Clinically Sufficient Vitamin D Levels With Survival and Cardiovascular Outcomes in a Prospective Cohort of 3,995 Individuals Diagnosed With Invasive Breast Cancer

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Abstract

Background: Vitamin D deficiency is prevalent in patients with breast cancer. The existing body of literature links vitamin D to lower total cancer mortality, yet the evidence on cardiovascular health is mixed. As there have been no randomized clinical trials on vitamin D supplementation in patients with breast cancer, evidence from large prospective studies is valuable to inform recommendations for this patient population. **Patients and Methods:** We measured serum 25-hydroxyvitamin D (25OHD) levels in 3,995 women with incident breast cancer in a prospective cohort, which were categorized based on clinical cut points and evaluated with cancer survival outcomes and incident cardiovascular events. **Results:** The median follow-up was 12.2 (range, 0.2–16.3) years. Patients with sufficient versus deficient vitamin D levels had better overall survival (adjusted hazards ratio [HR], 0.76; 95% CI, 0.62–0.93; *P* for trend =.005), second primary cancer–free survival (HR, 0.75; 95% CI, 0.63–0.90; *P* for trend =.003), and disease-free survival (HR, 0.82; 95% CI, 0.70–0.97; *P* for trend =.05). The associations were stronger in patients with stage ≥II disease (*P* for interaction <.05). Sufficient vitamin D levels were also associated with lower risk of any incident cardiometabolic risk factors (subdistribution HR [sHR], 0.67; 95% CI, 0.54–0.83; *P* for trend <.001), diabetes, and dyslipidemia, with suggestive lower hazards of cardiovascular disease (CVD), but not CVD-related death (sHR, 0.74; 95% CI, 0.47–1.15; *P* for trend =.19). **Conclusions:** Our study provides strong evidence supporting the association between vitamin D sufficiency and both improved cancer survival outcomes and cardiometabolic benefits in women following a breast cancer diagnosis. It may be advisable to routinely screen for vitamin D deficiency in this patient population and treat it when clinically indicated through daily vitamin D supplementation to improve cancer prognosis and cardiometabolic health.

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Background

At diagnosis, the majority of US patients with breast cancer have insufficient or deficient vitamin D levels.[1] Beyond its role in preventing bone loss and fractures, the benefits of maintaining sufficient vitamin D levels after a breast cancer diagnosis have long been a question for both patients and health care providers. Experimental data from cell culture and animal models support the anticancer properties of vitamin D,[2] yet results from observational studies and randomized clinical trials (RCTs) have been less clear. In meta-analyses and systematic reviews, there is no evidence that vitamin D is associated with a reduced risk of developing cancer; however, a consistent trend indicates that higher vitamin D levels are linked to lower total cancer mortality.[3,4] In patients with breast cancer, a similar mortality trend was observed in observational studies,[5–7] as breast cancer–specific survival (BCSS) data were not available from RCTs.

Beyond its potential anticancer effects, vitamin D has also been extensively studied for its potential cardiovascular benefits. Results from RCTs on vitamin D supplementation have largely been null, showing no reduction in cardiovascular disease (CVD) risk or mortality.[8,9] However, recent meta-analyses of RCTs report favorable effects of vitamin D supplementation on lowering blood pressure, total cholesterol, and blood glucose, and hemoglobin A1C levels,[10] as well as preventing the development of diabetes in individuals with prediabetes.[11]

Given the existing evidence on vitamin D and cancer and cardiovascular outcomes, it was alarming when a recent analysis within the Women's Health Initiative (WHI) RCT reported that, in postmenopausal women, vitamin D and calcium supplementation versus placebo was associated with a 7% reduction in cancer mortality but a 6% increase in CVD mortality after >20 years of follow-up.[12] Nevertheless, it was difficult to disentangle the effects of vitamin D from calcium supplementation when given simultaneously. Moreover, to our knowledge, no prior studies have examined the association between vitamin D and cardiovascular outcomes in patients with breast cancer, who are at increased risk of CVD and cardiometabolic complications due to cardiotoxic cancer treatment.[13,14]

In the present study, we assessed clinically defined vitamin D levels and their association with breast cancer and cardiovascular outcomes in a large prospective cohort after long-term follow-up.

Patients and Methods

Patients

Data and biospecimens for this study were drawn from the Pathways Study, an ongoing prospective cohort established to investigate breast cancer survivorship. A total of 4,504 women with

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newly diagnosed incident invasive breast cancer were enrolled within 2 months of diagnosis between 2006 and 2013 from Kaiser Permanente Northern California (KPNC) and have been followed to date. The Pathways Heart Study was established later to focus on cardiovascular health in breast cancer survivors and included participants from the Pathways Study. Details of the Pathways Study and Pathways Heart Study have been published elsewhere.[13–15] All patients provided written informed consent. The study was reviewed and approved by the Institutional Review Boards of KPNC and Roswell Park Comprehensive Cancer Center.

Clinical and Questionnaire Data Collection

At enrollment, participants completed an in-person questionnaire to collect data on a wide range of epidemiologic factors relevant to breast cancer survivorship. Regular follow-ups were conducted for updates on lifestyle factors, health outcomes, and comorbidities. Diagnosis and treatment data were obtained from the KPNC Cancer Registry and other electronic clinical and administrative databases. Potential recurrences and second primary cancers identified from both self-report and electronic health record (EHR) were confirmed by medical record review. Death information and causes of death came from multiple sources.

