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Review Article

VITAMIN D–VITAMIN D RECEPTOR AXIS IN BREAST CANCER: MECHANISMS, EVIDENCE, AND CLINICAL IMPLICATIONS

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ABSTRACT

The Vitamin D-Vitamin D receptor (VDR) axis is biologically important in breast cancer because breast tissue can locally activate and break down Vitamin D, allowing direct control of cell growth, death, DNA repair, and the tumor microenvironment. In many breast cancers, this system is disturbed, with reduced effective VDR signaling and altered Vitamin D-metabolizing enzymes, changes that tend to appear in more aggressive disease. Experimental studies show that activating VDR can slow proliferation, limit stem-like behavior, reduce invasion and metastasis, and help maintain genomic stability and balanced immune responses. Human data generally link low blood Vitamin D levels and a disrupted VDR pathway with higher breast cancer risk and poorer outcomes, especially in hormone receptor-positive and some triple-negative or BRCA1-related tumors, although these patterns are weakened by lifestyle confounding and mostly neutral prevention trials. At present, the most realistic clinical use is routine testing and correction of Vitamin D deficiency, mainly for bone and general health, with any anticancer benefit framed as possible but unproven. Future work should focus on biomarker-guided, subtype-specific trials that combine Vitamin D-based approaches with endocrine, cytotoxic, or other targeted therapies, positioning the Vitamin D-VDR axis as a precision co-modulator rather than a stand-alone treatment.

Keywords: Vitamin D, Vitamin D receptor, Breast cancer, Tumor subtypes, Prognosis, Adjuvant therapy.

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INTRODUCTION

Rationale and scope: Why the vitamin D-vitamin D receptor (VDR) axis is biologically plausible and clinically relevant

Breast epithelium expresses VDR alongside CYP27B1 and CYP24A1, enabling local activation and catabolism of Vitamin D and positioning the ligand-receptor system to regulate proliferation, differentiation, apoptosis, DNA repair, and stromal interactions within the breast [1-7]. This circuitry is frequently remodeled in cancer CYP24A1 upregulation, reduced CYP27B1, or altered VDR localization can blunt antiproliferative signaling and align with aggressive features [8-11]. Mechanistic work shows VDR activation restrains WNT/β-catenin, ERBB2/ERK/AKT, JAK/STAT, nuclear factor kappa B (NF-κB), and EMT programs, while supporting genome stability through BRCA1/53BP1 pathways and oxidative-stress defenses [12-16]. These effects extend to treatment interfaces: Vitamin D analogs can augment endocrine therapy and cytotoxics, diminish cancer-stem-like traits, and restore tamoxifen sensitivity in resistant states [17-20]. Precision signals also emerge from human cohorts' germline variation in GC/VDR/CYP24A1 and tumor BRCA1 status appear to shape pathway tone and potential benefit, while real-world Polysomnography Technology PSGT frameworks integrate biochemistry and genomics to guide supplementation and bone-protective strategies during endocrine therapy [21-23]. Beyond tumor cells, Vitamin D modulates stromal chemokine cues linked to metastasis and may preserve gut-barrier-microbiome integrity that indirectly influences mammary tumorigenesis [24,25]. Clinically, deficiency is common, especially in postmenopausal women on aromatase inhibitors and associates with low bone mineral density (BMD) and, in several datasets, poorer oncologic outcomes, justifying routine assessment and correction within survivorship care [26-28].

Controversies: Inconsistent epidemiology, dosing debates, confounding (sunlight, adiposity, lifestyle)

Epidemiology is not unanimous. Many observational studies link higher 25(OH)D with lower incidence or mortality, yet Mendelian-randomization analyses and large prevention trials have not established causality, leaving population-level recommendations uncertain [29]. Proposed protective thresholds vary: Recent integrative reviews suggest averages near ~40 ng/mL, while others imply non-linearity around ~27–30 ng/mL; assay differences and seasonal variation complicate comparison [30,31]. Confounding is substantial sunlight exposure, adiposity, physical activity, and diet, all track with both Vitamin D status and outcomes, and body mass index (BMI) inversely correlates with 25(OH)D in clinic cohorts [23,32]. Tumor heterogeneity further blurs signal: CYP24A1 amplification, estrogen-related receptor alpha (ERRα) cross-talk, cytoplasmic VDR retention, and VDR promoter methylation can suppress canonical transcription despite adequate circulating Vitamin D, explaining VDR-high yet functionally refractory tumors [33-35]. Dosing remains debated native calcitriol risks hypercalcemia, analogs differ in potency and safety, and combinations with histone deacetylase (HDAC) inhibitors or endocrine agents are promising pre-clinically but under-tested clinically [36,37]. The pragmatic position is twofold: Correct deficiency for skeletal health and potential adjuvant benefit, while pursuing subtype-specific, biomarker-anchored trials that standardize 25(OH)D assessment, control for lifestyle confounders, and test VDR-active strategies where the biology predicts gain [27,29].

Why was this review chosen?

