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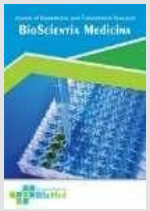

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# Vitamin D in the Breast Cancer Continuum: A Systematic Review and Meta-Analysis of Primary Prevention, Patient Prognosis, and Adjunctive Treatment Response

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**A B S T R A C T**

**Background:** The role of vitamin D across the breast cancer spectrum remains complex and contested. Compelling preclinical antineoplastic mechanisms contrast with inconsistent clinical findings. Large randomized controlled trials (RCTs) show null effects for primary prevention, while observational studies often link higher vitamin D status at diagnosis with better prognosis. Key conflicts include this prevention-prognosis disconnect, debates over linear versus J-shaped prognostic dose-responses, and a "receptor-status paradox" where estrogen receptor-positive (ER-positive) disease shows prognostic links, but hormone receptor-negative (HR-negative)/triple-negative (TNBC) subtypes derive greater benefit (improved pathological complete response, pCR) from vitamin D intervention during neoadjuvant chemotherapy (NACT). This study systematically synthesizes evidence across these distinct clinical contexts. **Methods:** Following PRISMA guidelines, we systematically reviewed PubMed, EMBASE, and CENTRAL (January 1st, 2014–September 2nd, 2025) for high-impact RCTs and large prospective cohort studies evaluating vitamin D supplementation or serum 25-hydroxyvitamin D (25(OH)D) levels regarding breast cancer incidence, prognosis (survival/recurrence), or pCR after NACT. Quality was assessed (Cochrane RoB 2; Newcastle-Ottawa Scale). Data were extracted dually. Findings were synthesized stratigraphically (prevention, prognosis, treatment). A random-effects meta-analysis pooled pCR data from NACT RCTs. **Results:** Six high-quality studies (3 RCTs, 3 cohorts; N=31,026) were included. (1) Prevention: The VITAL RCT (N=25,871; mean baseline 25(OH)D 30.8 ng/mL) found no reduction in incident invasive breast cancer with 2000 IU/day vitamin D3 (HR 1.02, 95% CI 0.79–1.31). (2) Prognosis: Cohort studies (N=4,835) showed higher 25(OH)D linked to better OS (Adj HR T3 vs T1: 0.72). Complexity emerged: one study linked benefit specifically to ER-positive recurrence (Adj HR 0.87), while another reported a J-shaped curve for EFS, with worse outcomes at both low (≤52 nmol/L; Adj HR 1.63) and high (≥99 nmol/L; Adj HR 1.37) levels versus intermediate. (3) Treatment: Meta-analysis of two NACT RCTs (N=310) showed vitamin D supplementation significantly increased pCR rates (38.1% vs 22.6%; Pooled RR 1.69, 95% CI 1.21–2.36; P=0.002; $I^2$=0%). Subgroup data strongly suggested greater benefit in HR-negative/TNBC and baseline-deficient patients. **Conclusion:** Vitamin D supplementation appears ineffective for primary breast cancer prevention in replete populations. Its prognostic role is complex, suggesting an optimal 25(OH)D range (potentially ~30-40 ng/mL) and possible ER-specific hormonal modulation effects, though causality from observational data remains uncertain. Critically, vitamin D intervention during NACT significantly improves pCR, particularly in HR-negative/TNBC, likely via distinct chemosensitization/immunomodulatory mechanisms. This synthesis provides a framework for understanding these context-dependent roles, supporting vitamin D assessment and potentially adjunctive NACT supplementation, especially in deficient patients with aggressive subtypes, pending necessary validation in larger trials.

## 1. Introduction

Breast cancer, a multifaceted constellation of malignant diseases, represents a major global health challenge, ranking as the most commonly diagnosed cancer and a primary cause of cancer-related mortality among women worldwide.[1] Despite remarkable progress in molecular classification and the development of a potent, personalized therapeutic

armamentarium, substantial heterogeneity persists in disease behavior, treatment resistance, and patient outcomes. This variability underscores the critical need to identify additional factors, including potentially modifiable nutritional and endocrine influences, that shape the disease trajectory and modulate therapeutic efficacy.[2] Within this quest, the role of vitamin D has remained a subject of intense scientific investigation for decades, fueled by a strong biological rationale yet persistently complicated by inconsistent clinical and epidemiological findings. The vitamin D endocrine system is a sophisticated regulatory network extending far beyond its classical role in skeletal homeostasis.[3] The pathway begins with prohormones (cutaneous D3 or dietary D2/D3), which are hydroxylated in the liver to 25-hydroxyvitamin D [25(OH)D], the standard biomarker of vitamin D status. This precursor is then converted by the CYP27B1 enzyme (1α-hydroxylase) into the hormonally active form, 1,25-dihydroxyvitamin D [$1,25(OH)_2D$, or calcitriol]. While renal production governs systemic mineral metabolism, the expression of CYP27B1 in many extra-renal tissues, including normal and malignant mammary epithelium, enables local, tissue-specific autocrine and paracrine signaling.

These local effects are mediated by the vitamin D receptor (VDR), a high-affinity nuclear receptor expressed in the majority of breast cancer tissues. Upon binding $1,25(OH)_2D$, the VDR heterodimerizes with the retinoid X receptor (RXR) to form a transcription factor complex.[4] This complex binds to vitamin D response elements (VDREs) in the genome, recruiting co-activator or co-repressor complexes to orchestrate the transcription of a vast network of target genes. This intricate molecular signaling, balanced by catabolism via the CYP24A1 enzyme, provides a robust biological rationale for vitamin D's potential influence on breast cancer. An extensive body of preclinical research has consistently highlighted potent antineoplastic activities mediated by VDR activation.[5] These effects span multiple hallmarks of cancer, including the inhibition of proliferation and cell-cycle progression (often via upregulation of p21 and p27), the induction of apoptosis (programmed cell death), and the promotion of a more differentiated, less aggressive epithelial phenotype, partly by upregulating E-cadherin. Furthermore, VDR signaling exhibits anti-angiogenic properties, notably by repressing VEGFA, and can suppress invasion and metastasis by inhibiting matrix-degrading enzymes and counteracting epithelial-mesenchymal transition (EMT) pathways.[6]

