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The Effect of Various Vitamin D Supplementation Regimens in Breast Cancer Patients

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Abstract

Purpose—Vitamin D deficiency in patients treated for breast cancer is associated with numerous adverse effects (bone loss, arthralgia, and falls). The first aim of this study was to assess vitamin D status, determined by 25-OH vitamin D levels, among women diagnosed with breast cancer according to demographic/clinical variables and bone mineral density (BMD). The second aim of this study was to evaluate the effect of daily low-dose and weekly high-dose vitamin D supplementation on 25-OH vitamin D levels.

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Methods—This retrospective study included 224 women diagnosed with Stage 0-III breast cancer who received treatment at the James P. Wilmot Cancer Center at the University of Rochester Medical Center. Total 25-OH vitamin D levels (D_2 + D_3) were determined at baseline for all participants. Vitamin D deficiency was defined as a 25-OH vitamin D level < 20 ng/mL, insufficiency as 20-31 ng/mL, and sufficiency as ≥ 32 ng/mL. BMD was assessed during the period between 3 months prior to and 6 months following the baseline vitamin D assessment. Based on the participants' baseline levels, they received either no supplementation, low-dose supplementation (1,000 IU/day), or high-dose supplementation (≥ 50,000 IU/week), and 25-OH vitamin D was reassessed in the following 8-16 weeks.

Results—Approx 66.5% had deficient/insufficient vitamin D levels at baseline. Deficiency/insufficiency was more common among non-Caucasians, women with later-stage disease, and those who had previously received radiation therapy ($p<0.05$). Breast cancer patients with deficient/insufficient 25-OH vitamin D levels had significantly lower lumbar BMD ($p=0.03$). Compared to the no supplementation group, weekly high-dose supplementation significantly increased 25-OH vitamin D levels, while daily low-dose supplementation did not significantly increase levels.

Conclusions—Vitamin D deficiency and insufficiency were common among women with breast cancer and associated with reduced BMD in the spine. Clinicians should carefully consider vitamin D supplementation regimens when treating vitamin D deficiency/insufficiency in breast cancer patients.

Introduction

While the frequency of deficiency for most vitamins is low in the United States, mainly due to dietary intake and multivitamin use, vitamin D deficiency is common [1, 2]. The prevalence of vitamin D deficiency (35-60%) is much higher than that of other vitamins among Americans.[3-5] The high frequency of vitamin D deficiency stems from the fact that most vitamin D is produced naturally from skin exposure to sunlight, and exposure to sunlight is limited for a large percentage of Americans who live in northern latitudes and for those who practice sun avoidance. Additionally, only small amounts of vitamin D come from dietary sources and multivitamins. Vitamin D plays an important role in a number of body functions including calcium absorption, bone metabolism, immune function, muscle function, and cellular regulation, and its deficiency has widely pervasive consequences such as hypocalcaemia, bone loss, and muscle weakness.[6-10]

The preponderance of epidemiologic data indicates vitamin D deficiency is associated with an increased incidence of breast cancer.[11-13] Furthermore, recent studies show that low vitamin D levels are associated with increased breast cancer recurrence and mortality rates.[14-17] In addition, breast cancer patients are at increased risk for a number of medical complications associated with vitamin D deficiency including bone loss, falls, fractures, and infection.[10, 18-20] Cancer-treatment-induced bone loss (CTIBL) is of particular concern and is experienced by up to 80% of breast cancer patients.[21] The annual loss of bone mineral density (BMD) in breast cancer patients may be up to 7 times greater than the annual loss of BMD by postmenopausal women without cancer.[22] This loss of BMD produces a significant increase in the risk of fractures compared to healthy postmenopausal

women,[23-25] which results in increased mortality, disability, and negative psychological consequences.[26-28] Breast cancer patients, therefore, must maintain adequate vitamin D levels to minimize their chances for negative outcomes.

25-OH vitamin D is the accepted assessment of vitamin D status and provides a comprehensive measure of vitamin D from all sources (diet, sunlight, and supplementation). Although there is not a “standard” definition of vitamin D status, a widely accepted classification is deficiency at <20 ng/ml, insufficiency at 20-31 ng/ml, and an optimal range of ≥32 ng/ml.[29-31] Despite a number of clinical trials, researchers and clinicians remain divided on the proper supplementation amount to achieve a normal 25-OH vitamin D level. The current recommendation by the Food and Nutrition Board (FNB) of the Institute of Medicine is for 400 IU a day of vitamin D for adults, with 2,000 IU a day as the tolerable upper intake level.[32] However, numerous clinical trials administering low-dose vitamin D supplementation (≤ 800 IU/day) to participants with sub-optimal vitamin D levels failed to achieve optimal 25-OH vitamin D levels.[33-36] A recent study of breast cancer patients receiving treatment found supplementation with almost 2,000 IU a day of vitamin D failed to normalize 25-OH levels in 50% of participants.[37] Vitamin D deficient individuals often require a short course (4-16 weeks) of high-dose vitamin D supplementation (≥ 40,000 IU/week) to achieve an optimal 25-OH vitamin D level, although experimental evidence is severely limited.[33, 38] While the FNB defines 2,000 IU a day of vitamin D as the upper intake level, high-dose vitamin D supplementation is well-tolerated among a variety of participant populations, including those with cancer.[39-42]