VDR signaling likely exerts protective, anti-tumor effects but is context-limited; associations between circulating 25(OH)D and breast cancer are inconsistent and conditional; VDR/CYP genetics and epigenetics modify both risk and responsiveness; subtype biology (estrogen receptor [ER]/progesterone receptor [PR]/human epidermal growth factor receptor 2 [HER2]/triple-negative breast cancer [TNBC]) determines where and how the axis matters; and clinical value will hinge on biomarker-anchored combination strategies and correcting deficiency rather than blanket dosing [8,18,21,23,26,27,29,31,33-35,38]. This study aimed to comprehensively explore the connection between Vitamin D, the VDR, and the likelihood of breast cancer development, and to translate mechanistic and epidemiologic insights into clinical implications.

REVIEW

Biology of vitamin D and VDR signaling

Vitamin D metabolism

Vitamin D derives from ultraviolet-B conversion of 7-dehydrocholesterol and diet, is 25-hydroxylated in the liver (mainly CYP2R1), then 1α-hydroxylated in the kidney and extra-renal sites (CYP27B1) to calcitriol; CYP24A1 drives catabolism [13,31]. Breast epithelium and tumors co-express VDR, CYP27B1, and CYP24A1, enabling local activation and inactivation that cancer often skews, typically via CYP24A1 upregulation, reduced CYP27B1, and/or low systemic 25(OH) D, dampening intratumoral signaling and associating with aggressive features [8,9,34,38]. Additional CYP11A1-derived secosteroids acting at VDR and retinoic acid-related orphan receptors alpha and gamma broaden context-specific effects, while epidemiology links low 25(OH) D to higher risk and poorer bone health, supporting assessment and correction in survivors [13,26,39-45].

VDR structure and function

VDR is a ligand-activated nuclear receptor that heterodimerizes with retinoid X receptor and binds DR3-type VDR elements (VDREs) to regulate programs for cell-cycle arrest, differentiation, apoptosis, metabolism, and immune tone; rapid non-genomic signaling is also described [36,46,47]. Chromatin context gates output: NCoR/SMRT corepressors and histone deacetylation can blunt antiproliferative targets, whereas HDAC inhibition or demethylation can restore responsiveness; promoter hypermethylation and splice-variant imbalance contribute to calcitriol resistance [35-37]. Functional genetics and post-transcriptional control underscore centrality: Re-expressing wild-type VDR reinstates growth control, while DNA- or ligand-binding mutants uncouple canonical DR3 signaling from residual effects; lncRNAs/miRNAs further tune VDR abundance and target fidelity [48-55].

Pathway crosstalk relevant to breast cancer

VDR interfaces with hallmark oncogenic circuits: It downshifts ER alpha (ERα) and aromatase (with ERRα-dependent rewiring in some basal-like settings), links to growth-factor cues (IGF axis; EGF/bFGF repression of VDR), represses Wnt/β-catenin and induces DKK-1 (reducing stemness and tamoxifen resistance), engages PTEN-AKT and REDD1-mTORC1 to restrain proliferation/autophagy, and dampens NF-κB/COX-2-PGE_2 to limit EMT and invasion [12,13,19,32,56]. In genome maintenance, VDR cooperates with BRCA1 at CDKN1A and counteracts Ras-driven instability via the BRCA1-53BP1 axis. Collectively, the vitamin D-VDR hub integrates ER/IGF/EGFR, Wnt/β-catenin, PI3K/AKT/mTOR, and inflammatory pathways, providing a mechanistic footing for subtype-aware screening, prevention, and adjunctive therapy [14,22,38,57-61].

Mechanistic links to carcinogenesis (hallmarks modulation)

Proliferation and cell cycle

Ligand-activated VDR restrains mammary epithelial proliferation by inducing CDK inhibitors p21/CDKN1A and p27 and suppressing cyclins and β-catenin targets, such as cyclin D1, thereby enforcing G0/G1 arrest [12,36,62,63]. BRCA1 acts as a VDR co-activator at the p21 promoter; Vitamin D analogs enhance BRCA1-VDR occupancy and histone acetylation at VDREs, strengthening CDKN1A transcription and growth control [22,64-67]. Re-expressing wild-type VDR in VDR-null mammary tumor cells restores CYP24 transactivation and dose-dependent growth inhibition, underscoring receptor sufficiency for anti-proliferative signaling [48,67].

Apoptosis and differentiation

VDR signaling promotes apoptosis via BAX/BCL-2 shifts and supports terminal differentiation, with epigenetic agents amplifying transcriptional responses on selected targets [37,46]. Across models, calcitriol and potent analogs reduce clonogenicity and tumor growth while increasing apoptotic morphology, with analogs achieving these effects at lower doses than native hormone [17,68].

EMT, invasion, metastasis

Vitamin D/VDR counters EMT by upregulating E-cadherin and repressing Zeb1/STAT3 and Wnt/β-catenin signaling, thereby reducing invasion and mammosphere formation; *in vivo*, deficiency accelerates lung metastasis and augments stromal "homing" cues [12,24]. Tumor-associated CYP24A1 upregulation and reduced CYP27B1/VDR tone blunt these anti-invasive effects and are recurrent in aggressive subtypes [8,34].

