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Exploring factors that influence vitamin D deficiency continuum across breast cancer patients' care: insights from a tertiary health population

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Abstract Vitamin D deficiency has prognostic implications in breast cancer care. Identifying patients at high risk for vitamin D deficiency across the breast cancer care continuum can improve testing and supplementation strategies. This study aimed to describe serum vitamin D distributions in patients receiving breast cancer care and to identify predictors of vitamin D deficiency.

Method A retrospective cross-sectional analysis of 14,773 patients with at least one serum 25-hydroxyvitamin D (25(OH)D) measurement was performed. Patients were categorized into three breast diagnostic groups based on their ICD-10 code: current breast cancer (C50), screening (Z12.39), and personal history (Z85.3). 25(OH)D levels were classified as deficient (<20 ng/mL), insufficient (20–29.9 ng/mL), and sufficient (≥30 ng/mL), with severe deficiency defined as <10 ng/mL and <15 ng/mL. One-way ANOVA compared the mean of 25(OH)D levels across different breast diagnostic groups. Multivariable logistic regression examined predictors of low 25(OH)D levels (<10 ng/mL and <15 ng/mL), adjusting for age, breast diagnostic group, and ethnicity.

Result Of the 14,773 patients, 99.8% were female, with a mean age of 54.8 ± 12.9 years. The overall mean serum 25(OH)D concentration was 37.3 ± 19.5 ng/mL. Serum 25(OH)D levels were higher in patients with current breast cancer (42.1 ng/mL) and those with a personal history (42.5 ng/mL) than in screening attendees (35.7 ng/mL). Significant differences among the groups were confirmed by ANOVA ($F(2, 14{,}770) = 152.2$, $p < 0.0001$). Overall, 14.4% were deficient (<20 ng/mL), with 6.8% severely deficient (<15 ng/mL). Severe deficiency was most common in Z12 (7.6%), followed by C50 (4.2%) and Z85 (3.4%). Increasing age was protective against deficiency, with each 10-year increase reducing the odds (aOR = 0.88 for <10 ng/mL; aOR = 0.84 for <15 ng/mL). Women with breast cancer had lower odds of deficiency than screening patients (C50: aOR 0.66; Z85: aOR 0.56). Hispanic women had higher odds of deficiency at <15 ng/mL (aOR 1.44) than non-Hispanic women.

Conclusion Vitamin D deficiency is prevalent among younger women, those undergoing breast cancer screening, and Hispanic women. Targeted testing by age, diagnostic group, and ethnicity has the potential to optimize resource allocation for at-risk patients and improve supplementation strategies throughout the breast oncology care continuum.

Keywords Breast cancer · Vitamin D · Women · Predictor · Continuum

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Introduction

Vitamin D insufficiency has been associated with the adverse outcomes of various musculoskeletal and non-skeletal diseases, including the prognosis of malignancies such as breast cancer [1–4]. Several observational studies have reported high rates of 25(OH)D deficiency in populations with or at risk of breast cancer [5]. Additionally, serum 25(OH)D levels have been shown to have an inverse relationship with the risk of breast cancer [6, 7]. The protective effects of 25(OH)D against breast cancer have been associated with its ability to regulate the cell cycle, promote apoptosis, inhibit angiogenesis, and suppress metastasis [8, 9]. However, routine vitamin D testing practices in breast health services are not consistent, and the specific subgroups at risk of deficiency across the breast cancer care continuum remain poorly defined. This is because vitamin D testing in breast health services has not been standardized [10].

Current guidelines do not recommend universal vitamin D screening in the general population because evidence is insufficient to support routine screening of asymptomatic adults [11]. This marks a shift from the early 2000s, when vitamin D testing was strongly recommended [12]. However, breast oncology guidance supports targeted assessment, especially before initiating chemotherapy, with an emphasis on monitoring bone mineral density throughout the breast cancer continuum [10, 13]. Secondary causes of bone loss, such as vitamin D deficiency, are evaluated before antiresorptive therapy is initiated, particularly for women receiving aromatase inhibitors or ovarian suppression [10]. Therefore, vitamin D testing has been integrated into breast oncology practice to monitor bone loss, though vitamin D is not recognized as a universal breast cancer biomarker [10, 13]. Even so, this practice varies across institutions. This variation reflects the scarcity of randomized trials on the protective effect of vitamin D supplementation on breast cancer risk, except in postmenopausal women [13, 14]. Vitamin D supplementation has been associated with approximately a 12% lower risk of breast cancer in postmenopausal women in observational studies [14, 15].

In most healthcare settings, the breast cancer care continuum includes risk assessment and screening, diagnostic evaluation, treatment, and survivorship follow-up [16, 17]. Access to this care may not be available to everyone and can be influenced by factors such as race, socioeconomic status, and geographic location [18, 19]. Notably, patients at different stages of this continuum may differ in age, comorbidities, lifestyle, and exposure to interventions, including vitamin D supplementation. For instance, women undergoing active treatment or who are in survivorship care may receive more intensive bone health assessment and supplementation than asymptomatic screening patients. As a result, the vitamin D levels observed in oncology clinics may not accurately represent the distribution in the broader at-risk population served by breast health services [20].

Although the role of vitamin D in breast cancer has attracted considerable interest and has been well documented in the last decade [6, 21], large-scale studies using real-world data that characterize vitamin D levels across the full spectrum of patients, from preventive to therapeutic and follow-up stages, in tertiary-level health care systems are lacking. Most previous studies focus on newly diagnosed breast cancer patients, high-risk populations, the community-based screening population, and case-control studies without directly comparing these groups or incorporating women with a personal history of breast cancer who are undergoing long-term observational follow-up care; these clinical states have generally been studied separately [5, 22]. Studies have also shown significant differences in vitamin D levels between breast cancer patients and healthy individuals [23]. In most of these studies, critical health information such as age, diagnostic categories, and ethnicity, which may have a confounding effect on vitamin D levels, is missing, and their predictive performance for clinically relevant vitamin D deficiency has not been assessed.

Furthermore, at both primary and tertiary health care institutions, vitamin D testing volume represents a substantial and significant growing expenditure [24, 25]. However, there is no clear evidence to support universal screening in all breast cancer patients across the care continuum. Instead, there is a pressing need to identify pragmatic, risk-based strategies that prioritize testing for individuals most likely to be deficient. Identifying predictors of vitamin D deficiency in a real-world breast health population can potentially inform more efficient

testing algorithms and help target interventions to the highest-risk groups. To our knowledge, studies that have examined the clinical importance of vitamin D testing across the breast cancer continuum from screening, current breast cancer, and post-treatment using large real-world breast cancer cohorts are scarce. These differences in care intensity, therapy, and vitamin D supplementation across the continuum remain poorly characterized.

