



An Updated Meta-Analysis on Serum Vitamin D Levels and the Risk of Breast Cancer

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ARTICLE INFO

Received:

17 December 2025

Revised:

30 June 2026

Accepted:

10 July 2026

Keywords:

breast neoplasms, vitamin D, meta-analysis, 25-hydroxyvitamin D, risk factors

ABSTRACT

Background: Although numerous observational studies suggest that higher vitamin D levels are associated with a reduced risk of breast cancer, the overall evidence remains inconclusive. This study aimed to comprehensively evaluate this association through a systematic review and meta-analysis.

Methods: A systematic literature search was conducted in PubMed, Scopus, and Google Scholar up to February 16, 2024. Relevant articles were extracted, and title and abstract screening followed by full-text screening was carried out. Quality assessment was followed by data extraction and analysis for selected articles. All pooled analyses were performed on the natural log scale and exponentiated to obtain valid odds ratios (ORs).

Results: Nineteen case-control studies, comprising 12 541 cases and 29 272 controls, were included. Lower circulating vitamin D levels were significantly associated with an increased risk of breast cancer (OR, 1.70; 95% CI, 1.31–2.23; $P < .001$). Between-study heterogeneity was high ($I^2 = 96.4\%$). In a prespecified subgroup analysis by study design, nested case-control studies showed a modest but statistically significant increase in risk (OR, 1.20; 95% CI, 1.06–1.36; $I^2 = 0.0\%$), whereas retrospective studies showed a larger but highly heterogeneous increase in risk (OR, 2.06; 95% CI, 1.38–3.08; $I^2 = 98.1\%$).

Conclusions: This meta-analysis, using a harmonized log-scale approach, supports a significant inverse association between vitamin D levels and breast cancer risk. The most reliable evidence from nested case-control studies suggests a modest increase in risk, while retrospective studies likely overestimate the association due to reverse causality. Further well-designed prospective studies are warranted.

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INTRODUCTION

Breast cancer is the most common cancer and the leading cause of cancer-related death in the female population worldwide.¹

In recent decades, it has become the leading cause of cancer death among women in the United States.² According to 2022 GLOBOCAN data, breast cancer is the most commonly diagnosed



cancer among women, with approximately 2.3 million new cases and 665 684 deaths every year.³

Vitamin D₃ is a natural form of vitamin D that is obtained either exogenously through dietary intake (for example, by eating fatty fish) or endogenously through its synthesis in the skin upon exposure to 290- to 320 nm ultraviolet B radiation from the precursor 7-dehydrocholesterol.⁴⁻⁶ In the 1980s, Garland and colleagues first suggested that sun exposure could reduce the risk of breast cancer.⁷ Since then, numerous preclinical and epidemiologic studies have been conducted to determine the association of serum 25-hydroxyvitamin D [25(OH)D] with the incidence and progression of breast cancer.⁸ In addition, its anticancer effects against colon, prostate, and breast cancer have been proven.⁹

Research has found that calcitriol, the active form of vitamin D, is involved in multiple aspects of tumor development and progression, such as apoptosis, proliferation, inflammation, differentiation, angiogenesis, invasion, and metastasis, by acting on several signaling pathways,⁹ which could modulate tumor growth and progression.¹⁰

In addition, vitamin D may influence the activity of endogenous estrogen, a recognized promoter of breast cancer, by inhibiting aromatase expression and estrogen production in breast fatty tissue and reducing estrogen receptor α (ER- α).¹⁰ Levels of 25(OH)D, the standard determinant of vitamin D status, can be safely increased through the consumption of fortified foods, dietary supplements, fatty fish, and carefully timed sun exposure. It has, therefore, been suggested that vitamin D could offer a relatively simple strategy to support breast cancer prevention.¹¹

Observational studies on the association between breast cancer risk and vitamin D status date back to the 1970s,¹² but these studies were inadequate.¹³ Variations in vitamin D status measurements and the criteria used to determine sufficiency can be ascribed to different study methodologies, populations studied, patient attributes, and the timing of these measurements.

Recent meta-analyses have provided further insights into this association. For instance, a 2019 meta-analysis based mainly on case-control studies by Hossain *et al.* found a significant link between vitamin D deficiency and increased breast cancer risk,⁸ whereas a comprehensive pooled analysis of prospective cohorts published in 2023 reported no significant overall association.¹¹ A more recent review from 2024 suggests a potential protective effect at higher vitamin D levels.¹⁴ These inconsistencies and the limitations discussed in these reviews, including methodological differences and the need for subtype- and context-specific analyses, highlight the ongoing need for updated and focused research in this area.

This meta-analysis aims to provide an up-to-date overview of the association between circulating serum 25(OH)D concentrations and breast cancer risk across different populations. By synthesizing observational case-control evidence using robust statistical methods, we seek to clarify the form and magnitude of

this association and to explore potential sources of heterogeneity, including menopausal status and study design. These findings are intended to inform ongoing discussions about the role of vitamin D in breast cancer etiology and to guide priorities for future epidemiologic research.

METHODS

Study design

This systematic review and meta-analysis was conducted to evaluate the association between vitamin D levels and breast cancer risk. The review included observational case-control designs and excluded randomized clinical trials based on predefined eligibility criteria. Eligible studies comprised both retrospective case-control studies, in which vitamin D was typically measured at or after diagnosis, and nested case-control studies, in which blood samples were collected before diagnosis within established cohorts. Randomized clinical trials were not included because they generally evaluate vitamin D supplementation rather than naturally occurring circulating 25(OH)D concentrations. Including both nested prospective and retrospective case-control designs allowed us to synthesize the available observational evidence while also examining the timing of exposure assessment as an important source of heterogeneity and potential reverse causality.

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines throughout the research process to ensure transparency and reproducibility in our methodology.¹⁵ The protocol for this systematic review and meta-analysis was registered prospectively in the International Prospective Register of Systematic Reviews (PROSPERO) database (Registration number: CRD420251029665).

Search strategy

We conducted a comprehensive literature search in PubMed, Scopus, and Google Scholar up to February 16, 2024. The search strategy used combinations of Medical Subject Headings (MeSH) and free-text words related to vitamin D and breast cancer. Key search terms included “vitamin D,” “25-hydroxyvitamin D,” “cholecalciferol,” “breast cancer,” “breast neoplasm,” “mammary carcinoma,” and “breast tumor.” We did not apply any language restrictions. The complete search strategy for each database is shown in Table 1. In addition, we manually searched reference lists of included studies and relevant reviews to identify missing articles. Two reviewers independently screened all records, resolving disagreements through discussion. When consensus could not be reached, a third reviewer was consulted to make the final decision.

Inclusion and exclusion criteria

Studies were included in the meta-analysis if they met the following criteria:

1. Case-control study design.
2. Assessment of the association between vitamin D

**Table 1.** Search Strategy for Selected Databases.

Database	Search strategy	Search date	Total results
PubMed	("Breast Neoplasms"[Mesh] OR breast cancer[Title/Abstract] OR breast neoplasm*[Title/Abstract] OR mammary carcinoma*[Title/Abstract]) AND ("Vitamin D"[Mesh] OR vitamin D[Title/Abstract] OR 25-hydroxyvitamin D[Title/Abstract] OR 25(OH)D[Title/Abstract] OR cholecalciferol[Title/Abstract])	February 16, 2024	1477
Scopus	TITLE-ABS(breast cancer OR breast neoplasm* OR mammary carcinoma*) AND TITLE-ABS("vitamin D" OR "25-hydroxyvitamin D" OR "25(OH)D" OR cholecalciferol)	February 16, 2024	2153
Google Scholar	allintitle: ("vitamin D" OR "25-hydroxyvitamin D" OR "25(OH)D") ("breast cancer" OR "breast neoplasm" OR "mammary carcinoma")	February 16, 2024	1308

levels and breast cancer risk as a primary outcome.