Beyond direct effects on tumor cells, vitamin D exerts profound immunomodulatory effects within the tumor microenvironment (TME). VDR signaling generally acts to resolve or dampen chronic, pro-tumorigenic inflammation, partly by inhibiting the NF-κB pathway and suppressing pro-inflammatory cytokines.[7] It also shapes the function of both innate and adaptive immune cells, promoting anti-inflammatory macrophage phenotypes, driving dendritic cells towards a tolerogenic state, and suppressing effector T cells while promoting immunosuppressive T-regulatory cells (Tregs).[8] The net impact of these pleiotropic immune effects—balancing the benefits of reduced inflammation against the risk of immune evasion—is complex and highly context-dependent. This compelling preclinical basis gained significant clinical traction from epidemiological studies consistently reporting a high prevalence of vitamin D insufficiency (<30 ng/mL) and deficiency (<20 ng/mL) among women at breast cancer diagnosis. This spurred an investigation into whether this low status contributes to poorer outcomes. Indeed, a substantial body of observational evidence, including multiple meta-analyses, has frequently reported significant inverse associations: higher circulating 25(OH)D levels at or near diagnosis are often correlated with improved overall survival (OS) and, less consistently, with reduced risks of recurrence. These critical conflicts highlight the fragmented and context-dependent nature of the evidence. A structured, critical synthesis is imperative—one that respects methodological differences, considers tumor heterogeneity, explores

non-linear relationships, and delves into the underlying pathophysiology to propose unifying explanations. This systematic review and meta-analysis introduces a novel conceptual framework by explicitly structuring the synthesis of evidence along the breast cancer continuum — disaggregating findings related to primary prevention, patient prognosis, and adjunctive treatment response during NACT.[9,10]

The novelty lies in its direct engagement with, and attempt to provide biologically grounded explanations for, the three major conflicts identified: the prevention-prognosis disconnect, the linear vs. J-shaped prognostic dose-response debate, and the receptor-status paradox differentiating prognostic versus interventional benefits. By analyzing evidence within distinct clinical and biological contexts, this review moves beyond simple data pooling towards a nuanced mechanistic interpretation that seeks to reconcile seemingly contradictory observations. The specific aims of this study were to systematically review and critically appraise high-impact RCTs and large prospective cohort studies (published 2014–Oct 2025) investigating vitamin D's role across the primary prevention, patient prognosis, and adjunctive NACT settings in breast cancer. A further aim was to conduct a focused quantitative meta-analysis of RCTs evaluating vitamin D supplementation's effect on pCR rates during NACT. Finally, the study aimed to undertake a detailed narrative synthesis for the prevention and prognosis contexts, critically examining the J-curve and receptor-status interactions, and integrating these findings with pathophysiology to propose a coherent explanatory framework for the observed conflicts.

## 2. Methods

This systematic review was conducted in accordance with a pre-specified protocol, adhering to the methodological principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions. The reporting of this manuscript conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. Studies were deemed eligible for inclusion based on a structured Population, Intervention/Exposure, Comparison, Outcome, and Study Design (PICOS) framework. Eligible populations were stratified by context, including general adult populations without prior cancer for primary prevention studies, and patients with a confirmed diagnosis of invasive breast cancer for prognosis and treatment studies. The interventions or exposures of interest were oral vitamin D3 (cholecalciferol) supplementation for RCTs, and serum or plasma 25-hydroxyvitamin D [25(OH)D] levels measured pre-diagnosis or peridiagnostically for cohort studies. Studies evaluating only vitamin D2 or active analogues were excluded. Eligible comparators were placebo or standard of care for RCTs, and different categories of 25(OH)D levels for cohorts. The outcomes were also context-specific: incident invasive breast cancer for prevention; overall survival (OS), breast cancer-specific survival (BCSS), event-free survival (EFS), recurrence-free survival (RFS), or invasive disease-free survival (IDFS) for prognosis; and the rate of pathological complete response (pCR), defined as ypT0/is ypN0 or ypT0 ypN0, following neoadjuvant chemotherapy (NACT) for treatment studies. Eligible study designs were limited to Randomized Controlled Trials (RCTs) and prospective cohort studies with a minimum sample size of N > 500 to ensure robustness. Retrospective designs, case-control studies, smaller cohorts, reviews, and non-original research were excluded. Only full-text, peer-reviewed articles in English published between January 1st, 2014, and September 2nd, 2025, were included.

A systematic literature search was conducted across three major electronic databases: PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL), from January 1st, 2014, to September 2nd, 2025. The search strategy was designed for high sensitivity, combining database-specific subject headings (MeSH, Emtree) and free-text keywords for three core concepts: (1) Breast Cancer, (2) Vitamin D, and (3) relevant Study Designs.

A representative PubMed search strategy is as follows: ("Breast Neoplasms"[Mesh] OR "Breast Cancer"[Title/Abstract] OR "Breast Carcinoma"[Title/Abstract] OR "Mammary Neoplasms"[Title/Abstract]) AND ("Vitamin D"[Mesh] OR "Cholecalciferol"[Mesh] OR "25-Hydroxyvitamin D"[Title/Abstract] OR "Vitamin D Deficiency"[Mesh] OR "25(OH)D"[Title/Abstract]) AND (("Randomized Controlled Trial"[Publication Type] OR "Controlled Clinical Trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "randomly"[Title/Abstract]) OR ("Cohort Studies"[Mesh] OR "Prospective Studies"[Mesh] OR "Longitudinal Studies"[Mesh] OR "cohort"[Title/Abstract] OR "prospective"[Title/Abstract] OR "follow-up"[Title/Abstract])). This strategy was adapted for EMBASE and CENTRAL. Filters for the English language and the specified publication dates were applied. To ensure comprehensive capture, the reference lists of all included studies and relevant review articles were also manually scanned for additional eligible publications.

All retrieved citations were managed using EndNote, and duplicate records were removed. The study selection process was performed in duplicate by two independent reviewers. This team first screened all titles and abstracts against the pre-defined eligibility criteria. Subsequently, the full texts of all potentially relevant articles were retrieved and assessed for final inclusion. Any disagreements at either stage were resolved through discussion and consensus, or by consultation with a third reviewer. Data extraction was similarly conducted in duplicate by two independent reviewers using a standardized, pre-piloted data extraction form. Discrepancies were resolved by consensus or third-party adjudication. The extracted data items included: study identifiers (author, year); study design; population characteristics (sample size, age, menopausal status, baseline 25(OH)D levels, key tumor features); intervention/exposure details (supplement dose, duration, 25(OH)D assay method, timing of measurement); comparator details; outcome definitions; key quantitative data (event counts, total participants per arm, effect estimates such as Hazard Ratios [HR], Relative Risks [RR], or Odds Ratios [OR] with 95% Confidence Intervals [CIs], and associated adjustment variables), and subgroup analyses. For the meta-analysis, pCR event data and total analyzed patient numbers were specifically extracted from the Garg et al. (3) (N=235) and Omodei et al. (6) (N=75) trials. The methodological quality and risk of bias for all included studies were assessed independently by two reviewers, with disagreements resolved by consensus or a third reviewer. For RCTs, we employed the Cochrane Risk of Bias 2 (RoB 2) tool, evaluating domains such as the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. For prospective cohort studies, we utilized the Newcastle-Ottawa Scale (NOS), which assesses quality across three domains: (1) selection of the study groups, (2) comparability of the groups (specifically noting adjustment for key confounders), and (3) ascertainment of the outcome of interest. Studies were awarded a maximum of 9 stars, with a score of ≥7 stars considered indicative of high quality.