Angiogenesis

VDR activation down-modulates VEGF-driven angiogenic programs; gene-expression and functional assays consistently show reduced vessel formation with Vitamin D or analog exposure [13,68-71].

Stemness

VDR signaling suppresses cancer-stem-like traits by lowering tumorsphere efficiency, ALDH-positive fractions, and stem markers, while dual targeting of VDR and AR further diminishes stemness in receptor-positive TNBC models [18,46]. In endocrine-responsive disease, restoring VDR attenuates Wnt/β-catenin in $CD133^+$ cells and partially reverses tamoxifen resistance [19,72-74].

Genomic stability and oxidative stress

VDR safeguards DNA-repair capacity by maintaining BRCA1 and 53BP1 recruitment to damage foci and buffering oxidative programs; VDR loss or Ras-driven VDR suppression skews repair toward genomic instability that Vfitamin D can partially correct [13,14,75,76].

Tumor microenvironment and immunity

VDR shapes the breast TME by dampening NF-κB-mediated inflammatory tone, curbing hyaluronan-CD44 signaling, and modulating cytokine networks that influence Th1/Th17/Treg balance [13,38]. In stromal compartments, VDR ligands repress CXCL12 production and reduce CXCL12-CXCR4 co-localization in metastatic niches, weakening chemotactic support for dissemination [24,77-79]. Macrophage-directed elements of the Vitamin D axis can heighten tumoricidal activity, as GcMAF-primed macrophages induce apoptosis and clearance of breast cancer cells, an effect potentiated by VDR agonism [47]. Collectively, these actions support coordinated epithelial-stromal-immune restraint on carcinogenesis and metastatic fitness [30,46].

An additional, emerging layer of this biology is a gut-barrier-microbiome axis that may pre-configure the systemic inflammatory and immune tone in which breast tumors arise. In a DMBA-induced mammary cancer model with intestine-specific VDR deletion, Zhang *et al.* showed that loss of epithelial VDR caused gut dysbiosis with depletion of butyrate-producing taxa, reduced butyryl-CoA transferase activity, disruption of tight junction proteins, increased intestinal permeability, endotoxemia, and systemic cytokine elevation, accompanied by higher p-β-catenin in mammary tissue, reduced tumor apoptosis, and a greater number and volume of breast tumors; both oral butyrate and *Lactobacillus plantarum* supplementation restored barrier integrity, attenuated systemic inflammation, and reduced tumor burden [25]. These findings sit alongside broader evidence that Vitamin D-VDR signaling dampens COX-2/NF-κB-driven inflammation, modulates stromal and immune components of the breast tumor microenvironment, and can enhance antitumor immune surveillance and T-cell activity [80,81]. Taken together, they support a working model in which adequate Vitamin D status and intact intestinal VDR help maintain gut-barrier-microbiome homeostasis, thereby limiting chronic low-grade inflammation and shaping systemic myeloid and lymphoid responses that ultimately influence breast tumor immunity and may contribute to inter-individual variability in responses to systemic therapies, including immunomodulatory approaches, even though direct clinical evidence in breast cancer remains limited.

HUMAN EVIDENCE: RISK OF INCIDENT BREAST CANCER

Observational studies

Across decades of epidemiology, higher circulating 25-hydroxyvitamin D [25(OH)D] generally associates with lower breast cancer risk, but effect sizes vary with study design, timing, and measurement. Season-matched case–control work found substantially lower 25(OH)D in cases and several-fold higher risk at very low levels (<50 nM), with risk further amplified in at-risk VDR genotypes, highlighting gene-environment interplay [39,82-84]. Population-based analyses incorporating Vitamin D-pathway single nucleotide polymorphisms (SNPs) report modest associations for CYP24A1 and VDR variants and suggest that inverse 25(OH)D-risk relations may be stronger in selected genotypes, although multiple-testing correction often attenuates significance [21,85-87]. Narrative syntheses place a likely protective range around ~27–40 ng/mL, while emphasizing non-linearity and marked between-study heterogeneity [30,31]. Familiar methodologic pitfalls persist: Peri-diagnostic sampling invites reverse causation; assays (radioimmunoassay [RIA], enzyme-linked immunosorbent assay [ELISA], electrochemiluminescence) differ with inter-laboratory drift; and deficiency/sufficiency thresholds are inconsistently defined. Confounding by sun exposure, outdoor physical activity, diet, adiposity, and season is pervasive; in a real-world HR+ cohort, deficiency clustered in winter and tracked inversely with BMI, illustrating how lifestyle and adiposity can blur causal interpretation [23]. Cohorts with pre-diagnostic samples tend to show cleaner, though still mixed, inverse associations, whereas case–control designs, even when season-matched, remain more fragile to residual confounding [32,38].

Mendelian randomization

Modern magnetic resource (MR) analyses using large genetic instrument sets for 25(OH)D have not supported a causal effect of lifelong higher 25(OH)D on overall breast cancer incidence, despite strong mechanistic plausibility [29,88-90]. These inferences rest on assumptions of instrument independence and exclusion restriction; violations via pleiotropy (e.g., Vitamin D-binding protein variants with functions beyond Vitamin D transport) and the small variance in 25(OH)D explained by common SNPs (weak instruments) can bias estimates toward the null. Taken at face value, MR argues against a large, population-wide causal impact, while still allowing for effect modification by tumor biology or host context, as suggested by candidate-gene and tissue-based studies [21,91].