3. Female participants diagnosed with breast cancer.

4. Clear definitions of breast cancer and vitamin D levels were used in the study. This criterion ensured that each included study provided clear and usable definitions for both breast cancer diagnosis and the measurement of vitamin D levels.

5. Reported threshold levels defining vitamin D sufficiency and insufficiency.

Studies were excluded if they involved experimental designs, animal subjects, participants with cancer diagnoses other than breast cancer, or outcomes unrelated to breast cancer.

Data extraction and synthesis

Two evaluators independently gathered information using a standardized template. The data collection process included the following variables: primary author, publication year, country of origin, study methodology, sample size, participant demographics (including age and menopausal status), method of measuring 25(OH)D, 25(OH)D levels (mean or median, categorized), criteria used for defining and assessing breast cancer, effect estimations with 95% CIs, and adjusted covariates. Inconsistencies were addressed through dialogue or consultation with a third evaluator.

Harmonization of effect estimates

To ensure a consistent interpretation across all included studies and to align with the direction of the forest plots, we standardized all effect estimates to represent the comparison of lowest vs highest circulating vitamin D levels, such that an OR greater than 1 consistently reflects an increased risk associated with lower vitamin D levels. For studies that originally reported the reverse comparison, we applied the reciprocal transformation: the inverted OR was calculated as $(1/OR)$, and the inverted 95% CI was calculated as $(1/CI_{upper}, 1/CI_{lower})$. For studies that already reported the highest vs lowest comparison but yielded an OR greater than 1 (indicating higher risk with higher vitamin D levels), we again inverted the OR and its CI to convert the direction of effect. Supplementary Table 1 provides a detailed record for each study, including the originally reported OR and 95% CI, the original reference category description, the transformation applied (if any), and the final OR and 95% CI used in the meta-analysis.

This procedure follows standard recommendations for the meta-analysis of observational studies to ensure reproducibility and transparency.

For subgroup analysis, studies were categorized based on how vitamin D exposure was defined: (1) fixed clinical cutoffs, (2) multilevel categorical classifications, (3) quartiles, (4) quintiles, and (5) supplement-based categorization. Cutoffs were defined based on the thresholds reported in the original studies, especially serum 25(OH)D concentrations such as < 20 ng/mL for deficiency and ≥ 30 ng/mL for sufficiency. Quartile and quintile classifications were determined within each study population. This categorization approach enabled meaningful comparisons across studies despite substantial heterogeneity in vitamin D definitions and reporting methods.

Quality assessment and bias evaluation

The methodological quality and risk of bias in the studies under review were appraised using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case-Control Studies. We selected the JBI checklist because it is specifically tailored to observational case-control designs and provides structured criteria for evaluating confounding control and exposure timing, which were central concerns in this review. Quality assessment was carried out independently by two reviewers, with any discrepancies resolved through consensus.

Statistical analysis

All statistical analyses were conducted using Stata, version 18 (StataCorp). To ensure mathematically valid pooling of ORs, all study-level effect estimates were first transformed to the natural log scale $[\ln(OR)]$, and the meta-analysis was performed on the log scale. We exponentiated the pooled log estimate and its confidence limits to obtain ORs with asymmetric intervals, which are appropriate for ratio measures. The primary analysis employed random-effects models using the restricted maximum likelihood (REML) method to compute pooled ORs and 95% CIs, accounting for expected heterogeneity across studies. Heterogeneity was measured using the I^2 statistic¹⁶ and the τ^2 estimate, with an I^2 value exceeding 50% signifying substantial heterogeneity.¹⁷

Examination of publication bias was carried out through a visual assessment of funnel plot symmetry and quantitatively using the Egger regression test for



small-study effects. The threshold for significance was set at $P < .10$ for the Egger test, as recommended for meta-analyses with a moderate number of studies.

Given the substantial heterogeneity observed in the overall analysis, a prespecified subgroup analysis was performed according to the study design: nested case-control studies vs retrospective case-control studies. Additionally, subgroup analyses were conducted based on the studies' definitions for vitamin D cutoff levels (fixed cutoff, multilevel, quartiles, quintiles, supplements) and according to menopausal status. A leave-one-out sensitivity analysis was conducted to assess the influence of each individual study on the pooled effect size after log transformation. The statistical significance level for the main pooled effect was established at two-sided $P < .05$.

RESULTS

Study selection and characteristics

The PRISMA flowchart of the study selection process is shown in Figure 1. After a preliminary database search, 4938 records were found. These records were reviewed after removing 1112 duplicates, resulting in a total of 3826 records. After reviewing the titles and abstracts, 3647 records were removed from the group. After evaluating 179 full-text articles, 19 studies met the inclusion criteria and were ultimately summarized in this meta-analysis. Table 2 lists the research attributes that were part of the analysis. Sample sizes ranged from 22 218 to 20 767,¹⁹ while publication dates ranged from 2005²⁰ to 2024.¹⁴ Seven studies were conducted in the United States,^{21–27} a total of 5 in European countries,^{14,20,21,28,29} 4 in the Middle East,^{18,30–32} 3 in Asia,^{19,33,34} and 1 in Australia.³⁵ A column has been added to Table 2 indicating which of the studies included in our meta-analysis were also part of the recent pooled analysis by Visvanathan *et al.*¹¹

Participant demographics

The mean age of the participants across all studies ranged from 36.5 to 79.0 years. Most studies included both premenopausal and postmenopausal women, with some focusing specifically on premenopausal³¹ or postmenopausal women.²⁶ The total number of breast cancer cases across all studies was 12 541, with 29 272 controls.

Quality assessment

All the included studies were assessed for their methodological quality using the JBI Critical Appraisal Checklist for case-control studies. The tool assesses various aspects, including participant selection, exposure measurement, identification and control of confounding factors, and outcome assessment. Two reviewers independently performed the quality assessment and resolved disagreements by consensus. Overall, the studies fulfilled most JBI criteria, but several common limitations were noted, particularly regarding the timing of vitamin D measurement relative to diagnosis and the extent of confounder adjustment (Supplementary Table 2).

Association between vitamin D status and breast cancer

To achieve a uniform direction of effect (comparing lowest vs highest vitamin D level, with OR > 1 indicating increased risk), we transformed the originally reported effect estimates for 16 of the 19 studies. After harmonization, all effect sizes were converted to the natural log scale [$\ln(\text{OR})$], and meta-analysis was performed on the log scale using a random-effects REML model. The final pooled ORs were obtained by exponentiation (eform), producing asymmetric confidence intervals as required for ratio measures. Full details are provided in Supplementary Table 1.