To address these gaps, we retrospectively analyzed routinely collected serum 25(OH)D data from a tertiary breast cancer health service to achieve three related objectives. First, described the distribution of 25(OH)D levels among the three breast diagnostic patient groups: those undergoing breast cancer screening (ICD CODE Z12), those currently diagnosed with breast cancer (C50), and those patients with a personal history of breast cancer (Z85). Next, we compared the prevalence of vitamin D deficiency across these groups using both conventional and more stringent thresholds. Third, we identified independent clinical predictors of vitamin D deficiency and evaluated the discriminative performance of a simple clinical model based on age, diagnostic category, and demographic factors such as ethnicity. Together, this study seeks to provide a large-scale real-world analysis to inform more targeted vitamin D assessment and optimization strategies across the breast cancer care continuum. However, this study is not intended to identify a causal effect of breast cancer status or vitamin D treatment; it uses a cross-sectional population study to identify patterns and predictors of deficiency across the three distinct groups of the breast cancer continuum.

Materials and methods

Population

This retrospective cross-sectional study included patients who received breast cancer care at the Indiana University Health System between 2022 and 2025 and underwent routine serum 25-hydroxyvitamin D testing. We initially retrieved 196,726 patient records from the electronic health record. Of these, only 14,773 patients were active with a breast diagnostic code (C50), in the clinic for breast cancer screening (Z12.39), or had a personal history of breast cancer (Z85.3). Each group was treated as mutually exclusive, and no patient contributed to more than one group. Therefore, all eligible test episodes from 2022–2025 without duplicate testing were included in this study, and the sample size was determined by the number of available eligible patients. Inclusion criteria included confirmed breast cancer with breast diagnostic code (ICD-10) C50, patients in the clinic for breast cancer screening (Z12.39), and a personal history of breast cancer (Z85.3) who had total 25-hydroxyvitamin D testing done in the lab. Patients with incomplete lab information were excluded from this study. Patients' ages were grouped into clinically meaningful strata (e.g., <40, 40–49, 50–59, 60–69, ≥70 years). The subjects were also categorized by ethnicity (Not Hispanic or Latino, Hispanic or Latino, and other/unknown), based on information available in the patients' electronic records. 25-hydroxyvitamin D was evaluated as both continuous and categorical (deficient, insufficient, sufficient). The study protocol was reviewed and approved by the Institutional Review Board (IRB) at Indiana University School of Medicine, Indianapolis, Indiana (IRB approval number: 27013).

During the review period, total serum 25(OH)D was measured using the DiaSorin LIAISON XL 25-OH Vitamin D Total direct competitive chemiluminescence immunoassay. The assay linear range is 4.0 to 150.0 ng/mL. Results greater than 150 ng/mL are diluted up to 1:4, and the final value is calculated using the dilution factor before reporting. The maximum reportable concentration is 400 ng/mL. Two-level quality controls (QC) are run before analyses begin each day, and analyzers are recalibrated every 7 days, before changing to a new reagent lot, after a QC failure, and when QC performance is unacceptable.

Statistical analysis

Serum 25(OH)D was analyzed both as a continuous variable (ng/mL) and as a categorical variable. For categorical summaries, 25-hydroxyvitamin D status was classified as deficient (<20 ng/mL), insufficient (20–29.9 ng/

mL), or sufficient (≥30 ng/mL). In addition, three binary deficiency thresholds were defined: <10 ng/mL, <15 ng/mL, and <20 ng/mL. The <10 ng/mL and <15 ng/mL thresholds were used as the primary outcomes for regression modeling, while <20 ng/mL was included in secondary receiver operating characteristic (ROC) analyses. All analyses were conducted using R for Windows version 4.5.2 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined as a two-sided $p < 0.05$.

To compare mean 25(OH)D levels across the three breast diagnostic groups (C50, Z12, and Z85), we conducted a one-way analysis of variance (ANOVA) with 25(OH)D as the dependent variable and the breast diagnostic group as the independent factor. When the global ANOVA F-test was statistically significant, we performed pairwise comparisons using Tukey's Honest Significant Difference (HSD) method: C50 vs. Z12, Z85 vs. Z12, and Z85 vs. C50. To evaluate the model's assumptions, we visually examined residual plots and normal quantile-quantile plots. We assessed homogeneity of variance using Levene's test; because it indicated heterogeneity, we performed Welch's one-way ANOVA as a variance-robust sensitivity analysis. After Welch's one-way ANOVA, we conducted pairwise comparisons among the breast diagnostic groups using the Games-Howell procedure to accommodate unequal variances and unequal group sizes. The combination of the conventional ANOVA/Tukey HSD and Welch/Games-Howell analyses helps determine the rigor of our data and concordance among the diagnostic groups.

In this study, we determined the adjusted odds ratio (aOR) with their 95% confidence intervals (CI) for logistic regression using profile likelihood methods in R. We assessed the prevalence of severe vitamin D deficiency (defined as <15 ng/mL) based on various factors, including breast diagnostic group, age range (under 40, 40–49, 50–59, 60–69, and 70 years and older), ethnicity, gender, and state (Indiana compared to other states). For each subgroup, we compiled the number and percentage of patients with 25(OH)D levels <15 ng/mL. Two main logistic regression models were fitted with binary outcomes: vitamin D <10 ng/mL and <15 ng/mL, respectively. In both models, the following predictors were included a priori based on clinical relevance: age (scaled per 10-year increase), breast diagnostic group (C50 and Z85 with Z12 as the reference), ethnicity (Hispanic versus Not Hispanic; Other/Unknown versus Not Hispanic), and state of residence (non-Indiana versus Indiana). Odds ratios (ORs) with 95% CIs and p-values were derived from the model coefficients.

To evaluate the models' discriminatory performance, we used predicted probabilities from the fitted logistic regressions to construct receiver operating characteristic (ROC) curves. For the primary model focused on vitamin D levels below 15 ng/mL, we calculated the area under the ROC curve (AUC) and its 95% CI using the DeLong method to quantify discrimination. In a secondary analysis, we also generated ROC curves and AUCs for models predicting deficiencies at thresholds of <10 ng/mL and <20 ng/mL. We displayed all three ROC curves on a single plot to allow visual comparison of discrimination across the thresholds, and we also included a graph showing the most clinically important concentration (<15 ng/mL).

Secondary statistical analyses

To assess the robustness of this study, three prespecified secondary analyses were conducted using the primary analytical cohort. We modeled the outcome with ordinary least squares regression, using breast cancer diagnostic category, age, and ethnicity as predictors, with screening for breast cancer (Z12) and Not Hispanic as the reference categories. Age was treated as continuous, and HC3 robust standard errors were used. Adjusted mean differences and model-adjusted group means at age 54.84 years and Not Hispanic ethnicity were reported with 95% CIs. We also reevaluated group differences using the Kruskal-Wallis test, followed by Holm-adjusted pairwise Wilcoxon tests; effect size was quantified with epsilon-squared. Finally, we calculated AUCs with 95% CIs; the overall prediction error was assessed using the Brier score, calibration intercept and slope, and calibration across predicted-risk deciles. In addition, internal validity was evaluated using 200 bootstrap resamples (seed 12345). Afterward, mean optimism was subtracted from the apparent AUC to obtain an optimism-corrected estimate.

