of BC cells proliferation.

### Calcitriol as enhancer of endocrine therapy

Approximately 75% of BC are ER positive and are supposed to be responsive to endocrine therapy. The hormone therapies used to treat ER-positive BC are designed to antagonize the mitogenic effects of estrogens and include: selective ER modulators (SERMs) such as tamoxifen (TAM) and raloxifene that bind to ER and act as antagonists in the breast (Frasor et al. 2004); selective ER down-regulators (SERDs) such as fulvestrant that bind to and target ER for degradation in any tissues (Woode et al. 2012); and aromatase inhibitors (AIs) that inhibit the activity of aromatase (CYP19A1) (Johnston and Dowsett 2003).

TAM, as a first generation breast cancer drug treatment, is the main adjuvant endocrine therapy for premenopausal and postmenopausal ER-positive BC. It undergoes hepatic bioactivation by cytochrome P450 (CYP) enzymes, CYP3A4/5 and CYP2D6, to produce primary metabolites N-desmethyl tamoxifen (NDT) and 4-OH-tamoxifen (HDT) and the active metabolite endoxifen (EDF) (Brauch et al. 2009; Higgins and Stearns 2011; Zembutsu 2015). Teft et al. (2013) indicated for the first time that environmental factors such as sunlight exposure and vitamin D status may impact tamoxifen metabolism in their prospective study of 196 breast cancer patients on tamoxifen over a 24-month periods: EDT levels were 20% lower during winter months than mean levels across seasons, which was also associated with lower vitamin D levels. Marina V. Antunes's group also found concentrations of EDF and HTF in summer were 24 and 42% higher compared with winter, which means vitamin D is involved in TAM metabolism, but they pointed that vitamin D level does not interfere tamoxifen biotransformation through CYP3A4, but maybe through other mechanisms (Antunes et al. 2015).

Although the importance of vitamin D deficiency is recognized in the BC treatment, much less is known about how vitamin D levels can be changed during cancer treatment. Studies have found that during chemotherapy, serum vitamin D levels are low and cannot be corrected by supplementation (Crew et al. 2009; Kailajarvi et al. 2004; Santini et al. 2010). Kim's study showed this consistent result that vitamin D levels decrease during chemotherapy but recover after treatment ends. And his research is also one of the first studies to examine the effect of tamoxifen treatment on serum 25OH-D levels in BC patients: Unlike chemotherapy, anti-hormone therapy with tamoxifen causes serum vitamin D levels to increase. Whether the increased serum vitamin D affects the anti-tumor effect of the tamoxifen has yet to be determined (Kim et al. 2014). Escaleira et al. (1993) for the first time reported that VDR content was upregulated in a dose-dependent fashion by TAM treatment in BC cell line (T47D) alone. However, there are still limited studies to establish the influence on vitamin D levels changes during TAM treatment.

Currently, AIs are the first-line therapy to prevent BC progression in postmenopausal women following primary surgery/radiotherapy therapies (Riemsma et al. 2010). The treatment is associated with adverse effects due to inhibition of aromatase in bone cells, and a large group of patients develop resistance to the AI. High-dose vitamin D supplementation can reduce aromatase inhibitor-induced arthralgia (Khan et al. 2010). With administration of the combinations of calcitriol and AIs, David Feldman et al. observed enhanced growth inhibitory effects in cell culture (MCF-7) and statistically significant increases in xenograft tumor shrinkage in nude mice compared to the individual agents at the doses tested (Krishnan et al. 2010b). Besides, Lundqvist et al. (2013) combined a low dose of a vitamin D analogue commercialized by Tocris Biosciences (Minneapolis, MN), EB1089, with low doses of clinically used AIs. The authors demonstrated that the combination was able to effectively inhibit aromatase-dependent growth of BC cells. In addition, a study using an induced estrogen receptor (ER)-positive mammary tumor and an ER-negative mammary tumor models from Lee et al. (2008) suggested that Gemini vitamin D analogues may be potent agents for the prevention and treatment of both ER-positive and ER-negative BC without hypercalcemia toxicity. Based on their respective studies, it can be concluded that calcitriol or its analogue can act as selective aromatase modulators (SAM), selectively decreasing aromatase expression in breast, but allowing estrogen synthesis at other desirable sites such as bones. Therefore, patients should be given vitamin D supplements not only to overcome therapeutic adverse effects like musculoskeletal symptoms, osteoporosis, and arthralgia but also function as an enhancer of endocrine therapy.

### Calcitriol and resistance to endocrine therapy

As mentioned above, TAM, as a successful ER antagonist for pre- and postmenopausal women of BC, fulvestrant another ER antagonist especially for postmenopausal women with metastatic BC, and AIs, which show greater efficacy than TAM for post-menopausal women, are the best drugs available to combat BC. However, during treatment, either de novo or acquired resistance is observed in most patients. Various complex mechanisms support endocrine resistance such as ER variants; ER/aromatase mutations; posttranscriptional/translational modifications of aromatase; or non-genomic ER signaling pathways leading to ER activation (Jeselsohn et al. 2015; Montemurro et al. 2013), but one of the key steps is activation of ER or change in ER behavior (Chan et al. 2015). As already described, VDR down-regulates ER expression and suppresses aromatase expression by independent mechanisms. Christensen et al. (2004) demonstrated a sequential treatment with combination between anti-estrogens and EB1089 in anti-estrogen and vitamin D-resistant BC cell lines, demonstrating that vitamin D analogues such as EB1089 may be a possible combinatory treatment option after development of anti-estrogen resistance and that VDR can be a potential predictive marker for response to EB1089 treatment. Yde et al. (2012) provided evidence that NFκB signaling is enhanced in anti-estrogen-resistant BC cells and plays an important role for anti-estrogen-resistant cell growth and sensitivity to tamoxifen treatment in resistant cells. Afterward, Lundqvist et al. (2014) demonstrated that calcitriol is able to strongly decrease the growth of both tamoxifen-sensitive and resistant BC cells and that this anti-proliferative effect might be mediated via inhibition of the NFκB pathway, reported as a key element for growth of anti-estrogen-resistant BC cells and estrogen-independent growth stimulatory pathway. As such, we can hypothesize that VDR determination can probably be a basis for the development of new targeted therapy to escape some resistance to anti-estrogen, as independent molecules or most presumably in combination with other drugs.