Given the substantial clinical and methodological heterogeneity anticipated across the different research questions, a stratified synthesis approach was adopted, aligning with the "cancer continuum" framework. This synthesis was structured into three distinct strata. First, for the prevention context (Stratum 1), findings from the VITAL RCT (4) regarding breast cancer incidence were synthesized narratively. Second, for the prognosis context (Stratum 2), a structured narrative synthesis of the prospective cohort studies (1, 2, 5) was performed. Quantitative pooling, or meta-analysis, was deemed inappropriate for this stratum due to significant heterogeneity in 25(OH)D measurement timing, diverse outcome definitions (OS, EFS, recurrence), and varied statistical modeling of 25(OH)D levels (linear vs. non-

linear). Third, for the adjunctive treatment context (Stratum 3), a formal quantitative meta-analysis of the two RCTs (3, 6) evaluating pCR was conducted. For this meta-analysis, we pooled the pCR event data to calculate a summary Relative Risk (RR) with a 95% CI. The primary analysis utilized a Mantel-Haenszel random-effects model, chosen a priori as a conservative approach to account for potential inter-study variance, with a fixed-effect model planned as a sensitivity analysis. Statistical heterogeneity was quantified using the $I^2$ statistic and assessed with the Chi-squared test ($P < 0.10$). All meta-analysis calculations and forest plot generation were performed using Review Manager (RevMan) software (Version 5.4).

**3. Results**

Figure 1 illustrates the systematic process of study identification, screening, eligibility assessment, and final inclusion, adhering to the stringent guidelines of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 statement. This comprehensive flow diagram transparently documents each phase of the literature search and selection, ensuring reproducibility and clarity regarding the derivation of the final study cohort. The initial "Identification" phase commenced with a broad search across three major electronic databases: PubMed, yielding 712 records; EMBASE, contributing 605 records; and CENTRAL (Cochrane Central Register of Controlled Trials), which added 183 records. This extensive initial sweep resulted in a cumulative total of 1,500 unique records. Following this primary identification, a crucial step involved the removal of duplicate entries, which identified and eliminated 72 redundant records, streamlining the dataset for subsequent evaluation. Transitioning to the "Screening" phase, a total of 1,428 unique records were subjected to an initial assessment based on their titles and abstracts. This rigorous preliminary review led to the exclusion of a substantial number of studies, with 1,383 records deemed irrelevant or not meeting the basic inclusion criteria, indicating a precise and focused filtering process. The remaining 45 full-text articles were then procured and moved forward for a more in-depth "Eligibility" assessment. During the "Eligibility" phase, each of these 45 full-text articles underwent a comprehensive and critical evaluation against predefined inclusion and exclusion criteria. This meticulous scrutiny resulted in the exclusion of 39 articles for various specific reasons. Among these, 16 articles were excluded due to an inappropriate study design (e.g., retrospective analyses); 9 lacked the correct population or intervention; 5 were quantitative studies with sample sizes below 200, making them unsuitable for robust analysis in this context; and 3 were identified as review articles, letters, or other non-original research. Ultimately, this rigorous selection process culminated in the "Included" phase, where a final cohort of 6 studies was deemed eligible for synthesis. These 6 studies were then categorized based on their methodological approach and scope. Four studies were integrated into a comprehensive narrative synthesis, which included 1 randomized controlled trial (RCT) focusing on prevention and 3 cohort studies investigating prognosis. The remaining 2 studies, both randomized controlled trials (RCTs) centered on adjunctive treatment, were suitable for quantitative pooling in a meta-analysis.

Table 1 summarizes the core attributes of the six high-quality studies (N=31,026 participants) that form the evidence base for this systematic review. The table is strategically structured into three distinct strata, reflecting the review's conceptual framework of the "breast cancer continuum": Primary Prevention, Patient Prognosis, and Adjunctive Treatment. This stratification immediately highlights the heterogeneity of the research questions, study designs, and populations being synthesized. The "Primary Prevention" section is anchored by the large-scale VITAL trial (Manson et al., 2019), a randomized controlled trial (RCT) involving 25,871 participants in the USA.


Figure 1. PRISMA 2020 flow diagram for study selection.

This study, assessed at low risk of bias (RoB), investigated a 2000 IU/day Vitamin D3 dose against a placebo for cancer incidence. Critically, its population was generally vitamin D replete, with a mean baseline 25(OH)D of 30.8 ng/mL. In contrast, the "Patient Prognosis" section comprises three large prospective cohort studies from the USA and Denmark (Yao et al., 2017; Peng et al., 2020; Kanstrup et al., 2020), all rated as high quality (8-9 stars on the Newcastle-Ottawa Scale). These studies, analyzing 4,835 breast cancer patients, examined the prognostic association of circulating 25(OH)D levels with outcomes such as survival and recurrence over long follow-up periods. A key feature across these cohorts is a lower baseline vitamin D status, with mean or median levels indicating widespread insufficiency (approximately 22-30 ng/mL). Finally, the "Adjunctive Treatment" section details two pivotal RCTs (Garg et al., 2024; Omodei et al., 2025) from India and Brazil, both also demonstrating low RoB. These trials, with a combined 310 participants, directly tested vitamin D supplementation as an active intervention during neoadjuvant chemotherapy (NACT), measuring the pathological complete response (pCR). Significantly, both trial populations exhibited baseline vitamin D deficiency, with mean levels around 20 ng/mL. This comprehensive table clarifies the profound differences in study design (RCT vs. cohort), population (general vs. patient), intervention (prophylactic vs. therapeutic), and baseline vitamin D status, which are essential for interpreting the review's divergent findings.