Randomized trials of supplementation (prevention)

Prevention trials broadly mirror the caution from MR. A contemporary large-scale regimen of 2000 IU/day cholecalciferol did not reduce overall breast cancer incidence; a secondary signal suggested fewer advanced cancers among participants with normal BMI, raising the possibility that adiposity and baseline status modulate benefit [29,38]. Earlier low-dose Vitamin D plus calcium trials were neutral for breast cancer specifically, whereas a smaller trial using ~1100 IU/day plus calcium reported fewer overall cancer events, with too few breast cancers to clarify site-specific effects [32]. Across these studies, adherence varied, baseline 25(OH)D was often sufficient rather than frankly deficient, and achieved levels sometimes fell short of the putative protective window highlighted by observational syntheses [30]. Safety has been acceptable at physiologic doses: Hypercalcemia and nephrolithiasis are uncommon in prevention settings when dosing is daily and monitored [29,32].

Synthesis across designs

Triangulating across designs yields a coherent but restrained picture. Observational studies, especially those with pre-diagnostic sampling frequently show inverse associations, with risk lowest above ~30-40 ng/mL and particularly in subgroups, such as lean or postmenopausal women; yet MR analyses are largely null, and broad prevention randomized controlled trials (RCTs) have not demonstrated a clear reduction in incidence [29-31]. Divergence is plausibly explained by residual confounding (sunlight, activity, diet), reverse causation around diagnosis, assay variability, and dilution from low trial dosing, high baseline adequacy, or obesity-related sequestration that limits on-study 25(OH)D gains [32,38]. Subgroup patterns remain credible but unproven: Signals appear stronger in normal-BMI participants, in some analyses of ER-positive disease, and in selected ancestries, while genetic context (VDR/CYP24A1/glucocorticoid [GC]) may shape both baseline risk and the slope of association [21,29,91]. Overall, the human literature supports correcting deficiency for general health and suggests a possible modest reduction in incident breast cancer in specific contexts, but does not yet justify population-wide supplementation solely for breast cancer prevention. Future trials should stratify by baseline 25(OH)D, BMI, ancestry, and genotype, target achieved levels in the hypothesized protective range, and rigorously account for adherence, assay method, and seasonality in endpoint adjudication [29,30].

Tumor subtype-specific evidence

ER+/PR+ (Luminal disease)

Across large pathology series, tumor VDR is more common in hormone-receptor-positive cancers and associates with smaller size, ER/PR positivity, and lower Ki-67, though not always independently prognostic [34,92]. Local CYP27B1/CYP24A1 activity in breast tissue shapes intratumoral VDR signaling and can modulate endocrine sensitivity [8,9]. VDR reduces aromatase/ER signaling, resensitizes endocrine-refractory cells, and VDR agonists augment tamoxifen/AI effects, including in stem-like, tamoxifen-resistant compartments via Wnt/β-catenin downregulation [17,19,57]. Clinically, higher 25(OH)D is more frequent in ER-positive tumors, links to earlier stage, and shows stronger survival associations in ER-positive disease, although trials are underpowered and constrained by assay/seasonality issues [32,50,93]. CYP24A1 amplification/overexpression in ER-positive, highly proliferative tumors may blunt benefit unless metabolically targeted [38].

HER2-enriched

Subtype-specific evidence is limited. In a large TMA, VDR did not consistently track with HER2 status, implying heterogeneous signaling [92,94-96]. Mechanistic work indicates VDR can dampen ERBB2/ERK/AKT and WNT pathways, while an ERRα-dependent VDR-CYP24A1-ERRα high-expression signature associates with worse survival in basal-like tumors, suggesting context-dependent effects [33,38]. Neoadjuvant cohorts hint that sufficient baseline 25(OH)D improves response and PFS overall, but robust HER2-specific effects are lacking. Thus, biology supports an inhibitory role of VDR on ERBB2, yet clinical signals remain preliminary [27,38].

TNBC and BRCA1-related disease

TNBC shows lower overall VDR positivity and, in some series, more cytoplasmic than nuclear localization, both linked to adverse features and subtype-specific patterns [34,91,97]. Vitamin D preserves BRCA1 and 53BP1, countering BRCA1-like, CTSL-mediated 53BP1 loss, and constrains EMT, stemness, and chemotaxis; in PyMT models, sufficiency reduced Zeb1/STAT3 signaling and stromal CXCL12, limiting lung metastasis [14,24,98,99]. BRCA1 is required for full VDR-mediated p21 induction, offering a mechanistic basis for variable TNBC responsiveness [22]. An AR+/VDR+ TNBC subset responds to dual agonism and taxane/platinum combinations with reduced viability and stem-cell traits [18]. However, CYP24A1-driven inactivation and ERRα-linked rewiring can erode benefit and predict worse prognosis in basal-like tumors, mandating molecular stratification [33,38]. TNBC patients often have the lowest 25(OH)D, and some cohorts link adequacy to better survival, but causality remains uncertain; VDR loss in engineered models accelerates onset and metastasis, underscoring a tumor-suppressive role [12,57,100-102].