## Vitamin D signaling in HER2-positive breast cancers

The epidermal growth factor receptor (EGFR) consists of four closely related receptor tyrosine kinases (RTKs): EGFR (ErbB-1), HER2/c-neu (ErbB-2), Her3 (ErbB-3), and Her4 (ErbB-4) (Elster et al. 2015; Roskoski 2014). This family of receptors functions primarily through a process of signal transduction (Karunagaran et al. 1996): the ligand-binding to the receptors induces homo- or

hetero-dimerization, activates the kinase domain, and then activates downstream signaling such as the Ras/MAPK and PI3K/AKT signaling pathways (Hynes and Lane 2005). Aberrant signal transduction through the EGFR family of RTKs is a common feature of many types of solid tumors (Yarden and Sliwkowski 2001). HER2, a transmembrane protein RTK, hetero-dimerizing with ErbB3 (Baselga and Swain 2009) is an oncogenic driver of the growth of HER2-positive BC. Either HER2 gene amplification or protein overexpression was independent of all other prognostic factors in BC (Ross et al. 2003). Approximately 15–20% of breast carcinomas are HER2 positive (HER2+), and half are ER negative (Olson et al. 2013; Wolff et al. 2013) which is generally considered to be a poor prognostic marker associated with more aggressive disease and a higher risk of metastasis. Nonetheless, the approval of newer HER2-targeted agents, e.g., trastuzumab, succeeds in the last 10 years in improving the prognosis of these patients (Zurawska et al. 2013).

Beside many hypothesis based on cell model results, Zeichner' study was the first to report a significant improvement in the DFS in a cohort of 308 HER2-positive patients. Patients received vitamin D supplementation (10,472 IU/week) concurrently with trastuzumab-based neoadjuvant therapy for HER2-positive non-metastatic BC regardless of ER status (Zeichner et al. 2015). In their one previous study (Lee et al. 2010), using a MMTV-ErbB2 transgenic mouse model (ER-negative/HER2-positive subtype of BC), they demonstrated that a Gemini vitamin D analogue, BXL0124 (commercialized by BioXell, Inc. (Nutley, NJ)), reduced ErbB2-regulated downstream signaling in both ErbB2-amplified mammary tumors in vitro and in vivo, determined by down-regulation of the phosphorylation of ErbB2, AKT, and ERK, and inhibited the expression of cyclin D1 as a downstream molecular target of cell proliferation. The specific mechanism for vitamin D-mediated VDR signaling suppression is still unknown. Furthermore, another study from them identified again that BXL0124 targeted multiple components of the ErbB2 signaling pathway and delayed the development of ErbB2-overexpressing mammary tumors. In this study, BXL0124 decreased mammary tumor burden by 30%, although the effect was lower than previously reported (54%). It has been noted that MMTV-ErbB2/neu mice were previously administered BXL0124 by intraperitoneal injection, whereas identical MMTV-ErbB/neu mice were given BXL0124 by oral gavage in the latter study (So et al. 2013).

The complete efficacy of the ligands for VDR has then not been reported in MMTV-ErbB2/neu mice model, which may indicate that the natural calcitriol and classic synthetic ligands alone have limited activity in ErbB2-positive BC. However, Gemini vitamin D analogues, especially BXL0124, used in combination, may be potent agents for prevention of different types of human BC without toxicity, especially for the HER2 overexpressing one.

## Vitamin D signaling in triple-negative breast cancers

Triple-negative breast cancers (TNBCs) represent 15–20% of all BCs (Kalimutho et al. 2015) and are defined by a lack of ER, PR, and HER2 expression, resulting in limited treatment options. TNBCs are more aggressive, affect younger women, than ER or HER2-positive BC, and are higher in incidence among women of African descent. In addition, TNBC have demonstrated both a higher rate of recurrence and a worse clinical outcome compared to the other subtypes of BC. Due to the lack of well-defined clinical targets, limited treatment options are offered and standard chemotherapy, combined or not with radiation therapy, is currently the only treatment option for women with TNBC, and there are no available preventive drugs (den Hollander et al. 2013). The TNBC phenotype appears as exhibiting the lowest average vitamin D level (50 ± 20 nmol/L) and the highest percentage (87%) of patients that are vitamin D deficient (Rainville et al. 2009). Moreover, among premenopausal BC women only, 25OH-D concentrations were significantly lower in women with tumors with poor prognostic characteristics (high grade, ER negative, and triple negative) than those with better prognostic features (Yao et al. 2011).

Recently, separate pre-clinic studies raised the possibility of developing novel VDR-targeted therapies for TNBC. Thakkar et al. (2016) previously discovered that approximately two-thirds of TNBCs express VDR and demonstrate that VDR agonist can be used in combination with chemotherapy to inhibit proliferation of TNBC cell lines (BT-549, SUM-1315, BT-20, MDA-MB-468, SUM-159PT, MFM-223, and CAL-148) by increased apoptosis and G1/S arrest. In addition, this hormone inhibits TNBC cancer stem cells phenotype and induces differentiation. Another research showed that both calcitriol and MART-10, the newly synthesized calcitriol 3 analog, could effectively attenuate TNBCs (MDA-MB-231 and MDA-MB-453) metastatic potential through repression of epithelial mesenchymal transition (EMT) process and induction of cadherin switching (up-regulation of E-cadherin and down-regulation of N-cadherin) with MART-10 much more potent than calcitriol (Chiang et al. 2016). Another two reports also show that the SUM159-PT and WT145 cell line are both triple negative and sensitive to growth inhibition by calcitriol or vitamin D analogue (Flanagan et al. 2003; LaPorta and Welsh 2014). Nonetheless, Richards et al. (2015) showed quite an unexpected result that three examples of TNBC cell lines (MDA-MB-157,

MDA-MB-231 and MDA-MB-468) are resistant to the anti-proliferative effects of vitamin D in their study. It is possible that due to the p53 status of these cells with lacking p53 (MDA-MB-157) or a mutant form (MDA-MB-231 and MDA-MB-468), non-function of p53 could turn vitamin D from pro-apoptotic to anti-apoptotic, based on a paper by Stambolsky et al. (2010). But most of TNBCs are p53 mutant (Hirshfield and Ganesan 2014), so further studies are needed to clarify the issue and make a comparison of growth inhibition with vitamin D between these cell lines and TNBC cell lines with normal p53 status. Be that as it may, vitamin D may not play a key role in the treatment of TNBC on his own, but may contribute to improve the efficacy of other targeted drugs in combination. In addition, Santos-Martinez et al. (2014) demonstrated that calcitriol induces the expression of ERα and restores the response to anti-estrogens in both primary and established ERα-negative BC cell lines (SUM-229PE) by a VDR-dependent mechanism. The combined treatment with calcitriol and anti-estrogens could then represent a new therapeutic strategy in ERα-negative BC patients including TNBC. It should be pointed that all the findings were observed only in BC cell lines, so in vivo studies regarding the application of calcitriol or its analogue to treat TNBC are warranted.

Another major breakthrough in targeted therapy was the finding that TNBCs are exquisitely sensitive to poly-ADP-ribose polymerase inhibitors (PARPi), especially when BRCA1/2 is mutated (Farmer et al. 2005; Helleday et al. 2005; Livraghi and Garber 2015).