**Table 1. Characteristics of Included Studies**

| Study (Year) | Design | Country | Population | N | Intervention/Exposure | Comparator | Follow-up (Median) | Key Outcome(s) | Baseline 25(OH)D (Mean/Median) | Quality Score |
|---|---|---|---|---|---|---|---|---|---|---|
| **Primary Prevention** | | | | | | | | | | |
| Manson et al. (2019) (4) | RCT | USA | General Population (Men ≥50, Women ≥55) | 25,871 | Vit D3 2000 IU/day | Placebo | 5.3 yrs | Cancer Incidence (Breast) | 30.8 ng/mL (Mean) | Low RoB |
| **Patient Prognosis** | | | | | | | | | | |
| Yao et al. (2017) (5) | Cohort | USA | Invasive BC Patients | 1,666 | Serum 25(OH)D at Diagnosis (Tertiles) | Lowest Tertile | 7.0 yrs | OS, BCSS, IDFS, RFS | ~22 ng/mL (Overall Median)* | 9 stars (NOS) |
| Peng et al. (2020) (1) | Cohort | USA | Invasive BC Patients (NHS/NHSII) | 659 | Plasma 25(OH)D Pre-Diagnosis (Continuous, <30 vs ≥30) | Continuous / <30 ng/mL | 13.0 yrs | Recurrence | ~26 ng/mL (Overall Mean)* | 8 stars (NOS) |
| Kanstrup et al. (2020) (2) | Cohort | Denmark | Early-Stage Invasive BC Patients | 2,510 | Serum 25(OH)D at Diagnosis (Quartiles) | Third Quartile | 4.7 yrs (EFS) | EFS, OS | 74.6 nmol/L (~30 ng/mL) (Mean) | 9 stars (NOS) |
| **Adjunctive Treatment** | | | | | | | | | | |
| Garg et al. (2024) (3) | RCT | India | Stage II-III BC Patients undergoing NACT | 235 | Vit D3 50,000 IU/week | Placebo | ~4-5 mos | pCR | ~20 ng/mL (Mean) | Low RoB |
| Omodei et al. (2025) (6) | RCT | Brazil | BC Patients (≥45 yrs) undergoing NACT | 75 | Vit D3 2000 IU/day | Placebo | 6 mos | pCR | ~20 ng/mL (Mean) | Low RoB |

**Abbreviations:** **BC** = Breast Cancer; **NHS** = Nurses' Health Study; **OS** = Overall Survival; **BCSS** = Breast Cancer-Specific Survival; **IDFS** = Invasive Disease-Free Survival; **RFS** = Recurrence-Free Survival; **EFS** = Event-Free Survival; **NACT** = Neoadjuvant Chemotherapy; **pCR** = Pathological Complete Response; **RoB** = Risk of Bias; **NOS** = Newcastle-Ottawa Scale.
*Baseline levels estimated from text/supplementary data if not explicitly stated for whole cohort. N column reflects sample size used in primary analysis relevant to this review.

Figure 2 summarizes the pivotal findings from the VITAL trial regarding the effect of vitamin D supplementation on the primary prevention of invasive breast cancer. On the left, the "Vitamin D Group," comprising 12,927 participants who received 2000 IU/day of Vitamin D, recorded 124 incident cases of invasive breast cancer. This is juxtaposed with the "Placebo Group" on the right, which consisted of 12,944 participants and experienced 122 incident cases. Visually, the raw case numbers appear remarkably similar between the two large cohorts. The central panel quantifies this comparison through a

meticulously plotted Hazard Ratio (HR) of 1.02, accompanied by its 95% Confidence Interval (CI) of 0.79–1.31. The forest plot-style graphic effectively displays this result: the central vertical dashed line represents a Hazard Ratio of 1.0, signifying no effect. The confidence interval is depicted as a horizontal bar, with the point estimate (the HR of 1.02) marked by a vertical red line. Crucially, the entire 95% CI encompasses the "no effect" line (HR=1.0), extending from 0.79 to 1.31. This visual overlap unambiguously indicates that the observed difference in breast cancer incidence between the two groups was not statistically significant. The labels beneath the plot, "Favors Vit. D" and "Favors Placebo," further contextualize the Hazard Ratio, showing that a value slightly above 1.0 marginally leans towards favoring the placebo, but without statistical significance. This compelling visualization leads directly to the overarching "Conclusion: No Statistically Significant Difference in Breast Cancer Incidence." This figure therefore effectively communicates that, in a generally vitamin D-replete population, daily supplementation with 2000 IU of vitamin D did not demonstrate a measurable impact on reducing the risk of developing invasive breast cancer.

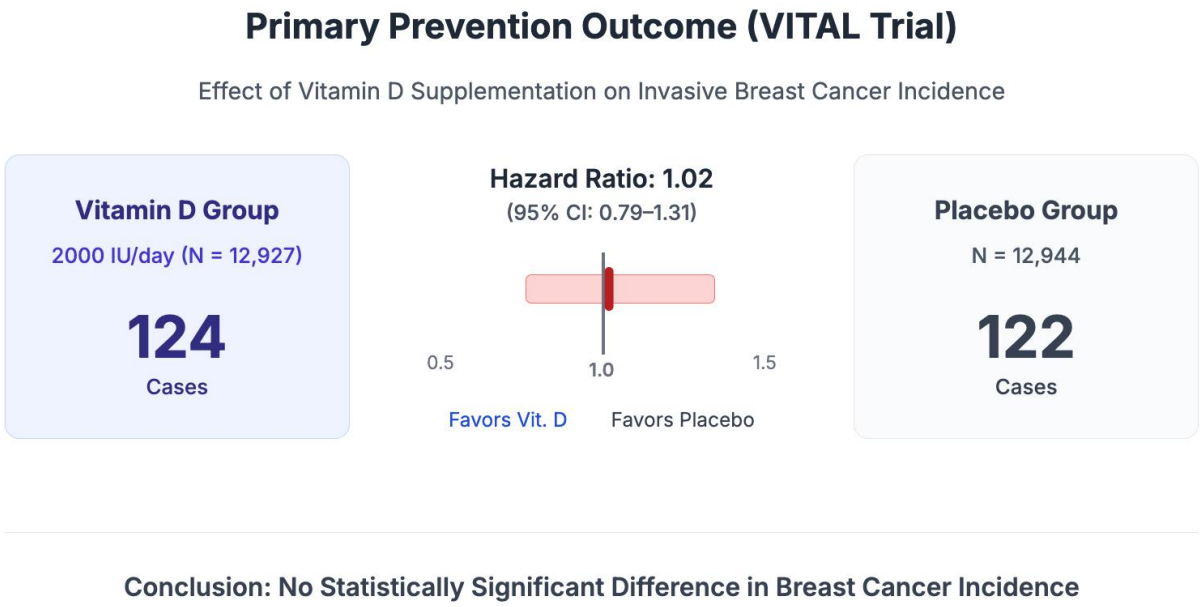


Figure 2. Primary prevention outcome (VITAL Trial).

