Increased vitamin D and calcium intake associated with reduced mammographic breast density
among premenopausal women

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Abbreviations

AAFFQ; Harvard African American Food Frequency Questionnaire

BMI ; Body Mass Index

DNA; Deoxyribonucleic acid

MI; Melanin index

MUA ; Medically Underserved Area

MUPs; Medically Underserved Populations

ng/mL; Nanogram/Milliliter

NGH-BHC ; Nashville General Hospital's Breast Health Center

RR; Relative Risk

SAS; Statistical Analysis Software

Abstract

Vitamin D has been identified as a weak protective factor for postmenopausal breast cancer (relative risk [RR]~0.9), while high breast density has been identified as a strong risk factor (RR~4-6). To test the hypothesis that there is an association between vitamin D intake, but not circulating vitamin D levels, and mammographic breast density among women in our study we conducted a cross-sectional study of 165 screening mammography patients at Nashville General Hospital's Breast Health Center (NGH-BHC), a public facility serving medically indigent and underserved women. Dietary and total (dietary plus supplements) vitamin D, calcium intakes were estimated by the AAFQ and blood samples were analyzed for 25-Hydroxyvitamin D [25(OH)D3]. Average percent breast density for the left and right breasts combined was estimated from digitized films using an interactive-thresholding method available through Cumulus software. After statistical adjustment for age, race and body mass index, the results revealed there were significant trends of decreasing breast density with increasing vitamin D and calcium intake among premenopausal, but not among postmenopausal women. There was no association between serum vitamin D and breast density in pre- or postmenopausal women. Confirmation of our findings in larger studies may assist in clarifying the role of vitamin D in breast density.

Keywords: Mammography, Vitamin D, Cross-Sectional Studies, Medically Underserved

1. Introduction

Vitamin D has been identified as a weak protective factor for postmenopausal breast cancer (relative risk [RR]~0.9),[1] while high mammographic breast density, defined here as the percentage of fibroglandular tissue in the breast, has been identified as a strong risk factor (RR~4-6)[2]. Vitamin D has anti-proliferative and pro-differentiation effects in normal breast tissue, and could have direct or indirect influences on breast tissue composition [3]. A recent systematic review of the association between vitamin D and mammographic breast density included comparisons of four studies of vitamin D intake and four studies of circulating vitamin D levels [4]. Two of the studies of vitamin D intake reported significantly higher adjusted mean percent breast density for the highest versus lowest intake among all and premenopausal Hispanic women[5] and among all premenopausal women,[6] but in one study the reverse was true for postmenopausal women,[7] and the final study showed no association[8]. None of the four studies of circulating vitamin D levels conducted among pre- and postmenopausal women reported significant findings for adjusted mean percent density [9-12]. The above studies did not investigate the vitamin D and mammographic breast density association in Black women separately; however, findings in studies among mixed race populations have varied [7, 9, 12-14].

In view of the emerging evidence that vitamin D might be a breast cancer risk reduction factor, and the noted predilection for vitamin D deficiency in African American women, we propose to examine the association of vitamin D with breast density, an established marker of increased breast cancer risk. The relative risk associated with highly dense breasts is greater than most traditional risk factors such as nulliparity and early menarche making it an attractive target

1 for intervention. Unlike most other breast cancer risk factors, breast density may be influenced
2 by alterations in lifestyle, [15] including possibly improvement of vitamin D status.

3 We conducted a cross-sectional analysis of diet and serum vitamin D in relation to breast
4 density in a screening population with a large proportion of medically underserved African
5 American women. Medically Underserved Populations (MUPs) include groups of persons who
6 face economic, cultural or linguistic barriers to health care. Our primary research question was
7 to examine whether low serum D is associated with breast cancer through its association with
8 greater breast density. The study hypothesis was there would be an association between vitamin
9 D intake, but not circulating vitamin D levels, and mammographic breast density among women
10 in our study. The main objective of this project was to examine whether vitamin D, as measured
11 in the serum, effectively discriminates women with high and low risk breasts based on
12 mammographic findings. In order to examine this hypothesis we collected information on diet
13 and lifestyle, and obtained blood samples to store the serum and DNA. Plasma vitamin D
14 metabolite concentrations were examined among all of the women, and related to levels of breast
15 density measured in digitized mammogram. Overall our goals are to contribute important new
16 information on a potentially modifiable breast cancer risk factor, address disparities in breast
17 cancer research in an underserved African-American population that is at high risk for both
18 vitamin D deficiency and breast cancer, and provide critical pilot data for more definitive full-
19 scale studies.

2. Methods and Materials

We conducted a cross-sectional study to investigate the relationship between vitamin D and mammographic breast density. Eligible participants were medically underserved women aged 40 and older with no history of *in situ* or invasive breast cancer. The women were recruited from a county hospital mammography center located in a federally designated medically underserved area (MUA)[16]. An additional source of recruitment was ResearchMatch.org, a portal for linking interested individuals with active research studies[17]. A total of 165 women completed in-person interviews, blood draws, body measurements, and analog mammograms from December 2009 through February 2011(See Figure 1).