The primary meta-analysis of all 19 studies showed that lower circulating vitamin D levels were significantly associated with an increased risk of breast cancer (OR, 1.70; 95% CI, 1.31–2.23; $P < .001$). However, between-study heterogeneity was very high ($I^2 = 96.4\%$, $\tau^2 = 0.289$, $Q = 113.99$, $df = 18$, $P < .001$), indicating that the overall estimate should be interpreted with caution. The forest plot for the harmonized analysis is shown in Figure 2.

Subgroup analysis by study design (nested vs retrospective case-control)

Because the overall analysis showed substantial heterogeneity, and because the timing of vitamin D measurement (prediagnostic vs postdiagnostic) is a major methodological concern, we performed a prespecified subgroup analysis according to study design: nested case-control studies (6 studies, all using prediagnostic blood samples) vs retrospective case-control studies (13 studies, using blood samples collected at or after diagnosis). The results are presented in Figure 3.

- Nested case-control studies: Lower vitamin D levels were associated with a modest but statistically significant increase in breast cancer risk (pooled OR, 1.20; 95% CI, 1.06–1.36). There was no evidence of heterogeneity ($I^2 = 0.0\%$, $\tau^2 = 0.000$, $Q = 2.67$, $df = 5$, $P = .751$).

- Retrospective case-control studies: Lower vitamin D levels were associated with a larger and highly statistically significant increase in risk (pooled OR, 2.06; 95% CI, 1.38–3.08). However, heterogeneity was extremely high ($I^2 = 98.1\%$, $\tau^2 = 0.465$, $Q = 111.26$, $df = 12$, $P < .001$).

The test for subgroup differences was statistically significant ($Q = 6.34$, $df = 1$, $P = .012$), indicating that the effect size was significantly larger in retrospective studies compared with nested studies.

Subgroup analysis by vitamin D cutoff

To explore potential sources of heterogeneity, subgroup analyses were performed according to the vitamin D classification method (fixed cutoff, multilevel categories, quartiles, quintiles, and supplement-based assessment). A borderline statistically significant difference was observed between subgroups ($Q_b(4) = 9.26$, $P = .055$), indicating that effect sizes varied modestly according to the cutoff approach used. Studies applying fixed cutoffs (7 studies) showed a pooled OR of 2.29 (95% CI, 1.15–4.57) with very

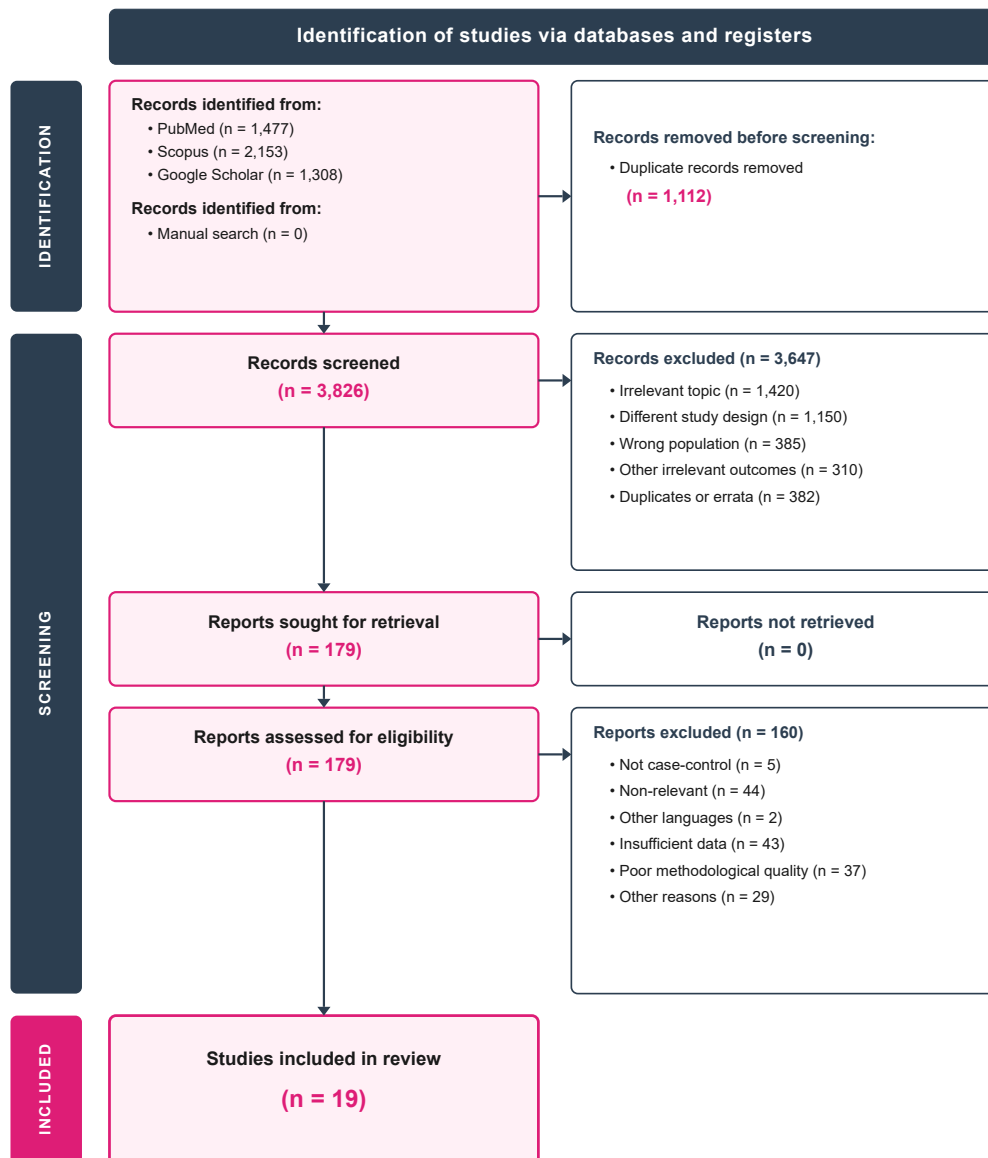


Figure 1. PRISMA Flow Diagram of Study Selection.

high heterogeneity ($I^2 = 98.8\%$, $\tau^2 = 0.822$). In the multilevel subgroup (3 studies), the pooled OR was 1.77 (95% CI, 0.97–3.24) with moderate heterogeneity ($I^2 = 57.7\%$, $\tau^2 = 0.153$), and the effect was not statistically significant ($P = .096$ for Q). Studies using quartiles (5 studies) demonstrated a pooled OR of 1.51 (95% CI, 1.05–2.16) with substantial heterogeneity ($I^2 = 69.5\%$, $\tau^2 = 0.098$). For quintiles (3 studies), the pooled estimate was 1.20 (95% CI, 0.98–1.47) with no heterogeneity ($I^2 = 0.0\%$, $\tau^2 = 0.000$), and the effect was not statistically significant ($P = .96$ for Q). The supplement-based category (single study) showed an OR of 1.11 (95% CI, 1.04–1.18). Overall, the pooled effect size across all studies (using the harmonized log-scale meta-analysis) was 1.70 (95% CI, 1.31–2.23), with high between-study heterogeneity ($I^2 = 96.4\%$). These findings suggest that the vitamin D categorization method explains only a modest proportion of the observed variability, whereas the consistently high heterogeneity across most subgroups points to other factors—notably study design—as

more influential drivers (Figure 4).