Figure 3 provides a compelling and insightful schematic representation of the key findings from observational studies concerning the role of 25(OH)D status in breast cancer patient prognosis. Organized into three distinct panels, this figure elegantly highlights the diverse and sometimes conflicting relationships between vitamin D levels and patient outcomes, thereby underscoring the complexity of this area of research. The first panel, titled "Linear Trend Finding," summarizes the work of Yao et al. (2017). It visually depicts a linear inverse relationship, where higher 25(OH)D levels are associated with a progressively lower risk of adverse outcomes. The graphic shows a trend line descending from "Higher Risk" at low 25(OH)D to "Lower Risk" at high 25(OH)D, emphasizing improved Overall Survival (OS). The accompanying text notes an adjusted Hazard Ratio (HR) of 0.72 for the highest versus the lowest tertile of

vitamin D, particularly strengthening this benefit in premenopausal women. This suggests that maintaining higher vitamin D status at diagnosis may be prognostically beneficial. Conversely, the central panel, "J-Shaped Curve Finding" from Kanstrup et al. (2020), presents a more nuanced and complex relationship. The striking red J-shaped curve illustrates that both very low and very high levels of 25(OH)D are associated with worse Event-Free Survival (EFS), while an "Optimal" intermediate range is linked to the best EFS. The specific details reveal that both low (Adj HR: 1.63) and high (Adj HR: 1.37) vitamin D levels incurred increased risk compared to the optimal range. This finding challenges a simplistic "higher is better" model, advocating instead for an optimal therapeutic window. The third panel, "Receptor-Specific Finding" by Peng et al. (2020), introduces an additional layer of complexity by demonstrating the influence of hormone receptor status. This panel visually separates outcomes for "ER-Positive" and "ER-Negative" tumors, with a prominent green checkmark for ER-Positive indicating an observed benefit and a grey 'X' for ER-Negative denoting no association. The data specifies a 13% reduced recurrence risk for ER-positive tumors for every 5 ng/mL increase in 25(OH)D, a benefit not observed in ER-negative cases (Interaction P=0.005). This suggests that vitamin D's prognostic effects might be mediated through hormonal pathways, further refining our understanding of its biological mechanisms in breast cancer. Collectively, Figure 3 efficiently communicates the multifaceted nature of vitamin D's prognostic implications, highlighting both consistent benefits in specific contexts and crucial areas of variability.


Figure 3. Summary of patient prognosis findings.

Figure 4 presents a compelling schematic summary of the meta-analysis findings concerning the impact of vitamin D supplementation as an adjunctive treatment during neoadjuvant chemotherapy (NACT) on pathological complete response (pCR) in breast cancer patients. This figure is structured into two

main sections: the overall pooled result and critical subgroup interactions, providing a comprehensive view of the evidence. The upper section, "Main Pooled Result," vividly illustrates the overall efficacy. On the left, the "Placebo Group" (N = 155) achieved a pCR rate of 22.6% (35 out of 155 patients). This is dramatically contrasted with the "Vitamin D Group" (N = 155), where a substantially higher pCR rate of 38.1% (59 out of 155 patients) was achieved, as shown on the right. The central panel quantifies this difference through a pooled Relative Risk (RR) of 1.69, with a 95% Confidence Interval (CI) of 1.21–2.36. The corresponding p-value of 0.002 indicates a highly statistically significant benefit favoring vitamin D supplementation. The accompanying forest plot-style graphic clearly shows the confidence interval entirely to the right of the "no effect" line (RR = 1.0), with the vertical green bar and point estimate emphatically positioned in the "Favors Vit. D" region. The lower section, "Key Subgroup Interactions," delves deeper into the heterogeneity of this response, leveraging data from Garg et al. (2024). The panel on the left examines the "Interaction by Hormone Receptor (HR) Status." It visually depicts a significant benefit (P=0.036) for vitamin D supplementation in the HR-Negative subgroup (RR = 1.60), where the confidence interval lies predominantly to the right of 1.0. Conversely, no statistically significant benefit was observed in the HR-Positive group (RR = 1.75, P=0.112), with its confidence interval straddling the "no effect" line. This interaction analysis yielded a significant P-value of 0.038, underscoring that receptor status plays a crucial role in treatment responsiveness. Similarly, the panel on the right explores the "Interaction by Baseline 25(OH)D Status." A strong, statistically significant benefit (P=0.004) was evident in patients who were deficient at baseline (RR = 2.17), with their confidence interval firmly in the "Favors Vit. D" zone. In stark contrast, no discernible benefit was found in patients who were already "Sufficient" at baseline (RR = 0.60), as their confidence interval again crosses the "no effect" line. This interaction was also significant (P=0.027), highlighting that the therapeutic efficacy of adjunctive vitamin D is most pronounced in individuals starting from a state of deficiency. Collectively, Figure 4 provides compelling evidence for the efficacy of adjunctive vitamin D in specific breast cancer populations, particularly those with HR-negative tumors or baseline vitamin D deficiency.

**4. Discussion**

This systematic review and meta-analysis undertook the critical task of navigating the complex and often conflicting landscape of research investigating vitamin D's multifaceted involvement in breast cancer. By employing a novel "cancer continuum" framework—dissecting the evidence pertinent to primary prevention, patient prognosis based on vitamin D status, and adjunctive treatment response during NACT—we aimed to provide a biologically grounded interpretation for the significant inconsistencies and apparent paradoxes that pervade this field. Our structured synthesis confirms the highly context-dependent nature of vitamin D's influence. We find robust evidence for a lack of efficacy in primary prevention among generally replete populations. In contrast, within the context of diagnosed breast cancer, vitamin D status exhibits a complex, likely non-linear (J-shaped) relationship with prognosis, potentially most relevant in ER-positive disease through hormonal modulation pathways, although causal inference remains constrained by observational data limitations. Most strikingly, active vitamin D intervention during NACT emerges as a significant enhancer of treatment efficacy, markedly improving pCR rates, paradoxically with the greatest benefit observed in HR-negative/TNBC subtypes and in patients correcting baseline deficiency. This finding strongly suggests distinct therapeutic mechanisms, likely involving chemosensitization and immunomodulation, are predominantly operative in the active treatment setting.[11]