Menopausal status and adiposity strata

Host context shapes subtype relationships. In postmenopausal HR-positive women, hypovitaminosis D is common, BMI inversely correlates with 25(OH)D, and bone-health issues intersect with endocrine therapy factors integrated in a pathology-supported genetic-testing workflow linking deficiency, GC/VDR genotypes, and seasonal dips to tailored care [23,103-105]. In a postmenopausal ER-positive cohort on endocrine therapy, almost all had <30 ng/mL, and higher

25(OH)D clustered with a "healthier-bone" phenotype via lumbar BMD, justifying routine assessment and correction [26]. Reviews suggest stronger incidence signals for higher 25(OH)D in premenopausal women, while survivorship and bone outcomes dominate postmenopause [31,32]. Adiposity may dilute effective exposure; in prevention trials, reduced advanced cancers with Vitamin D were most evident in normal-BMI participants, and among survivors with BMI ≥25 kg/m^2, VDR polymorphisms modulated metabolic responses to supplementation [29,106-110].

Taken together, the Vitamin D-VDR axis is most trial-ready in luminal disease, where endocrine pathways provide cooperative entry points, and most experimentally promising in TNBC/BRCA1-like subsets, where DNA repair, EMT control, and AR/VDR co-targeting might be exploited. Variability in VDR localization, CYP27B1/CYP24A1 balance, and host factors (menopause, BMI, genotype) likely governs effect size, emphasizing the need for subtype-specific, biomarker-enriched trials and rational combinations [34,38,111].

PROGNOSIS AND TREATMENT CONTEXT

Prognostic associations

Across observational and translational datasets, lower circulating 25(OH)D at or near diagnosis generally tracks with more aggressive disease and poorer control, although effect sizes vary by study design and adjustment [27,38,46,57]. A PRISMA-guided meta-analysis of neoadjuvant cohorts reported that sufficient baseline 25(OH)D associates with higher response odds and longer progression-free survival (OR ≈0.78; HR ≈0.65), supporting 25(OH)D as a biomarker of treatment sensitivity [27]. Narrative syntheses consistently link deficiency with inferior disease-free and overall survival, while emphasizing confounding from adiposity, season, and lifestyle [38,46,57]. Tumor VDR expression shows a biological gradient higher in ER-positive, lower-proliferation phenotypes, but independent prognostic value is mixed: Some cohorts report better breast cancer-specific or overall survival with higher VDR, whereas a large hospital series found no outcome separation despite favorable clinicopathologic correlates [34,92]. Subcellular localization appears critical: Nuclear VDR correlates with ER positivity and lower grade, while cytoplasmic-dominant or lost VDR associates with nodal involvement and worse histology, implying that mislocalization blunts canonical signaling [91]. Vitamin D metabolic context also carries prognostic weight. CYP24A1, often upregulated or amplified, reduces intratumoral ligand availability; its inhibition restores 1,25(OH)$_2$D antiproliferative effects, and clinical-omics datasets link CYP24A1 gain to adverse features, including in ER-positive/high-proliferation disease [8,34,38]. An ERRα-VDR-CYP24A1 high-expression signature associates with poorer overall survival in basal-like tumors, while epigenetic repression of functional VDR isoforms adds a resistance layer that may obscure otherwise favorable associations [33,35,112-116].

VDR pathway resistance mechanisms and targeted strategies

Several recurrent lesions can attenuate Vitamin D-VDR signaling despite adequate circulating 25(OH)D and preserved receptor expression. First, CYP24A1 amplification and overexpression accelerate catabolism of 1,25(OH)$_2$D, uncoupling robust CYP24A1 induction from antiproliferative target activation and contributing to more aggressive, therapy-resistant phenotypes in breast tumors [9,34,35,39,40,116-118]. Second, epigenetic repression of the VDR locus, including promoter hypermethylation and skewing toward truncated splice variants, can reduce full-length, transcriptionally competent VDR and blunt VDRE-driven programs; demethylation restores VDR expression and resensitizes calcitriol-refractory cells in experimental models [36,37,118]. Third, altered VDR localization, with predominant cytoplasmic rather than nuclear staining, is repeatedly linked to higher grade, nodal involvement, and adverse biology in population cohorts, whereas nuclear VDR associates with more differentiated tumors [59,93,94,99]. In parallel, corepressor-dominated and chromatin-restricted VDR signaling driven by NCoR/SMRT complexes and histone deacetylases can selectively maintain CYP24A1 induction yet weaken growth-suppressive transcripts [37,38]. Finally, non-coding RNA networks add another layer of resistance: Specific miRNAs and lncRNAs can down-regulate VDR or remodel its downstream transcriptome, while others integrate VDR with BRCA1 and metabolic or EMT programs, potentially altering both tumor behavior and responsiveness to Vitamin D-based strategies [50,51,61,100,101].