Although numerous studies have examined the association between vitamin D levels and breast cancer incidence, few have examined vitamin D levels and the prevalence of vitamin D deficiency in patients with breast cancer. It is especially important to monitor vitamin D levels in these patients because of their increased vulnerability to fractures during and after cancer treatment. The primary aim of this study was to determine the prevalence of vitamin D deficiency/insufficiency among women receiving clinical care for non-metastatic breast cancer. The study also aimed to examine the association between baseline vitamin D levels and BMD. Patients with sub-optimal 25-OH vitamin D levels (< 32 ng/ml) were prescribed vitamin D supplementation, in the course of clinical care, while patients with optimal 25-OH vitamin D levels (≥ 32 ng/ml) were instructed to continue their existing regimen. 25-OH vitamin D levels were reassessed after 8-16 weeks. The final aim of this study was to determine the efficacy of both lowand high-dose vitamin D supplementation.

Methods and Materials

Study Population

The medical records of all women who were diagnosed with Stage 0-III breast cancer and currently receiving treatment (chemotherapy, radiotherapy, and/or hormone therapy) at the James P. Wilmot Cancer Center in the University of Rochester Medical Center were reviewed. All breast cancer patients who had a 25-OH vitamin D value collected during a 4 year period between April 2006 and March 2010 were identified and included in this analysis. Patients taking over-the-counter vitamin D supplements were included. Clinical

data and demographics, including age at diagnosis, stage, treatment history (chemotherapy, radiation, and hormone therapy), race/ethnicity, and bisphosphonate usage were collected.

Information from BMD testing performed during the period between 3 months prior to and 6 months following the baseline 25-OH vitamin D assessment was included in the analyses. BMD was measured by dual energy X-ray absorptiometry using a Lunar densitometer made by General Electric. The Lunar model is extremely precise, with short-term in vivo coefficient of variation of 0.41% for the spine and 0.53% for the hip.[43] Bone density is expressed in grams per square centimeter and in terms of t-score for the comparison of patients with young– normal populations of the same race and sex. BMD was determined for the lumbar spine (L1-L4) and the total hip, which includes the femoral neck, trochanter, intertrochanter, and Ward's triangle. Measurements at these sites follow the recommendations of the International Society of Clinical Densitometry (ISCD) for osteoporosis surveillance and diagnosis.[44]

We used the total 25-OH vitamin D level, which was the sum of 25-OH Vitamin D_2 and 25-OH vitamin D_3, as our measure of vitamin D level. Serum samples were collected at the University of Rochester and stored in aliquots at -80°C until measurement. Between January 2004 and June 2009 (66.7% of all samples), total 25-OH vitamin D was assessed by chemiluminescent immunoassay (CIA) by the Associated Regional and University Pathologists (ARUP) laboratory in conjunction with the University of Utah. Total 25-OH vitamin D levels after June 24, 2009, were performed by a liquid chromatography-tandem mass spectrometry (LC/MS) assay at the University of Rochester (33.3% of all samples). On average, total 25-OH vitamin D levels were 14% higher after controlling for age, race, and month of test when determined by LC/MS than CIA.

Vitamin D supplementation amounts were determined based on baseline total 25-OH vitamin D levels. Participants with total 25-OH vitamin D levels of 25-31 ng/ml were prescribed low-dose vitamin D supplementation (1,000 IU/day), and those with levels ≤ 24 ng/ml were prescribed high-dose supplementation (total 25-OH levels 15-24 ng/ml: 50,000 IU/week; total 25-OH levels < 15 ng/ml: 100,000 IU/week). Participants prescribed low-dose vitamin D supplementation were instructed to obtain the vitamin D over-the-counter. The high-dose vitamin D supplementation regimen was administered once weekly. After 8-16 weeks, 25-OH vitamin D levels were reassessed. Although this study did not use pill diaries or pill counts, all patients were encouraged to take the supplements as recommended. Of the 224 patients with baseline 25-OH vitamin D values, 126 patients returned in the 8-16 week follow-up window for 25-OH vitamin D reassessment.