Sensitivity analysis

In the leave-one-out sensitivity analysis, the study by Atoum and Al-Khatib¹⁸ had the greatest influence on the pooled estimate; when this extreme outlier was omitted, the pooled OR decreased from 1.70 to 1.45, while the association remained in the same direction and the main conclusion was unchanged (Figure 5).

Publication bias

Publication bias was assessed using a visual inspection of the funnel plot and the Egger regression test. The funnel plot (Figure 6) showed asymmetry.

The Egger test for small-study effects was statistically significant ($\beta = 2.74$, $SE = 0.721$, $z = 3.80$, $P = .001$), indicating evidence of publication bias or other small-study effects. Because the nested case-control studies (which are less prone to bias) showed a consistent effect ($I^2 = 0.0\%$), the bias likely originates from retrospective studies and does not invalidate the

**Table 2.** Characteristics of the Included Studies.

Author/year	Country/design	Participants/age	25(OH)D/reference	Association
Fernández Madrigal <i>et al.</i> ¹⁴ (2024)	Spain Case-control	BC, 231 localized luminal cases (stage I–III); C, 324 Age: BC median 62 years (34–88); C median 65 years (45–78)	Mean: BC 21 ng/mL; C 24 ng/mL Reference: >20 ng/mL	Deficiency higher in BC patients than C; OR, 2.08 (95% CI, 1.4–2.7). ^a
Islam <i>et al.</i> ³⁴ (2023)	Malaysia Case-control	BC, 231; C, 693; age-matched Age: Matched within ± 5 years; mean 54.20 (6.76) years	Mean: BC 42.43 (± 22.53) nmol/L; C 44.30 (± 21.88) nmol/L Reference: ≥ 75 nmol/L	No significant association
Shamsi <i>et al.</i> ³³ (2020)	Pakistan Matched case-control	BC, 411 newly diagnosed; C, 784 Age: Various groups; substantial proportion aged 35–44 years	Median: BC 15.3 ng/mL; C 16.7 ng/mL Reference: >30 ng/mL	Lower 25(OH)D associated with higher risk; OR, 1.65 (95% CI, 1.10–2.50)
Atoum and Al-Khatib ¹⁸ (2017)	Jordan Case-control	BC, 122; C, 100 Age: >50% of BC patients aged 50–59 years	BC: 8.1 ± 0.3 ng/mL; C: 21.2 ± 0.6 ng/mL Reference: >20 ng/mL	Inverse association between serum 25(OH)D and BC risk. ^a
Jamshidinaeini <i>et al.</i> ³² (2016)	Iran Case-control	BC, 135; C, 135; age/menopause matched Age: BC mean 50.4 years; C mean 50.0 years	BC: 24 ± 13.36 IU/d; C: 30.56 ± 19.28 IU/d Reference: Not stated	Higher serum 25(OH)D associated with lower BC risk
Deschasaux <i>et al.</i> ²⁹ (2016)	France Nested case-control	BC, 233; C, 466; matched Age: Mean 49 ± 6 years	BC: 18.9 ± 11.3 μ g/L; C: 18.8 ± 10.2 μ g/L Reference: Severe deficiency <10 ng/mL; insufficiency <20 ng/mL	Association modified by BMI and alcohol. ^a
Park <i>et al.</i> ¹⁹ (2015)	Korea Case-control	BC, 3634; C/general population, 17 133 Age: BC mean 50.7 ± 10.5 years; C 49.7 ± 16.3 years	Mean: BC 15.1 ± 7.2 ng/mL; C 17.1 ± 6.3 ng/mL Reference: ≥ 20 ng/mL	Deficient 25(OH)D associated with 27% higher risk than sufficient levels
Arbabi Bidgoli and Azarshab ³¹ (2014)	Iran Case-control	BC, 60 newly diagnosed premenopausal; C, 116 Age: BC mean 36.45 ± 7.02 years; C 34.2 ± 5.7 years	BC: 15.2 ± 8.15 ng/mL; C: 15.5 ± 7.45 ng/mL Reference: Not stated; <20 ng/mL implied deficient	No significant difference; vitamin D/calcium supplementation associated with lower premenopausal BC risk
Yousef <i>et al.</i> ³⁰ (2013)	Saudi Arabia Case-control	BC, 120; C, 120 Age: Mean 47.8 years	Mean: BC 9.4 ± 6.4 ng/mL; C 15.4 ± 12.3 ng/mL Reference: ≥ 20 ng/mL	Inverse association between serum 25(OH)D and BC risk
Scarmo <i>et al.</i> ²¹ (2013)	US and Sweden Nested case-control	BC, 1585 incident; C, 2940 Age: Mean at enrollment 54 years	Median: BC 53.0 nmol/L; C 54.2 nmol/L Reference: 50–74 nmol/L adequate; ≥ 75 nmol/L adequate to high	No overall association; possible protective effect in younger women. ^a
Mohr <i>et al.</i> ²⁷ (2013)	US Nested case-control	BC, 600 incident; C, 600; matched Age: Mean 39.6 years	Mean (SD): BC $24.8 (12.2)$ ng/mL; C $25.9 (12.3)$ ng/mL Reference: Not stated	No significant principal association; inverse association in subgroup with blood collected within 90 days before diagnosis



Table 2 (continued)

Author/year	Country/design	Participants/age	25(OH)D/reference	Association
Kühn <i>et al.</i> ²⁸ (2013)	Germany, France, Denmark, Greece, Italy, Norway, Spain, Sweden, Netherlands, UK Nested case-control within EPIC	BC, 1391 incident; C, 1391 Age: Mean baseline 50.7 years; diagnosis 54.8 years	Mean plasma 25(OH)D: BC 53.1 nmol/L; C 52.8 nmol/L Reference: Not stated	No significant association between season-standardized 25(OH)D and BC risk. ^a
Bilinski and Boyages ³⁵ (2012)	Australia Observational case-control	BC, 214 newly diagnosed women; C, 852; matched Age: <50 years and ≥50 years	Median 25(OH)D: BC 53.0 nmol/L; C 62.0 nmol/L Reference: ≥75 nmol/L	Lower 25(OH)D associated with significantly higher BC risk
Neuhouser <i>et al.</i> ²⁶ (2012)	US Nested case-control within the Women's Health Initiative Calcium and Vitamin D Clinical Trial	BC, 1080; C, 1080 Age: Postmenopausal women, 50–79 years	Serum 25(OH)D measured; specific BC/C levels not provided Reference: Not stated	No significant association after adjustment; OR, 1.06 (95% CI, 0.78–1.43). ^a
Peppone <i>et al.</i> ²⁵ (2012)	US Case-control	BC, 194 women; C, 194 cancer-free Age: 40–70 years	BC: 32.7 ng/mL; C: 37.4 ng/mL Reference: ≥32.0 ng/mL	BC cases had lower 25(OH)D than C; lower levels associated with worse prognostic indicators
Yao <i>et al.</i> ²⁴ (2011)	US Case-control and case-series	BC, 579 incident women; C, 574 Age: Matched on age and blood-draw time	BC: 22.8 ng/mL; C: 26.2 ng/mL Reference: ≥30.0 ng/mL	Higher serum 25(OH)D associated with reduced BC risk, especially in high-grade, ER-negative, or triple-negative cancers in premenopausal women
Crew <i>et al.</i> ²³ (2009)	US Population-based case-control	BC, 1026 incident; C, 1075 population-based Age: BC mean 58.6 years; C 56.1 years	Mean plasma 25(OH)D: BC 27.1 ± 13.0 ng/mL; C 29.7 ± 15.1 ng/mL Reference: >32 ng/mL for bone mineral metabolism; ≥40 ng/mL suggested for BC prevention	Inverse association; higher plasma 25(OH)D associated with lower BC risk
McCullough <i>et al.</i> ²² (2009)	US Nested case-control	BC, 516; C, 516 Age: 47–85 years at baseline	BC: 56.5 nmol/L; C: 56.2 nmol/L Reference: ≥75 nmol/L	No association. ^a
Lowe <i>et al.</i> ²⁰ (2005)	UK Matched case-control	BC, 179; C, 179 Age: BC median 58 years (34–84); C median 58 years (36–80)	Mean: BC 80.1 nmol/L (SD 43.4); C 97.8 nmol/L (SD 41) Reference: 50–200 nmol/L	Low 25(OH)D associated with increased BC risk. ^a