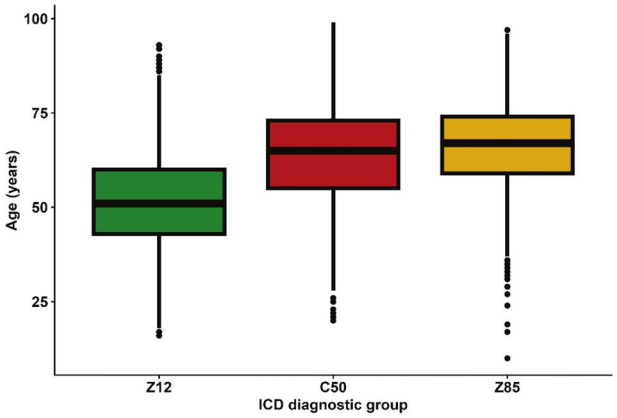


Fig. 1 Age distribution between breast diagnostic groups. Patients attending the hospital for breast cancer screening were younger (51.8 ± 11.5 years). Abbreviations: Screening (Z12), Current breast cancer (C50), and personal history (Z85)

Table 1 Age distribution by Breast Cancer Diagnostic Group

Breast cancer diagnostic groups	N	Age (years) (Mean ± SD)	Median (Years)	Q1-Q3	Maximum Age (Years)
Z12	11278	51.8 ± 11.5	51	43–60	93
C50	2317	63.8 ± 12.6	65	55–73	99
Z85	1178	66.0 ± 11.6	67	59–74	97

Results

Patient characteristics and study population

A total of 14,773 patients with at least one serum 25-hydroxyvitamin D result were included in the study. Only 0.1% (16) of the cohort identified as men; 2 (0.01%) identified as non-binary/other; and for 5 (0.03%) patients, gender was not available. The remaining 99.8% of the cohort identified as women. Because the number of participants who did not identify as women was small, all multivariable regression models were restricted to women.

The mean age of the overall cohort was 54.8 ± 12.9 years. Patients attending the breast cancer screening clinic had the lowest mean and median ages (51.8 ± 11.5 years and 51 years, respectively). The mean and median ages of patients with current breast cancer (C50) were 63.8 ± 12.6 years and 65 years, respectively, and those of patients with a personal history of breast cancer (Z85.3) were 66.0 ± 11.6 years and 67 years, respectively, which were similar (Fig. 1 and Table 1).

Most patients were identified as Not Hispanic or Latino (14,158; 95.8%), while 3.4% (506) were identified as Hispanic or Latino. The ethnicity of a few of our participants was unavailable (0.5%; n = 72) or they declined to disclose it (0.3%; n = 37). Only 1% of the cohort (148) were from other states, while 99% of participants were from Indiana.

Serum vitamin D distribution

Figure 2A and B show the distribution of serum 25(OH)D concentrations across all diagnostic groups. The mean 25-hydroxyvitamin D concentration across the population was 37.3 ± 19.5 ng/mL (range 4.0–279.6 ng/mL), with a median of 33.8 ng/mL and an interquartile range (IQR) of 25.0–45.3 ng/mL. Specifically, Table 2 shows that the mean serum 25(OH)D level in women with current breast cancer (C50) was 42.1 ± 20.1 ng/mL (median = 39.0 ng/mL and IQR = 29.1–50.7 ng/mL); in women with a personal history of breast cancer (Z85; n = 1178), the mean was 42.5 ± 20.9 ng/mL (median = 38.4 ng/mL and IQR = 29.3–51.5 ng/mL); and in screening subjects (Z12; n = 11,278), the mean was lower at 35.7 ± 19.0 ng/mL (median = 32.3 ng/mL and IQR = 23.9–43.2 ng/mL) (Fig. 2A

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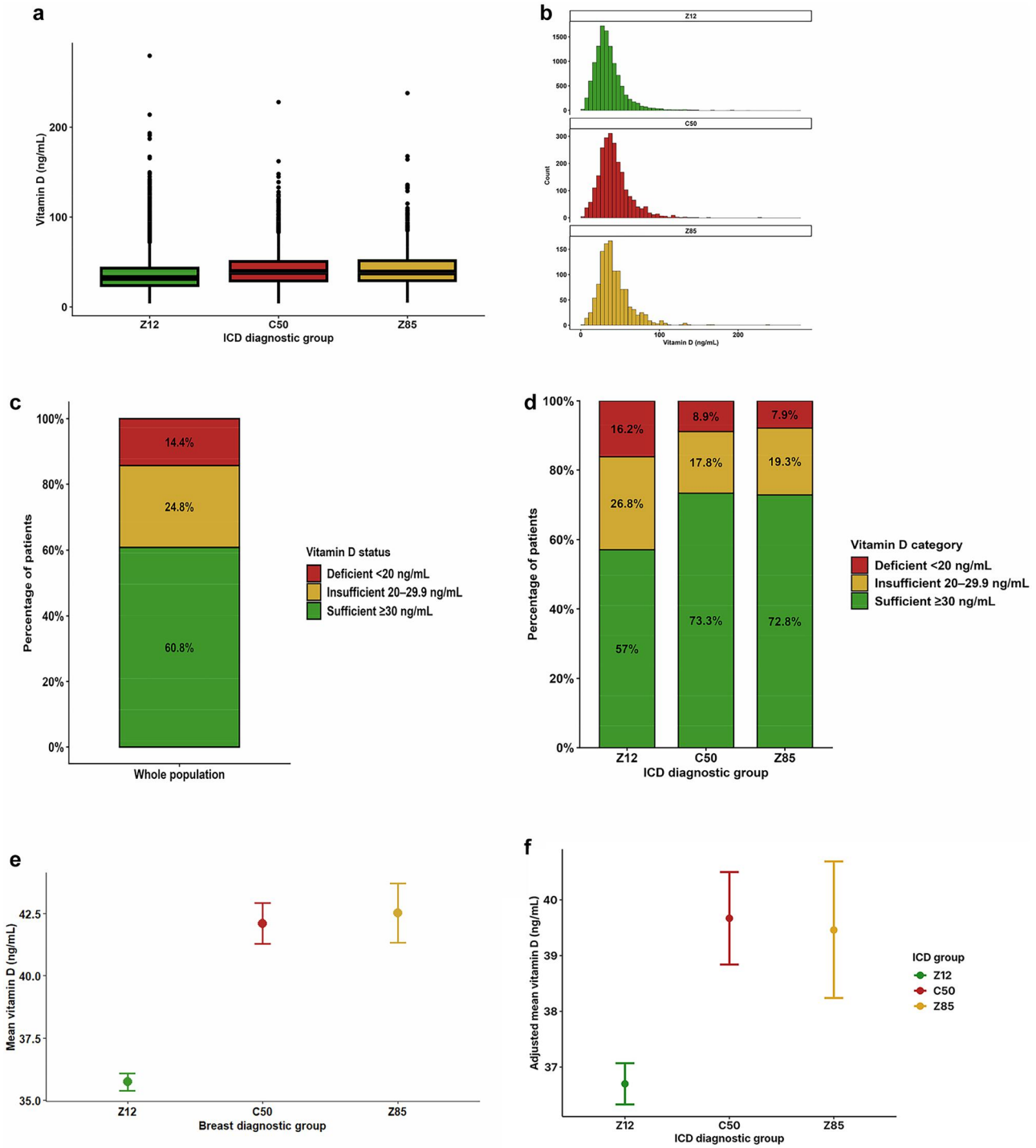