Statistical Analysis

The percentages of breast cancer patients with vitamin D deficiency and insufficiency were calculated for the entire group and according to demographic (menopausal status and race) and clinical (stage, chemotherapy, radiotherapy, hormone therapy, and bisphosphonate use) variables. Mean baseline 25-OH vitamin D levels were calculated by demographic and clinical variables using ANCOVA models, controlling for the season (winter/spring, summer/autumn) of blood draw and age. Mean BMD and corresponding t-scores were calculated according to 25-OH vitamin D status (normal and insufficient/deficient) using

ANCOVA models controlling for age, stage, and bisphosphonate use. The mean change in 25-OH vitamin D levels was calculated by supplementation level (none prescribed, low-dose supplementation, high-dose supplementation) using an ANCOVA model, controlling for baseline 25-OH vitamin D level, season of blood draw, stage, and age. All P values were calculated using exact Pearson chi-square tests, and a P-value < 0.05 was considered significant.

Results

Baseline 25-OH vitamin D levels according to demographic and clinical variables are shown on Table 1. Among the 224 participants who had their 25-OH vitamin D assessed, 23.2% had deficient levels, 43.3% had insufficient levels, and 33.5% had sufficient levels. No significant differences in baseline 25-OH vitamin D levels were seen with age at diagnosis, menopausal status at diagnosis, chemotherapy, hormone therapy, or bisphosphonate therapy. Participants who were non-Caucasian, had a later stage at diagnosis, and who underwent radiation therapy all had significantly lower baseline 25-OH vitamin D levels.

Table 2 shows the mean BMD and mean t-scores at the hip and lumbar region by categorical baseline 25-OH vitamin D status (normal, insufficient/deficient). Mean levels were determined using an ANCOVA model and adjusting for age, race, month of serum test, stage, hormone therapy and bisphosphonate use. Breast cancer patients with 25-OH vitamin D levels < 32 ng/ml had a significantly lower mean BMD (≥ 32 ng/ml: 1.23 vs. < 32 ng/ml: 1.11; p=0.03) and mean t-score (≥ 32 ng/ml: 0.40 vs. < 32 ng/ml: −0.60; p=0.02) in the lumbar region than those with 25-OH vitamin D levels ≥ 32 ng/ml. While the mean BMD (≥ 32 ng/ml: 0.97 vs. < 32 ng/ml: 0.91; p=0.14) and t-score (≥ 32 ng/ml: −0.25 vs. < 32 ng/ml: −0.72; p=0.11) at the hip were lower for those with 25-OH vitamin D levels < 32 ng/ml than for those with 25-OH vitamin D levels ≥ 32 ng/ml, the difference was not statistically significant.

Table 3 shows the changes in 25-OH vitamin D levels from baseline to follow-up (8-16 weeks after baseline) in the three groups (no supplementation, low-dose supplementation, high-dose supplementation). The mean changes in 25-OH vitamin D levels were determined using an ANCOVA model adjusting for age, race, stage, baseline 25-OH vitamin D level, month of baseline test, and month of follow-up test. Among all those with baseline 25-OH vitamin D levels, 9 out of 58 participants (16%) in the no supplementation group, 64 out of 104 (61%) participants in the low-dose supplementation group, and 53 out of 62 (85%) participants in the high-dose supplementation group returned for follow-up 25-OH vitamin D testing. Breast cancer patients who received no supplementation had a mean increase of 3.1 ng/ml in 25-OH vitamin D, while patients receiving low-dose supplementation had a mean increase of 9.4 ng/ml, and patients receiving high-dose supplementation had a mean increase of 24.3 ng/ml. Compared to those who received no vitamin D supplementation, the increase in 25-OH vitamin D levels for those in the low-dose supplementation group was not statistically significant (p=0.15). However, the increase in 25-OH vitamin D levels for those in the high-dose supplementation group was statistically significant (p<0.01) when compared to the group not receiving vitamin D supplementation.

Discussion

In this heterogeneous group of women diagnosed with breast cancer, vitamin D insufficiency and deficiency, as determined by 25-OH vitamin D levels, were highly prevalent (66.5%). The overall prevalence of vitamin D insufficiency and deficiency in our study is similar to other studies of vitamin D levels in breast cancer patients[36, 37, 45, 46] and other cancer sites.[47, 48] Sub-optimal vitamin D levels were more common in women with later stage disease, non-Caucasians, and those who received radiation therapy. It is possible that non-Caucasians had lower 25-OH vitamin D levels due to higher levels of melanin, which reduces the amount of endogenously produced vitamin D.[49] It is also possible that those with later-stage disease and those who received radiation therapy reduced their sunlight exposure and/or altered their diet due to the nature of their treatment. Recent research shows that lower vitamin D levels are associated with increased breast cancer mortality rates, as are later stages of disease and non-Caucasian race.[14, 50]

Vitamin D plays a role in a number of important bodily functions, many of which are of particular importance for breast cancer patients. One of those functions is bone health; women with breast cancer have higher rates of bone loss and fractures than women without cancer.[22, 23, 25] Our findings show that women with 25-OH vitamin D levels below 32 ng/ml had significantly lower lumbar BMD than women with levels ≥ 32 ng/ml. This finding demonstrates the importance of maintaining a 25-OH vitamin D level ≥ 32 ng/ml to preserve BMD and reduce the likelihood of fractures in breast cancer patients.