Taken together, these mechanisms support a view of VDR as a context-dependent tumor suppressor whose impact depends not only on receptor abundance but also on metabolic balance (CYP27B1 vs. CYP24A1), epigenetic accessibility of VDRE targets, receptor localization, and the surrounding ncRNA and co-regulator landscape. Clinically, this underpins the paradox of VDR-high yet functionally refractory tumors and suggests that prognostic or predictive use of the pathway should incorporate compartment-specific VDR staining, CYP24A1 levels, and selected epigenetic or transcriptional biomarkers rather than VDR expression alone [34-39,50,51,93,94,100,101,116-118]. These resistance nodes also open avenues for intervention, such as 24-hydroxylase–resistant analogs or CYP24A1 inhibitors, demethylating agents, and HDAC inhibitors to restore canonical VDR signaling, and biomarker-driven combinations with endocrine or cytotoxic therapies, which are summarized in Table 1 and further discussed in the dosing and combination subsections [18,19,34-38,64,116-119].

Therapeutic interactions

Endocrine therapy

Mechanistic data support bidirectional reinforcement between the VDR axis and endocrine therapy. Calcitriol down-regulates ERα and prostaglandin-driven aromatase, augments anti-estrogen effects in ER-positive models, and can resensitize stem-like, tamoxifen-resistant cells by suppressing Wnt/β-catenin [19,46,57,117,118]. Early pharmacology showed strong additivity between tamoxifen and VDR agonists, such as EB1089 and KH1060 at lower analogue doses than calcitriol, with preserved activity in tamoxifen-resistant lines [17]. In practice, pathology-supported genetic testing integrates Vitamin D status, bone-health risk, and tumor genomics to refine endocrine regimens (e.g., tamoxifen switch, AI-associated bone-loss mitigation) while correcting deficiency, illustrating how host status can inform endocrine planning [23,26].

Chemotherapy and radiotherapy

Higher pre-treatment 25(OH)D levels associate with better neoadjuvant outcomes, in line with the meta-analytic signal [27,119,120]. Pre-clinical studies show enhanced effects when VDR agonists are combined with taxanes or platinum agents and when AR/VDR co-activation is layered onto cytotoxics in receptor-positive TNBC models, reducing tumorsphere formation and ALDH-high fractions [18]. Reviews also highlight radiosensitizing potential via effects on cell-cycle control, DNA-damage signaling, and EMT restraint, although human data remain preliminary and confounded [29,57].

Immuno-microenvironment

VDR signaling modulates stromal and immune tone by curbing HAS2/HA-CD44 pathways, dampening inflammatory circuits, and, in murine models, restraining EMT and CXCL12-driven metastatic "homing"; macrophage-activating components of the Vitamin D axis may cooperate with VDR ligands to enhance tumoricidal activity [24,38,47]. Integrative reviews describe miRNA-mediated immunomodulation and increased cytotoxic T-cell activity with higher Vitamin D status, but translation to checkpoint-based immunotherapy remains an early, inconclusive signal rather than established practice [30,50].

Vitamin D analogs and dosing considerations

Hypercalcemia limits systemic calcitriol, prompting the development of low-calcemic analogs (e.g., seocalcitol/EB1089, KH1060) that reproduce or exceed antiproliferative activity at lower concentrations, show additivity with tamoxifen and chemotherapy, and may target cancer-stem traits, especially when combined with epigenetic

Table 1: VDR pathway resistance mechanisms in breast cancer and potential therapeutic strategies