In the Pathways Heart Study, cardiometabolic risk factors (hypertension, diabetes, and dyslipidemia) were identified using KPNC EHR diagnostic codes, abnormal laboratory results, and the use of relevant medications. CVD events (arrhythmia, heart failure or cardiomyopathy, cardiac arrest, myocarditis or pericarditis, ischemic heart disease, transient ischemic attack, stroke, carotid disease, valvular disease, venous thromboembolism, and CVD-related death) were assessed as incidence occurring after the date of breast cancer diagnosis. These events were ascertained based on EHR codes from inpatient, ambulatory, and emergency department encounters, and/or hospital discharge records. Follow-up time for CVD outcomes began at the date of breast cancer diagnosis.

Measurement of Serum 25-Hydroxyvitamin D Levels

Blood samples were collected from approximately 90% of participants at a median of 69 days after diagnosis. Approximately 30% of the blood samples were collected after the initiation of cancer chemotherapy. Serum samples available from a total of 3,995 patients were analyzed for total 25-hydroxyvitamin D (25OHD) concentrations (D_2 and D_3) by an immunochemiluminometric assay performed at Heartland Assays. The assays were performed in 2 separate batches—one in 2013 and the other in 2019, with the latter batch including 48 samples from the 2013 batch for quality control (QC) purposes. The assay demonstrated high reproducibility (r=0.99; Supplementary Figure S1, available in the supplementary materials). Based on the QC results, the 2019 batch data were recalibrated to the 2013 batch data and merged for analysis. Vitamin D levels were classified according to clinical cut points (deficient: <20.0 ng/mL; insufficient: 20.0–29.9 ng/mL; sufficient: ≥30.0 ng/mL).

Statistics

Means and standard deviations of 25OHD concentrations were calculated across descriptive characteristics and formally compared using *t* tests or ANOVA, with linear regression used to test for trends (*P* for trend) when ordinal assumptions were met. Stepwise linear regression was used to evaluate the contribution of a set of variables to the variance in 25OHD concentrations, as measured by R^2. To analyze differences in 25OHD concentrations by tumor histopathologic characteristics, least square (LS) means and corresponding standard errors were derived after adjusting for covariates.

In time-to-event analysis, the time scale was defined from the date of blood sample collection to the earliest of the event of interest, health plan disenrollment, death, or the last health status update on December 31, 2021. The median follow-up time was 12.2 (range, 0.2–16.3) years, with 9% loss to active follow-up via telephone interviews; passive follow-up through electronic medical records continues. Because vitamin D was measured using a single sample collected at the time of diagnosis and its relevance to clinical outcomes might become weaker over time, the longest follow-up time for analysis was capped at 12 years. Analyses were repeated using the full follow-up time.

Five cancer outcomes were assessed—overall survival (OS), BCSS, recurrence-free survival, second primary cancer–free survival, and disease-free survival (DFS),—using standardized definitions from the STEEP system.[16] Kaplan-Meier (KM) survival curves were plotted according to clinical vitamin D levels, with differences between curves assessed using the log-rank test. Cox proportional hazards models were employed to examine the associations of clinically defined vitamin D levels with patient survival outcomes. Hazard ratios (HRs) and 95% confidence intervals were calculated, adjusting for age at diagnosis, body mass index (BMI), race and ethnicity, season of blood collection, physical activity, smoking status, tumor stage, tumor grade, cancer subtype, and receipt of surgery, radiation therapy, chemotherapy, and endocrine therapy. In 2 separate analyses, we further adjusted for Elixhauser comorbidity index at diagnosis, or calcium supplement use after diagnosis, to account for potential confounding effects by these variables. We also conducted a sensitivity analysis restricted to patients without calcium supplement use after diagnosis. For any covariate violating the proportional hazards assumption, an interaction term of the covariate and time scale was added to the model. To examine whether the associations of vitamin D levels and survival outcomes were modified by cancer stage, tumor estrogen receptor (ER) status, or BMI, stratified analyses were performed, followed by inclusion of an interaction term in the Cox models, which was tested using likelihood ratio statistics.

For incident cardiometabolic risk factors and CVD events, cumulative incidence curves were plotted by vitamin D levels and the differences between the curves were examined using the log-rank test. Fine and Gray hazards models were used to examine the associations of vitamin D levels with incident cardiometabolic risk factors and CVD events, treated all-cause death as a competing risk. Subdistribution hazards ratio (sHR) and 95% confidence intervals were estimated, adjusting for age at diagnosis, BMI, menopausal status, smoking status, primary care utilization, annual household income, educational attainment, cancer treatment (including cardiotoxic chemotherapy, radiation therapy, and endocrine therapy), Elixhauser comorbidity index, calcium supplement use, and prevalent non-outcome cardiometabolic risk factors or CVD events. In addition, when modeling any specific event of interest, women with a history of that event were excluded. All analyses were conducted using R version 4.2.0 (R Foundation for Statistical Computing), with 2-sided $P \leq .05$ considered statistically significant.

