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Effects of Vitamin D Use on Health-Related Quality of Life of Breast Cancer Patients in Early Survivorship

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Abstract

Background: Vitamin D supplements may prevent recurrence, prolong survival, and improve mood for women with breast cancer, although evidence for these effects is preliminary. **Methods:** This report describes vitamin D supplement use by 553 breast cancer patient/survivors (193 who used a naturopathic oncology [NO] provider and 360 who did not) participating in a matched cohort study of breast cancer outcomes. **Results:** We found that more than half of breast cancer patients reported using vitamin D supplements. Women who received care from NO providers in early survivorship may be more likely to use vitamin D supplements ($P < .05$). Approximately 30% of breast cancer patients with blood levels recorded in their medical chart were potentially vitamin D deficient (<30 ng/mL). Vitamin D supplement use at study enrollment was associated with higher levels of self-reported health-related quality of life (HRQOL) at enrollment ($P < .05$) and predicted better HRQOL at 6-month follow-up ($P < .05$). Sufficient blood levels of vitamin D recorded between enrollment and follow-up were also associated with better HRQOL at follow-up ($P < .05$). **Conclusions:** Vitamin D supplementation by breast cancer patients is common both during and after treatment for breast cancer, but deficiency may also be common. NO and conventional providers may be able to promote vitamin D sufficiency through vitamin D supplementation and by encouraging healthy solar exposure. Further studies should be undertaken examining whether vitamin D supplementation and higher blood levels might improve HRQOL among women with breast cancer in early survivorship.

Keywords

vitamin D, health-related quality of life, breast cancer, survivorship, CAM

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Use of vitamin D supplements is nominally a complementary and alternative medicine (CAM) activity; however, some conventional doctors also encourage cancer patients to take supplemental vitamin D during and after breast cancer treatment. Epidemiological evidence suggests that solar exposure, through its influence on vitamin D blood levels, may prevent cancer and improve outcomes for diagnosed patients.[1,2] Thus far, the evidence for vitamin D's effectiveness in preventing cancer is mixed,[3,4] but studies have found evidence that low levels of vitamin D (25(OH)D) in the blood are associated with increased risk of recurrence and death in early-stage breast cancer patients.[5] Studies also found that women with breast cancer in the highest tertile of 25(OH)D blood levels have superior overall survival (OS), breast cancer–specific survival, and invasive disease-free survival compared with those with lower levels.[6] Other cohort examinations found higher blood levels of 25(OH)D associated with survival and lower recurrence rates, although the results have not always been statistically significant.[7-9]

Systemically, vitamin D may influence breast cancer because activation of its receptor induces autophagy and an autophagic transcriptional signature in breast cancer cells that correlates with increased survival in patients and is

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progressively lost in metastatic breast cancer models.[10] The mechanism by which vitamin D might influence mood is less clear, but there is consistent evidence that there are receptors for vitamin D in the brain and that depression and a variety of mood disorders are associated with low blood levels of 25(OH)D.[11,12]

What is less clear is the effectiveness of vitamin D supplements as a way to reduce incidence or improve survival after cancer. Studies of D supplement use for cancer prevention have provided mixed results.[3,13-15] Studies of vitamin D supplementation among breast cancer patients describe high rates of deficiency (>60% of references), particularly after neoadjuvant chemotherapy, and often describe insignificant changes associated with supplementation at levels of 400IU and 1000 IU daily,[16] although 1 study did report that high doses of supplements did increase blood levels of vitamin D[17] in this setting. Studies of very high supplemental doses of vitamin D of 10 000 IU per day or 50 000 IU per week or dosage levels sufficient to increase blood levels to 40 ng/mL found these recommendations safe and associated with reductions in pain associated with use of aromatase inhibitors,[18,19] although data on overall HRQOL were not presented.

There is evidence that vitamin D supplement use and higher blood levels of vitamin D may improve mood.[20] Studies that found D supplement use is effective for mood-related conditions include an RCT finding that supplementation reduced levels of depression[21] and an RCT finding that supplementation enhanced mood in healthy participants during winter[22]; these studies did not focus on cancer patients. We sought to examine vitamin D supplement use by breast cancer survivors and its effects on health-related quality of life (HRQOL) of these women during treatment and early survivorship. Studies describing CAM use among cancer patients generally find that CAM use is common but rarely break down the frequency with which various specific herbs and other supplements are used.

This study, a secondary analysis of a study of breast cancer survivors who seek and do not seek to use naturopathic physicians who specialize in oncology (NO) care to supplement their conventional oncology treatment, sought to explore the role of vitamin D in detail. In this report, we describe the percentage of women with breast cancer who used vitamin D supplements at various points in their cancer treatment course, the levels of supplemental vitamin D taken, and the effects of D supplement use. We also sought to describe the percentage of patients who report receiving a physician (conventional or NO) recommendation for vitamin D supplementation and the frequency with which physicians monitor blood levels of vitamin D in breast cancer patient/survivors. We also asked, "What are the rates of vitamin D deficiency?" and "Is vitamin D deficiency or supplementation associated with an improved sense of well-being or functional HRQOL for breast cancer patients in early survivorship?"