Fig. 2 Serum vitamin D distribution by breast diagnostic group. **a** Serum vitamin D distribution by breast diagnostic group. **b** Histogram showing left and right distribution of vitamin D by breast diagnostic group. **c** Overall categorized threshold distribution of vitamin D status of the whole population. **d** Mean vitamin D status by breast diagnostic category. **e** Mean vitamin D by each of the breast cancer diagnostic groups. **f** Age- and ethnicity-adjusted mean serum vitamin D by breast diagnostic groups. Abbreviations: Current breast cancer (C50), screening (Z12), and personal history (Z85)

Table 2 Serum 25-hydroxyvitamin D concentrations (ng/mL) by Breast Cancer Diagnosis Category

Breast cancer diagnosis category	N	Mean ± SD (ng/mL)	Median(ng/mL)	Q1-Q3	Maximum Vitamin D(ng/mL)
Z12	11278	35.7 ± 19.0	32.3	23.9–43.2	279.6
C50	2317	42.1 ± 20.1	39	29.1–50.7	228
Z85	1178	42.5 ± 20.9	38.4	29.3–51.5	238

Table 3 Group comparison (One-way ANOVA): The overall F-test was highly significant (F = 152.2, df = 2, $p < 0.001$), indicating that the mean 25-hydroxyvitamin D levels differed across categories

Source	Sum of squares	df	F (*p*-value)
Diagnostic category	113845	2	152.2 ($p < 0.0001$)
Residual	5525386	14,770	

Table 4 Tukey HSD pairwise comparisons of mean serum 25-hydroxyvitamin D ng/mL (difference in means)

Comparison	Mean diff	95% CI	p
C50 − Z12	6.39	5.35–7.42	<0.001
Z85 − Z12	6.80	5.42–8.19	<0.001
Z85 − C50	0.42	−1.21–2.04	0.82

Table 5 Levene's Test for homogeneity of variance

Effect	Df	F-value	*P*-value
group	2 14770	11.48	$p < 0.0001$

and D). When the whole population was categorized using conventional thresholds, 2125 (14.4%) patients were vitamin D deficient (<20 ng/mL), 3661 (24.8%) were vitamin D insufficient (20–29.9 ng/mL), and 8987 (60.8%) were vitamin D sufficient (≥30 ng/mL) (Fig. 2C).

Figure 2D shows the distribution of vitamin D across breast diagnostic groups: among women with C50, 8.9% were deficient, 17.8% insufficient, and 73.3% sufficient; among Z12 subjects, 16.2% were deficient, 26.8% insufficient, and 57.0% sufficient; and among women with Z85, 7.9% were deficient, 19.3% insufficient, and 72.8% sufficient (Suppl. Table 1). Thus, screening patients (Z12) were more likely to be vitamin D deficient or insufficient than those with current or prior breast cancer. Boxplots and histograms illustrate that the vitamin D distributions in the C50 and Z85 groups are right-shifted relative to Z12 (Fig. 2A and B). Notably, after adjustment for age and ethnicity, the difference in serum vitamin D levels among the breast cancer diagnostic categories remained (Fig. 2F).

Analysis of variance (ANOVA) analysis of breast diagnostic groups

Table 3 showed a significant overall effect of diagnostic group on mean vitamin D, $F(2, 14{,}770) = 152.2$, $p < 0.0001$, confirming that mean vitamin D levels differ across the three breast diagnostic groups. Post hoc pairwise comparisons using Tukey's Honest Significant Difference (HSD) procedure were consistent with the descriptive means (Table 4) and further showed that the main difference was between patients attending clinic for breast cancer screening and the other two groups in the breast cancer continuum. Women with current breast cancer (C50) had a mean vitamin D level 6.39 ng/mL higher than screening attendees (Z12; 95% CI 5.35–7.42; $p < 0.001$). Women with a personal history of breast cancer (Z85) had a mean 6.80 ng/mL higher than Z12 (95% CI 5.42–8.19; $p < 0.001$) (Table 4). The difference between Z85 and C50 was not statistically significant (mean difference of 0.42 ng/mL; 95% CI: −1.21–2.04; $p = 0.82$) (Table 4). However, Levene's test demonstrated heterogeneity of variance in the data ($F(2, 14{,}770) = 11.48$, $p < 0.001$) (Table 5). Due to the violation of equal variance,

Table 6 Welch one-way ANOVA

Test	F-value	Numerator Df	Denominator Df	*P*-value
Welch one-way ANOVA	141.3	2	2521.1	$p<0.0001$

Table 7 Games-Howell pairwise comparisons

Group 1	Group 2	Mean difference	CI lower	CI upper	Adjusted *P*-value	Significance
Z12	C50	6.39	5.32	7.45	<0.0001	****
Z12	Z85	6.80	5.32	8.29	<0.0001	****
C50	Z85	0.42	−1.32	2.15	>0.05	ns

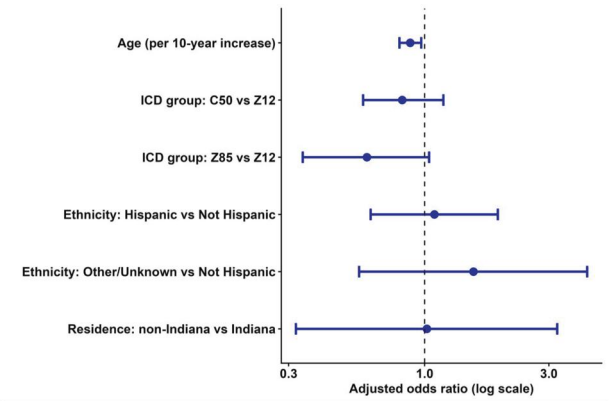


Fig. 3 Predictors of severe vitamin D deficiency (<10 ng/mL model)

Table 8 Prevalence of 25-hydroxyvitamin D deficiency by Breast Cancer Diagnostic Group

Breast Cancer Groups	N	N (<10 ng/mL)	<10 ng/mL	N (<15 ng/mL)	<15 ng/mL	N (<20 ng/mL)	<20 ng/mL
Z12	11278	268	2.4	861	7.6	1826	16.2
C50	2317	39	1.7	97	4.2	206	8.9
Z85	1178	14	1.2	40	3.4	93	7.9

Welch's ANOVA was performed to ensure robust sensitivity analysis, followed by Games–Howell post hoc comparisons. Table 6 shows that Welch's ANOVA confirmed significant differences across the breast cancer diagnostic category ($F(2, 2521.1) = 141.3$, $p<0.001$). In addition, Games–Howell post hoc comparisons were consistent with our observations from the conventional ANOVA and Tukey HSD analyses (Table 7).