Table 1. Serum Vitamin D Concentrations by Patient Characteristics

Variable	n (%)	Mean [SD]	*P* Value
Age at diagnosis			<.001
<50 y	860 (22)	21.1 [9.1]	
50–59 y	1,163 (29)	22.9 [10.5]	
60–69 y	1,171 (29)	25.4 [10.6]	
≥70 y	801 (20)	26.8 [10.5]	
BMI			<.001
Normal	1,324 (33)	27.1 [11]	
Overweight	1,255 (31)	24.5 [10.1]	
Obese	1,416 (35)	20.6 [9.1]	
Self-reported race and ethnicity			<.001
Asian	474 (12)	22.5 [10.4]	
Hispanic	436 (11)	20.0 [9.4]	
Non-Hispanic Black	296 (7)	19.5 [10.2]	
Non-Hispanic White	2,696 (67)	25.5 [10.4]	
Other[a]	93 (2)	22.7 [9]	
Nonsedentary physical activity			<.001
Q1	994 (25)	21.8 [10.2]	
Q2	992 (25)	23.3 [9.5]	
Q3	994 (25)	25.3 [10.6]	
Q4	992 (25)	25.7 [11.0]	
Smoking status			.001
Never	2,242 (56)	23.9 [10.5]	
Former	1,544 (39)	24.5 [10.4]	
Current	198 (5)	21.7 [10.6]	
Education attainment			<.001
High school or less	599 (15)	22.6 [10.5]	
Some college	1,408 (35)	23.6 [10.6]	
College graduate	1,097 (28)	24.3 [9.9]	
Postgraduate	885 (22)	25.3 [10.7]	
Marital status			<.001
Married/Live as married	2,443 (61)	24.3 [10.3]	
Widow	457 (11)	25.1 [10.4]	
Separated/Divorced	765 (19)	23.6 [11.4]	
Single	317 (8)	21.2 [8.8]	
Employment status			<.001
Full-time	1,359 (34)	22.4 [10.3]	
Part-time	491 (12)	24.9 [11.3]	
Unemployed	183 (5)	22.6 [9.2]	
Retired	1,280 (32)	26.5 [10.4]	
Disability	373 (9)	20.7 [8.5]	
Homemaker	202 (5)	24.5 [11.0]	
Other	71 (2)	24.6 [10.1]	
Vitamin D supplement use			<.001
No	3,388 (88)	22.9 [9.6]	
Yes	473 (12)	32.0 [12.8]	
Dietary vitamin D status			<.001
Q1	848 (25)	22.8 [11.0]	
Q2	848 (25)	24.2 [10.4]	
Q3	848 (25)	24.3 [9.7]	
Q4	848 (25)	25.8 [10.2]	
Season of blood collection			.03
Spring (Feb–Apr)	1,051 (26)	23.4 [11.0]	
Summer (May–Jul)	1,002 (25)	24.4 [10.1]	
Fall (Aug–Oct)	1,004 (25)	24.6 [10.2]	
Winter (Nov–Jan)	938 (23)	23.6 [10.5]	
Vitamin D status			NA
Deficient (<20 ng/mL)	1,518 (38)	14.2 [3.9]	
Insufficient (20–29.9 ng/mL)	1,487 (37)	24.9 [2.8]	
Sufficient (≥30 ng/mL)	990 (25)	37.7 [8.5]	

(*continued in next column*)

Table 1 (cont.). Serum Vitamin D Concentrations by Patient Characteristics

Variable	n (%)	LS Means (95% CI)	*P* Value
AJCC stage			<.001
I	2,157 (54.7)	22.5 (21.6–23.4)	
II	1,360 (34.5)	20.9 (20.0–21.8)	
III	374 (9.5)	19.6 (18.3–20.8)	
IV	55 (1.4)	21.1 (18.4–23.7)	
Tumor histologic grade			<.001
Well-differentiated	1,050 (28.3)	22.2 (21.3–23.2)	
Moderately differentiated	1,686 (45.5)	21.7 (20.8–22.6)	
Poorly differentiated	972 (26.2)	21.0 (20.0–22.0)	
Tumor ER status			<.001
Positive	3,289 (83.4)	21.8 (21.0–22.7)	
Negative	655 (16.6)	20.6 (19.6–21.7)	
Tumor IHC subtype			<.001
Luminal A	2,825 (74.8)	21.9 (21.0–22.7)	
Luminal B	327 (8.7)	20.9 (19.6–22.2)	
HER2-enriched	174 (4.6)	21.0 (19.4–22.7)	
Triple-negative	450 (11.9)	20.4 (19.3–21.6)	

Abbreviations: BMI, body mass index; ER, estrogen receptor; IHC, immunohistochemistry; LS, least square; NA, not applicable; Q, quarter.
[a]Self-reported race/ethnicity other from non-Hispanic White, non-Hispanic Black, Asian, or Hispanic.
[b]Derived from linear models adjusted for age at diagnosis, self-reported race/ethnicity, season of blood collection, BMI, physical activity, smoking status, marital status, and employment status.

Results

Patient Characteristics

Descriptive patient characteristics are summarized in Table 1. The mean [SD] age at diagnosis was 59.6 [12.1] years, and older women (aged ≥60 years) tended to have higher 25OHD concentrations. Higher BMI, non-Hispanic Black race/ethnicity, lower physical activity, current smoking, lower education attainment, being single, disability status, and both unemployment and full-time employment were associated with lower 25OHD concentrations. Women reporting vitamin D supplement use had markedly higher 25OHD concentrations than those who did not (32.0 vs 22.9 ng/mL), whereas higher dietary vitamin D intake was associated with modest increases in 25OHD concentrations (Q4 versus Q1: 25.8 vs 22.8 ng/mL). Only modest differences were noted in 25OHD concentrations by season of blood collection (Supplementary Figure S2). Based on clinical cut points, 38% of patients had vitamin D deficiency and only 25% had vitamin D sufficiency. Calcium supplement use after diagnosis differed significantly by clinical vitamin D status ($P<.001$). Among women with sufficient vitamin D levels, 15.9% reported calcium supplement use, compared with 12.9% among those with insufficient levels and 9.5% among those with deficient levels.

In analyses of tumor histopathologic characteristics, after adjusting for nonclinical factors, patients with more aggressive cancer, including higher stage, poor differentiation, and ER-negative and triple-negative subtype, had significantly lower vitamin D concentrations (Table 1).