Methods

Institutional review boards at Fred Hutchinson Cancer Research Center and Bastyr University approved the study methods and questionnaires. The women involved in this study are part of a longitudinal assessment of 2 matched cohorts of women with breast cancer (NCT01366248). Breast cancer patients in our NO cohort were eligible for the study if they spoke English fluently enough to complete surveys, were older than 21 years, and received a breast cancer diagnosis less than 2 years prior to their visit to a NO clinic. Usual care (UC) cohort members were selected from the cancer registry based on their similarity to an enrolled NO clinic patient in age, race, stage at diagnosis, and other demographic characteristics. Potential participants received a packet containing the informed consent form, a medical records release, and the enrollment questionnaire. Analyses describing the similarities and differences between the 2 cohorts are described elsewhere.[23,24] Women seeking NO care either consented in the clinic or during a telephone call, with the documents returned by mail. Women identified through the cancer registry completed consent documents by mail. Details regarding study recruitment and retention for the cohorts are in Figure 1. Reasons women were determined ineligible for analyses included failure to complete the medical records release or identification at the NO clinic or in the registry for a second rather than first primary cancer diagnosis. In addition, 5 women originally identified as UC comparison participants later chose to visit a NO clinic, disqualifying them from the UC cohort. These women participated in the NO cohort after their clinic enrollment, and additional comparison women were recruited for the UC cohort. In total, 553 women (193 in the NO cohort and 360 from the UC cohort) are included in these analyses.

Measures

In addition to standard assessments of demographics, the study enrollment questionnaire included items assessing CAM supplement use and a measure of overall HRQOL.[25] Participants also signed medical records releases that allowed collection and retention of information about their diagnosis and treatment for breast cancer from the cancer registry and from their personal medical records. Trained study personnel abstracted medical records beginning at the date of initial breast cancer diagnosis. This report includes records abstracted to 6 months postenrollment. Additional information about study procedures is available in prior reports that describe the cost and content of NO care provided to the NO cohort and in reports that describe the pilot

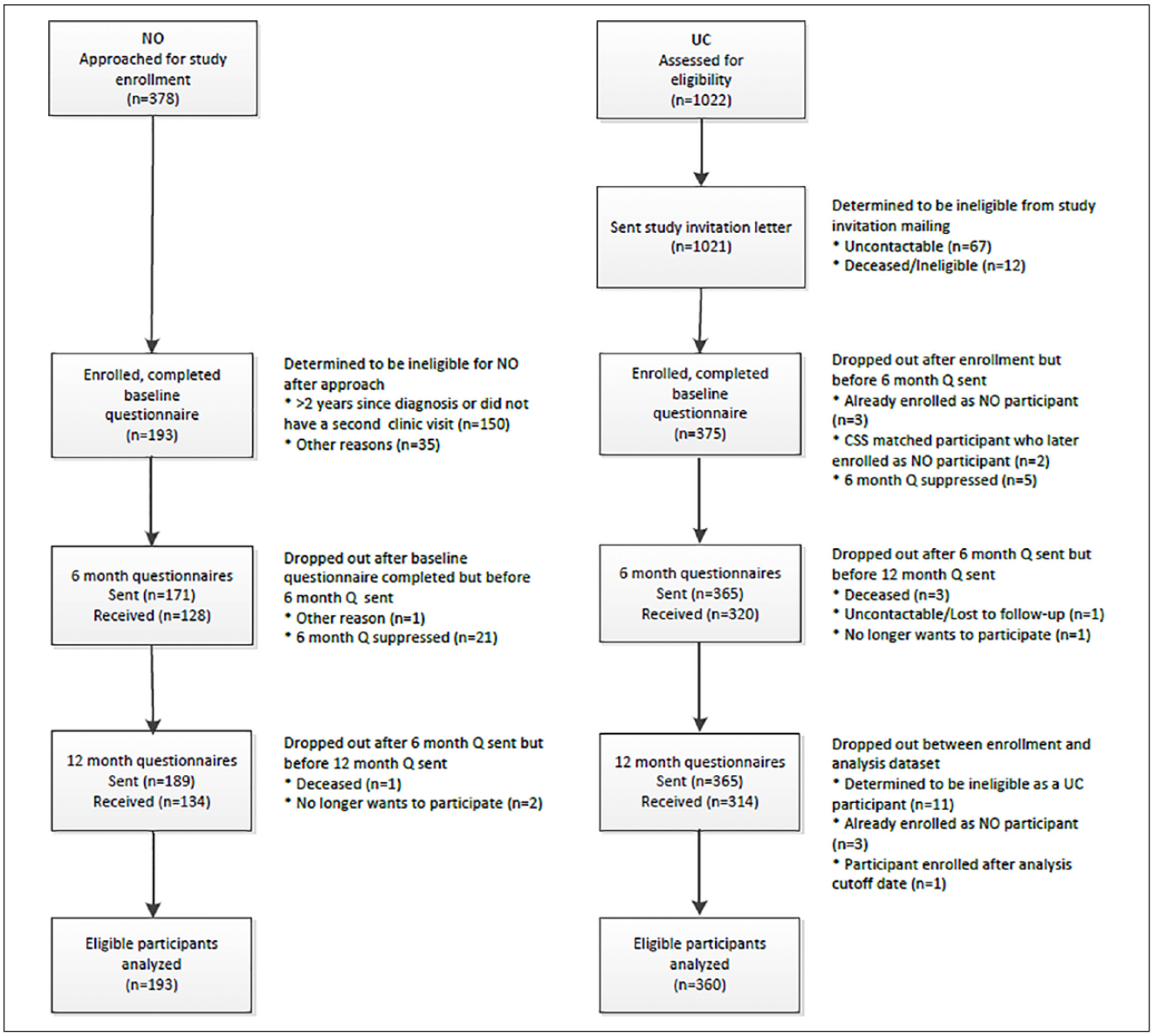

Figure 1. Participant flow through the protocol.