Prevalence and predictors of severe vitamin D deficiency (<10 ng/mL)

Severe vitamin D deficiency is defined by the Centers for Disease Control (CDC) as a level below 12 ng/mL [26]. To address this cut-off, we explored two severe vitamin D models: 10 ng/mL and 15 ng/mL. Using the 10 ng/mL model, only 2.2% (321 of 14, 773) of the overall patients are severely deficient with patients having the highest prevalence seen in the breast diagnostic screening population, followed by patients with current breast cancer, and the least in participants with personal history of breast cancer: 268/11,278 (2.4%) in Z12, 39/2317 (1.7%) in C50, and 14/1178 (1.2%) in Z85, respectively.

Concentrating exclusively on female patients, a multivariable logistic regression model was initially developed with severe deficiency (<10 vs ≥10 ng/mL) as the outcome. The predictors included age (10-year increments), breast diagnostic group, ethnicity, and residence (Indiana vs. other states), with Z12 and non-Hispanic women as reference categories. Age was significantly associated with lower odds of severe deficiency (aOR = 0.88 per 10-year increase; 95% CI, 0.80–0.97; $p=0.008$) (Fig. 3 and Tables 8, 9). Compared with Z12, women with C50

Table 9 25-hydroxyvitamin D <15 ng/mL by ethnicity

Ethnicity	N	Severe deficiency n (<15 ng/mL)	Severe deficiency %
Hispanic or Latino	506	53	10.5
Not Hispanic or Latino	14158	935	6.6
Patient Declined	37	3	8.1
Patient Unavailable	72	7	9.7

Table 10 Adjusted odds ratios (OR) of Vitamin D <10 ng/mL with 95% CI

Predictor	OR	95% CI lower	95% CI upper	*P* value
Age (per 10-year increase)	0.88	0.80	0.97	0.008
ICD group: C50 vs Z12	0.82	0.57	1.16	0.284
ICD group: Z85 vs Z12	0.60	0.33	1.01	0.071
Ethnicity: Hispanic vs Not Hispanic	1.09	0.59	1.83	0.770
Ethnicity: Other/Unknown vs Not Hispanic	1.54	0.47	3.70	0.402
Residence: non-Indiana vs Indiana	1.02	0.25	2.72	0.972

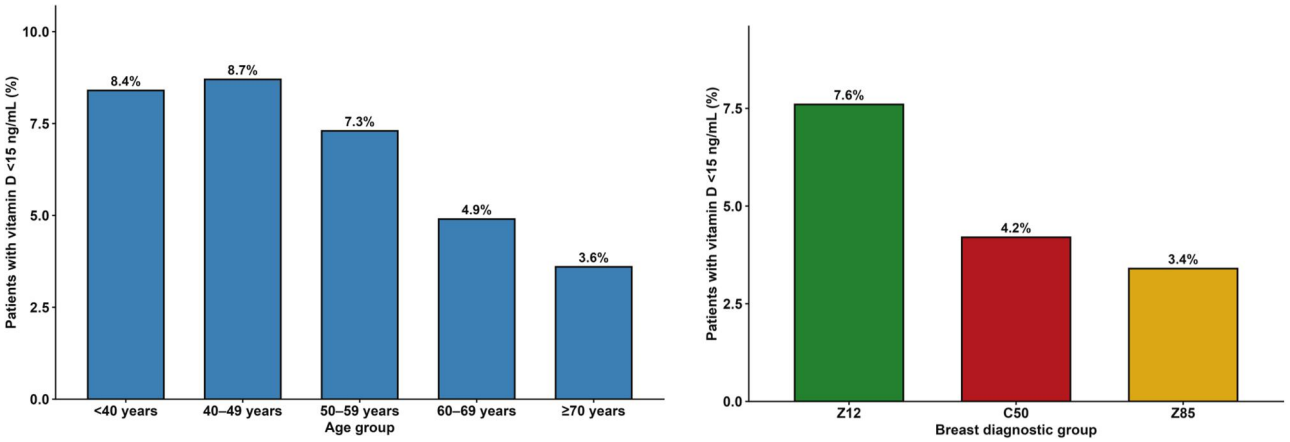


Fig. 4 **a**) Prevalence of severe deficiency decreases with age (% with VitD <15) **b**) Prevalence of severe deficiency by breast diagnostic categories (% with VitD <15)

had lower but non-significant odds (aOR 0.82, 95% CI 0.58–1.18, $p=0.284$), and those with Z85 had even lower, borderline non-significant odds (aOR 0.60, 95% CI 0.33–1.01, $p=0.071$). Ethnicity (Hispanic vs non-Hispanic; other/unknown vs non-Hispanic) and residence outside Indiana were not statistically significant predictors of severe deficiency (Fig. 3 and Table 10).

Prevalence and predictors of severe vitamin D deficiency (<15 ng/mL)

To ensure we capture a wider range of clinically relevant vitamin D concentrations, we broaden the definition of deficiency to <15 ng/mL. With this definition, 998 of 14,773 (6.8%) of the patients for breast cancer continuum care were deficient. The pattern by diagnostic group again showed the highest burden among screening patients: 97/2317 (4.2%) in C50, 861/11,278 (7.6%) in Z12, and 40/1178 (3.4%) in Z85 (Fig. 4B) (Suppl. Table 2). The prevalence of severe deficiency decreased with increasing age (Fig. 4A) (Suppl. Table 3).

A multivariable logistic regression model using the same predictors as the <10 ng/mL model (age, breast diagnostic group, ethnicity, and residence) revealed stronger, statistically significant associations (Fig. 5). For every 10-year increase in age, the odds of deficiency decreased by 16% (OR 0.84, 95% CI 0.79–0.89, $p<0.001$) (Table 11). Compared with the Z12 screening group, women currently diagnosed with breast cancer (C50) had 34% lower odds of deficiency (OR 0.66, 95% CI 0.52–0.82, $p<0.001$) (Table 11), while those with a personal history of breast cancer (Z85) had 44% lower odds (OR 0.56, 95% CI 0.39–0.77, $p<0.001$) (Table 11). Hispanic

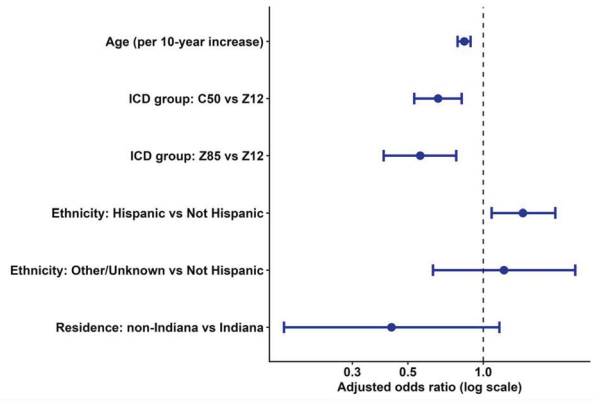


Fig. 5 Predictors of severe vitamin D deficiency (<15 ng/mL model)

Table 11 Adjusted Predictors of vitamin D (<15 ng/mL) odds ratios (OR) with 95% CI