Vitamin D plays an important role in other health issues that breast cancer patients face including arthralgias and falls. Arthralgias affect a significant proportion of breast cancer patients and represent one of the leading reasons for the discontinuation of aromatase inhibitor therapy.[51, 52] High-dose vitamin D supplementation in breast cancer patients significantly reduces aromatase inhibitor-induced arthralgia.[37, 45] Falls, usually caused by a loss in balance associated with a decrease in muscular strength, are a major cause of excess morbidity and mortality.[53] Vitamin D is directly involved in the regulation of muscular function, and clinical trials demonstrate that vitamin D supplementation significantly reduces the incidence of falls.[54, 55] Due to the important roles vitamin D plays in a variety of health issues that are highly relevant to breast cancer patients, it is imperative that proper 25-OH vitamin D levels are maintained in this population. However, no official guidelines exist for specific vitamin D supplementation regimens, resulting in confusion among clinicians.

In order to correct sub-optimal 25-OH vitamin D levels, breast cancer patients were prescribed various oral vitamin D supplementation regimens. Women were prescribed either weekly high-dose vitamin D supplementation (baseline 25-OH vitamin ≤ 24 ng/ml), daily low-dose vitamin D supplements (25-31 ng/ml), or no supplementation (≥ 32 ng/ml). Following 8-16 weeks of supplementation, women receiving high-dose vitamin D supplementation had an average increase in 25-OH vitamin D of 24 ng/ml, which was significantly ($p<0.01$) greater than the 3 ng/ml increase in the no supplementation group. The 10 ng/ml increase in 25-OH vitamin D for the low-dose supplementation group was not significantly ($p=0.15$) greater than the no supplementation group, which shows that daily

low-dose vitamin D supplementation may not be enough to normalize vitamin D levels for those who are deficient. These results are in agreement with other studies that also show that daily low-dose vitamin D (≤ 1,000 IU/day) is not sufficient to correct vitamin D deficiency in cancer patients.[36, 45] Oncologists need to carefully monitor 25-OH vitamin D levels and supplement as necessary to decrease the risk of treatment-related issues such bone loss, arthralgia, and falls.

Several methodological issues should be considered when interpreting the results of this study. First and foremost, this study was performed in the course of normal clinical care and was not randomized, controlled, and blinded; the vitamin D supplementation regimen was based on the patient's baseline 25-OH vitamin D levels. The type of vitamin D supplement taken by the patient was also not controlled because some pharmacies dispensed D3 whereas others dispensed D2. It is possible there was contamination in terms of vitamin D supplementation across the groups, as participants in the no-supplementation group were not explicitly prohibited from taking over-the-counter vitamin D supplementation on their own accord. Furthermore, compliance by pill count was not performed although all participants were urged to take the supplement as prescribed. Additionally, causality cannot be inferred in the relationship between 25-OH vitamin D levels and BMD because the measurements were cross-sectional. Lastly, we were unable to control for body mass index (BMI), which can affect 25-OH vitamin D levels.[5]

This study also had a number of strengths, including a relatively large heterogeneous sample of breast cancer patients. Because of the large diverse sample, we were able to examine vitamin D status by a number of clinical and demographic variables. In addition, this study used 25-OH vitamin D levels to assess vitamin D status, which is considered the best method.[56] 25-OH vitamin D is a comprehensive measure that takes into account both endogenous production from skin exposure and exogenous intake from dietary and supplement sources. It also accounts for genetic and aging factors that influence vitamin D status.[5] While we were unable to control for BMI, we were able to control for a number of other factors that affect vitamin D levels such as age, race, and the season of the blood draw.