Determinants of Serum 25OHD Concentrations

The top 4 factors explaining at least 1% of the variance in 25OHD concentrations were vitamin D supplement use (9.0%), BMI (7.0%), race and ethnicity (3.4%), and age at diagnosis (1.2%) (Supplementary Table S1). In addition, several other factors were

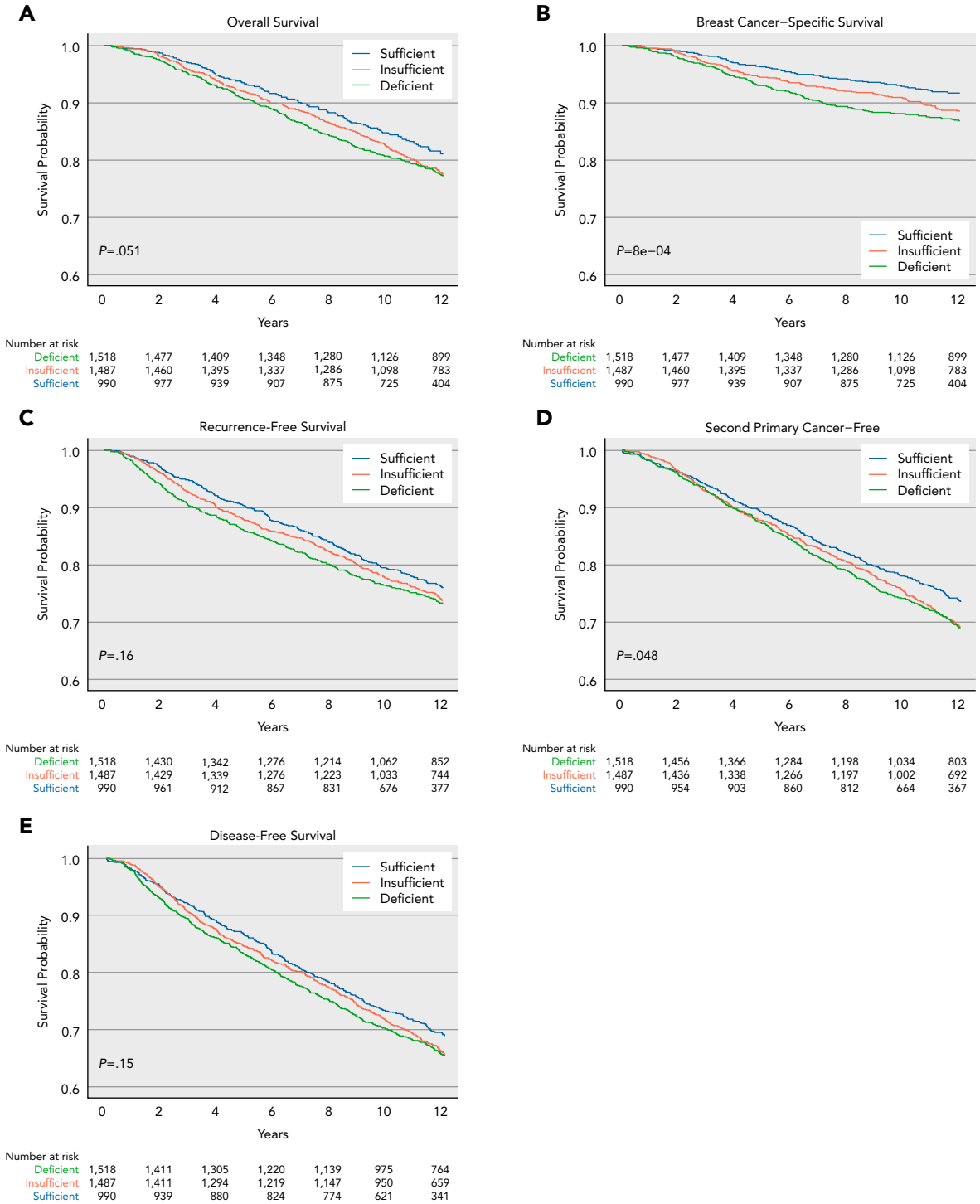

Figure 1. Kaplan-Meier curves of breast cancer survival outcomes by serum vitamin D levels: **(A)** overall survival, **(B)** breast cancer-specific survival, **(C)** recurrence-free survival, **(D)** second primary cancer-free survival, and **(E)** disease-free survival. Vitamin D status was classified using clinical cut points: deficient (<20 ng/mL), insufficient (20-29.9 ng/mL), and sufficient (≥30 ng/mL). *P* values were derived from the log-rank test.

also significant in the model but explained <1% of the variance, including cancer stage (0.8%), physical activity (0.6%), employment status (0.5%), season of blood collection (0.4%), dietary vitamin D intake (0.3%), and menopausal status at diagnosis (0.1%). These factors together explained a total of 22.5% of the variance of serum 25OHD concentrations.

Associations of Clinical Vitamin D Levels and Breast Cancer Survival Outcomes

Figure 1 shows the KM curves of survival outcomes by clinical vitamin D levels. Patients with sufficient vitamin D levels had the best survival probability and those with deficient levels had the worst, with the differences being significant for OS (P=.05), BCSS

Table 2. Associations of Serum Vitamin D Levels With Breast Cancer Survival Outcomes

Survival Outcome	Vitamin D Level[a]	Events/Patients	HR (95% CI)	*P* for Trend
Overall survival	Deficient	337/1,518	Ref	.005
	Insufficient	316/1,487	1.02 (0.86–1.22)	
	Sufficient	175/990	**0.76 (0.62–0.93)**	
Breast cancer–specific survival	Deficient	190/1,518	Ref	.78
	Insufficient	156/1,487	1.13 (0.88–1.43)	
	Sufficient	75/990	0.87 (0.64–1.17)	
Recurrence-free survival	Deficient	400/1,518	Ref	.07
	Insufficient	374/1,487	1.02 (0.87–1.19)	
	Sufficient	225/990	0.85 (0.70–1.02)	
Second primary cancer–free survival	Deficient	458/1,518	Ref	.003
	Insufficient	435/1,487	0.96 (0.83–1.12)	
	Sufficient	245/990	**0.75 (0.63–0.90)**	
Disease-free survival	Deficient	512/1,518	Ref	.05
	Insufficient	485/1,487	0.96 (0.84–1.11)	
	Sufficient	290/990	**0.82 (0.70–0.97)**	