of these study methods and the enrollment characteristics of our cohorts.[23,24,26,27] This report supplements one describing the HRQOL of women in the 2 cohorts[26] that found women in the NO cohort versus the UC cohort to report reduced levels of HRQOL on study enrollment but slightly higher levels of HRQOL at the 6-month follow-up. This report describes use of vitamin D by women in both study cohorts and the results of laboratory assessments of 25(OH)D blood levels ordered by patients' personal physicians and described in medical records in an effort to understand the contribution of vitamin D recommendation and use to any effects of NO care. Other reports that describe the women in this cohort do not include their use of vitamin D.

Assessment of Vitamin D Use

The baseline assessment asked study enrollees about vitamin D use and about their routine consumption of more than 50 other herbs and supplements taken by or recommended for cancer patients. That item asked women about use of a variety of supplements, including vitamin D prior to diagnosis, during chemotherapy or radiation treatment, following completion of therapy, and current use. It did not ask about the dose of the supplement they took but did ask how frequently they took the supplements and included the following choices: "Less than once per week," "At least once per week," "At least 5×/wk," and "Daily." Women were also asked, "Who prescribed or recommended this

Table 1. Calculation of Daily Average Vitamin D Doses.

Questionnaire Frequency Choices	Multiplier for Weekly Use			
Less than once per week	0.5	Multiply by combined dosage from both categories	Divide by 7	To get daily dose
At least once per week	3.5			
At least 5×/wk	5.5			
Daily	7.0			

substance?" with the options "Conventional Health Care Provider," "Complementary/Alternative Health Care Provider," "Self/Friend," and "Not sure/Don't remember."

When it became clear that the percentage of women using vitamin D as an individual supplement was particularly high, we added a second set of questions to a later version of the questionnaire that requested more detail about vitamin D supplement use. Up to 90 women in the NO cohort and 244 women in the UC cohort completed this supplemental set of questions at one or more time points. This set of items asked women about their use of multivitamins, vitamin D and calcium combination formulas, and supplements containing only vitamin D. Women also indicated within a range the doses of vitamin D they took in each form of supplement not including multivitamins on days they took supplements. The ranges offered for each supplement included "less than 1000 IU," "1000 to 2000 IU," and ">2000 IU." To calculate individual exposure for vitamin D with calcium combinations or a single supplement D, total dose estimates were calculated using a middle value for the doses of each supplement reported, such that "<1000" was treated as 500, and "1000 to 2000" as 1500, and ">2000" as 3000, for the purposes of combining the combination and noncombination dosages. We then combined dose information for supplements with information on frequency of vitamin D supplement use to create an estimated average amount per day. Table 1 describes the methods used to calculate average daily dose.

Health-Related Quality of Life

The SF-36 is a widely used self-report measure of functional status and overall HRQOL, which is frequently used in intervention and longitudinal studies.[28] The SF-36 measures quality of life across a broad range of general function levels and is sensitive to changes in life function common in both healthy and ill populations. The SF-36 was scored by calculating 8 subscales, including functional status, role-physical function, role-emotional function, pain, general health, mental health, vitality, and social functioning.

Abstracted Data

Abstracted data used in this report included data on laboratory tests performed assessing 25(OH)D blood levels recorded in participants' medical charts. Abstractors recorded all laboratory values for vitamin D found in participants' medical records by date within 2 abstraction windows. Abstraction windows included diagnosis to study enrollment and study enrollment to 6-month follow-up postenrollment. If multiple values were found within an abstraction window, the most recent value was recorded as the value for the time period. For women in the NO cohort, both conventional charts and NO clinic charts were abstracted. Laboratory reports of 25(OH)D found in NO charts were recorded for abstraction windows where no conventional chart laboratory value was recorded. In addition, abstractors recorded the treatment recommendations and prescriptions provided by the NO physician. This allowed us to identify the percentage of women in the NO cohort who received a recommendation or prescription for vitamin D supplementation at their first NO office visit and for visits between study enrollment and 6-month follow-up. Finally, for purposes of describing vitamin D blood levels in clinically meaningful terms, blood levels recorded in patient charts were categorized. Levels below 30 ng/mL were considered "potentially D-deficient," 30 to 50 ng/mL "adequate," 50 to 99 ng/mL "ideal," and greater than 100 ng/mL "of potential concern." Although, any categorization of D levels is to some degree arbitrary, these cutoff values were based on the participating NO clinicians' (LJS, ES) reports of their preferences for patients and the literature suggesting deficiency in patients with levels less than 30 ng/mL.[29,30]