## Calcitriol and BRCA1

BRCA1-mutant cancers are a clearly identifiable subset of TNBCs (Hirshfield and Ganesan 2014). BRCA proteins including BRCA1 and 2 have distinct functions in related DNA repair processes; comparing to BRCA2, BRCA1 seems to have a relatively broad cellular role, having been implicated in a range of cellular processes such as DNA repair, transcriptional regulation, and chromatin remodeling (Romagnolo et al. 2015). BRCA1 is the most frequently mutated tumor suppressor gene in BC. Carriers of germline mutations in the BRCA1 gene have a significant increased lifetime risk of being diagnosed with BC (Friebel et al. 2014). A report showed that two non-calcemic analogues of calcitriol, EB1089 and QW-1624F2-2, collaborate with BRCA1 in mediating growth inhibition of BC cells and BC stem-like cells. EB1089 induces a G1/S phase growth arrest that coincides with induction of p21waf1 expression only in BRCA1-expressing cells. Furthermore, BRCA1 associates with VDR and the complex co-occupies VDRE at the CDKN1A promoter (encoding p21waf1) and enhances acetylation of histone H3 and H4 at these sites. Thus, BRCA1 expression is critical for mediating the biological impact of calcitriol in BC cells (Pickholtz et al. 2014). Loss of BRCA1 leads to activation of cysteine protease cathepsin L (CTSL)-mediated degradation of 53BP1 and that calcitriol via activation of VDR can inactivate this pathway. CTSL-mediated degradation of 53BP1 pathway will be discussed in the next paragraph. For the moment, chemoprevention (risk-reducing medication) reducing BC incidence in high-risk populations is potentially confined to ER-positive tumors (Jatoi and Benson 2016). Referring women who carry BRCA mutations for risk-reducing, bilateral prophylactic mastectomy is the only safe option to save their life. Besides, preventive agents can be considered with non-steroidal anti-inflammatory drugs, including aspirin, COX-2 inhibitors, retinoids, and rexinoids (Litzenburger and Brown 2014). This suggests that targeting VDR signaling may represent a plausible, non-surgical prevention option to evaluate for BRCA mutation carriers.

## Calcitriol and PARPi

The use of PARPi as single agents or in combination with radiation and chemotherapy represents a leading strategy for the management of BC, especially TNBC. However, a significant fraction of these cancers acquires also resistance to PARPi. One of the reasons is that loss of 53BP1 protein induces resistance of BRCA1-deficient cells to PARPi (Jaspers et al. 2013). 53BP1 is a key factor in DNA double-strand breaks (DSBs) repair, and its deficiency is associated with genomic instability and cancer progression. Interesting studies (Gonzalez-Suarez et al. 2011; Gonzalo 2014) revealed that calcitriol can stabilize 53BP1 level and inhibit CTSL-mediated degradation of 53BP1 pathway, in which CTSL inhibits mechanisms of DNA repair, contributing to BC with the poorest prognosis (Grotsky et al. 2013). Consequently, a triple biomarker signature was introduced (nuclear expression levels of VDR, CTSL, and 53BP1) for the identification of patients that could benefit from the treatment.

It is important to point out that calcitriol could induce the *de novo* expression of the epithelial differentiation marker E-cadherin by Cadherin 1 (CDH1) promoter demethylation in the highly metastatic, triple-negative MDA-MB-231 breast cancer cell line (Lopes et al. 2012). This is the first report of the *de novo* induction of E-cadherin in BC by calcitriol due to promoter demethylation, thereby revealing a novel mechanism for the action of calcitriol in BC cells. The induction of differentiation promoted by calcitriol in metastatic TNBC may decrease the aggressiveness of this subtype of mammary carcinomas and improve patient outcome, but further studies are necessary to confirm this hypothesis.

## Vitamin D supplement and vitamin D analogues

Despite compelling data from experimental and observational studies, there is still insufficient data from clinical trials to make recommendations for vitamin D supplementation for BC prevention or treatment. Calcitriol and its structural analogues have been evaluated as therapeutic agents in cancer patients, but most of the clinical trials were conducted in prostate cancer, with relatively few studies in other malignancies, and none of them is currently used in the clinic for the treatment of cancer (Crew 2013; Leyssens et al. 2014). A large randomized clinical trial WHI showed that administering 400 IU vitamin D and 1000 mg of calcium versus placebo to women did not reduce the risk of BC (Chlebowski et al. 2008). The Institute of Medicine (IOM) concluded that for cancer and vitamin D, the evidence was inconsistent and insufficient to inform nutritional requirements (Ross et al. 2011). Therefore, vitamin D supplementation for BC prevention or treatment is uncertain. However, an inverse association between vitamin D levels and BC risk was explicit in the majority of studies (Abbas et al. 2008; Bertone-Johnson et al. 2005; Chen et al. 2013; Gandini et al. 2011; Kim et al. 2011; Kim and Je 2014; Lowe et al. 2005; Rose et al. 2013; Yin et al. 2010). Further investigation should focus on gaining a better understanding of the biological effects of vitamin D in breast tissue and better define the clinical impact of vitamin supplementation in BC development, and then a more accurate dosage of vitamin D for both prophylactic and therapeutic purposes can be established. Several vitamin D analogues have been approved for treating psoriasis, osteoporosis, and secondary hyperparathyroidism and are often used as first- or second-line treatment option. Different combinations of vitamin D analogues and standard cancer therapies should be further explored as well as the correct duration and timing of administration. There is a long way to go but development of actual and new vitamin D analogues may improve to be very important for new targeted therapy in the future. In addition, vitamin D concentrations should be measured regularly. With the low cost of supplement and little adverse effects, vitamin D can be suggested to apply for high-risk women and BC survivors as a modified risk factor (Crew 2013).

## Conclusion

The mechanisms for vitamin D-mediated suppression of BC-relevant gene expression appear as being complex and have still to be deciphered. Nonetheless, it has been reported that VDR can bind both to promoter regions and within gene introns and exons in breast normal and cancer tissues and therefore alter the gene expression. In this comprehensive review, we outlined the potential therapeutically influence of vitamin D signaling on ER and HER2 which thus provide more possibilities and new approaches for future research in BC: VDR can be new prognostic biomarker of BC, and VDR may be subtype specific in BC; vitamin D and its analogues, combined with AIs or TAM, might improve therapy and decrease resistances.

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**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest.