Bold indicates statistically significant *P* value.
Multivariable Cox proportional hazards models were adjusted for age at diagnosis, BMI, self-reported race/ethnicity, season of blood collection, physical activity, smoking status, tumor stage, grade, IHC subtype, and breast cancer treatment, including surgery, radiation therapy, chemotherapy, and endocrine therapy. For covariates that violated the proportional hazards assumption, an interaction term between the covariate and time was included in the model. Follow-up time was capped at 12 years.
Abbreviations: BMI, body mass index; HR, hazard ratio; IHC, immunohistochemistry.
[a]Vitamin D levels were classified based on serum 25-hydroxyvitamin D concentrations as deficient (<20 ng/mL); insufficient (20–29.9 ng/mL); sufficient (≥30 ng/mL).

(*P*=.0008), and second primary cancer–free survival (*P*=.05). In multivariable, fully adjusted Cox hazards models, women with sufficient vitamin D levels had better OS (HR, 0.76; 95% CI, 0.62–0.93; *P* for trend =.005), second primary cancer–free survival (HR, 0.75; 95% CI, 0.63–0.90; *P* for trend =.003), and disease-free survival (HR, 0.82; 95% CI, 0.70–0.97; *P* for trend =.05) (Table 2). When the analyses were repeated without a maximum cap of follow-up at 12 years, the separation of KM curves for BCSS remained, yet the curves for other outcomes converged after approximately 12 years (Supplementary Figure S3). The associations in multivariable models became slightly attenuated and remained significant for OS and second primary cancer–free survival (Supplementary Table S2).

In further analyses stratified by cancer stage, associations of higher vitamin D levels and survival outcomes—except for BCSS—appeared to be stronger among patients with stage ≥II advanced disease (*P* for interaction ≤.02; Supplementary Table S3). No significant differences were observed by tumor ER status or BMI category (*P* for interaction >.05). Adjusting additionally for Elixhauser comorbidity index at diagnosis did not significantly change the associations between vitamin D sufficiency and survival outcomes (Supplementary Table S5). To tease apart the impact of calcium supplementation, further adjustment for postdiagnosis supplement use and sensitivity analyses restricted to patients who did not uses calcium supplements after diagnosis were conducted, yielding results similar to those of the original model (Supplementary Table S6).

Associations of Clinical Vitamin D Levels With Cardiometabolic Risk Factors and CVD Events

Sufficient vitamin D levels were also associated with a lower risk of incident cardiometabolic risk factors, diabetes, and dyslipidemia, as shown in the cumulative incidence curves in Figure 2. These associations remained significant after adjustment for all covariates. The strongest association was observed for incident cardiometabolic risk factors, with women who had sufficient vitamin D levels experiencing 33% lower hazards compared with those with deficient levels (sHR, 0.67; 95% CI, 0.54–0.83; *P* for trend <.001) (Table 3).

For incident CVD events, there was no apparent difference in incidence by vitamin D levels; however, in multivariable fully adjusted models, women with sufficient vitamin D levels had nonsignificant lower hazards (sHR, 0.82; 95% CI, 0.66–1.02; *P* for trend =.06). Vitamin D sufficiency was also associated with a potential lower risk of venous thromboembolic events (sHR, 0.67; 95% CI, 0.44–1.03; *P* for trend =.07). KM curves showed a higher incidence of stroke among women with sufficient versus deficient vitamin D levels (*P*=.06), which was no longer apparent after covariate adjustment (sHR, 1.04; 95% CI, 0.62–1.72; *P* for trend =.88). Finally, no association was observed between vitamin D levels and CVD-related death (sHR, 0.74; 95% CI, 0.47–1.15; *P* for trend =.19).

The associations of vitamin D levels with cardiometabolic risk factors and CVD events did not change substantially when the analyses were repeated using the full follow-up time (Supplementary Table S4) or when adjusted for Elixhauser comorbidity index or postdiagnosis calcium supplement use (Supplementary Table S7).

Discussion

In this large prospective breast cancer cohort with long-term follow-up, we found that women with sufficient versus deficient vitamin D levels at diagnosis had better survival outcomes, independent of known prognostic and treatment factors. Notably, we did not observe increased CVD mortality with higher vitamin D levels; instead, sufficiency was linked to a lower incidence of cardiometabolic risk factors posttreatment.