^a Included in the pooled analysis by Visvanathan *et al.* (2023).¹¹

BC, breast cancer; C, controls; 25(OH)D, 25-hydroxyvitamin D; EPIC, European Prospective Investigation into Cancer and Nutrition; SD, standard deviation. Data are presented as mean (SD), median (range), or group-specific values as reported.

modest increase in the risk observed in nested studies.

DISCUSSION

Comparison with previous research

Our finding of a statistically significant association between lower circulating vitamin D levels and increased breast cancer risk (pooled OR for lowest vs highest category, 1.70; 95% CI, 1.31–2.23) contrasts with the conclusions of a large, recent international pooled analysis of prospective cohorts by Visvanathan *et al.*¹¹, who did not observe a clear relationship between prediagnostic vitamin D status and subsequent breast cancer incidence. In that analysis of 17 cohorts, the summary estimates were close to the null, highlighting potential

differences between prospective and case-control evidence.

However, our result is broadly consistent with earlier meta-analyses based mainly on case-control studies, such as Hossain *et al.*, which also reported a protective association of higher vitamin D levels with breast cancer risk. Several factors may explain the discrepancies across the literature. First, methodological differences—including our use of a REML random-effects model, harmonization of exposure contrasts (highest vs lowest vitamin D category), and performance of the meta-analysis on the natural log scale—yield more statistically valid estimates compared with some prior syntheses.

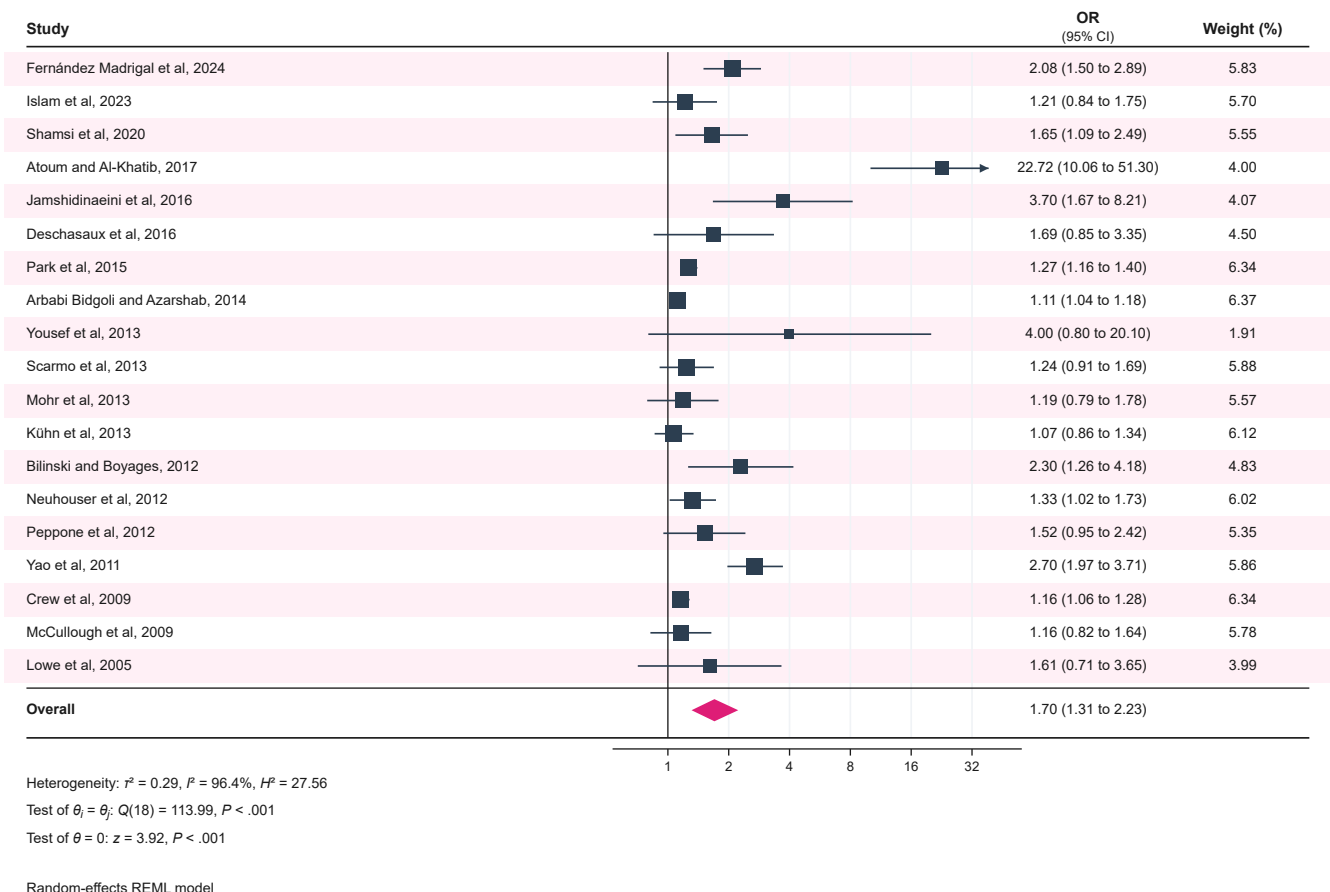


Figure 2. Forest Plot of the Association Between Vitamin D Levels and Breast Cancer Risk.

Second, variations in study design (retrospective case-control vs nested case-control) and in the underlying populations are likely to produce differing effect sizes and levels of statistical significance.

Despite the overall inverse association observed in our analysis, the very high and largely unexplained heterogeneity ($I^2 \approx 96.4\%$) indicates that the relationship between vitamin D and breast cancer is not uniform across studies or populations. This pattern suggests that the association is likely modified or obscured by numerous confounding and contextual factors that are not fully captured in existing research.