In summary, this study found that a high proportion of breast cancer patients suffered from vitamin D insufficiency and deficiency. Non-Caucasian and later stage breast cancer patients were more likely to have sub-optimal 25-OH vitamin D levels. We also found that sub-optimal 25-OH vitamin D were associated with lower BMD in the lumbar region after controlling for relevant covariates. The final part of the study showed that there was no statistically significant increase in 25-OH vitamin D levels for breast cancer patients receiving daily low-dose vitamin D supplementation (1,000 IU/day) compared to those not receiving supplementation. However, weekly high-dose vitamin D supplementation (≥ 50,000 IU/day) was shown to be safe and well tolerated among breast cancer patients and significantly increased 25-OH vitamin D levels compared to breast cancer patients receiving no supplementation. It is imperative that breast cancer patients maintain optimal vitamin D levels to minimize the risk of treatment-related problems such as bone loss, arthralgias, and falls. Clinicians need to carefully consider the vitamin D regimen (amount and type) when treating vitamin D deficiency in breast cancer patients due to the limited efficacy of daily low-dose supplementation.

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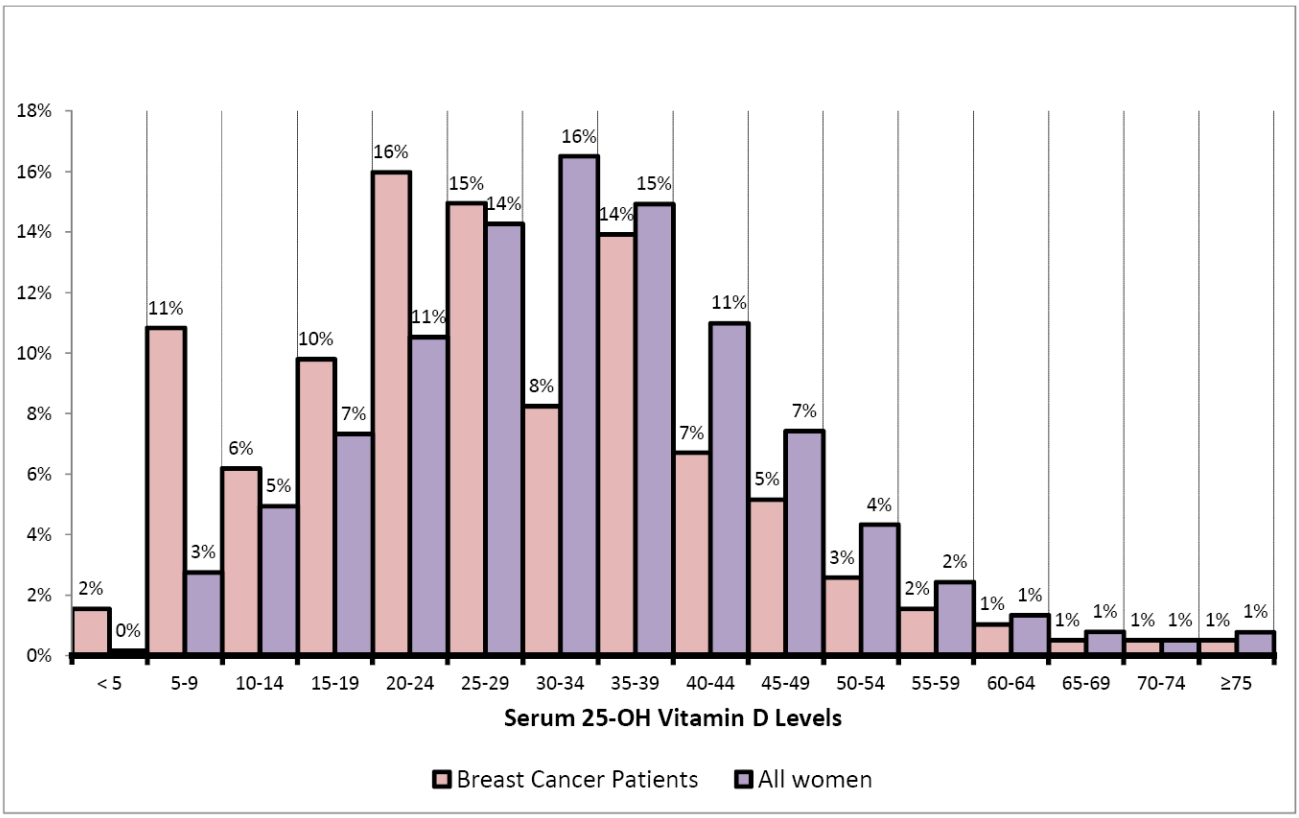

Figure 1.