Given the lack of RCTs specifically examining vitamin D supplementation in patients with breast cancer, the best available evidence comes from prospective cohort studies measuring circulating vitamin D levels. At least 4 studies,[17–20] including ours, showed a dose-dependent survival benefit, as confirmed in a meta-analysis.[5] Expanding our analysis to nearly 4,000 women with extended follow-up strengthens the evidence that sufficient vitamin D levels are associated with improved cancer survival outcomes. We also found that vitamin D sufficiency was associated with lower hazards of

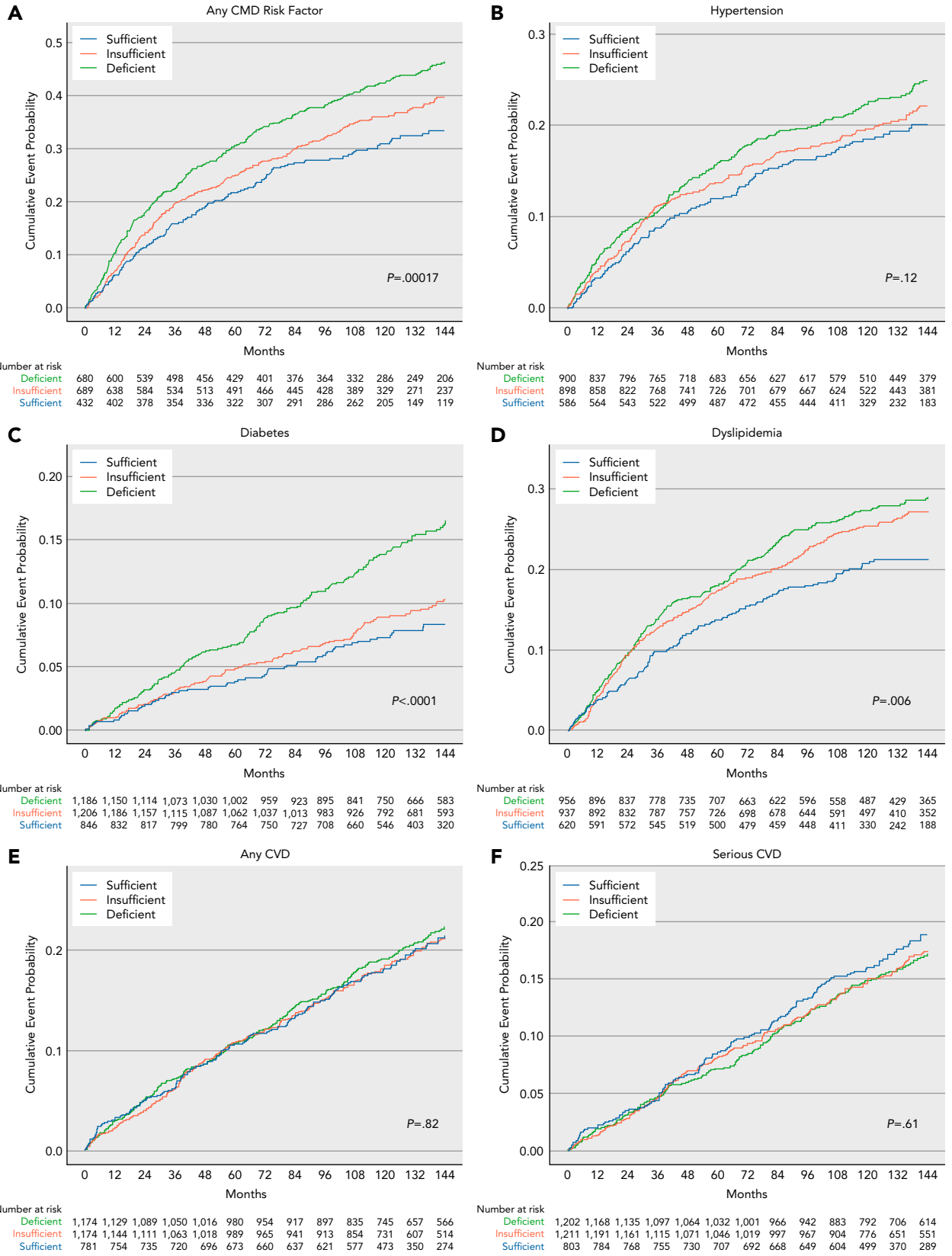

Figure 2. Cumulative incidence curves of incident cardiometabolic risk factors and CVDs by serum vitamin D levels. Cardiometabolic risk factors include **(A)** any CMD risk factors, **(B)** hypertension, **(C)** diabetes, and **(D)** dyslipidemia. Cardiovascular diseases include **(E)** any CVD, and **(F)** serious CVD. Cardiometabolic risk factors include **(G)** arrhythmia, **(H)** heart failure or cardiomyopathy, **(I)** ischemic heart disease, **(J)** stroke, **(K)** venous thromboembolic event, and **(L)** CVD-related death. Serum 25-hydroxyvitamin D levels were classified using clinical cut points as deficient (<20 ng/mL), insufficient (20–29.9 ng/mL), and sufficient (≥30 ng/mL). Abbreviations: CMD, cardiometabolic disease; CVD, cardiovascular disease.