Crucially, although the pooled estimate suggests a protective effect of higher vitamin D levels, the results were not consistent across all studies. Several factors could have contributed to the varying results among studies:

1. **Study Design:** Differences between retrospective case-control studies and nested case-control studies contribute substantially to inconsistent results. In our prespecified subgroup analysis, nested case-control studies showed a modest but statistically significant increase in risk (OR, 1.20; 95% CI, 1.06–1.36) with no heterogeneity ($I^2 = 0.0\%$), whereas retrospective case-control studies showed a much larger but highly heterogeneous increase in risk (OR, 2.06; 95% CI, 1.38–3.08; $I^2 = 98.1\%$). The test for subgroup differences was significant ($P = .012$). This suggests that retrospective studies are particularly

vulnerable to reverse causality, because vitamin D levels can be influenced by cancer-related weight loss, treatment, or postdiagnosis lifestyle changes.³⁶ Although prospective studies also have limitations—such as reliance on a single baseline measurement—they assess vitamin D status before cancer diagnosis and are therefore generally less susceptible to reverse causality and selection bias.²⁷

2. **Population Variations:** Genetic background, lifestyle, and environmental exposure can all affect the association between vitamin D and breast cancer risk.^{37,38}

3. **Vitamin D Measurement:** Inconsistent results may arise from using different techniques to measure vitamin D and from using different definitions of sufficiency across different studies.³⁹

4. **Breast Cancer Subtypes:** Vitamin D may only affect certain types of breast cancer, as mentioned in the limitations. Breast cancer is a heterogeneous disease.⁴⁰ Subtype-specific associations may be obscured by the fact that many studies lack subtype-specific analyses.⁴¹

Biological mechanisms

Many biological mechanisms support the protective effects of vitamin D against breast cancer. Some of these mechanisms are explained below:

1. **Anticancer Properties:** Vitamin D has been shown to promote apoptosis in cancer cells.⁴² The active form, 1,25(OH)₂D, binds to the vitamin D

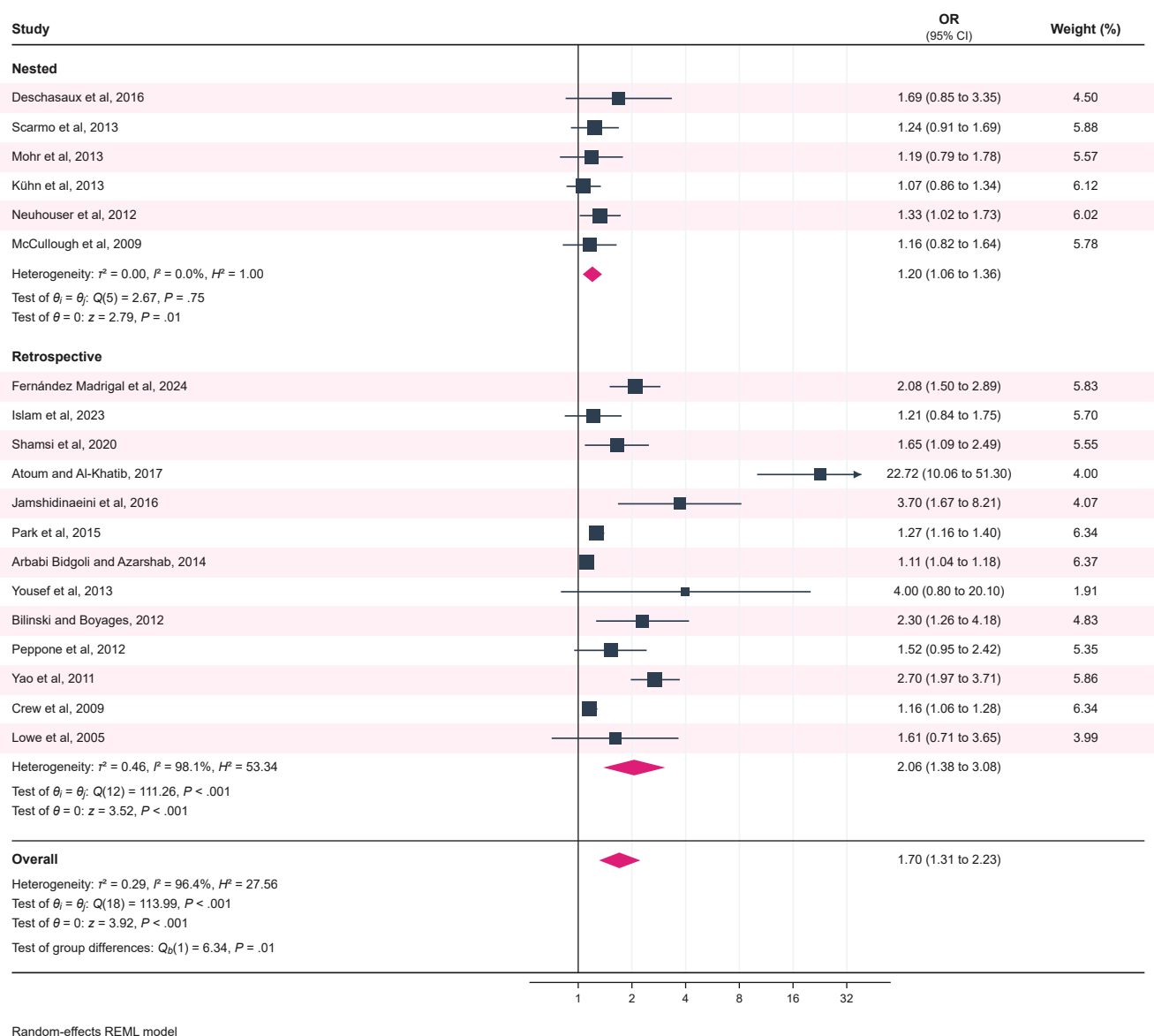


Figure 3. Forest Plot of the Subgroup Analysis by Study Design.

receptor in normal breast cells, regulates cell growth, promotes differentiation, improves cell adhesion, protects against DNA damage, regulates immune responses, and reduces inflammation.⁴³

2. **Gene Regulation:** The active form of vitamin D binds to the vitamin D receptor to modulate the transcription of target genes such as c-fos, p21, p27, and c-myc, which are involved in cell cycle control and oncogenesis, respectively.⁴⁴

3. **Immune System Modulation:** Vitamin D appears to be involved in both the innate and adaptive immune systems and represents an additional mechanism for its anticancer activities.^{45,46}

4. **Mammary Gland Development:** Vitamin D has been shown to play an important role in the development and function of the mammary gland. It acts not only in vitro but also in vivo models of mouse mammary tumor cells.^{47,48}

5. **Vitamin D–Regulated Pathways:** One review suggests that breast cancer in humans can be prevented,

among other things, by restoring or activating pathways regulated by vitamin D.⁴⁹

These mechanisms provide a biologically plausible framework for a potential protective role of vitamin D in breast carcinogenesis and point to avenues for intervention and prevention strategies. While our study focused on observational epidemiologic data, a recent review by Kanwal *et al.*⁵⁰ highlighted how vitamin D may modulate the breast cancer tumor microenvironment by influencing immune cell infiltration and stromal interactions. The apparent tension between strong biological plausibility and highly variable epidemiologic estimates may reflect the contributing factors discussed above, including study design (nested vs retrospective), population heterogeneity, environmental exposures, and differences in breast cancer subtypes. Importantly, the consistent effect in nested case-control studies ($I^2 = 0\%$) with prediagnostic sampling provides stronger support for a genuine protective effect, even if modest, compared with the exaggerated estimates from