Resistance mechanism	Molecular/biological feature	Functional impact on Vitamin D-VDR signaling	Potential therapeutic strategies (examples)
CYP24A1 amplification/ overexpression	20q13 gain and strong CYP24A1 induction in breast tumors and aggressive, hormone-resistant lines; CYP24A1 expression often uncoupled from antiproliferative gene programs [9,34,35,39,40,116-118]	Accelerated catabolism of $1,25(OH)_2D$; reduced intratumoral ligand availability; VDR-high but functionally "ligand-starved" tumors with poorer outcomes and reduced sensitivity to calcitriol [34,35,39,116-118]	Use of 24-hydroxylase-resistant VDR agonists (e.g., EB1089, seocalcitol, KH1060); experimental CYP24A1 inhibitors; avoiding very low 25(OH) D; biomarker-guided selection of patients with high CYP24A1 for analog- or inhibitor-based combination strategies [18,19,34,39,64,116-118]
VDR promoter methylation and splice-variant imbalance	CpG-island hypermethylation in the VDR 5′ region in tumors versus normal tissue; preferential expression of truncated VDR transcripts with reduced transcriptional competence [36,118]	Reduced full-length VDR expression and impaired VDRE-dependent transcription; attenuated anti-proliferative, pro-differentiation and DNA-repair programs despite exogenous calcitriol [36,37,118]	DNA-methyltransferase inhibitors (e.g., 5-aza-deoxycytidine) and HDAC inhibitors to restore VDR expression and canonical target induction; rational sequencing of epigenetic therapy followed by VDR agonists in selected patients (experimental) [36-38,64,118]
Cytoplasmic VDR retention and nuclear loss	Predominantly cytoplasmic VDR with reduced nuclear staining in a subset of invasive breast cancers and TNBC; cytoplasmic VDR linked to higher grade and nodal disease; nuclear VDR enriched in ER-positive, better-differentiated tumors [59,93,94,99]	Impaired canonical nuclear VDR transcription despite total VDR positivity; potential shift toward non-genomic signaling; VDR IHC that does not distinguish compartments may overestimate functional sensitivity [59,93,94,99]	Incorporating nuclear versus cytoplasmic VDR into prognostic assessment and trial stratification; exploring agents or conditions that favor nuclear translocation; combining VDR agonists with endocrine or AR-directed strategies in subtypes with preserved nuclear VDR [19,59,93,94,99]
Corepressor-dominated/ epigenetically constrained VDR signaling	Increased NCoR/SMRT and HDAC recruitment at VDR target loci; epigenetic context that maintains CYP24A1 induction while blunting cell-cycle and differentiation targets; gene-specific chromatin effects of HDAC inhibitors [37,38]	VDR present but tumor-suppressive transcriptional outputs dampened; partial or transient responses to calcitriol; context-dependent sensitivity of individual targets (e.g., GADD45A, TRPV6) [37,38]	Short-course HDAC inhibitor co-therapy to re-open chromatin and enhance VDR-dependent transcription; careful dosing to balance antitumor effects with toxicity; selection of patients based on epigenetic/VDR signatures (research stage) [37,38,64]
Non-coding RNA-mediated modulation (miRNAs and lncRNAs)	VDR-linked lncRNAs (e.g., LINC00511, MALAT1, SNHG16) and miRNAs that directly target VDR or its downstream effectors; miRNA-VDR crosstalk influencing EMT, stemness, metabolism, and DNA repair [50,51,61,100,101]	Post-transcriptional suppression or re-wiring of VDR signaling despite adequate receptor levels; subtype-specific patterns that may shift sensitivity to Vitamin D or analogs [50,51,61,100,101]	Emerging strategies include targeting oncogenic miRNAs/lncRNAs or using their expression as biomarkers to select VDR-directed therapies; currently pre-clinical with no approved interventions, but highly relevant for trial stratification and mechanistic studies [50,51,61,100,101]

VDR: Vitamin D receptor, HDAC: Histone deacetylase

modulators [17,18,36,121,122]. Resistance mechanisms, including CYP24A1 overexpression, VDR methylation or alternative splicing, and ERRα-mediated metabolic rewiring, support biomarker-guided selection and, in some contexts, CYP24A1 inhibition or chromatin-targeted co-therapy to sustain intratumoral ligand action [8,13,33,35]. Overall, the most defensible near-term strategy is systematic correction of deficiency and incorporation of VDR pathway status (VDR level/ localization, CYP27B1/CYP24A1 balance, endocrine context) into combination designs, with prospective trials needed to define dose, schedule, and the subtypes most likely to benefit [29,38,46].

Measurement, targets, and dosing

Assays and calibration; cut-points and seasonality. Circulating 25(OH)D is measured by RIA, ELISA, or electrochemiluminescence, and method heterogeneity contributes to differences in absolute values and risk thresholds [27]. Even with external quality control, as in the Long Island Breast Cancer Study Project, the 2-3-week half-life of 25(OH)D and pre-analytical factors add noise around peri-diagnostic samples [21]. Most syntheses define deficiency as <20 ng/mL (≈50 nmol/L), insufficiency 20-29 ng/mL, and sufficiency ≥30 ng/mL, and suggest an "optimal" 30-60 ng/mL window for extra-skeletal effects; epidemiologic data support higher risk at levels <50 nmol/L and lower risk around 40 ng/mL [30-32,39]. Because 25(OH)D varies with season and adiposity, winter dips and higher BMI justify retesting 8–12 weeks in a similar season and using the same laboratory [21,23,106].

Dosing strategies and achievable targets. Daily cholecalciferol is the best studied strategy. Large trials using 2000 IU/day did not reduce overall breast-cancer incidence, although fewer advanced cancers appeared in normal-BMI subgroups [29]. Smaller studies suggest that 1000–4000 IU/day typically moves patients with insufficiency into the ≥30-40 ng/mL range, including breast-cancer survivors with low baseline levels [31,106]. High-dose weekly regimens can safely achieve >40 ng/mL in high-risk settings, but prevention or survival benefits remain unproven, and adherence, BMI, and season often drive achieved levels more than schedule [23,32,46].

Targets, co-supplementation, and safety. In oncology, authors aim to keep 25(OH)D ≥30 ng/mL, with 30-50 ng/mL a pragmatic range for bone and adjunctive benefit, while emphasizing that observational associations with response or progression do not establish causality [27,29,31,32]. Calcium is often co-prescribed for skeletal protection, but makes any cancer-prevention signal difficult to attribute to Vitamin D alone [32,46]. Hypercalcemia limits calcitriol and analogs, so low- or non-calcemic agents and Vitamin D-based combinations with endocrine or cytotoxic therapies are best explored within biomarker-anchored clinical trials [13,18,27,46]. A practical approach is to document baseline status, choose a daily dose guided by BMI and baseline 25(OH)D, recheck after 8–12 weeks in the same laboratory, adjust for season, add calcium where bone protection is indicated, and prioritize correction of deficiency over pursuit of supra-physiologic targets [23,31,32,106].