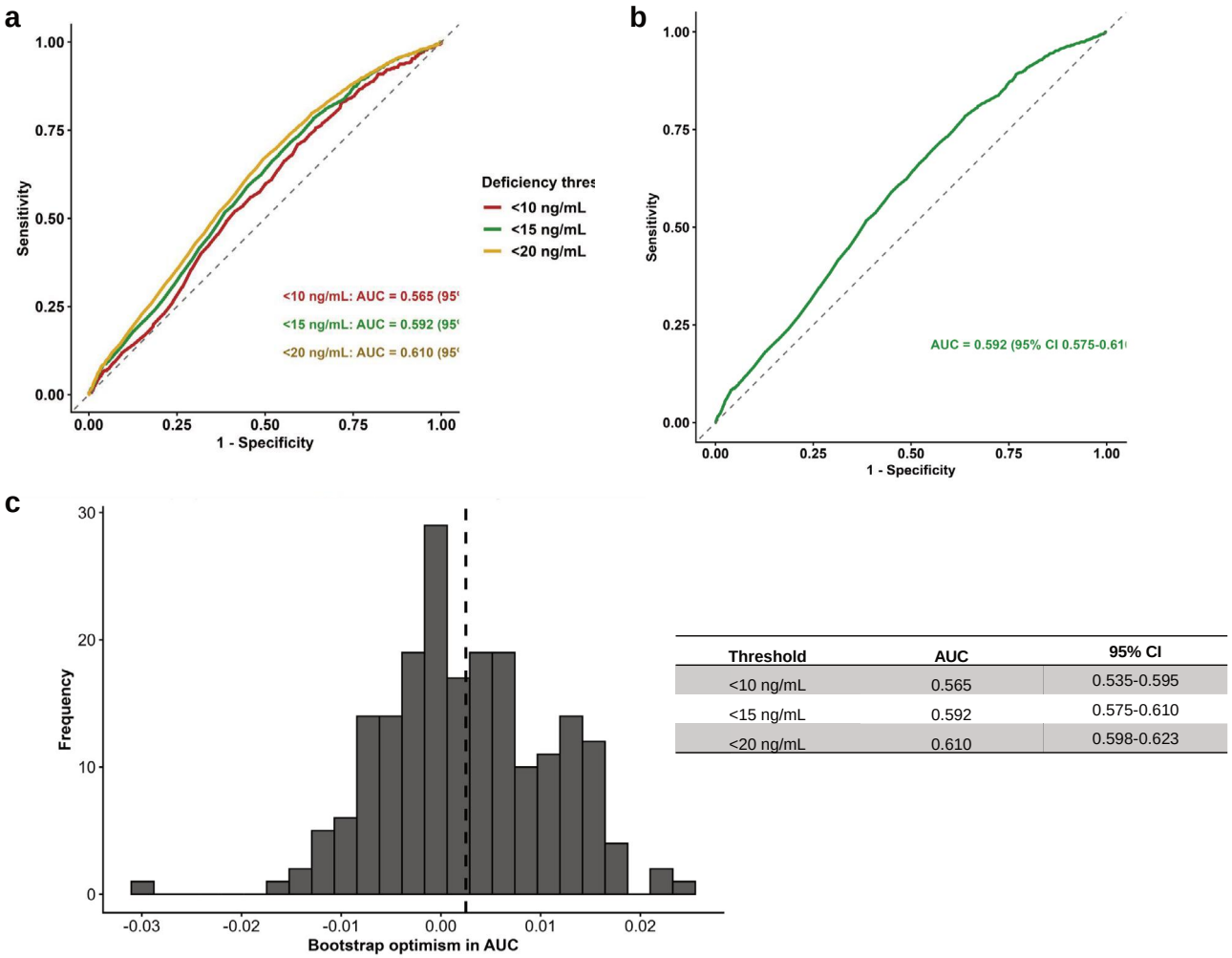
Predictor	OR	95% CI lower	95% CI upper	P value
Age (per 10-year increase)	0.84	0.79	0.89	<0.001
ICD group: C50 vs Z12	0.66	0.52	0.82	<0.001
ICD group: Z85 vs Z12	0.56	0.39	0.77	<0.001
Ethnicity: Hispanic vs Not Hispanic	1.44	1.06	1.92	0.014
Ethnicity: Other/Unknown vs Not Hispanic	1.21	0.59	2.22	0.569
Residence: non-Indiana vs Indiana	0.43	0.13	1.02	0.095

women had significantly higher odds of deficiency than non-Hispanic women (OR 1.44, 95% CI 1.06–1.92, $p=0.014$). In contrast, women identified as other/unknown ethnicity did not differ significantly from their non-Hispanic counterparts. Living outside Indiana showed a non-significant trend toward lower odds of deficiency (OR 0.43, 95% CI 0.13–1.02, $p=0.095$). Notably, we believe these findings should be interpreted as associations rather than causal effects because this is a retrospective cross-sectional study.

Furthermore, the logistic regression model for vitamin D deficiency, defined as <15 ng/mL, showed modest discrimination, with an area under the ROC curve (AUC) of 0.59 (95% CI 0.58–0.61), which is modestly different from the other categories; <10 ng/mL, 0.56 (95% CI 0.53–0.59), and <20 ng/mL, 0.61 (95% CI 0.60–0.62) (Fig. 6A and B). In addition, multivariable logistic regression models improved as the vitamin D deficiency threshold increased from 10 ng/mL to 20 ng/mL (Supplemental Table 12), but provided limited explanatory power for predicting vitamin D deficiency in these models. All pseudo-R^2 measures remained low (McFadden R^2: 0.0062–0.0244 and Nagelkerke R^2: 0.0069–0.0355) (Supplemental Table 12). This suggests that the predictors we included in our observational association study model might not fully explain the variability in vitamin D deficiency status observed across the breast cancer continuum.

Secondary statistical analyses

We conducted several secondary analyses to assess whether the primary findings persist. Notably, after adjusting for age and ethnicity, the association between breast cancer diagnostic categories and continuous vitamin D concentration remained (Fig. 2F and Supplemental Tables 6 and 7). Current breast cancer patients had a mean serum vitamin D level 2.97 ng/mL higher (C50; 95% CI 2.03–3.91; $p<0.001$), and patients with a personal history of breast cancer had a mean serum vitamin D level 2.76 ng/mL higher (Z85; 95% CI 1.45–4.07; $p<0.001$) than the screening group (Supplemental Table 6). Age was also independently associated with serum vitamin D levels, with an estimated 0.28 ng/mL increase per year (95% CI 0.25–0.31; $p<0.001$) (Supplemental Table 6). Notably, the adjusted linear model confirmed lower mean vitamin D in the Hispanic women population (−2.89 ng/mL, 95% CI −4.50 to −1.28; $p<0.001$) (Supplemental Table 7). In addition, Kruskal-Wallis analysis corroborated a significant difference in the overall distribution of vitamin D across breast cancer categories ($H=414.69$, $df=2$,



Threshold	AUC	95% CI
<10 ng/mL	0.565	0.535-0.595
<15 ng/mL	0.592	0.575-0.610
<20 ng/mL	0.610	0.598-0.623

Fig. 6 **A** Receiver Operating Characteristic (ROC) curve showing modest differences between the three deficient thresholds. **B** ROC curve for models predicting vitamin D deficiency (<15 ng/mL). **C** Bootstrap optimism in AUC for the vitamin D <15 ng/mL model

$p<0.001$) (Supplemental Table 8). Holm-adjusted pairwise Wilcoxon nonparametric analyses confirmed these differences among the diagnostic groups, with significant differences between C50 vs Z12 (adjusted $p<0.001$) and Z85 vs Z12 (adjusted $p<0.001$), but not for Z85 vs C50 (adjusted $p=0.979$) (Supplemental Table 9).