Analysis Plan

In describing participants' use of vitamin D and the effects of vitamin D on HRQOL, we report first descriptive analyses of women's self-reports of vitamin D supplement use since diagnosis, at enrollment, and at 6-month follow-up. Descriptive analyses also include recommenders of vitamin D supplements and doses of D used by women in each cohort. Next, we describe an analysis of abstracted medical records describing the frequency with which participants' 25(OH)D blood levels were assessed and the blood levels found by the cohort for study windows that included both postdiagnosis prior to study enrollment and study enrollment to 6-month follow-up. Comparisons between the cohorts included χ^2 and *t*-tests. Finally, we combined

women from both cohorts for analyses describing the associations of supplement use with HRQOL at study enrollment and then predictive analyses describing the effects of use at enrollment on HRQOL reported at 6-month follow-up. Similar analyses were conducted examining the predictive effects of 25(OH)D levels documented prior to enrollment on HRQOL at enrollment and of 25(OH)D levels documented postenrollment but prior to 6-month follow-up on HRQOL at follow-up. Analyses of HRQOL included both simple unadjusted *t*-tests and multiple regression analyses allowing for control of potential confounders of HRQOL, including age, time since diagnosis, race, ethnicity, cancer stage, marital status, use of chemotherapy or radiation, or type of surgery received, and in analyses of 6-month outcomes baseline HRQOL. All analyses were conducted using the R statistical package.

Results

Analyses of Supplemental Vitamin D Use Reported by Patients

Participants' retrospective self-reports of supplemental vitamin D use are shown in Table 2. The data presented include reports of use of vitamin D supplements prior to diagnosis, during primary treatment with chemotherapy and/or radiation, and after completing initial treatment.

In total, almost 90% (n = 130) of patients in the NO and 73% (n = 262) of the UC cohort reported ever using vitamin D supplements, excluding multivitamins, at the time of their enrollment in the study. Differences in supplemental D use between the cohorts prior to study enrollment suggest higher levels of use by NO cohort women prior to initiating NO care. Women in the NO cohort reported more use of vitamin D prior to diagnosis (n = 88, 60.7%, vs 141, 39.2%; $P < .001$), although reported rates of use during treatment and since treatment but prior to study enrollment were not significantly different between the cohorts. Women in the NO cohort did appear more likely to use vitamin D supplements at study enrollment ($P < .01$).

At the time of study enrollment, members of both cohorts reported past use of vitamin D at the recommendation of both conventional and complementary non-NO CAM medical providers. Of those taking vitamin D, more than half (51.9%) of those in the UC cohort reported doing so based on a recommendation from their conventional medical provider, whereas of those in the NO cohort taking vitamin D, only 26.9% reported a similar recommendation ($P < .05$). NO cohort women taking vitamin D were more likely to report the recommendation of an alternative medicine provider (46.9% vs 13% of NO vs UC patients taking vitamin D, respectively; $P < .05$). Both cohorts included women who reported taking vitamin D at the recommendation of friends or family members (33% and 21% NO and UC women taking vitamin D, respectively; differences not statistically significant). Rates of NO provider recommendation in the NO group reflect a combination of the recommendations of any of a variety of CAM providers (eg, primary care naturopathic doctors, chiropractors), similar to the variety of CAM providers seen by the UC cohort and the recommendations of the NO clinic providers who enrolled them in this study. A total of 27 women completed the enrollment questionnaire after their first office call visit with the NO provider and received a recommendation for vitamin D at that NO visit.

Women in both cohorts appeared to increase their use of vitamin D supplements over time. At the 6-month follow-up, approximately 57% of women in both cohorts reported using some form of vitamin D supplement (differences between the cohorts were not statistically significant). There was a nonsignificant trend toward higher use by the NO cohort at the 12-month follow-up [63.9% vs 54.1%, $\chi^2(1) = 3.64$, $P = .06$; data not shown].

Analyses progressed to examine the dose of vitamin D taken by women. For these analyses, we used only data from women who completed an additional section of the questionnaire assessing the types and doses of vitamin D supplements women used. Current use of vitamin D supplements at baseline and at the time of the 6-month follow-up are in Table 3. The rates of vitamin D use reported by women in this subgroup appears to be substantially higher than that of the sample as a whole, perhaps because women in this group were asked explicitly about multivitamins and vitamin D supplements combined with calcium, which may have helped women recall uses not reported in response to the original question. Still, of those taking vitamin D supplements, more than half reported taking less than 1000 IU, and again, there were no statistically significant differences found between the cohorts in the percentage of patients taking supplements, even at 6-month follow-up. This may be attributed to the fact that while vitamin D use increased substantially in the NO cohort, use among UC cohort women also increased over time.

Monitoring of Vitamin D Blood Levels

A review of medical charts revealed that blood levels of 25(OH)D were monitored by a minority of physicians, both conventional and naturopathic, treating breast cancer patients. Monitoring was similar among UC women and women who later enrolled in the NO cohort. Between diagnosis and enrollment, approximately 30% of each cohort group had at least 1 blood test recorded in their medical chart. After enrollment, testing for 25(OH)D levels was more common among NO cohort women than for those in the UC cohort [$\chi^2(1) = 14.73$; $P < .001$]. In the 6-month period following initiation of care at the NO clinic, 30% of NO women had a blood test for 25(OH)D recorded in their medical charts, as did only 16% of UC patients.