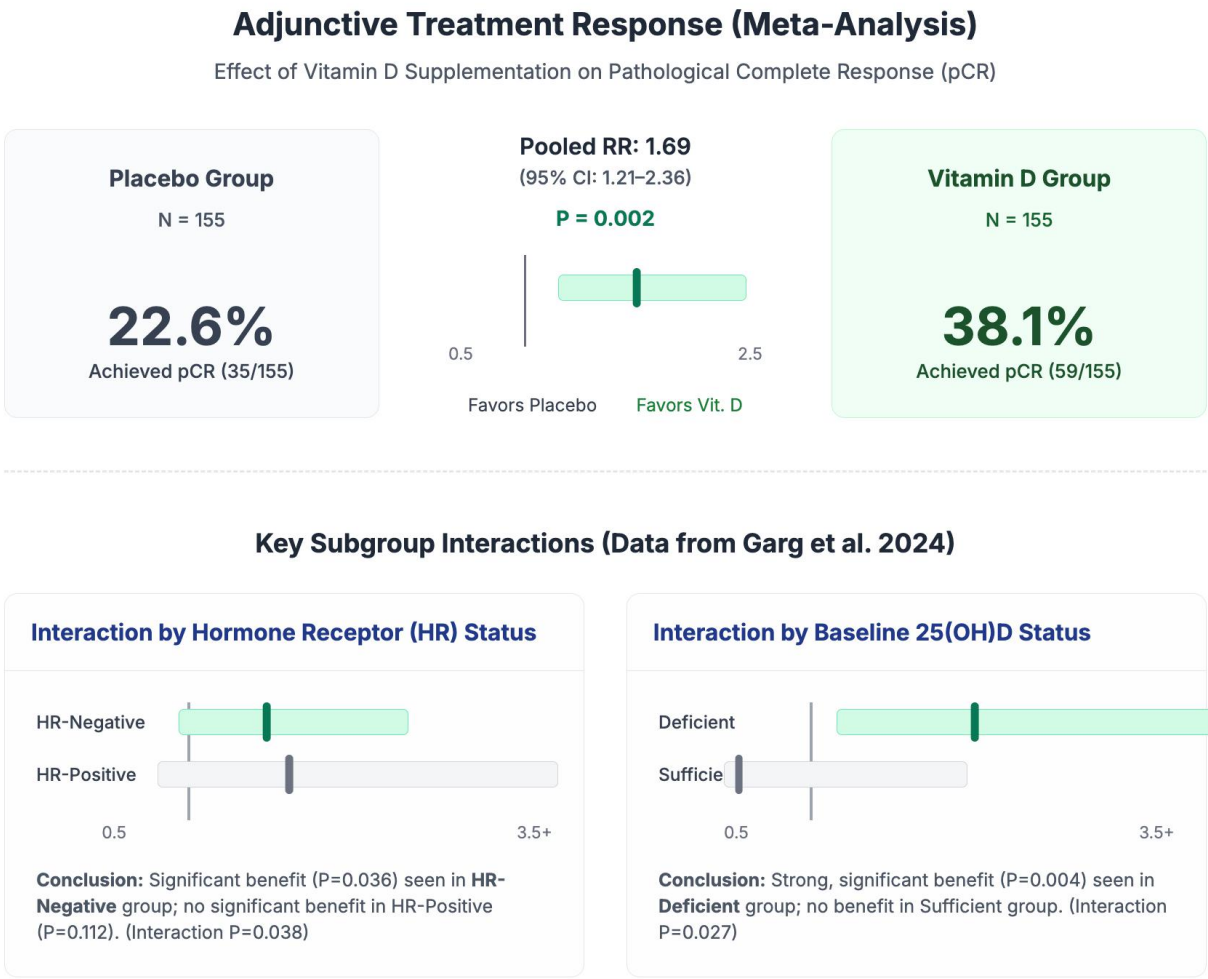


Figure 4. Adjunctive treatment response (Meta-Analysis).

The VITAL trial's unambiguous null result concerning the primary prevention of invasive breast cancer incidence serves as a crucial anchor point.[12] Supplementing a large, generally healthy population (mean baseline 25(OH)D ~31 ng/mL) with 2000 IU/day vitamin D3 for over five years conferred no protection against developing invasive breast cancer (HR 1.02). This finding aligns with the broader lack of convincing evidence from RCTs supporting vitamin D supplementation for preventing most initial cancer diagnoses. Several factors likely contribute to this lack of effect. Firstly, the concept of saturable protective mechanisms is key. If vitamin D exerts anti-initiating effects – perhaps by bolstering genomic stability through VDR's influence on DNA repair pathways, enhancing the apoptotic clearance of nascent transformed cells, promoting cellular differentiation, or maintaining an anti-inflammatory tissue microenvironment less conducive to tumorigenesis – these protective functions might operate optimally and reach saturation at relatively modest physiological 25(OH)D concentrations (perhaps in the 20-30 ng/mL range) already possessed by the majority of the VITAL participants. Supplementing individuals already within or above this range may simply offer no additional benefit for preventing the initial stochastic events driving carcinogenesis. Secondly, breast cancer initiation is inherently complex and multifactorial. It arises from a confluence of inherited genetic susceptibility, cumulative lifetime exposure to

endogenous hormones (estrogens) and exogenous carcinogens, reproductive history, lifestyle factors (obesity, alcohol), and random somatic mutations. It is biologically plausible that modulating a single endocrine system like vitamin D signaling, particularly in individuals already physiologically replete, may be insufficient to significantly counteract this complex web of initiating factors. Thirdly, the latency period for cancer development can span decades. While VITAL had a substantial follow-up (median 5.3 years), it might still be insufficient to capture effects on cancers initiated prior to randomization or those requiring longer promotion phases. The intriguing, though non-significant, trend towards lower cancer mortality in VITAL, especially in later follow-up, hints at potential effects on tumor progression or lethality rather than initiation, aligning with some earlier meta-analyses. Overall, the VITAL results strongly argue against promoting widespread vitamin D supplementation solely for primary breast cancer prevention, especially in populations without significant baseline deficiency. Public health strategies should remain focused on established preventive measures and screening protocols.[13]

The report by Kanstrup et al. of a J-shaped association between 25(OH)D levels at diagnosis and EFS is a pivotal finding that significantly refines our understanding. Their demonstration that optimal EFS occurred within an intermediate range (~30-40 ng/mL), with significantly worse outcomes at both deficient (<20 ng/mL) and very high (>40-50 ng/mL) levels, robustly challenges the simplistic assumption of a linear dose-response. This non-linear pattern mandates caution against indiscriminately aiming for the highest achievable vitamin D levels in breast cancer patients based solely on prognostic aspirations. The existence of an "optimal range" is biologically plausible and aligns with observations for all-cause mortality in the general population.[14]