First-time 25-OH Vitamin D Levels for All Women compared to Breast Cancer Patients who Visited URMC between 1/09 and 10/10

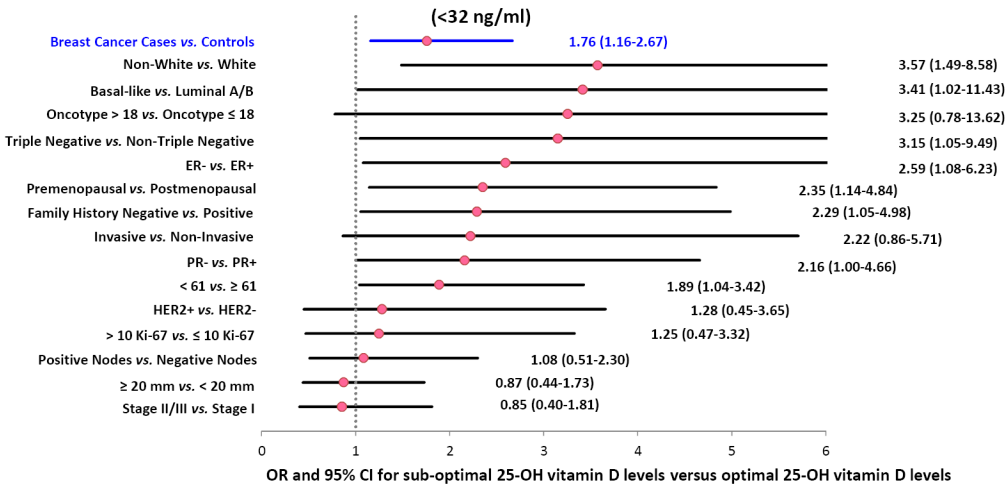

Figure 2.

OR and 95% CI by Case-Control Status and Prognostic Indicators for Sub-optimal 25-OH Vitamin D

Table 1

Odds ratios (OR) with 95% Confidence Intervals for Categorical 25-OH Vitamin D Levels

Vitamin D Status	Control	%	Breast Cancer	%	Breast Cancer Odds Ratio*	95% Confidence Interval	P-Value
Optimal (≥ 32 ng/ml)	119	61.3%	96	49.5%	1.00	Referent	
Insufficient (20-32 ng/ml)	55	28.4%	62	32.0%	1.52	0.95 - 2.41	0.08
Deficient (≤ 20 ng/ml)	20	10.3%	36	18.6%	2.41	1.30 - 4.48	<0.01
						P_{trend} <0.01	

Mean 25-OH Vitamin D Levels by Case-Control Status

	Mean 25-OH Vitamin D*	SD	P-Value
Control	37.4	15.9	
Breast Cancer	32.7	14.4	0.02

*Adjusted for age, laboratory, and month of blood draw.

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Table 2

Mean serum 25-OH vitamin D levels by prognostic demographic and tumor indicators for breast cancer cases

	N	%	Mean 25-OH Vitamin D	SD	P-Value
Race[†]					
Caucasian	157	83.1%	34.9	13.8	
Non-caucasian	32	16.9%	22.9	12.9	<0.01
Family History BC[*]					
No	105	69.1%	31.0	13.6	
Yes	47	30.9%	33.6	12.4	0.27
Age[‡]					
53 and younger	63	32.5%	28.8	11.6	
54-65	63	32.5%	32.9	13.3	
66 and older	68	35.1%	36.1	16.7	0.01
Menopausal Status[‡]					
Premenopausal	45	23.2%	29.2	11.7	
Postmenopausal	149	76.8%	34.0	14.9	0.04
ER Status[*]					
Negative	32	16.8%	28.1	12.8	
Positive	159	83.2%	33.4	14.4	0.04
PR Status[*]					
Negative	37	19.4%	28.9	12.7	
Positive	154	80.6%	33.4	14.5	0.08
HER2 Status[*]					
Negative	144	89.4%	31.7	14.8	
Positive	17	10.6%	32.6	11.0	0.80
Triple Negative[*]					
No	139	86.3%	33.3	14.3	
Yes	22	13.7%	26.2	12.9	0.02
Invasiveness[*]					
No	23	12.8%	37.4	13.5	

	N	%	Mean 25-OH Vitamin D	SD	P-Value
Yes	156	87.2%	32.0	14.6	0.09
Tumor Size*					
In-situ	23	12.8%	36.7	13.4	
≤ 0.2 cm	107	59.8%	34.9	11.8	
> 0.2	49	27.4%	31.7	15.0	0.20
Positive Lymph Nodes*					
No	136	77.7%	32.4	14.0	
Yes	39	22.3%	33.4	12.1	0.73
Oncotype Score*					
< 18	25	64.1%	31.5	12.0	
18-30	12	30.8%	25.3	12.5	
> 30	2	5.1%	12.3	14.8	0.07
Molecular Phenotype*					
In situ	23	12.4%	37.5	13.5	
Luminal A	102	55.1%	32.8	14.9	
Luminal B	34	18.4%	33.6	13.0	
HER2	7	3.8%	31.6	14.2	
Basal-like	19	10.3%	24.2	11.6	0.04
Season of Blood Draw§					
Winter/Spring	106	54.6%	30.8	13.8	
Summer/Autumn	88	45.4%	32.8	12.1	0.37

†Adjusted for age, laboratory, and month of blood draw.