Table 2. Characteristics of Participants.[a]

	NO Care, Percentage (n = 193)	Usual Care, Percentage (n = 360)
Total at baseline		
Age, mean (SD)	53.3 (11.19)	54.8 (10.3)
Race		
White	94.8 (183)	95.3 (343)
African American	0.0 (0)	0.6 (2)
Asian	3.6 (7)	3.6 (13)
Mixed	1.5 (3)	0.6 (2)
Ethnicity		
Hispanic	1.0 (2)	1.7 (6)
Non-Hispanic	99.0 (191)	98.3 (354)
Stage at enrollment		
Stage 0	10.4 (20)	8.3 (30)
Stage I	32.1 (62)	39.4 (142)
Stage II	39.9 (77)	35.5 (128)
Stage III	13.5 (26)	13.3 (48)
Stage IV	3.6 (7)	1.9 (7)
Unknown	0.5 (1)	1.4 (5)
Self-reported current use at time of baseline questionnaire[b]	49.0% (71/145)	51.1% (184/360)
Use of vitamin D before dx[c]	60.7 (88)	39.2 (141)
Use of vitamin D during chemotherapy	26.9 (39)	22.5 (81)
Use of vitamin D during radiation	13.8 (20)	21.4 (77)
Of patients reporting any use of vitamin D at baseline		
Daily users	85.4%	82.4 %
Of patients reporting any use of vitamin D at baseline		
Participants reporting "Conventional provider" prescribed[c]	26.9 (35)	51.9 (136)
Participants reporting "CAM provider" prescribed	46.9 (61)	13.0 (34)
Participants reporting "Self-friend" prescribed	33.1 (43)	21.0 (55)
Participants reporting "Don't remember" for prescription	0.8 (1)	1.1 (3)

Abbreviations: NO, naturopathic oncology; CAM, complementary and alternative medicine.
[a]Age, race, ethnicity are from the Western Washington Cancer Surveillance System (CSS). Stage is from abstracted medical records (MRs). If MR stage was not available, CSS stage was used. Stage dated >24 months before enrollment is treated as unknown. All other data are from patient questionnaires.
[b]This includes 27 women who completed their baseline questionnaire after their initial appointment with the NO clinic and who received a recommendation for vitamin D from the clinic at that initial visit. All items asking about vitamin D use 145 participants as the denominator for the NO cohort instead of 193 because only 145 of the NO cohort received any questions asking about supplement use.
[c]Differences significant at the $P < .05$ level or greater. All analyses conducted using χ^2 tests.

Analyses examining the predictors of vitamin D monitoring and presence of blood test results in the medical chart revealed no statistically significant predictors other than cohort and chemotherapy. Women who received chemotherapy as part of their treatment appear more likely to have their blood levels of vitamin D tested between diagnoses and study enrollment than did those who did not have chemotherapy ($P < .05$). Physicians do not appear more likely to order tests for women who do, or do not, report use of supplemental vitamin D either concurrently or in time-lagged analyses that would indicate monitoring after vitamin D supplement use was established (data not shown).

Average blood levels of 25(OH)D recorded are shown in Table 4. Levels when recorded were not significantly different between the cohorts. When values were evaluated for clinically significant ranges, approximately 30% of the women in each cohort were potentially deficient for vitamin D at study enrollment with levels <30 ng/mL The percentage of potentially vitamin D–deficient women appears to fall for those in the NO cohort at the 6-month follow-up, when only 6 (10%) of these women had blood levels <30 ng/mL (in contrast 16 [28%] of those in the UC cohort had levels <30 ng/mL). Similarly, 31% of those in the NO cohort and 21% of those in the UC cohort with any 25(OH) D value recorded had levels of 50 to 99 ng/mL None of the women at baseline or 6 months had blood levels >100 ng/mL recorded. These differences between the cohorts were not statistically significant.

In an effort to describe the effects of vitamin D supplementation on blood levels of 25(OH)D in breast cancer patients, we examined the subset of women (n = 160) who had recorded blood test results. These analyses found that

Table 3. Self-reported Use of Vitamin D Supplements in the Subgroup Completing Additional Questions About Use.[a]

	Baseline		6 Months		1 Year	
	NO Care, Percentage (n)	Usual Care, Percentage (n)	NO Care, Percentage (n)	Usual Care, Percentage (n)	NO Care, Percentage (n)	Usual Care, Percentage (n)
Total number of patients	(71)	(194)	(90)	(221)	(82)	(244)
Patients reporting any current use of vitamin D (including multivitamins)	85.9 (61)	73.2 (142)	97.8 (88)	81.9 (181)	98.8 (81)	80.3 (196)
Of those reporting current use: use of vitamin D with calcium combos	29.5 (18)	42.3 (60)	44.3 (39)	55.2 (100)	49.4 (40)	55.1 (108)
Of those reporting current use: vitamin D as a single supplement	86.9 (53)	72.5 (103)	85.2 (75)	63.5 (115)	82.7 (67)	63.3 (124)
Patients reporting current use of vitamin D (not in multivitamins)	83.1 (59)	68.0 (132)	96.7 (87)	75.1 (166)	96.3 (79)	74.6 (182)
Of those reporting combo or single supplement vitamin D use, self-reported dose						
<1000 IU	69.5 (41)	61.4 (81)	56.3 (49)	50.0 (83)	53.2 (42)	53.3 (97)
1000-2000 IU	18.6 (11)	32.6 (43)	27.6 (24)	38.5 (64)	29.1 (23)	33.0 (60)
>2000 IU	11.9 (7)	5.3 (7)	16.1 (14)	10.2 (17)	16.4 (13)	13.2 (24)
Dose not reported	0.0 (0)	0.8 (1)	0.0 (0)	1.2 (2)	1.3 (1)	0.5 (1)