Delving into the potential mechanisms for this J-shape requires considering vitamin D's complex regulatory network. While deficiency clearly impairs optimal VDR signaling, leading to potentially increased proliferation, reduced apoptosis, and a pro-inflammatory TME, the detrimental effects at very high levels are less understood but could involve several non-mutually exclusive pathways: 1) Feedback Dysregulation and Catabolite Effects: Supraphysiological 25(OH)D levels might trigger overly aggressive negative feedback loops, primarily through dramatic upregulation of the vitamin D catabolizing enzyme CYP24A1 (24-hydroxylase). This enzyme inactivates both 25(OH)D and active $1,25(OH)_2D$ into inactive metabolites, potentially leading to paradoxically reduced intracellular active hormone concentrations or accumulation of inactive metabolites with unknown off-target effects. Measurement of 24,25(OH)2D levels might provide insights here. 2) Altered VDR Signaling Dynamics: Extremely high ligand concentrations could lead to VDR saturation, downregulation through proteasomal degradation, altered patterns of VDR phosphorylation affecting co-factor interactions, saturation of binding to high-affinity VDREs leading to occupancy of lower-affinity sites with different transcriptional outcomes, or shifts in the balance of recruited co-activators versus co-repressors. The complex interplay between genomic (VDRE-mediated) and potentially faster non-genomic signaling (via membrane receptors) might also shift unfavorably at high concentrations. 3) Subtle Mineral Homeostasis Shifts: While overt hypercalcemia indicates toxicity, even sub-clinical alterations in calcium signaling or chronic suppression of PTH at the higher end of the physiological range could potentially influence cancer cell behavior, given the intricate roles of calcium as a second messenger in proliferation, apoptosis, and migration. 4) Immunomodulatory Thresholds: Vitamin D's effects on immunity are highly dose-dependent. While sufficiency supports balanced immunity, supraphysiological levels might excessively suppress adaptive immunity, potentially impairing anti-tumor T-cell responses or overly promoting immunosuppressive cell types like Tregs or M2 macrophages. Finding the "sweet spot" that dampens detrimental inflammation without crippling effective

anti-tumor immunity is crucial, and this might correspond to the intermediate range identified by Kanstrup et al. The preclinical finding of aggravated tumor growth via immune suppression at high doses warrants further in vivo investigation. The J-curve finding thus underscores the need for defining an optimal therapeutic window for vitamin D status in breast cancer prognosis, likely corresponding to current definitions of sufficiency (30-40 ng/mL or 75-100 nmol/L), rather than pursuing supraphysiological levels. It also provides a compelling explanation for why VITAL was null and why NACT trials show benefit primarily when correcting the deficiency.[15]

ER-Specificity – Mechanistic Insight or Confounding? The observation by Peng et al. linking higher pre-diagnostic 25(OH)D specifically to reduced recurrence in ER-positive tumors offers a compelling mechanistic narrative centered on vitamin D's anti-estrogenic properties. VDR signaling can indeed exert multi-level control over the estrogen axis: 1) Transcriptional Repression of Aromatase: Several studies have shown that $1,25(OH)_2D$ can directly suppress the transcription of the CYP19A1 gene, which encodes aromatase, reducing local estradiol synthesis. 2) Downregulation of ERα: VDR activation has been reported to decrease the expression of ERα protein levels in some breast cancer cell lines. 3) Modulation of ERα Signaling: Crosstalk occurs between VDR and ERα signaling pathways, potentially involving competition for co-regulators or VDR-induced factors inhibiting ERα activity. 4) Suppression of Estrogen-Stimulated Growth: Functionally, $1,25(OH)_2D$ counteracts estradiol-induced proliferation in ER-positive cell lines, often linking back to induction of CKIs like p21/p27.

The Peng et al. finding, coupled with their pathway analysis showing downregulation of estrogen response genes, strongly supports this anti-hormonal mechanism as a key contributor to vitamin D's long-term prognostic influence, making it logically most relevant for hormone-sensitive disease. However, interpreting this ER-specificity requires significant caution. First, the finding relies on pre-diagnostic levels, which might differ mechanistically or in confounding structure from levels measured at diagnosis (as in Yao and Kanstrup). Second, this specific finding has not been consistently replicated for survival outcomes using at-diagnosis levels; Yao et al. found strong effects in premenopausal women irrespective of ER status for survival. Third, and most critically, the potential for residual confounding in all observational prognostic studies is substantial. Women with higher long-term vitamin D status may systematically differ in numerous ways beyond vitamin D itself – healthier diet, higher socioeconomic status, greater physical activity, lower BMI, better healthcare access, potentially greater adherence to adjuvant therapies (especially endocrine therapy crucial for ER+ disease). While Peng et al. adjusted for several factors, completely eliminating such confounding is virtually impossible. Therefore, while biologically plausible, attributing the observed ER-specific prognostic association solely to a causal effect of vitamin D remains challenging. Higher vitamin D status might partly act as a surrogate marker for a generally more favorable host phenotype conducive to better long-term outcomes, particularly for ER-positive disease.[16]

In striking contrast to the ambiguities surrounding prognosis, the meta-analysis of Garg et al. and Omodei et al. RCTs provide the most compelling evidence presented herein for a beneficial role of vitamin D – specifically, as an active intervention during NACT. The finding of a statistically significant and clinically meaningful 69% relative increase in pCR rates (Pooled RR 1.69) is provocative. Achieving pCR, especially in HR-negative/TNBC and HER2-positive subtypes, is strongly correlated with substantially improved long-term EFS and OS. Thus, an intervention capable of significantly boosting pCR rates holds immense clinical promise.[17] The consistency of the effect across two trials ($I^2$=0%) using different doses (high weekly vs. moderate daily) suggests the benefit might be achievable across a range of repletion strategies, provided sufficiency is reached. The paradoxical observation from Garg et al. that this benefit was