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## References

Abbas S, Linseisen J, Slanger T, Kropp S, Mutschelknauss EJ, Flesch-Janys D, Chang-Claude J (2008) Serum 25-hydroxyvitamin D and risk of post-menopausal breast cancer–results of a large case-control study. Carcinogenesis 29:93–99. doi:10.1093/carcin/bgm240

Anderson WF, Chatterjee N, Ershler WB, Brawley OW (2002) Estrogen receptor breast cancer phenotypes in the surveillance, epidemiology, and end results database. Breast Cancer Res Treat 76:27–36

Antunes MV et al (2015) Influence of CYP2D6 and CYP3A4 phenotypes, drug interactions, and vitamin D status on tamoxifen biotransformation. Ther Drug Monit 37:733–744. doi:10.1097/FTD.0000000000000212

Baselga J, Swain SM (2009) Novel anticancer targets: revisiting ERBB2 and discovering ERBB3. Nat Rev Cancer 9:463–475. doi:10.1038/nrc2656

Beatson G (1896) On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment, with illustrative cases. Lancet 148:104–107. doi:10.1016/s0140-6736(01)72307-0

Bertone-Johnson ER, Chen WY, Holick MF, Hollis BW, Colditz GA, Willett WC, Hankinson SE (2005) Plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D and risk of breast cancer. Cancer Epidemiol Biomark Prev 14:1991–1997. doi:10.1158/1055-9965.EPI-04-0722

Bettoun DJ et al (2003) Retinoid X receptor is a nonsilent major contributor to vitamin D receptor-mediated transcriptional activation. Mol Endocrinol 17:2320–2328. doi:10.1210/me.2003-0148

Blackmore KM, Lesosky M, Barnett H, Raboud JM, Vieth R, Knight JA (2008) Vitamin D from dietary intake and sunlight exposure and the risk of hormone-receptor-defined breast cancer. Am J Epidemiol 168:915–924. doi:10.1093/aje/kwn198

Brauch H, Murdter TE, Eichelbaum M, Schwab M (2009) Pharmacogenomics of tamoxifen therapy. Clin Chem 55:1770–1782. doi:10.1373/clinchem.2008.121756

Brodie AM et al (2001) Aromatase and COX-2 expression in human breast cancers. J Steroid Biochem Mol Biol 79:41–47

Brueggemeier RW, Quinn AL, Parrett ML, Joarder FS, Harris RE, Robertson FM (1999) Correlation of aromatase and cyclooxygenase gene expression in human breast cancer specimens. Cancer Lett 140:27–35

Bulun SE, Simpson ER (2008) Aromatase expression in women's cancers. Adv Exp Med Biol 630:112–132

Bulun SE, Lin Z, Zhao H, Lu M, Amin S, Reierstad S, Chen D (2009) Regulation of aromatase expression in breast cancer tissue. Ann N Y Acad Sci 1155:121–131. doi:10.1111/j.1749-6632.2009.03705.x

Buras RR, Schumaker LM, Davoodi F, Brenner RV, Shabahang M, Nauta RJ, Evans SR (1994) Vitamin D receptors in breast cancer cells. Breast Cancer Res Treat 31:191–202

Cadoo KA, Fornier MN, Morris PG (2013) Biological subtypes of breast cancer: current concepts and implications for recurrence patterns. Quart J Nucl Med Mol Imag 57:312–321

Carson MW et al (2014) HDX reveals unique fragment ligands for the vitamin D receptor. Bioorg Med Chem Lett 24:3459–3463. doi:10.1016/j.bmcl.2014.05.070

Chan HJ, Petrossian K, Chen S (2015) Structural and functional characterization of aromatase, estrogen receptor, and their genes in endocrine-responsive and -resistant breast cancer cells. J Steroid Biochem Mol Biol. doi:10.1016/j.jsbmb.2015.07.018

Chen S (1998) Aromatase and breast cancer. Front Biosci 3:d922–d933

Chen P, Hu P, Xie D, Qin Y, Wang F, Wang H (2010) Meta-analysis of vitamin D, calcium and the prevention of breast cancer. Breast Cancer Res Treat 121:469–477. doi:10.1007/s10549-009-0593-9

Chen P et al (2013) Higher blood 25(OH)D level may reduce the breast cancer risk: evidence from a Chinese population based case-control study and meta-analysis of the observational studies. PLoS ONE 8:e49312. doi:10.1371/journal.pone.0049312

Cheng JB, Levine MA, Bell NH, Mangelsdorf DJ, Russell DW (2004) Genetic evidence that the human CYP2R1 enzyme is a key vitamin D 25-hydroxylase. Proc Natl Acad Sci USA 101:7711–7715. doi:10.1073/pnas.0402490101

Chiang KC et al (2016) The vitamin D analog, MART-10, attenuates triple negative breast cancer cells metastatic potential. Int J Mol Sci. doi:10.3390/ijms17040606

Chlebowski RT et al (2008) Calcium plus vitamin D supplementation and the risk of breast cancer. J Natl Cancer Inst 100:1581–1591. doi:10.1093/jnci/djn360

Christakos S, Dhawan P, Verstuyf A, Verlinden L, Carmeliet G (2016) Vitamin D: metabolism, molecular mechanism of action, and pleiotropic effects. Physiol Rev 96:365–408. doi:10.1152/physrev.00014.2015

Christensen GL, Jepsen JS, Fog CK, Christensen IJ, Lykkesfeldt AE (2004) Sequential versus combined treatment of human breast cancer cells with antiestrogens and the vitamin D analogue EB1089 and evaluation of predictive markers for vitamin D treatment. Breast Cancer Res Treat 85:53–63. doi:10.1023/B:BREA.0000021047.37869.95

Colston KW (2008) Vitamin D and breast cancer risk. Best Pract Res Clin Endocrinol Metab 22:587–599. doi:10.1016/j.beem.2008.08.002

Crew KD (2013) Vitamin d: are we ready to supplement for breast cancer prevention and treatment? ISRN Oncol 2013:483687. doi:10.1155/2013/483687

Crew KD, Shane E, Cremers S, McMahon DJ, Irani D, Hershman DL (2009) High prevalence of vitamin D deficiency despite supplementation in premenopausal women with breast cancer undergoing adjuvant chemotherapy. J Clin Oncol 27:2151–2156. doi:10.1200/JCO.2008.19.6162

Cross HS (2007) Extrarenal vitamin D hydroxylase expression and activity in normal and malignant cells: modification of expression by epigenetic mechanisms and dietary substances. Nutr Rev 65:S108–S112

Davies GL (2003) Cyclooxygenase-2 and chemoprevention of breast cancer. J Steroid Biochem Mol Biol 86:495–499

Davies G, Martin LA, Sacks N, Dowsett M (2002) Cyclooxygenase-2 (COX-2), aromatase and breast cancer: a possible role for COX-2 inhibitors in breast cancer chemoprevention. Ann Oncol ESMO 13:669–678

deConinck EC, McPherson LA, Weigel RJ (1995) Transcriptional regulation of estrogen receptor in breast carcinomas. Mol Cell Biol 15:2191–2196

DeLuca HF (2008) Evolution of our understanding of vitamin D. Nutr Rev 66:S73–S87. doi:10.1111/j.1753-4887.2008.00105.x

den Hollander P, Savage MI, Brown PH (2013) Targeted therapy for breast cancer prevention. Front Oncol 3:250. doi:10.3389/fonc.2013.00250