Clinical implications

Routine 25(OH)D assessment is justified at diagnosis and during survivorship, with special attention to postmenopausal women on aromatase inhibitors, patients with higher BMI, limited sun exposure, or low BMD [23,26]. Treat deficiency primarily for skeletal health and overall well-being; any anticancer benefit should be presented as possible but unproven at the population level given neutral Mendelian-randomization and large prevention RCT signals [29]. A pragmatic target is to avoid <20 ng/mL and maintain roughly 30-50 ng/mL, acknowledging assay and seasonal variation [30,31]. In practice: Start 1,000–2,000 IU/day cholecalciferol (consider 4,000 IU/day short-term in low-baseline or higher-BMI patients) and recheck in 8–12 weeks; add calcium when bone protection is indicated; use the same laboratory for follow-up to minimize inter-assay drift [21,106]. Counseling should be risk-informed: (1) Quantify baseline and season; (2) factor BMI, activity, and diet; (3) consider therapy context (e.g., AI-associated bone loss); (4) where feasible, integrate pathway cues VDR localization, CYP27B1/CYP24A1 balance, and germline GC/VDR variants to tailor supplementation intensity and discuss trial eligibility [23,34]. For oncology endpoints, frame expectations realistically: Observational and neoadjuvant data suggest better outcomes with sufficient status and VDR-intact biology, but causality remains uncertain; reserve active analogs or CYP24A1-targeted approaches for clinical trials or biomarker-anchored protocols [27,33].

Limitations of this review and future directions

Evidence synthesized here spans heterogeneous designs, assays, thresholds, and timepoints, which complicates direct comparison and causal inference; peri-diagnostic sampling, seasonality, and lifestyle confounding remain pervasive [21,32]. Prevention trials often enrolled largely sufficient populations and did not guarantee on-study achievement of hypothesized protective ranges, limiting interpretability [29]. Tumor heterogeneity, including CYP24A1 upregulation, epigenetic repression or mislocalization of VDR, and ERRα-mediated rewiring blunts pathway readouts and likely dilutes pooled effects [33-35]. Finally, small or early-phase studies of low-calcemic analogs and combination regimens restrict clinical generalizability [36].

Future work should prioritize biomarker-anchored trials that stratify by baseline 25(OH)D, BMI, ancestry, and GC/VDR/CYP24A1 genotype; standardize assays and seasonal timing; and target achieved levels within a pre-specified window [30,31]. Subtype-specific designs are needed luminal disease for endocrine co-therapy, TNBC/BRCA1-like settings for DNA-repair, EMT, and AR/VDR co-targeting with embedded pharmacodynamic readouts (p21, DKK1, Ki-67, VDR localization) and bone endpoints in AI-treated survivors [18,19,26]. Mechanistic trials should test CYP24A1 inhibition or epigenetic co-modulation to overcome calcitriol resistance, alongside next-generation analogs with lower calcemic risk [8,37]. Finally, integrative PSGT frameworks that pair biochemistry with genomics and tumor context deserve prospective evaluation as care pathways for safe correction of deficiency and rational trial referral [23,38].

CONCLUSION

The Vitamin D-VDR axis in breast cancer is biologically compelling but clinically modest. Experimental data consistently show that sufficient ligand and intact VDR signaling curb proliferation, EMT, stemness, and genomic instability, yet these effects are strongly conditioned by local metabolism (CYP27B1/CYP24A1), VDR expression/localization, and host factors, such as BMI, menopause, and GC/VDR/CYP variants. Human studies broadly link low 25(OH)D and disrupted pathway tone with more aggressive disease and poorer outcomes, especially in luminal and selected TNBC/BRCA1-like settings, while epidemiology, Mendelian-randomization, and large prevention trials do not support a major, population-wide causal effect on incident breast cancer. At present, the most defensible practice is systematic detection and correction of deficiency, targeting roughly 30–50 ng/mL for skeletal and possible adjunctive benefit, with clear counseling that anticancer effects remain uncertain. Future progress hinges on biomarker-anchored, subtype-specific trials that integrate VDR pathway status and host context, and test low-calcemic analogs and rational combinations, positioning Vitamin D-VDR as a precision co-modulator rather than a stand-alone anticancer therapy.

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CONFLICTS OF INTEREST

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AUTHORS' CONTRIBUTIONS

Conceptualization and overall design of the review: Kuppusamy Baskaran and Arumugam Suresh. Literature search, study selection, and data extraction: Vemuri Helena and Natrajan Muninathan. Drafting of the initial manuscript: Vemuri Helena, with substantial input from Arumugam Suresh. Critical revision of the manuscript for important intellectual content and integration of mechanistic, translational, and clinical sections: Kuppusamy Baskaran and Natrajan Muninathan. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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