The <15 ng/mL logistic model shows modest apparent discrimination (AUC 0.593, 95% CI 0.575–0.610) (Fig. 6A and B). Bootstrap internal validation with 200 resamples yielded a mean AUC optimism of 0.0021 and an optimism-corrected AUC of 0.590 (Fig. 6C and Supplemental Table 10). The approximately 0.002 difference in AUC suggests limited internal overfitting and indicates that the model is likely to perform similarly in a comparable patient population. Calibration is also close to ideal, with an intercept of approximately 0 and a slope of 1.0 (Supplemental Tables 10 and 11), indicating good agreement between predicted and observed risk even with the limited discrimination (Supplemental Fig. 1 and Supplemental Table 11). Nevertheless, validation in an independent external population is required to confirm the generalizability of this finding. It may not apply to populations with different demographic characteristics, vitamin D supplementation practices, test-ordering policies, or patterns of sunlight exposure. Differences in assay platforms, clinical workflows, and healthcare settings may also affect the pattern of vitamin D distribution.

Discussion

Breast cancer is the most common cancer in women and the leading cause of cancer-related deaths among women worldwide [21]. Vitamin D deficiency has been associated with breast cancer risk [27, 28]. This study, for the first time, revealed a coherent and detailed picture of serum 25(OH)D status among patients attending a tertiary breast health system from screening through survivorship. Our results show that women attending breast cancer screening clinics (Z12.39) present with the lowest mean level, a higher proportion of deficiency, and insufficiency of vitamin D compared with women with current breast cancer (C50) and those with prior breast cancer (Z85.3). This finding was further confirmed after correcting for age and ethnicity and performing several secondary analyses; women with current breast cancer (C50) and those with a personal history of breast cancer (Z85.3) have lower odds of having a deficiency of serum 25(OH)D compared with those attending screening clinics.

One main limitation in previously published studies on serum 25(OH)D in breast cancer-related subjects is that most studies have looked into each group separately, not as a continuum, limiting the ability to compare each group with the others [5, 29–31]. Our study is unique because we use a large dataset from a real-world tertiary breast health cohort (N = 14,773) with three distinct breast cancer continuum groups from the same clinical setting. We also ensure no patient overlap and use a single run per subject. Our design enables a cross-sectional comparison of vitamin D distributions and deficiency prevalence. A previous study in breast cancer survivors suggests a higher rate of insufficiency of serum 25(OH)D, with a mean of 24.8 ± 10.4 ng/mL [30]. This is inconsistent with the findings of the current study. The mean serum 25(OH)D in patients with a personal history of breast cancer in our study was 42.5 ± 20.9 ng/mL (median 38.4 ng/mL and IQR 29.3–51.5 ng/mL). Although other factors, including age, sunlight exposure, seasonality, higher latitudes, geographical location, skin pigmentation, ethnicity, obesity, malabsorption, chronic liver disease, or chronic kidney disease, can contribute to serum 25(OH)D levels [2, 30, 32–34], we cannot rule out the role of the study design. Other factors may also explain differences in vitamin D levels between the breast cancer population in our study and that of Momivand et al. [5]; this may reflect differences in study group characteristics and measurement context. Zemlin et al. reported significantly higher serum 25(OH)D among supplement users and higher levels in summer, while Neuhouser et al. reported variation by race/ethnicity, geography, season, body mass index, physical activity, treatment, and supplement use [30, 35]. Momivand et al. reported that the mean serum level of 25(OH)D was 31.9 ± 28.27 ng/mL. In contrast, the mean serum level of 25(OH)D in patients with current breast cancer (C50) in this study was 42.1 ± 20.1 ng/mL, with a median of 32.3 ng/mL and an interquartile range (IQR) of 23.9 to 43.2 ng/mL. Importantly, both continuous and categorical analyses revealed consistent differences by breast diagnostic group: patients with current or prior breast cancer had higher mean vitamin D levels and a larger proportion in the sufficient category compared with screening attendees. Boxplots and histograms visually reinforced these findings, demonstrating right-shifted vitamin D distributions for the C50 and Z85 groups relative to the Z12 group.

It is plausible that, once patients are within the oncology and survivorship group, vitamin D status is maintained at a clinically beneficial threshold regardless of whether they are undergoing active treatment or long-term follow-up, due to robust vitamin D supplementation. It has been reported that serum 25(OH)D level ≥40.26 ng/mL may confer a protective effect against breast cancer [36]. The continued supplementation after diagnosis of breast cancer might explain why, despite being older and likely having more comorbidities, women with current or prior breast cancer are more vitamin D replete than screening subjects in this current study. In addition, there is no significant difference between C50 and Z85, suggesting that greater attention to bone health and supplementation in oncology and survivorship care pathways, while women seen only for screening may not have had a previous vitamin D assessment or targeted supplementation. This suggests that a combination of lifestyle changes and supplementation in patients with a history of breast cancer and current breast cancer pathology might have contributed to these differences. This hypothesis is supported by a recent study that indicated that vitamin D supplementation is common among breast cancer survivors [37]. The question remains of the daily dosage needed to help maintain the needed concentration of vitamin D in breast cancer patients. The National Cancer Institute

recommends 15 µg per day for individuals aged 1–70 years, including pregnant or lactating women, and 20 µg per day for women ≥70 years or older [38]. However, it has been suggested that due to the aromatase inhibitors that utilize CYP3A4 in breast cancer, vitamin D daily requirements in breast cancer patients might be higher than those of the general population [39]. Several studies of women with breast cancer receiving a combination of aromatase inhibitors and vitamin D have shown that vitamin D levels significantly mitigate against loss of bone density and improve musculoskeletal symptoms [39–41]. Despite these pilot studies, there is a need for further study to determine the dosage of vitamin D needed to maintain musculoskeletal health in breast cancer patients.

Beyond differences in breast cancer diagnostic groups, age consistently emerges as an important protective factor in this study, as older women are less likely to be deficient and have higher average vitamin D levels, patterns evident in both stratified tables and regression coefficients. Notably, in the <10 ng/mL model, although only 2% of women were deficient, age is the only statistically significant independent predictor, with a 10-year increase in age associated with approximately a 12% reduction in the odds of severe deficiency. The threshold for deficiency increases to 7% in the <15% model; age remains the strongest predictor of vitamin D deficiency, with approximately a 16% reduction in the odds of deficiency. This finding is consistent with Rosso et. al. [22]. They found that patients with Vitamin D deficiency tended to be younger and more frequently obese compared to those with sufficient levels [22]. Conversely, in a cross-sectional study of breast cancer patients in Hamadan, Iran, researchers found a weak positive correlation between serum Vitamin D levels and patient age, but it was not statistically significant [5]. Another study showed that higher Vitamin D levels were associated with smaller tumors across all women; the effect was greater in premenopausal women [42]. Interestingly, the study also reported that the vitamin D-insufficient patient population was slightly younger [42]. The inconsistent reports suggest that the impact of age on the vitamin D status of breast cancer patients needs further evaluation. Consistent with previous discussions, the current study finds that compared with patients presenting for breast cancer screening (Z12), women with current breast cancer (C50) had about one-third lower odds of deficiency. Those with a personal history of breast cancer (Z85) had even lower odds, suggesting a more intensive vitamin D monitoring and supplementation in these groups.