Diaz L, Diaz-Munoz M, Garcia-Gaytan AC, Mendez I (2015) Mechanistic effects of calcitriol in cancer biology. Nutrients 7:5020–5050. doi:10.3390/nu7065020

Ditsch N et al (2012) The association between vitamin D receptor expression and prolonged overall survival in breast cancer. J Histochem Cytochem 60:121–129. doi:10.1369/0022155411429155

Ditsch N et al (2013) Thyroid hormone receptor (TR)alpha and TRbeta expression in breast cancer. Histol Histopathol 28:227–237

Elster N, Collins DM, Toomey S, Crown J, Eustace AJ, Hennessy BT (2015) HER2-family signalling mechanisms, clinical implications and targeting in breast cancer. Breast Cancer Res Treat 149:5–15. doi:10.1007/s10549-014-3250-x

Enjuanes A et al (2003) Regulation of CYP19 gene expression in primary human osteoblasts: effects of vitamin D and other treatments. Eur J Endocrinol 148:519–526

Escaleira MT, Sonohara S, Brentani MM (1993) Sex steroids induced up-regulation of 1,25-(OH)2 vitamin D3 receptors in T 47D breast cancer cells. J Steroid Biochem Mol Biol 45:257–263

Farmer H et al (2005) Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 434:917–921. doi:10.1038/nature03445

Feldman D, Krishnan AV, Swami S, Giovannucci E, Feldman BJ (2014) The role of vitamin D in reducing cancer risk and progression. Nat Rev Cancer 14:342–357. doi:10.1038/nrc3691

Flanagan L, Packman K, Juba B, O'Neill S, Tenniswood M, Welsh J (2003) Efficacy of Vitamin D compounds to modulate estrogen receptor negative breast cancer growth and invasion. J Steroid Biochem Mol Biol 84:181–192

Frasor J, Stossi F, Danes JM, Komm B, Lyttle CR, Katzenellenbogen BS (2004) Selective estrogen receptor modulators: discrimination of agonistic versus antagonistic activities by gene expression profiling in breast cancer cells. Cancer Res 64:1522–1533

Friebel TM, Domchek SM, Rebbeck TR (2014) Modifiers of cancer risk in BRCA1 and BRCA2 mutation carriers: systematic review and meta-analysis. J Natl Cancer Inst 106:dju091. doi:10.1093/jnci/dju091

Gandini S et al (2011) Meta-analysis of observational studies of serum 25-hydroxyvitamin D levels and colorectal, breast and prostate cancer and colorectal adenoma. Int J Cancer 128:1414–1424. doi:10.1002/ijc.25439

Garland CF, Gorham ED, Mohr SB, Garland FC (2009) Vitamin D for cancer prevention: global perspective. Ann Epidemiol 19:468–483. doi:10.1016/j.annepidem.2009.03.021

Gonzalez-Suarez I et al (2011) A new pathway that regulates 53BP1 stability implicates cathepsin L and vitamin D in DNA repair. EMBO J 30:3383–3396. doi:10.1038/emboj.2011.225

Gonzalo S (2014) Novel roles of 1 alpha, 25(OH)2D3 on DNA repair provide new strategies for breast cancer treatment. J Steroid Biochem Mol Biol 144(Pt A):59–64. doi:10.1016/j.jsbmb.2013.09.009

Grotsky DA et al (2013) BRCA1 loss activates cathepsin L-mediated degradation of 53BP1 in breast cancer cells. J Cell Biol 200:187–202. doi:10.1083/jcb.201204053

Harris RE, Casto BC, Harris ZM (2014) Cyclooxygenase-2 and the inflammogenesis of breast cancer. World J Clin Oncol 5:677–692. doi:10.5306/wjco.v5.i4.677

Hart CD, Migliaccio I, Malorni L, Guarducci C, Biganzoli L, Di Leo A (2015) Challenges in the management of advanced, ER-positive, HER2-negative breast cancer. Nat Rev Clin Oncol 12:541–552. doi:10.1038/nrclinonc.2015.99

Heaney RP, Horst RL, Cullen DM, Armas LA (2009) Vitamin D3 distribution and status in the body. J Am Coll Nutr 28:252–256

Helleday T, Bryant HE, Schultz N (2005) Poly(ADP-ribose) polymerase (PARP-1) in homologous recombination and as a target for cancer therapy. Cell Cycle 4:1176–1178

Higgins MJ, Stearns V (2011) Pharmacogenetics of endocrine therapy for breast cancer. Annu Rev Med 62:281–293. doi:10.1146/annurev-med-070909-182545

Hirshfield KM, Ganesan S (2014) Triple-negative breast cancer: molecular subtypes and targeted therapy. Curr Opin Obstet Gynecol 26:34–40. doi:10.1097/GCO.0000000000000038

Hynes NE, Lane HA (2005) ERBB receptors and cancer: the complexity of targeted inhibitors. Nat Rev Cancer 5:341–354. doi:10.1038/nrc1609

James SY, Mackay AG, Binderup L, Colston KW (1994) Effects of a new synthetic vitamin D analogue, EB1089, on the oestrogen-responsive growth of human breast cancer cells. J Endocrinol 141:555–563

Jaspers JE et al (2013) Loss of 53BP1 causes PARP inhibitor resistance in Brca1-mutated mouse mammary tumors. Cancer Discov 3:68–81. doi:10.1158/2159-8290.CD-12-0049

Jatoi I, Benson JR (2016) Management of women with a hereditary predisposition for breast cancer. Future Oncol 12:2277–2288. doi:10.2217/fon-2016-0186

Jeselsohn R, Buchwalter G, De Angelis C, Brown M, Schiff R (2015) ESR1 mutations-a mechanism for acquired endocrine resistance in breast cancer Nature reviews. Clin Oncol 12:573–583. doi:10.1038/nrclinonc.2015.117

Johnston SR, Dowsett M (2003) Aromatase inhibitors for breast cancer: lessons from the laboratory. Nat Rev Cancer 3:821–831. doi:10.1038/nrc1211

Jones G (2007) Expanding role for vitamin D in chronic kidney disease: importance of blood 25-OH-D levels and extra-renal 1alpha-hydroxylase in the classical and nonclassical actions of 1alpha,25-dihydroxyvitamin D(3). Semin Dial 20:316–324. doi:10.1111/j.1525-139X.2007.00302.x

Kailajarvi ME, Salminen EK, Paija OM, Virtanent AM, Leino AE, Irjala KA (2004) Serum bone markers in breast cancer patients during 5-fluorouracil, epirubicin and cyclophosphamide (FEC) therapy. Anticancer Res 24:1271–1274

Kalimutho M, Parsons K, Mittal D, Lopez JA, Srihari S, Khanna KK (2015) Targeted therapies for triple-negative breast cancer: combating a stubborn disease. Trends Pharmacol Sci. doi:10.1016/j.tips.2015.08.009