Abbreviation: NO, naturopathic oncology.
[a]Data are for patients who were given a version of the questionnaire that asked about use and dosages of vitamin D, both standalone and in combination with calcium.

Table 4. 25(OH)D Testing and Blood Levels as Recorded in Medical Charts.

	NO Care, n = 193		Usual Care, n = 360	
	Percentage (n)	25(OH)D Level, Mean (SD)	Percentage (n)	25(OH)D Level, Mean (SD)
Lab values recorded for diagnosis to enrollment	29.5% (57)	41.6 (17.2)	28.6% (103)	37.6 (16.1)
Lab values recorded for enrollment to 6 months	30.1% (58)	45.1 (13.8)	16.1% (58)	40.1 (15.3)

Abbreviation: NO, naturopathic oncology.

women who reported taking vitamin D supplements at study enrollment had higher blood levels of 25(OH)D assessed in blood levels taken between enrollment and the 6-month follow-up than nonusers, but these differences did not achieve statistical significance ($P = .07$). Similarly, women who reported taking vitamin D appeared less likely to be potentially vitamin D–deficient during the 6-month postenrollment assessment window than nonusers, but again, these analyses only suggested a trend ($P = .06$) and were not statistically significant (data not shown).

We also chose to examine the HRQOL reported by users and nonusers of vitamin D supplements and combined the 2 cohorts for these analyses. Analyses examining the predictors of vitamin D use other than cohort included, age, race, ethnicity, stage, time since diagnosis, marital status, surgery type, use of radiation, and use of chemotherapy. These analyses found few differences between users and nonusers; the only statistically significant difference predicting vitamin D supplement use other than cohort [$\chi^2(df = 1) = 10.37$; $P < .01$] found was time since diagnosis [$f(df = 1) = 31.66$; $P < .01$]. Because time since diagnosis did differ substantially between the cohorts and could influence HRQOL, it was included as a covariate in all analyses predicting HRQOL.

Using Vitamin D Supplements at Study Enrollment as a Predictor of HRQOL

The Welch 2-sample *t*-test found that users of supplemental vitamin D reported better physical function, role-physical function, social function, and role-emotional function on the SF-36 HRQOL assessment subscales at baseline

Table 5. Self-reported HRQOL at Enrollment and 6-Month Follow-up Associated With Vitamin D Supplement Use at Enrollment.

SF-36 Scales	Vitamin D Supplement	Use Categories	Advantage to Vitamin D Users	*P* Value
Baseline HRQOL	No (n = 298)	Yes (n = 255)		
Physical function	75.98	81.34	5.36	$t = -2.89$; $P < .01$
Role-physical	45.00	55.43	10.43	$t = -2.78$; $P < .01$
Pain	68.28	71.22	2.94	NS
General health	71.14	73.38	2.24	NS
Vitality	48.68	50.83	2.15	NS
Social functioning	66.62	72.04	5.42	$t = -2.47$; $P < .05$
Role-emotional	63.91	71.98	8.07	$t = -2.27$; $P < .05$
Mental health	71.48	73.70	2.22	NS
6-Month HRQOL	No (n = 228)	Yes (n = 211)		
Physical function	81.06	84.68	3.62	$t = -1.77$; $P = .08$
Role-physical	61.35	73.81	12.46	$t = -3.24$; $P < .01$
Pain	73.02	78.06	5.04	$t = -2.20$; $P < .05$
General health	70.63	76.31	5.68	$t = -3.11$; $P < .01$
Vitality	53.15	58.88	5.73	$t = -2.67$; $P < .01$
Social functioning	74.44	82.36	7.92	$t = -3.53$; $P < .01$
Role-emotional	77.82	77.35	−0.47	NS
Mental health	72.40	75.59	3.19	$t = -1.87$; $P = .06$

Abbreviation: HRQOL, health-related quality of life.

($P < .05$ in all cases; see Table 5). At the 6-month follow-up, vitamin D supplement users at baseline reported better role-physical function, less pain, better general health, and greater vitality and social function ($P < .05$ in all cases). Differences in physical function and mental health also favored supplement users but only trended toward statistical significance. Differences in most cases were within a range of scores generally considered clinically significant. Users of vitamin D supplements at 6-month follow-up also reported better social function and mental health when assessed at the 12-month follow-up ($P < .05$ in all cases; data not shown).