*Adjusted for age, laboratory, race, and month of blood draw.

‡Adjusted for race, laboratory, and month of blood draw.

§Adjusted for age, laboratory, and race.

Table 3

Odds ratios (OR) with 95% Confidence Intervals for Categorical 25-OH Vitamin D Levels by Prognostic Demographic and Tumor Characteristics: Case Series Analysis

	Race				Non-White			
	White	**%**	**Non-White**	**%**	**Odds Ratio†**	**95% Confidence Interval**		**P-Value**
Optimal (≥ 32 ng/ml)	87	55.4%	8	25.0%	1.00	Referent		
Insufficient (20-32 ng/ml)	52	33.1%	9	28.1%	1.77	0.63	4.97	0.28
Deficient (≤ 20 ng/ml)	18	11.5%	15	46.9%	8.72	3.18	23.92	<0.01
							P_{trend} <0.01	
	Age				**< 61**			
	≥ 61	**%**	**< 61**	**%**	**Odds Ratio‡**	**95% Confidence Interval**		**P-Value**
Optimal (≥ 32 ng/ml)	56	56.6%	40	42.1%	1.00	Referent		
Insufficient (20-32 ng/ml)	27	27.3%	35	36.8%	1.86	0.96	3.58	0.06
Deficient (≤ 20 ng/ml)	16	16.2%	20	21.1%	1.95	0.82	4.62	0.12
							P_{trend} =0.02	
	Menopausal Status				**Premenopausal**			
	Post-menopausal	**%**	**Pre-menopausal**	**%**	**Odds Ratio‡**	**95% Confidence Interval**		**P-Value**
Optimal (≥ 32 ng/ml)	81	54.4%	15	33.3%	1.00	Referent		
Insufficient (20-32 ng/ml)	42	28.2%	20	44.4%	2.58	1.19	5.57	0.02
Deficient (≤ 20 ng/ml)	26	17.4%	10	22.2%	1.88	0.69	5.17	0.22
							P_{trend} =0.04	
	ER Status				**ER Negative**			
	ER Positive	**%**	**ER Negative**	**%**	**Odds Ratio***	**95% Confidence Interval**		**P-Value**
Optimal (≥ 32 ng/ml)	85	53.5%	9	28.1%	1.00	Referent		
Insufficient (20-32 ng/ml)	47	29.6%	14	43.8%	2.75	1.02	7.40	0.04
Deficient (≤ 20 ng/ml)	27	17.0%	9	28.1%	3.39	1.01	11.31	0.04
							P_{trend} =0.04	
	PR Status				**PR Negative**			
	PR Positive	**%**	**PR Negative**	**%**	**Odds Ratio***	**95% Confidence Interval**		**P-Value**
Optimal (≥ 32 ng/ml)	81	52.6%	13	35.1%	1.00	Referent		

	Race				Non-White			
	White	**%**	**Non-White**	**%**	**Odds Ratio†**	**95% Confidence Interval**		**P-Value**
Insufficient (20-32 ng/ml)	46	29.9%	15	40.5%	2.17	0.93	5.07	0.08
Deficient (≤ 20 ng/ml)	27	17.5%	9	24.3%	2.14	0.81	5.68	0.13
							P_{trend} =0.09	
	Triple Negative				**Triple Negative**			
	No	**%**	**Yes**	**%**	**Odds Ratio***	**95% Confidence Interval**		**P-Value**
Optimal (≥ 32 ng/ml)	88	52.7%	5	22.7%	1.00		Referent	
Insufficient (20-32 ng/ml)	51	30.5%	9	40.9%	2.79	0.84	9.27	0.09
Deficient (≤ 20 ng/ml)	28	16.8%	8	36.4%	3.87	1.03	14.55	0.04
							P_{trend} =0.03	
	HER2				**HER2+**			
	No	**%**	**Yes**	**%**	**Odds Ratio***	**95% Confidence Interval**		**P-Value**
Optimal (≥ 32 ng/ml)	69	47.9%	8	47.1%	1.00		Referent	
Insufficient (20-32 ng/ml)	42	29.2%	7	41.2%	1.37	0.45	4.22	0.58
Deficient (≤ 20 ng/ml)	33	22.9%	2	11.8%	1.03	0.19	5.59	0.97
							P_{trend} =0.82	
	Invasive?				**Invasive**			
	No	**%**	**Yes**	**%**	**Odds Ratio***	**95% Confidence Interval**		**P-Value**
Optimal (≥ 32 ng/ml)	15	65.2%	74	47.4%	1.00		Referent	
Insufficient (20-32 ng/ml)	7	30.4%	48	30.8%	1.51	0.56	4.10	0.42
Deficient (≤ 20 ng/ml)	1	4.3%	34	21.8%	7.15	0.89	57.14	0.06
							P_{trend} =0.08	
	Tumor Size				**≥ 20 mm**			
	< 20 mm	**%**	**≥ 20 mm**	**%**	**Odds Ratio***	**95% Confidence Interval**		**P-Value**
Optimal (≥ 32 ng/ml)	53	49.5%	22	44.9%	1.00		Referent	
Insufficient (20-32 ng/ml)	34	31.8%	14	28.6%	0.75	0.33	1.74	0.51
Deficient (≤ 20 ng/ml)	20	18.7%	13	26.5%	1.31	0.54	3.21	0.55
							P_{trend} =0.47	
	Nodal Involvement				**Nodal Involvement**			
	No	**%**	**Yes**	**%**	**Odds Ratio***	**95% Confidence Interval**		**P-Value**