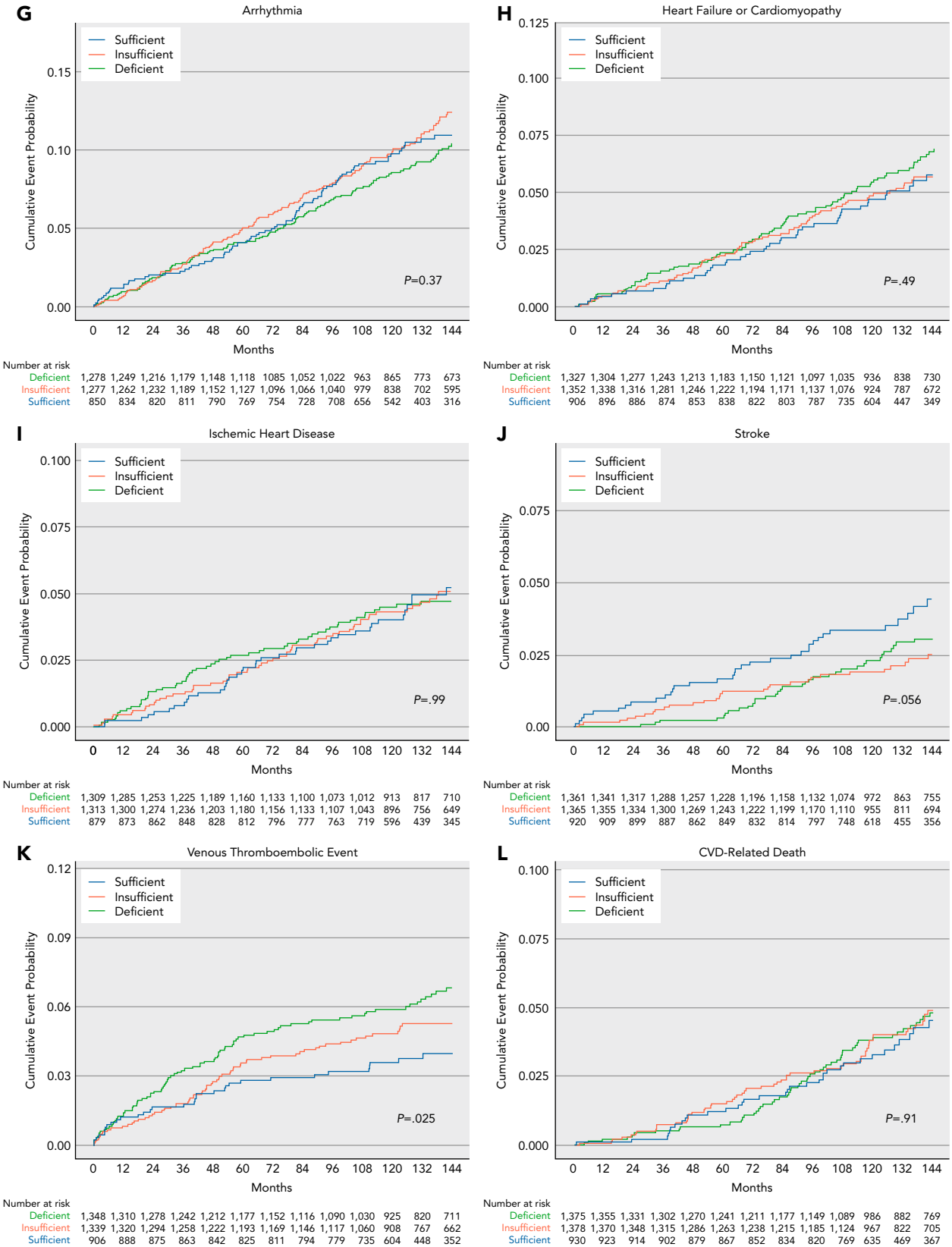

Figure 2. (cont.) Cumulative incidence curves of incident cardiometabolic risk factors and CVDs by serum vitamin D levels. Cardiometabolic risk factors include **(G)** arrhythmia, **(H)** heart failure or cardiomyopathy, **(I)** ischemic heart disease, **(J)** stroke, **(K)** venous thromboembolic event, and **(L)** CVD-related death. Serum 25-hydroxyvitamin D levels were classified using clinical cut points as deficient (<20 ng/mL), insufficient (20-29.9 ng/mL), and sufficient (≥30 ng/mL).
Abbreviation: CVD, cardiovascular disease.

Table 3. Associations of Serum Vitamin D Levels With Incident CMD Risk Factors and CVDs

Event	Vitamin D Level	Events/Patients	sHR (95% CI)	*P* for Trend
Any CMD risk factor	Deficient	288/680	Ref	<.001
	Insufficient	254/689	0.85 (0.72–1.02)	
	Sufficient	134/432	**0.67 (0.54–0.83)**	
Hypertension	Deficient	202/900	Ref	.36
	Insufficient	182/898	0.97 (0.78–1.19)	
	Sufficient	108/586	0.88 (0.69–1.14)	
Diabetes	Deficient	170/1,186	Ref	.009
	Insufficient	109/1,206	**0.75 (0.58–0.96)**	
	Sufficient	63/846	**0.69 (0.50–0.94)**	
Dyslipidemia	Deficient	252/956	Ref	.006
	Insufficient	236/937	0.96 (0.80–1.15)	
	Sufficient	123/620	**0.71 (0.56–0.90)**	
Any CVD	Deficient	237/1,174	Ref	.06
	Insufficient	225/1,174	0.89 (0.73–1.07)	
	Sufficient	151/781	0.82 (0.66–1.02)	
Serious CVD	Deficient	184/1,202	Ref	.32
	Insufficient	188/1,211	0.91 (0.74–1.12)	
	Sufficient	136/803	0.89 (0.70–1.13)	
Arrhythmia	Deficient	114/1,278	Ref	.58
	Insufficient	136/1,277	1.1 (0.85–1.42)	
	Sufficient	83/850	0.9 (0.67–1.22)	
Heart failure or cardiomyopathy	Deficient	78/1,327	Ref	.25
	Insufficient	67/1,352	0.85 (0.60–1.19)	
	Sufficient	44/906	0.8 (0.54–1.19)	
Ischemic heart disease	Deficient	56/1,309	Ref	.48
	Insufficient	58/1,313	0.95 (0.65–1.39)	
	Sufficient	39/879	0.85 (0.55–1.32)	
Stroke	Deficient	34/1,361	Ref	.88
	Insufficient	29/1,365	0.74 (0.44–1.23)	
	Sufficient	34/920	1.04 (0.62–1.72)	
Venous thromboembolic event	Deficient	83/1,348	Ref	.07
	Insufficient	65/1,339	0.88 (0.63–1.23)	
	Sufficient	33/906	0.67 (0.44–1.03)	
CVD-related death	Deficient	55/1,375	Ref	.19
	Insufficient	56/1,378	0.94 (0.65–1.38)	
	Sufficient	34/930	0.74 (0.47–1.15)	