Multiple regression analyses were then conducted to determine whether age, time since diagnosis, race, ethnicity, cancer stage, marital status, use of chemotherapy or radiation, or type of surgery received might be confounders and explain the associations of vitamin D use and HRQOL found in unadjusted analyses. Analyses that included cohort were also conducted and are not reported because the results did not differ substantially from the models that did not include cohort. Variables were selected as potential confounders based on theoretical or demonstrated potential to influence HRQOL. Adjusted analyses examining predictors of self-reported baseline HRQOL status revealed that adjusted models had modest explanatory power and that adjustment reduced to statistical insignificance the associations of vitamin D supplement use on the role-physical, social functioning, and role-emotional scales but that the association of vitamin D use with the physical functioning scale remained statistically significant. Vitamin D supplement users reported on average 8.88 points better physical functioning in adjusted analyses. A difference of this size on this scale is usually considered clinically significant (data not shown).

When similar adjusted models were used to examine the predictive effects of vitamin D supplement use at study enrollment on 6-month HRQOL status, analyses revealed the women using vitamin D supplements reported less pain, in addition to improved general health, vitality, and social functioning ($P < .05$, $P < .01$, and $P < .001$, respectively). Table 6 presents the results of regression analyses. The advantages associated with vitamin D use varied among the subscales found in the adjusted analyses and ranged from 4.17 to 6.34 points.

In an effort to examine dose effects, we compared HRQOL reported by those who did and did not report using more than 1000 IU in the subsample of women (n = 265) who provided dose information. Again, users of vitamin D supplements of greater than 1000 IU at study enrollment reported better HRQOL. Specifically, they reported better levels of vitality, role-emotional health, and mental health ($P < .05$ for each), with a trend toward better social functioning ($P = .07$; data not shown).

Looking at blood levels of 25(OH)D as predictors of HRQOL, we compared the scores of those who were potentially vitamin D–deficient between diagnosis and enrollment

Table 6. Predictors of Change in HRQOL at the 6-Month Follow-up.[a]

	Physical Functioning, β	Role-Physical, β	Bodily Pain, β	General Health, β	Vitality, β	Social Functioning, β	Role-Emotional β	Mental Health β
Vitamin D supplement use at baseline			6.34**	4.17**	5.74**	6.19***		
Age	−0.18*	10.86**				0.47***		
Time since dx	−2.53*		−4.64**	−1.84*	−2.54**	6.82***		−1.99*
Race: nonwhite	Reference					11.11*		
Race							21.70*	
Ethnicity: non-Hispanic	Reference							
Ethnicity: Hispanic								
Stage: early	Reference							
Stage; late								
Stage; unknown								−13.20*
Marital status: partnered	Reference							
Marital status: single					−4.61*			
Chemotherapy								
Radiation								
Surgery: breast conserving surgery	Reference							
Mastectomy								
None								
Model R^2	0.36	0.18	0.29	0.56	0.43	0.35	0.18	0.45
Model *F*	17.66***	8.90***	16.53***	51.54***	30.85***	22.46***	6.75***	33.70***

Abbreviation: HRQOL, health-related quality of life.
[a]β Values from the multiple regression provided where statistically significant. *$P < .05$; **$P < .01$; ***$P < .001$.

(n = 48) contrasted with those with blood levels greater than 30 ng/mL (n = 112) recorded in their chart for this time period. These blood values predicted at enrollment levels of the SF-36 general health subscale [$t(80.43) = -2.3925$; $P < .01$] showing that those with higher values had scores almost 8 points higher. A larger absolute difference of 14 points was found between women with potentially deficient 25(OH)D blood levels and those with levels greater than 30 ng/mL on the role-physical subscale also, though in that case, the differences failed to achieve statistical significance [$t(82.11) = -1.81$; $P = .07$]. A 7-point advantage to women with blood levels greater than 30 ng/mL was also found for vitality, though it too was not statistically significant [$t(103.9) = -1.89$; $P = .06$]. Multiple regression analyses adjusting for additional predictors of HRQOL, including age, time since diagnosis, race, ethnicity, stage, and marital status, revealed 25(OH)D blood levels and age to be the only significant predictors of general health status. After adjustment, the advantage associated with nondeficient blood levels was 6.31 points (data not shown).

Discussion

In this observational study of survivors who do and do not use NO care to supplement UC oncology treatment, we found that vitamin D supplement use is common. Many survivors report that a recommendation for vitamin D supplementation came from their conventional medical care provider, with those who see NO providers more likely to report receiving a recommendation for vitamin D supplement use from a CAM provider. Those who see a NO provider may be more likely to use vitamin D supplements than those who rely on UC alone. We also found that nondeficient blood levels of vitamin D and vitamin D supplement use are associated with better self-reported HRQOL on multiple scales in both cross-sectional and predictive analyses. Although there is no single standard by which SF-36 scale scores are determined to be clinically significant, minimal significant differences have been reported with 2-to 5-point improvements in individual scale scores.[31] In this study, the differences associated with vitamin D use are larger than that and likely reflect clinically significant differences. These differences associated with vitamin D use and 25(OH)D blood levels are also larger and more consistent than differences in HRQOL associated with use of NO that we previously reported in this data set.[26]