	Race				Non-White			
	White	**%**	**Non-White**	**%**	**Odds Ratio†**	**95% Confidence Interval**		**P-Value**
Optimal (≥ 32 ng/ml)	69	50.7%	17	43.6%	1.00	Referent		
Insufficient (20-32 ng/ml)	39	28.7%	14	35.9%	1.15	0.49	2.67	0.75
Deficient (≤ 20 ng/ml)	28	20.6%	8	20.5%	0.99	0.37	2.66	0.95
							P_{trend} =0.51	
	Stage				**Stage 2 or 3**			
	Stage 1	**%**	**Stage 2 or 3**	**%**	**Odds Ratio***	**95% Confidence Interval**		**P-Value**
Optimal (≥ 32 ng/ml)	45	48.9%	29	45.3%	1.00	Referent		
Insufficient (20-32 ng/ml)	28	30.4%	20	31.3%	0.81	0.37	1.80	0.61
Deficient (≤ 20 ng/ml)	19	20.7%	15	23.4%	0.95	0.40	2.28	0.92
							P_{trend} =0.82	
	Ki-67				**> 10**			
	≤ 10	**%**	**> 10**	**%**	**Odds Ratio***	**95% Confidence Interval**		**P-Value**
Optimal (≥ 32 ng/ml)	19	55.9%	17	50.0%	1.00	Referent		
Insufficient (20-32 ng/ml)	8	23.5%	14	41.2%	1.93	0.64	5.85	0.24
Deficient (≤ 20 ng/ml)	7	20.6%	3	8.8%	0.35	0.06	2.03	0.24
							P_{trend} =0.87	
	Oncotype				**≥ 18**			
	< 18	**%**	**≥ 18**	**%**	**Odds Ratio***	**95% Confidence Interval**		**P-Value**
Optimal (≥ 32 ng/ml)	13	52.0%	4	28.6%	1.00	Referent		
Insufficient (20-32 ng/ml)	7	28.0%	4	28.6%	1.98	0.36	10.86	0.43
Deficient (≤ 20 ng/ml)	5	20.0%	6	42.9%	4.72	0.83	26.68	0.08
							P_{trend} =0.05	
	Family History				**Positive Family History**			
	Yes	**%**	**No**	**%**	**Odds Ratio***	**95% Confidence Interval**		**P-Value**
Optimal (≥ 32 ng/ml)	28	56.0%	46	43.8%	1.00	Referent		
Insufficient (20-32 ng/ml)	14	28.0%	38	36.2%	2.23	0.93	5.35	0.07
Deficient (≤ 20 ng/ml)	8	16.0%	21	20.0%	2.40	0.80	7.23	0.11
							P_{trend} =0.25	
	Molecular Phenotype				**Basal-like**			

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	Race				Non-White			
	White	**%**	**Non-White**	**%**	**Odds Ratio†**	**95% Confidence Interval**		**P-Value**
	Luminal A/B	**%**	**Basal-like**	**%**	**Odds Ratio***	**95% Confidence Interval**		**P-Value**
Optimal (≥ 32 ng/ml)	72	52.9%	4	21.1%	1.00	Referent		
Insufficient (20-32 ng/ml)	39	28.7%	7	36.8%	3.01	0.81	11.12	0.10
Deficient (≤ 20 ng/ml)	25	18.4%	8	42.1%	4.24	1.01	17.75	0.04
							P_{trend} =0.02	

† Adjusted for age, laboratory, and month of blood draw.

‡ Adjusted for race, laboratory, and month of blood draw.

* Adjusted for age, laboratory, race, and month of blood draw.