Karunagaran D et al (1996) ErbB-2 is a common auxiliary subunit of NDF and EGF receptors: implications for breast cancer. EMBO J 15:254–264

Kawase T et al (2010) Association between vitamin D and calcium intake and breast cancer risk according to menopausal status and receptor status in Japan. Cancer Sci 101:1234–1240. doi:10.1111/j.1349-7006.2010.01496.x

Khan QJ, O'Dea AP, Sharma P (2010) Musculoskeletal adverse events associated with adjuvant aromatase inhibitors. J Oncol. doi:10.1155/2010/654348

Khan MI, Bielecka ZF, Najm MZ, Bartnik E, Czarnecki JS, Czarnecka AM, Szczylik C (2014) Vitamin D receptor gene polymorphisms in breast and renal cancer: current state and future approaches (review). Int J Oncol 44:349–363. doi:10.3892/ijo.2013.2204

Kim Y, Je Y (2014) Vitamin D intake, blood 25(OH)D levels, and breast cancer risk or mortality: a meta-analysis. Br J Cancer 110:2772–2784. doi:10.1038/bjc.2014.175

Kim HJ et al (2011) Vitamin D deficiency is correlated with poor outcomes in patients with luminal-type breast cancer. Ann Surg Oncol 18:1830–1836. doi:10.1245/s10434-010-1465-6

Kim HJ, Koh BS, Yu JH, Lee JW, Son BH, Kim SB, Ahn SH (2014) Changes in serum hydroxyvitamin D levels of breast cancer patients during tamoxifen treatment or chemotherapy in premenopausal breast cancer patients. Eur J Cancer 50:1403–1411. doi:10.1016/j.ejca.2014.02.026

Kinuta K, Tanaka H, Moriwake T, Aya K, Kato S, Seino Y (2000) Vitamin D is an important factor in estrogen biosynthesis of both female and male gonads. Endocrinology 141:1317–1324. doi:10.1210/endo.141.4.7403

Krishnan AV, Feldman D (2011) Mechanisms of the anti-cancer and anti-inflammatory actions of vitamin D. Annu Rev Pharmacol Toxicol 51:311–336. doi:10.1146/annurev-pharmtox-010510-100611

Krishnan AV, Swami S, Feldman D (2010a) Vitamin D and breast cancer: inhibition of estrogen synthesis and signaling. J Steroid Biochem Mol Biol 121:343–348. doi:10.1016/j.jsbmb.2010.02.009

Krishnan AV, Swami S, Peng L, Wang J, Moreno J, Feldman D (2010b) Tissue-selective regulation of aromatase expression by calcitriol: implications for breast cancer therapy. Endocrinology 151:32–42. doi:10.1210/en.2009-0855

Krishnan AV, Swami S, Feldman D (2012) The potential therapeutic benefits of vitamin D in the treatment of estrogen receptor positive breast cancer. Steroids 77:1107–1112. doi:10.1016/j.steroids.2012.06.005

LaPorta E, Welsh J (2014) Modeling vitamin D actions in triple negative/basal-like breast cancer. J Steroid Biochem Mol Biol 144(Pt A):65–73. doi:10.1016/j.jsbmb.2013.10.022

Lee HJ et al (2008) Gemini vitamin D analogues inhibit estrogen receptor-positive and estrogen receptor-negative mammary tumorigenesis without hypercalcemic toxicity. Cancer Prev Res (Phila) 1:476–484. doi:10.1158/1940-6207.CAPR-08-0084

Lee HJ et al (2010) Gemini vitamin D analog suppresses ErbB2-positive mammary tumor growth via inhibition of ErbB2/AKT/ERK signaling. J Steroid Biochem Mol Biol 121:408–412. doi:10.1016/j.jsbmb.2010.03.053

Leyssens C, Verlinden L, Verstuyf A (2014) The future of vitamin D analogs. Front Physiol 5:122. doi:10.3389/fphys.2014.00122

Litzenburger BC, Brown PH (2014) Advances in preventive therapy for estrogen-receptor-negative breast cancer. Curr Breast Cancer Rep 6:96–109. doi:10.1007/s12609-014-0144-1

Liu NQ, Hewison M (2012) Vitamin D, the placenta and pregnancy. Arch Biochem Biophys 523:37–47. doi:10.1016/j.abb.2011.11.018

Livraghi L, Garber JE (2015) PARP inhibitors in the management of breast cancer: current data and future prospects. BMC Med 13:188. doi:10.1186/s12916-015-0425-1

Lopes N et al (2012) 1Alpha,25-dihydroxyvitamin D3 induces de novo E-cadherin expression in triple-negative breast cancer cells by CDH1-promoter demethylation. Anticancer Res 32:249–257

Lowe LC, Guy M, Mansi JL, Peckitt C, Bliss J, Wilson RG, Colston KW (2005) Plasma 25-hydroxy vitamin D concentrations,

vitamin D receptor genotype and breast cancer risk in a UK Caucasian population. Eur J Cancer 41:1164–1169. doi:10.1016/j.ejca.2005.01.017

Lumachi F, Santeufemia DA, Basso SM (2015) Current medical treatment of estrogen receptor-positive breast cancer. World J Biol Chem 6:231–239. doi:10.4331/wjbc.v6.i3.231

Lundqvist J, Hansen SK, Lykkesfeldt AE (2013) Vitamin D analog EB1089 inhibits aromatase expression by dissociation of comodulator WSTF from the CYP19A1 promoter-a new regulatory pathway for aromatase. Biochim Biophys Acta 1833:40–47. doi:10.1016/j.bbamcr.2012.10.012

Lundqvist J, Yde CW, Lykkesfeldt AE (2014) 1alpha, 25-dihydroxyvitamin D3 inhibits cell growth and NFkappaB signaling in tamoxifen-resistant breast cancer cells. Steroids 85:30–35. doi:10.1016/j.steroids.2014.04.001

McCullough ML, Rodriguez C, Diver WR, Feigelson HS, Stevens VL, Thun MJ, Calle EE (2005) Dairy, calcium, and vitamin D intake and postmenopausal breast cancer risk in the Cancer Prevention Study II Nutrition Cohort. Cancer Epidemiol Biomark Prev 14:2898–2904. doi:10.1158/1055-9965.EPI-05-0611

Milani A, Geuna E, Mittica G, Valabrega G (2014) Overcoming endocrine resistance in metastatic breast cancer: Current evidence and future directions. World J Clin Oncol 5:990–1001. doi:10.5306/wjco.v5.i5.990

Montemurro F, Di Cosimo S, Arpino G (2013) Human epidermal growth factor receptor 2 (HER2)-positive and hormone receptor-positive breast cancer: new insights into molecular interactions and clinical implications. Annals Oncol/ESMO 24:2715–2724. doi:10.1093/annonc/mdt287