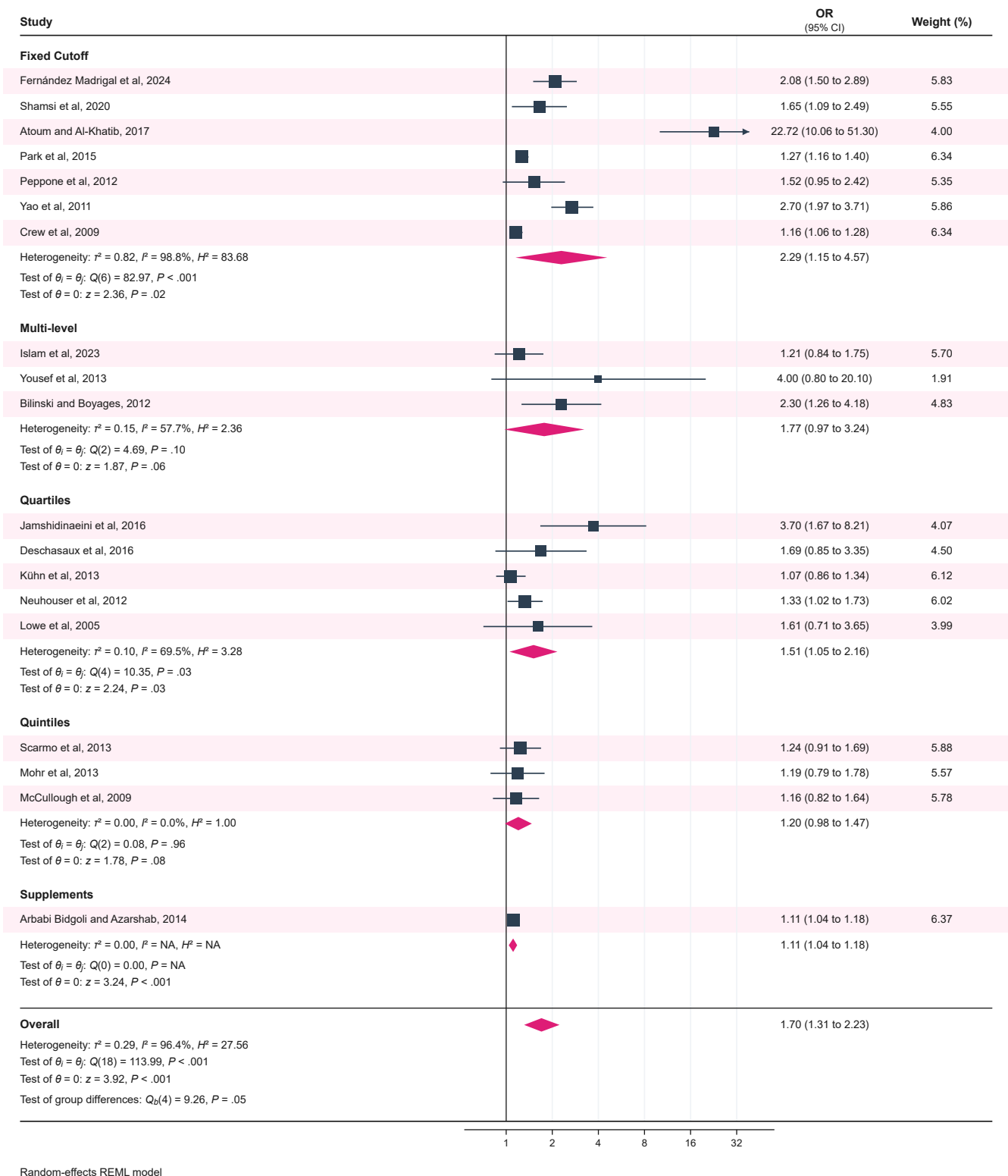


Figure 4. Forest Plot of the Subgroup Analysis by Vitamin D Sufficiency Cutoff Definition.

retrospective studies.

Strengths and limitations

The main strengths of this meta-analysis are the large combined sample size, the inclusion of studies from multiple world regions, the use of a structured quality assessment tool tailored to case-control designs, and the performance of the meta-analysis on the natural log

scale with exponentiation to produce valid asymmetric confidence intervals. Additionally, the prespecified subgroup analysis by study design (nested vs retrospective) allowed us to disentangle true association from reverse causality.

Nevertheless, important limitations must be acknowledged. First, the heterogeneity between studies was extremely high in the overall analysis

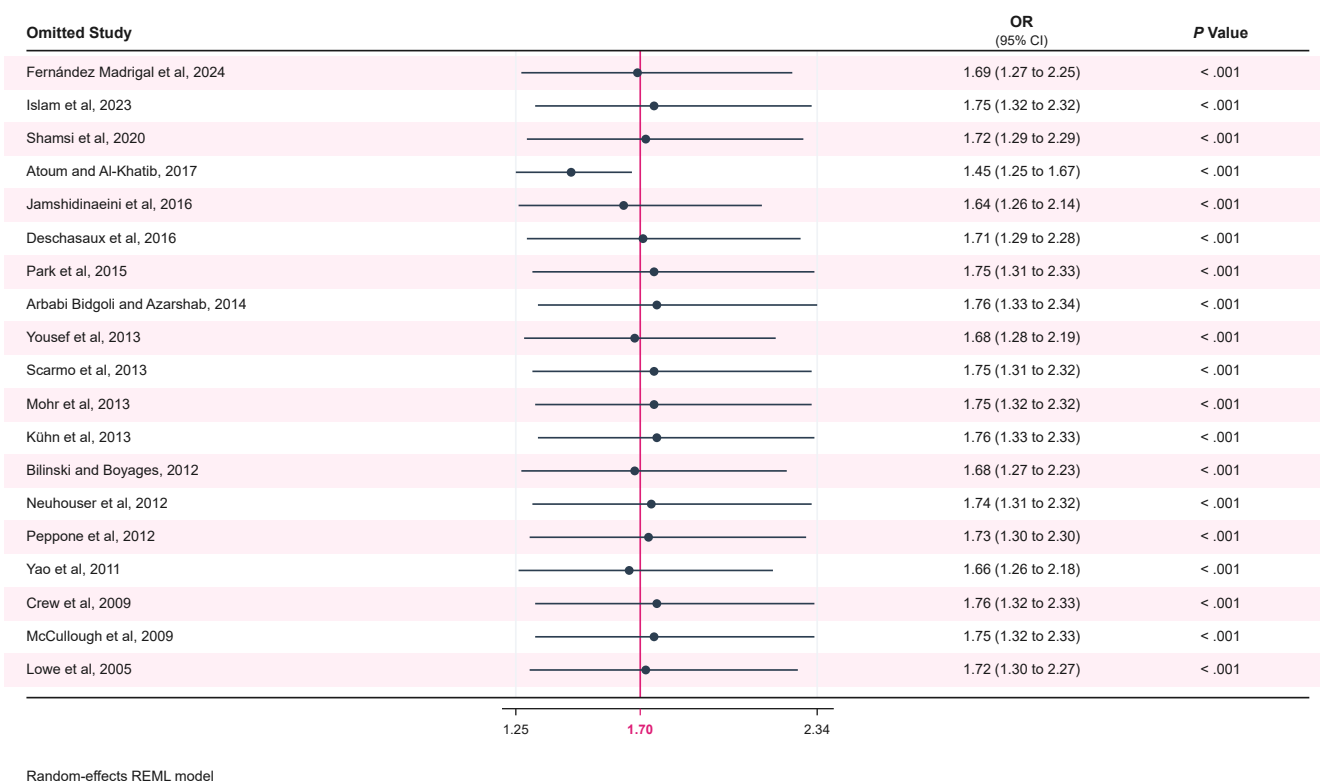


Figure 5. Forest Plot of the Leave-One-Out Sensitivity Analysis.