In addition, we found that most breast cancer survivors are not monitored for vitamin D blood levels, and perhaps 30% of those who are may be vitamin D–deficient at some time after diagnosis. Levels of vitamin D–deficiency appear

to drop in our study population as levels of supplementation increase over time and as time since diagnosis increases. Unfortunately, much uncertainty is linked to estimates of survivors' blood levels of vitamin D because we found that only a minority of physicians recorded blood levels in patient charts. That said, concerning levels of deficiency are consistent with reports suggesting that vitamin D deficiency is common among older women in clinical populations generally[32,33] and among women with breast cancer.[17,29,30,34] Indeed, the levels of deficiency found in this study are notably lower than those reported in other studies where a majority, more than 70% of patients, were deficient.[17,29,30,34] Our reliance on medical chart abstraction for 25(OH)D levels is a significant limitation of this study. We cannot determine whether women in our study were more likely to have adequate blood levels of vitamin D or whether physicians were not testing many of the women who were most likely to be deficient. Our study participants were also generally posttreatment, which gave us limited ability to compare during and after treatment levels. In some of the cited studies, vitamin D level assessment occurred during chemotherapeutic treatment, and this may have contributed to the low blood levels found in those studies.

We also found that women who see NO providers appear to have higher blood levels of vitamin D when compared with women receiving only UC, but differences between the cohorts did not reach statistical significance. We were also unable to document substantial changes in vitamin D blood levels associated with women's typical levels of supplement use. For both these analyses, we could only use the subset of our participants with recorded blood tests in medical charts, and the relatively small number of patients with blood levels recorded in charts reduced the power of these investigations. Thus, we only had power to find moderate or large effects. We did find that higher rates of vitamin D supplement use at 6-month follow-up appear to be associated with higher average blood levels and reduced rates of vitamin D deficiency, consistent with recommendations for supplementation.[35] Prior studies failed to find significant changes in vitamin D blood levels associated with modest levels (400-1000 IU daily) of supplement use. Some of these studies were small, but results of larger studies have been mixed, suggesting that supplementation with less than 1000 IU may be inadequate to improve blood levels to 30 in some populations, including breast cancer patients.[34,35] A larger study would presumably be required to understand the effects of vitamin D supplement use by breast cancer patient survivors on 25(OH)D levels when supplement use is in the range of doses commonly used by women commonly seen in community practices.

Why modest levels of supplementation and blood levels greater than 30 ng/mL are associated with improved HRQOL in this sample is unclear. Few studies have examined effects of vitamin D supplements on HRQOL in breast cancer survivors. Those that have studied functional status and pain among breast cancer survivors taking aromatase inhibitors have not found changes in pain, menopausal symptoms, or breast cancer–related quality of life similar to those we report,[16,29,36] although Khan et al[16] did find improvements in pain with high-dose supplementation. In the case of Shapiro et al,[36] their measure appears to have been more specific to hand pain. Changes found in our study may be more dependent on changes in mood contributing to perceptions of general health, vitality, and social functioning. Randomized controlled trials have found that vitamin D supplement use is effective in reducing levels of depression[21] and enhancing mood in healthy participants during winter.[22] Mood may respond to vitamin D supplementation at lower levels than pain. Mood may also be very responsive to nonsupplement strategies for improving vitamin D levels, including solar exposure. It is also possible that breast cancer survivors with less severe mood-related challenges are more likely to take supplements.

Limitations

Although we feel it is useful to understand common practices and effects of vitamin D supplement use by breast cancer patients who do and do not visit NO providers, it is important to note that this study did not adjust for physical activity, lifestyle exposure to sunlight, and other lifestyle differences that might be associated with supplement use. These activities might also be associated with NO provider use or healthy lifestyles generally and would influence blood levels of vitamin D and patient moods. Many of our NO providers may have recommended a variety of healthy activities in addition to vitamin D supplementation that might have helped improve the HRQOL of their patients as did at least some of our participants' conventional providers. We found that HRQOL effects associated with blood levels of vitamin D suggest that vitamin D blood levels may influence HRQOL among breast cancer survivors. Although we found similar effects associated with supplementation, this does not explain the degree to which supplementation versus other activities may have contributed to participants' mood and makes further work exploring the effectiveness of supplement use by survivors of breast cancer important.

Conclusions

This report is a secondary analysis following up on a report that found modest improvements in HRQOL associated with NO care use among these women.[26] The differences found here associated with vitamin D levels and supplement use are substantially stronger, suggesting that the extent to which NO providers encourage vitamin D supplement use or healthy practices that increase vitamin

D blood levels may be one of the means by which NO providers improve the HRQOL of their patients. Naturopathic providers who see breast cancer patients in early survivorship should be aware that a substantial proportion of their patients may be potentially deficient for vitamin D and may benefit from recommendations to improve vitamin D levels. This study found that both nondeficient blood levels of vitamin D and vitamin D supplement use are associated with better self-reported quality of life in this population. Although this study focused on the first 2 to 3 years of cancer survivorship, additional follow-up of this cohort might offer a unique opportunity to describe the effects of vitamin D supplement use on recurrence and survival. Additional studies of vitamin D supplementation for breast cancer survivors are needed to better describe the amount of vitamin D women need to take in order to improve 25(OH)D blood levels when they are deficient during and after cancer treatment. It will also be important to explore the extent to which findings associating improved mood with vitamin D use reflect supplement use and nonsupplementation lifestyle means of increasing 25(OH)D levels.

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