Mun MJ, Kim TH, Hwang JY, Jang WC (2015) Vitamin D receptor gene polymorphisms and the risk for female reproductive cancers: a meta-analysis. Maturitas 81:256–265. doi:10.1016/j.maturitas.2015.03.010

Musgrove EA, Sutherland RL (2009) Biological determinants of endocrine resistance in breast cancer. Nat Rev Cancer 9:631–643. doi:10.1038/nrc2713

Nadji M, Gomez-Fernandez C, Ganjei-Azar P, Morales AR (2005) Immunohistochemistry of estrogen and progesterone receptors reconsidered: experience with 5,993 breast cancers. Am J Clin Pathol 123:21–27

Narvaez CJ, Matthews D, LaPorta E, Simmons KM, Beaudin S, Welsh J (2014) The impact of vitamin D in breast cancer: genomics, pathways, metabolism. Front Physiol 5:213. doi:10.3389/fphys.2014.00213

Nemenqani DM, Karam RA, Amer MG (2015) Abd El Rahman TM. Vitamin D receptor gene polymorphisms and steroid receptor status among Saudi women with breast cancer Gene 558:215–219. doi:10.1016/j.gene.2014.12.065

Olson EM, Najita JS, Sohl J, Arnaout A, Burstein HJ, Winer EP, Lin NU (2013) Clinical outcomes and treatment practice patterns of patients with HER2-positive metastatic breast cancer in the post-trastuzumab era. Breast 22:525–531. doi:10.1016/j.breast.2012.12.006

Orlov I, Rochel N, Moras D, Klaholz BP (2012) Structure of the full human RXR/VDR nuclear receptor heterodimer complex with its DR3 target DNA. EMBO J 31:291–300. doi:10.1038/emboj.2011.445

Pickholtz I et al (2014) Cooperation between BRCA1 and vitamin D is critical for histone acetylation of the p21waf1 promoter and growth inhibition of breast cancer cells and cancer stem-like cells. Oncotarget 5:11827–11846. doi:10.18632/oncotarget.2582

Radermacher J, Diesel B, Seifert M, Tilgen W, Reichrath J, Fischer U, Meese E (2006) Expression analysis of CYP27B1 in tumor biopsies and cell cultures. Anticancer Res 26:2683–2686

Rainville C, Khan Y, Tisman G (2009) Triple negative breast cancer patients presenting with low serum vitamin D levels: a case series. Cases J 2:8390. doi:10.4076/1757-1626-2-8390

Reimers LL et al (2015) Vitamin D-related gene polymorphisms, plasma 25-hydroxyvitamin D, and breast cancer risk. CCC 26:187–203. doi:10.1007/s10552-014-0497-9

Richards SE, Weierstahl KA, Kelts JL (2015) Vitamin D effect on growth and vitamin D metabolizing enzymes in triple-negative breast cancer. Anticancer Res 35:805–810

Riemsma R, Forbes CA, Kessels A, Lykopoulos K, Amonkar MM, Rea DW, Kleijnen J (2010) Systematic review of aromatase inhibitors in the first-line treatment for hormone sensitive advanced or metastatic breast cancer. Breast Cancer Res Treat 123:9–24. doi:10.1007/s10549-010-0974-0

Ristimaki A et al (2002) Prognostic significance of elevated cyclooxygenase-2 expression in breast cancer. Cancer Res 62:632–635

Rochel N, Wurtz JM, Mitschler A, Klaholz B, Moras D (2000) The crystal structure of the nuclear receptor for vitamin D bound to its natural ligand. Mol Cell 5:173–179

Rollison DE et al (2012) Vitamin D intake, vitamin D receptor polymorphisms, and breast cancer risk among women living in the southwestern U.S. Breast Cancer Res Treat 132:683–691. doi:10.1007/s10549-011-1885-4

Romagnolo AP, Romagnolo DF, Selmin OI (2015) BRCA1 as target for breast cancer prevention and therapy. Anti Cancer Agents Med Chem 15:4–14

Rose AA, Elser C, Ennis M, Goodwin PJ (2013) Blood levels of vitamin D and early stage breast cancer prognosis: a systematic review and meta-analysis. Breast Cancer Res Treat 141:331–339. doi:10.1007/s10549-013-2713-9

Roskoski R Jr (2014) The ErbB/HER family of protein-tyrosine kinases and cancer. Pharmacol Res 79:34–74. doi:10.1016/j.phrs.2013.11.002

Ross JS et al (2003) The Her-2/neu gene and protein in breast cancer 2003: biomarker and target of therapy. Oncologist 8:307–325

Ross AC et al (2011) The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metabol 96:53–58. doi:10.1210/jc.2010-2704

Rubin GL, Zhao Y, Kalus AM, Simpson ER (2000) Peroxisome proliferator-activated receptor gamma ligands inhibit estrogen biosynthesis in human breast adipose tissue: possible implications for breast cancer therapy. Cancer Res 60:1604–1608

Santini D et al (2010) Longitudinal evaluation of vitamin D plasma levels during anthracycline- and docetaxel-based adjuvant chemotherapy in early-stage breast cancer patients. Ann Oncol 21:185–186. doi:10.1093/annonc/mdp497

Santos-Martinez N et al (2014) Calcitriol restores antiestrogen responsiveness in estrogen receptor negative breast cancer cells: a potential new therapeutic approach. BMC Cancer 14:230. doi:10.1186/1471-2407-14-230

Simboli-Campbell M, Narvaez CJ, van Weelden K, Tenniswood M, Welsh J (1997) Comparative effects of 1,25(OH)2D3 and EB1089 on cell cycle kinetics and apoptosis in MCF-7 breast cancer cells. Breast Cancer Res Treat 42:31–41

Simpson ER et al (2002) Aromatase–a brief overview. Annu Rev Physiol 64:93–127. doi:10.1146/annurev.physiol.64.081601.142703

So JY et al (2013) Oral administration of a gemini vitamin D analog, a synthetic triterpenoid and the combination prevents mammary tumorigenesis driven by ErbB2 overexpression. Cancer Prev Res 6:959–970. doi:10.1158/1940-6207.CAPR-13-0087

Stambolsky P et al (2010) Modulation of the vitamin D3 response by cancer-associated mutant p53. Cancer Cell 17:273–285. doi:10.1016/j.ccr.2009.11.025

Stocklin E, Eggersdorfer M (2013) Vitamin D, an essential nutrient with versatile functions in nearly all organs. Int J Vitam Nutr Res 83:92–100. doi:10.1024/0300-9831/a000151

Stoica A, Saceda M, Fakhro A, Solomon HB, Fenster BD, Martin MB (1999) Regulation of estrogen receptor-alpha gene expression by 1, 25-dihydroxyvitamin D in MCF-7 cells. J Cell Biochem 75:640–651