($I^2 \approx 96.4\%$), which likely reflects variability in the underlying association across populations, study designs, and analytic approaches. However, this heterogeneity was entirely eliminated in the nested case-control subgroup ($I^2 = 0.0\%$) and substantially reduced in some vitamin D categorization subgroups (quintiles: $I^2 = 0.0\%$). This suggests that the overall heterogeneity is driven primarily by the inclusion of retrospective studies. Such heterogeneity could be due to different methods of measuring vitamin D, differences in assay standardization, varying definitions of sufficient vitamin D concentration, and differences in how confounding variables were identified and adjusted for across studies. Second, despite the broad geographical spread, no eligible studies from African countries were identified, which limits the generalizability of our findings to regions with high breast cancer burden and high sunlight exposure. Third, because all included studies used a case-control design (though nested case-control studies are derived from prospective cohorts), the possibility of residual reverse causality cannot be entirely excluded, even in nested studies. However, the consistent and homogeneous effect in nested studies with prediagnostic sampling substantially reduces this concern. Given the combination of potential selective reporting and high between-study heterogeneity in retrospective studies, our summary estimates should be interpreted with caution. The nested case-control subgroup provides the most reliable evidence for a modest increase in risk

associated with lower vitamin D levels (OR, 1.20; 95% CI, 1.06–1.36; equivalent to OR, 0.83 for highest vs lowest).

Clinical implications

This meta-analysis found a statistically significant inverse association between circulating vitamin D levels and breast cancer risk. The strongest evidence came from nested case-control studies with prediagnostic sampling, showing a modestly higher risk with low vitamin D levels (OR, 1.20; equivalent to OR, 0.83 for high vs low). Adequate vitamin D may modestly reduce risk, but the effect is small and evidence is limited by substantial between-study heterogeneity. Thus, current evidence does not support routine population screening or high-dose supplementation solely for primary breast cancer prevention. Vitamin D sufficiency remains important for skeletal and other health outcomes and may form part of a broader risk-reduction strategy, but not a stand-alone breast cancer prevention target. Clinicians should prioritize established risk factors and proven prevention strategies, considering vitamin D assessment and supplementation according to general health guidelines and in patients at high risk of deficiency.

Future research

Better designed studies, with particular emphasis on large prospective cohorts with prediagnostic vitamin D measurements (nested case-control studies within cohorts) and adequately powered randomized clinical

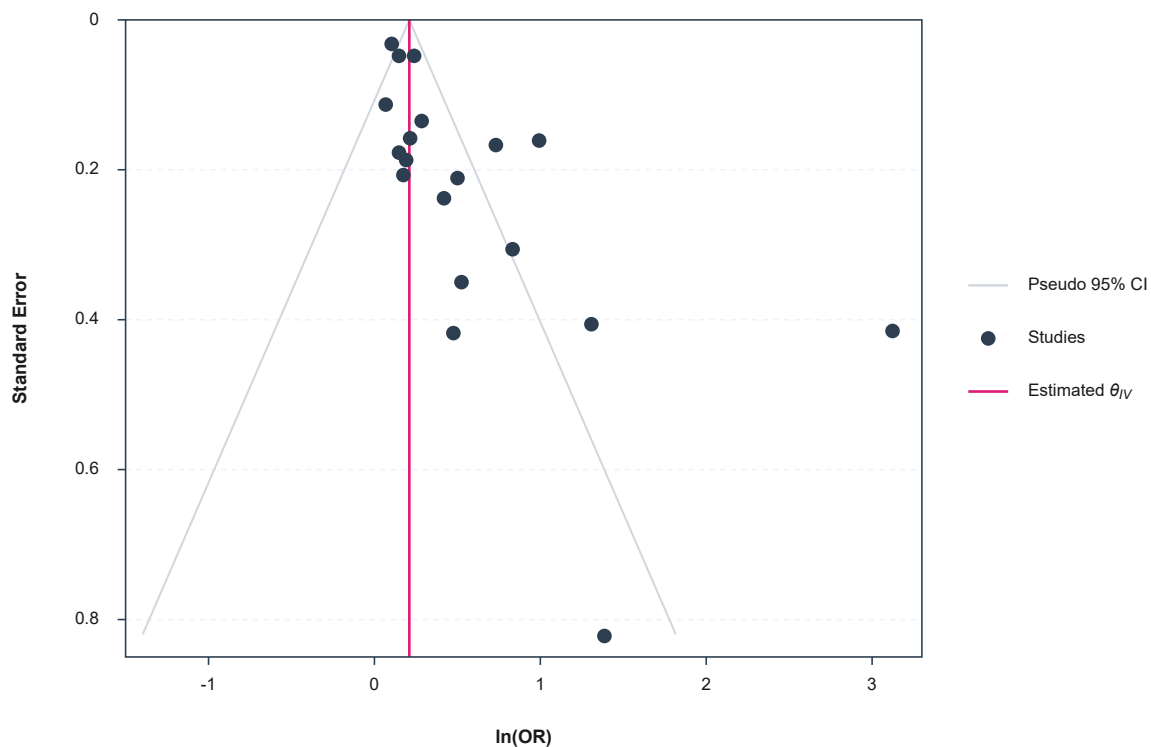


Figure 6. Funnel Plot for the Assessment of Publication Bias.

trials, could help clarify the causality of the association between vitamin D levels and breast cancer risk. Future research should also standardize vitamin D measurement and categorization methods to reduce heterogeneity. Subgroup analyses by breast cancer subtype and by menopausal status are needed to identify populations that may benefit most from vitamin D optimization.

Conclusions

This meta-analysis suggests that lower circulating vitamin D levels are significantly associated with an increased risk of breast cancer (OR, 1.70; 95% CI, 1.31–2.23). In nested case-control studies, the association remained significant but was more modest (OR, 1.20; 95% CI, 1.06–1.36) with no heterogeneity ($I^2 = 0.0\%$). The stronger effect in retrospective studies (OR, 2.06) likely reflects reverse causality. Therefore, maintaining adequate vitamin D levels may reduce breast cancer risk, although further prospective studies are warranted.

ETHICAL CONSIDERATIONS

Not applicable.

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DATA AVAILABILITY

Data are available upon request from the corresponding author.

CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest.

FUNDING

None.

ACKNOWLEDGMENTS

The authors would like to thank the researchers whose work was included in this study.

AI DISCLOSURE

During the preparation of this manuscript, DeepSeek-R1 was used to improve readability and English language. All the text was double-checked and approved by the authors.

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How to Cite This Article

Mehranpour G, Beigrezaee M, Atashgah AS, Taherkhani A, Ashrafi SZ, Piroti H, et al. An Updated Meta-Analysis on Serum Vitamin D Levels and the Risk of Breast Cancer. *Arch Breast Cancer*. 2026; 13(4):412-425. doi: 10.32768/abc.7391846250-317

Available from: <https://www.archbreastcancer.com/index.php/abc/article/view/1257>