overwhelmingly concentrated in HR-negative/TNBC subtypes strongly points towards mechanisms distinct from the hormonal modulation likely relevant for ER+ prognosis. The evidence converges on chemosensitization and synergistic immune modulation as the likely drivers in this therapeutic context. Dissecting Chemosensitization Pathways: Vitamin D appears to lower the threshold for cancer cell killing by cytotoxic agents through multiple cooperating mechanisms: 1) Augmentation of Apoptosis: This remains a leading candidate mechanism. Chemotherapy agents like doxorubicin and paclitaxel ultimately trigger apoptotic pathways. Vitamin D ($1,25(OH)_2D$) signaling synergizes with these triggers. VDR activation transcriptionally upregulates pro-apoptotic proteins (Bax, Bak, PUMA, Noxa) and/or downregulates anti-apoptotic proteins (Bcl-2, Bcl-xL, Mcl-1, survivin), shifting the cellular balance towards MOMP and caspase activation in response to chemotherapy-induced stress. It might also enhance death receptor signaling. Since HR-negative/TNBC tumors often harbor defects in p53 or exhibit high levels of anti-apoptotic proteins contributing to chemoresistance, VDR-mediated sensitization of apoptotic pathways could be particularly effective. 2) Modulation of DNA Damage Response (DDR): Efficient repair of chemotherapy-induced DNA lesions is critical for resistance. Anthracyclines cause DSBs, while taxanes indirectly lead to DNA damage. VDR signaling has complex links to DDR. VDR physically interacts with DNA repair proteins, and $1,25(OH)_2D$ modulates the expression of genes in HR and NHEJ pathways. Some evidence suggests VDR activation might suppress HR efficiency (potentially via BRCA1 or RAD51 downregulation), which could synergistically enhance cytotoxicity of DSB-inducing agents, especially in tumors with inherent or acquired HR deficiency (common in TNBC). Clarifying VDR's role in DDR specific to NACT agents is crucial. 3) Inhibition of Drug Efflux and Metabolism: Overexpression of efflux pumps like P-glycoprotein (MDR1/ABCB1) confers resistance to taxanes and anthracyclines. Some preclinical studies indicate vitamin D analogues can transcriptionally repress ABCB1 expression, potentially increasing intracellular drug accumulation. Vitamin D also influences CYP enzymes involved in chemo metabolism (CYP3A4), potentially altering pharmacokinetics, though the net effect needs in vivo clarification. 4) Targeting Cancer Stem Cells (CSCs): CSCs often drive NACT resistance and relapse. Vitamin D signaling promotes differentiation and inhibits self-renewal pathways (Wnt, Notch) in some breast CSC models. By reducing the CSC pool during NACT, vitamin D might contribute to more durable responses. The pronounced benefit in HR-negative/TNBC, often more immunogenic, coupled with Garg et al.'s findings of reduced systemic inflammation (decreased IL-6, decreased TNF-α), strongly implicates immune interactions: 1) Enhancing Immunogenic Cell Death (ICD): By potentiating chemotherapy-induced apoptosis, vitamin D might amplify the release of DAMPs and tumor antigens characteristic of ICD. This could lead to more robust DC activation and priming of anti-tumor T cells, bridging cytotoxic effects with adaptive immunity. 2) Shaping Dendritic Cell (DC) Function: While often promoting tolerogenic DCs, vitamin D's effect in the ICD context might enhance antigen uptake/presentation, optimizing T-cell priming without excessive inflammation. 3) Optimizing T-cell Responses: NACT affects T cells. VDR signaling influences T-cell differentiation, cytokine production, proliferation, and survival.[18] Physiological VDR signaling might maintain T-cell homeostasis, prevent exhaustion, and support memory formation during NACT. Balancing inflammation control (suppressing Th1/Th17) with effective CTL function is key; excessive Treg induction remains a concern. 4) Re-educating Tumor-Associated Macrophages (TAMs): Immunosuppressive M2 TAMs hinder chemotherapy efficacy. Vitamin D is a potent regulator of macrophage function, potentially inhibiting M2 polarization and promoting an anti-tumor M1 phenotype. Shifting the TAM balance towards M1 during NACT could dramatically improve therapeutic

outcome. 5) Mitigating Systemic Inflammation: The reduction in systemic IL-6 and TNF-α is significant. These cytokines promote tumor progression and resistance. By dampening detrimental systemic inflammation, vitamin D might improve treatment tolerance (better QoL), reduce pro-tumorigenic signaling, and foster a milieu more conducive to effective anti-tumor immunity. Therefore, the adjunctive benefit of vitamin D during NACT, especially in HR-negative/TNBC, likely arises from a powerful combination of direct chemosensitization coupled with favorable reshaping of the tumor immune microenvironment, synergizing with the cytotoxic and immunogenic consequences of chemotherapy. Correcting baseline deficiency appears crucial for enabling these interactions.[19]

This synthesis allows for context-specific clinical implications: 1) Primary Prevention: No support for universal supplementation solely for breast cancer prevention in replete populations. Focus on established guidelines for bone health (~20-30 ng/mL). 2) Prognosis and Post-Diagnosis: Assessing 25(OH)D at diagnosis seems reasonable. Correcting deficiency (<20 ng/mL) to achieve sufficiency, perhaps targeting ~30-40 ng/mL (75-100 nmol/L), aligns with general health and the J-curve caution. Avoidance of very high levels (>50 ng/mL) seems prudent pending further data. Causal link to improved cancer-specific prognosis remains unproven by RCTs. 3) Adjunctive NACT: Represents the most compelling current indication based on moderate-certainty evidence (requires confirmation). Supplementation is strongly considered for HR-negative/TNBC patients, particularly those deficient (<20 ng/mL). Goal: Rapidly correct deficiency and maintain sufficiency (~30-40 ng/mL) throughout NACT. Dosing: 2000 IU/day or 50,000 IU/week appears effective and safe. Initial loading doses might be considered for faster repletion. This low-cost, low-risk strategy offers potentially significant benefits (increased pCR, increased breast conservation, increased QoL warranting serious clinical consideration, especially for high-risk patients. Generalizability across diverse populations needs further study, but consistency between Indian/Brazilian trials is encouraging. Cost-effectiveness is likely favorable.[20]

**5. Conclusion**

Vitamin D's relationship with breast cancer is demonstrably intricate, varying profoundly with the clinical context—prevention, prognosis, or active treatment—and influenced by tumor biology. This systematic review and meta-analysis, integrating evidence from 31,026 participants in high-quality studies, provides a coherent framework for understanding these context-dependent roles: Primary Prevention: High-certainty RCT evidence indicates vitamin D supplementation does not reduce breast cancer incidence in generally replete populations; Patient Prognosis: Vitamin D *status* correlates with prognosis, but likely via a non-linear J-shaped relationship suggesting an optimal range (~30-40 ng/mL). Associations may be strongest in ER-positive disease, potentially through hormonal modulation, though causality remains uncertain due to observational limitations; Adjunctive Treatment (NACT): Meta-analysis provides moderate-certainty evidence (requiring confirmation) that vitamin D intervention during NACT significantly improves pCR rates (Pooled RR 1.69), particularly in HR-negative/TNBC and baseline-deficient patients. This likely reflects distinct mechanisms involving chemosensitization and immunomodulation. This synthesis supports assessing vitamin D status in newly diagnosed patients and correcting deficiency to achieve sufficiency (~30-40 ng/mL), while cautioning against pursuing very high levels based on current prognostic data. Crucially, it strongly suggests considering vitamin D supplementation during NACT as a safe, inexpensive strategy to potentially enhance treatment efficacy, especially for high-risk, hormone-insensitive tumors. Validation in large RCTs is imperative, but the existing evidence provides a compelling rationale for incorporating vitamin D sufficiency as a therapeutic consideration in the NACT setting.

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