Bold indicates statistically significant *P* value.
Cox proportional hazards models were used to examine the association between vitamin D levels and incident CMD risk factors or CVD, adjusting for age at diagnosis, baseline BMI, menopausal status, smoking status, primary care utilization in the year prior to diagnosis, household income, education level, breast cancer treatments (including anthracycline, anti-HER2 therapy, radiation therapy, and endocrine therapy), and prevalent CMD risk factors (for CVD outcomes) or prevalent CVD (for CMD outcomes). When modeling a specific event of interest, women with a history of that event were excluded. To account for competing risks from all-cause death, sHRs and 95% CI for incident CMD and CVD events were derived using Fine and Gray proportional hazards regression. Follow-up time was capped at 12 years.
Abbreviations: BMI, body mass index; CMD, cardiometabolic disease; CVD, cardiovascular disease; sHR, subdistribution hazard ratio.

cancer recurrence and second cancers, aligning with findings from the Nurses' Health Study, in which vitamin D levels were associated with lower recurrence risk among patients with ER-positive tumors.[21] When considered alongside meta-analyses demonstrating vitamin D's role in lowering total cancer mortality[3,4]—driven by 3 of the largest RCTs, including WHI,[12] VITAL,[9] and RECORD[22]—our findings support the conclusion that maintaining clinically recommended levels (≥30 ng/mL) may improve survival.

However, concerns remain regarding potential harms. A recent reanalysis of the WHI reported a 7% reduction in cancer mortality but a 6% increase in CVD mortality with combined vitamin D and calcium supplementation.[12] Although the increased CVD risk might be attributable to calcium,[23] the simultaneous administration of both supplements made it impossible to separate their individual effects. It is therefore possible that calcium, rather than vitamin D, contributed to the observed increase in CVD risk.[23] Differences in study populations (eg, age, baseline vitamin D status, comorbidities), supplementation regimens, and study designs may also have contributed to these contrasting findings. In our data, higher vitamin D levels were not associated with increased CVD mortality in patients with breast cancer; instead, they were linked to lower risks of diabetes, dyslipidemia, and any cardiometabolic risk factors. This aligns with a meta-analysis of 3 RCTs showing that vitamin D supplementation reduced diabetes risk in patients with prediabetes.[11] Given the increased cardiometabolic risk among breast cancer survivors, maintaining vitamin D sufficiency may confer additional health benefits.

Although accumulating evidence supports vitamin D's benefits in improving breast cancer survival, its effect on breast cancer risk remains unclear.[3,9] Previous studies have linked higher vitamin D levels to a lower risk of aggressive breast cancer subtypes, including later-stage, higher-grade, ER-negative, and triple-negative tumors.[20,24] These associations, confirmed in our current analysis, are consistent with findings from the VITAL

RCT, which demonstrated a reduced risk of metastatic or fatal cancer with vitamin D supplementation.[25] Additionally, our study suggests that the survival benefits of vitamin D may be stronger in patients with stage ≥II advanced disease, highlighting the need for further research on its effects in aggressive breast cancers. Although several key mechanisms of vitamin D have been delineated in preclinical studies, including the inhibition of cellular proliferation, promotion of apoptosis, anti-inflammatory effects, modulation of tumor microenvironment, and inhibition of angiogenesis and metastasis, more research is necessary to further elucidate these mechanisms in patients with breast cancer.[2,26,27]

Our findings confirm that supplementation is the most effective way to increase vitamin D levels. However, dosage and frequency are critical considerations. The D-Health Trial, using high-dose monthly supplementation (60,000 IU vitamin D3), showed no survival benefit and suggested increased mortality risks,[28] whereas the 3 RCTs showing benefits used lower daily doses.[9,12,22] Given the rising trend of vitamin D supplement use—3% of consumers now exceed the upper tolerable limit of 4,000 IU daily—safety concerns such as increased fall risk, hypercalcemia, kidney stones, and potential cancer risks must be considered.[29] Moderate daily doses below 4,000 IU appear safest.

A limitation of our study is the reliance on a single vitamin D measurement shortly after diagnosis, which may not reflect long-term levels. We focused on 25OHD because it is the most stable and widely accepted biomarker for assessing overall vitamin D status, as it reflects both dietary intake and endogenous synthesis.[26,27] In contrast, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], the active form, is tightly regulated by calcium and parathyroid hormone levels, has a short half-life, and may not accurately represent vitamin D stores.[26] Additionally, serum 1,25$(OH)_2$D levels often remain normal or elevated even in individuals who are deficient in 25OHD, particularly in the context of cancer.[26] Notably, KM survival curves separated by vitamin D status crossed after approximately 12 years. This may partly reflect smaller numbers of patients with the longest follow-up, but it may also indicate that a one-time vitamin D measurement becomes less representative of long-term vitamin D status over time. Another limitation is the unavailability of other prognostic factors, such as the ECOG performance status, in our dataset. However, as shown in Table 1, most of our cohort had early-stage breast cancer (89.2% with stage I or II) and would therefore be expected to have generally good performance status. We also incorporated the Elixhauser comorbidity index to account for baseline comorbidities, providing an indirect measure of overall health status.

Conclusions

With no RCTs on vitamin D supplementation in patients with breast cancer expected in the near future, our findings provide strong observational evidence supporting multiple extraskeletal benefits of maintaining vitamin D sufficiency after diagnosis. Routine screening for vitamin D deficiency in this patient population may be advisable, with correction through daily supplementation when clinically indicated—not only for the benefits of bone health, but also to potentially improve cancer prognosis and cardiometabolic health.

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