Swami S, Krishnan AV, Feldman D (2000) 1alpha,25-Dihydroxyvitamin D3 down-regulates estrogen receptor abundance and suppresses estrogen actions in MCF-7 human breast cancer cells. Clin Cancer Res 6:3371–3379

Swami S, Krishnan AV, Peng L, Lundqvist J, Feldman D (2013) Transrepression of the estrogen receptor promoter by calcitriol in human breast cancer cells via two negative vitamin D response elements. Endocr Relat Cancer 20:565–577. doi:10.1530/ERC-12-0281

Takeyama K, Kitanaka S, Sato T, Kobori M, Yanagisawa J, Kato S (1997) 25-Hydroxyvitamin D3 1alpha-hydroxylase and vitamin D synthesis. Science 277:1827–1830

Tanaka S, Haji M, Takayanagi R, Tanaka S, Sugioka Y, Nawata H (1996) 1,25-Dihydroxyvitamin D3 enhances the enzymatic activity and expression of the messenger ribonucleic acid for aromatase cytochrome P450 synergistically with dexamethasone depending on the vitamin D receptor level in cultured human osteoblasts. Endocrinology 137:1860–1869. doi:10.1210/endo.137.5.8612525

Teft WA et al (2013) CYP3A4 and seasonal variation in vitamin D status in addition to CYP2D6 contribute to therapeutic endoxifen level during tamoxifen therapy. Breast Cancer Res Treat 139:95–105. doi:10.1007/s10549-013-2511-4

Thakkar A, Wang B, Picon-Ruiz M, Buchwald P, Ince TA (2016) Vitamin D and androgen receptor-targeted therapy for triple-negative breast cancer. Breast Cancer Res Treat 157:77–90. doi:10.1007/s10549-016-3807-y

Thill M et al (2015) Combined treatment of breast cancer cell lines with vitamin D and COX-2 inhibitors. Anticancer Res 35:1189–1195

Tian XQ, Chen TC, Matsuoka LY, Wortsman J, Holick MF (1993) Kinetic and thermodynamic studies of the conversion of previtamin D3 to vitamin D3 in human skin. J Biol Chem 268:14888–14892

Voudouri K, Berdiaki A, Tzardi M, Tzanakakis GN, Nikitovic D (2015) Insulin-like growth factor and epidermal growth factor signaling in breast cancer cell growth: focus on endocrine resistant disease. Anal Cell Pathol 2015:975495. doi:10.1155/2015/975495

Welsh J (2007a) Targets of vitamin D receptor signaling in the mammary gland. J Bone Miner Res 22(Suppl 2):V86–V90. doi:10.1359/jbmr.07s204

Welsh J (2007b) Vitamin D and prevention of breast cancer. Acta Pharmacol Sin 28:1373–1382. doi:10.1111/j.1745-7254.2007.00700.x

Welsh J (2011) Vitamin D metabolism in mammary gland and breast cancer. Mol Cell Endocrinol 347:55–60. doi:10.1016/j.mce.2011.05.020

Welsh J, Wietzke JA, Zinser GM, Byrne B, Smith K, Narvaez CJ (2003) Vitamin D-3 receptor as a target for breast cancer prevention. J Nutr 133:2425S–2433S

Wolff AC et al (2013) Recommendations for human epidermal growth factor receptor 2 testing in breast cancer. Am Soc Clin Oncol 31:3997–4013. doi:10.1200/JCO.2013.50.9984

Woode DR, Aiyer HS, Sie N, Zwart AL, Li L, Seeram NP, Clarke R (2012) Effect of berry extracts and bioactive compounds on fulvestrant (ICI 182,780) sensitive and resistant cell lines. Int J Breast Cancer 2012:147828. doi:10.1155/2012/147828

Yanase T, Suzuki S, Goto K, Nomura M, Okabe T, Takayanagi R, Nawata H (2003) Aromatase in bone: roles of Vitamin D3 and androgens. J Steroid Biochem Mol Biol 86:393–397

Yao S et al (2011) Pretreatment serum concentrations of 25-hydroxyvitamin D and breast cancer prognostic characteristics: a case-control and a case-series study. PLoS ONE 6:e17251. doi:10.1371/journal.pone.0017251

Yarden Y, Sliwkowski MX (2001) Untangling the ErbB signalling network. Nat Rev Mol Cell Biol 2:127–137. doi:10.1038/35052073

Yde CW, Emdal KB, Guerra B, Lykkesfeldt AE (2012) NFkappaB signaling is important for growth of antiestrogen resistant breast cancer cells. Breast Cancer Res Treat 135:67–78. doi:10.1007/s10549-012-2053-1

Yen PM (2015) Classical nuclear hormone receptor activity as a mediator of complex biological responses: a look at health and disease. Best Pract Res Clin Endocrinol Metab 29:517–528. doi:10.1016/j.beem.2015.07.005

Yin L, Grandi N, Raum E, Haug U, Arndt V, Brenner H (2010) Meta-analysis: serum vitamin D and breast cancer risk. Eur J Cancer 46:2196–2205. doi:10.1016/j.ejca.2010.03.037

Zehnder D, Bland R, Williams MC, McNinch RW, Howie AJ, Stewart PM, Hewison M (2001) Extrarenal expression of 25-hydroxyvitamin d(3)-1 alpha-hydroxylase. J Clin Endocrinol Metabol 86:888–894. doi:10.1210/jcem.86.2.7220

Zeichner SB et al (2015) Improved clinical outcomes associated with vitamin D supplementation during adjuvant chemotherapy in patients with HER2+ nonmetastatic breast cancer. Clin Breast Cancer 15:e1–11. doi:10.1016/j.clbc.2014.08.001

Zella LA, Kim S, Shevde NK, Pike JW (2007) Enhancers located in the vitamin D receptor gene mediate transcriptional autoregulation by 1,25-dihydroxyvitamin D3. J Steroid Biochem Mol Biol 103:435–439. doi:10.1016/j.jsbmb.2006.12.019

Zembutsu H (2015) Pharmacogenomics toward personalized tamoxifen therapy for breast cancer. Pharmacogenomics 16:287–296. doi:10.2217/pgs.14.171

Zhang K, Song L (2014) Association between vitamin D receptor gene polymorphisms and breast cancer risk: a meta-analysis of 39 studies. PLoS ONE 9:e96125. doi:10.1371/journal.pone.0096125

Zhou D, Chen S (1999) Identification and characterization of a cAMP-responsive element in the region upstream from promoter 1.3 of the human aromatase gene. Arch Biochem Biophys 371:179–190. doi:10.1006/abbi.1999.1454

Zurawska U, Baribeau DA, Giilck S, Victor C, Gandhi S, Florescu A, Verma S (2013) Outcomes of her2-positive early-stage breast cancer in the trastuzumab era: a population-based study of Canadian patients. Curr Oncol 20:e539–e545. doi:10.3747/co.20.1523