Ethnicity is an independent predictor of 25(OH)D deficiency in this cohort, with Hispanic women experiencing a higher burden (10.5%) of deficiency at the <15 ng/mL threshold even after adjusting for other variables, highlighting a potential target group for enhanced assessment and intervention. In contrast to this result in a large study of 790 breast cancer survivors (the HEAL study), the overall mean vitamin D concentration was 24.8 ng/mL, with serum 25(OH)D levels of 18.1 ± 8.7 ng/mL in African Americans, and 22.1 ± 9.2 ng/mL in Hispanics [30]. Our study follows strict criteria for reported ethnicity as Hispanic or non-Hispanic and does not overlap with race (Caucasian, Asian, etc). This may have obscured the identification of the roles of race in vitamin D deficiency in this current study. Several studies have documented that serum 25(OH)D levels are lower in African Americans compared to those of Caucasians [43, 44]. Race-ethnicity has been identified as a strong and independent predictor of serum Vitamin D deficiency in breast cancer patients [30, 45], consistent with our results. It is therefore imperative that ethnicity be incorporated into guidance for vitamin D testing in the breast cancer care continuum to facilitate timely identification of deficiency and potentially optimize sufficiency, particularly for populations with historically lower concentrations and poorer survival outcomes.

The pseudo R^2 of the <15 ng/mL (pseudo $R^2 = 0.016$) is modest but higher than that of the <10 ng/mL (pseudo $R^2 = 0.006$) severe deficiency model in the multivariable analysis. This suggests that using a <15 ng/mL cut-off improves discrimination and better captures meaningful variation in deficiency status than an extreme cut-off. In addition to the modest pseudo R^2, the ROC curves for models predicting vitamin D deficiency at thresholds of <10, <15, and <20 ng/mL showed only modest differences in the area under the curve (AUC) (0.56, 0.59, and 0.6, respectively). These small variations reflect the underlying prevalence and event counts at each threshold. The modest pseudo R^2 values and AUCs observed in these deficiency models are not unexpected, given the limited number of predictors and the multifactorial nature of the determinants of vitamin D status [46]. The two metrics underscore the distinction between identifying broad risk patterns at the population level, which this study does very well, and constructing highly predictive individual-level tools, which would require data on behavioral

and environmental exposures. Overall, the synthesis across analyses supports a pragmatic, risk-based approach to vitamin D testing in breast health services with younger women, Hispanic women, and those attending for screening, representing priority groups for assessment and optimization. In contrast, women already embedded in oncology and survivorship pathways appear to be comparatively well managed with respect to vitamin D.

Overall, the differences we observed in this study may be associated with both biological factors and variations in care across the breast cancer continuum. For instance, patients with current or a history of breast cancer are most likely to receive more intensive bone health monitoring and vitamin D supplementation as part of their oncology or survivorship care. Conversely, patients in the continuum who are undergoing screening are not exposed to the same intensity of care as those with current or a history of breast cancer. The lower odds of deficiency with increasing age may similarly reflect greater cumulative preventive care associated with older age rather than a direct protective effect of aging. However, it is difficult to associate the higher risk of deficiency we observed among Hispanic women with a specific factor. Dietary, environmental, behavioral, and social determinants might have contributed to the high risk; however, because we do not have data on supplementation history, treatment history, body mass index, seasonality factors, diet, and sun exposure, we could not correct for those factors in this study.

This study has several limitations worth noting. First, it is a retrospective cross-sectional study with no data on comorbidities that can affect vitamin D levels. Second, the study lacks information on vitamin D supplementation, seasonality, body mass index, or diet. Accounting for vitamin D supplementation, including over-the-counter supplements across all groups, would have helped determine the true prevalence of vitamin D deficiency in each group. Because the study is limited to a single health system, generalizing these findings should be done cautiously. This is especially true since men were excluded from the multivariable analysis because their population was <0.1%. Lastly, therapeutic data are not included in this study, such as the use of aromatase inhibitors, which are commonly combined with high doses of vitamin D to mitigate the side effects of this therapy. Another notable limitation of using clinician-assigned ICD-10 codes is that clinicians sometimes misclassify patients, though we made efforts to minimize overlap to ensure subjects in this study are mutually exclusive across analytic groups.

Conclusion

To our knowledge, this is the first study to describe serum 25(OH)D status across the breast cancer care continuum using large, real-world data in a single tertiary breast health population, spanning the three distinct stages of the breast health continuum. Previous studies have largely focused on a single stage of the breast cancer continuum. For instance, Crew et al.'s study reported on serum 25(OH)D in women undergoing screening for breast cancer without a history of breast cancer, while the HEAL study focused on vitamin status in breast cancer survivors after diagnosis and treatment, and the Pathway Study is a prospective cohort of women with breast cancer [30, 31, 47]. Notably, our study is unique because it reduces the challenges associated with comparing studies from different clinical or cohort settings by directly comparing screening attendees, patients with current breast cancer, and patients with a personal history of breast cancer within the same real-world clinical dataset. However, these cross-sectional cohorts do not represent longitudinal transitions within the same individuals. Therefore, higher vitamin D levels should not be interpreted as the effect of breast cancer or cancer therapy. The lower odds of deficiency among women with current or personal history of breast cancer likely reflect more intensive assessment and supplementation in oncology and survivorship programs. However, the higher burden of deficiency among screening subjects and Hispanic women may suggest that risk-based testing and targeted supplementation may be more efficient than universal screening in this setting. Overall, vitamin D deficiency in a tertiary care breast health population is concentrated in younger women, those presenting for screening rather than cancer treatment or follow-up, and Hispanic women. Simple demographic information, diagnostic category, and ethnicity may be sufficient to guide selective vitamin D testing and optimization strategies, thereby improving bone and metabolic health while reducing unnecessary laboratory testing.

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Author contributions JO- Conceptualized the study, investigation, wrote the original manuscript, data analysis, data curation, figures visualization, and reviewed and edited.VA- Contributed to the data analysis process, reviewed, and edited the manuscriptRG- Manuscript drafting, reviewing, and editing of the manuscript.

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Data availability The data analyzed for this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate The study protocol was reviewed and approved by the Institutional Review Board (IRB) at Indiana University School of Medicine, Indianapolis, Indiana (IRB approval number: 27013).

Consent for publication All the authors agree with the content of the paper.

Consent to Participate declaration This is a retrospective cross-sectional study approved by the Indiana School of Medicine IRB. Individual participants' consent was not visible.

Declarations The study was conducted in accordance with the Helsinki Declaration.

Competing interests The authors declare no competing interests.

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