2.1 Study Procedures

In-person interviews were administered to assess lifestyle, sun exposure, family history of cancer, diet, reproductive history , demographic characteristics and established breast cancer risk factors. The Harvard African American Food Frequency Questionnaire (AAFFQ) and study-specific questions modified from the Collaborative Breast Cancer Study Questionnaire[18]were used to categorize dietary intake and supplement use of vitamin D and calcium into tertiles. The AAFFQ was used because it is a validated instrument that quantitatively measures dietary vitamin D. Serum vitamin D levels were assayed from blood samples [19-20] and categorized into tertiles and as deficient (<20 ng/mL). Plasma vitamin D metabolite concentrations were determined by radioimmunoassay (RIA), without knowledge of the mammographic findings of the subject. 25-Hydroxyvitamin D [25(OH)D3] was used as the marker of vitamin D status[21]. Vitamin D level results were classified into deficient, insufficient and sufficient Vitamin D levels [20, 22]. Anthropometric measurements included height and weight used to calculate body mass

index; waist and hips used to calculate waist-hip ratio; and for a subsample of women triceps, suprailiac and thigh skinfold thickness used to calculate body fat distribution [23].

Melanin index (MI) was estimated by measuring skin color at the underarm with the use of a Konica Minolta Portable Spectrophotometer (model CM-2600d). This device produces a direct and reproducible melanin index (MI) (Konica Minolta, Ramsey, NJ). The MI is the inverse amount of back-reflected light over the visible spectrum of wavelengths estimating light absorbed, accounting concentration of cutaneous melanin. . The melanin index provides a proxy estimate of vitamin D absorption through sun exposure [24]. Average percent breast density for the left and right breasts combined, was assessed from digitized films of analog mammograms using an interactive-thresholding method available through Cumulus software which is a well-validated computer-assisted planimetry program [25, 26]. Reliability of density measurements with this method is reported to be 90% or greater [15, 25]. Mammographic breast density measures were available for 154 women. The Institutional Review Boards of the participating institutions approved this study's protocol.

2.2 Statistical analyses

Statistical analyses were performed in SAS version 9.2. We calculated the power of the study to detect a range of odds ratios assuming 550 women are enrolled, of whom 40% will have $\geq 50\%$ breast density (the 'cases'). We further assume conservatively that 20% of those with lower breast density (the 'controls') will have low serum vitamin ($\leq 16\text{ng/ml}$). Under these assumptions, power will be adequate (80% or greater) to detect moderate main effect associations ($\text{ORs} \leq 0.57 / \geq 1.75$) at a p value of < 0.05 . We did not succeed in recruiting the planned number of subjects ($n=550$), however, the precision of our estimates from the study actually performed can be inferred from our 95% confidence intervals.

We used linear regression to estimate the mean percent breast density associated with vitamin D intake and circulating vitamin D levels while adjusting for confounding variables [27]. Race, age, educational level, marital status, household income, age at menarche, number of full-term pregnancies, age at first pregnancy, oral contraceptive use, diabetes, smoking, alcohol intake, body mass index (BMI), waist-hip ratio, melanin index, season of blood draw, age at menopause, and hormone replacement therapy were evaluated as potential confounders. Variables were considered confounders if their addition to the model changed the unadjusted mean by 10 percent or more. Findings are presented separately by menopausal status since breast density decreases during the menopausal transition [28]. We adjusted for age, race, and BMI which were confounders in our data, and additionally adjusted serum vitamin D analyses for season of blood draw.

3. Results

Premenopausal women were more likely than postmenopausal women to be white, more highly educated, divorced, widowed or separated, have a higher household income. Premenopausal women were also more likely, to have undergone a later age at menarche, and to be nulliparous, obese and to have a lower melanin index. Table 1 further illustrates the demographic characteristics and breast cancer risk factors of participants by menopausal status.

We observed a significant trend of decreasing breast density with increasing total vitamin D intake, vitamin D from food sources and total calcium intake after adjustment for age, race and BMI, in premenopausal women only. Similar associations were not observed among postmenopausal women. Table 2 presents mean breast density associated with dietary vitamin D and calcium intake by menopausal status.

Serum vitamin D was unrelated to mammographic breast density overall though a non-significant pattern of higher density with lower serum levels of vitamin D or a deficient state (<20 ng/mL) was observed in premenopausal women (N=57), after adjustment for age, race, BMI and season of blood draw. Table 3 further illustrates mean percent breast density in association with serum vitamin D levels and vitamin D deficiency by menopausal status.

4. Discussion

In the present study, our research hypothesis was accepted; increasing vitamin D intake was associated with reduced mammographic breast density in premenopausal women. Higher intake of calcium was also associated with more favorable patterns of breast density. Higher serum levels of vitamin D were also inversely associated with breast density in premenopausal women though findings were based on limited numbers of women and did not attain statistical significance. No similar associations were present among postmenopausal women. Our findings are consistent with those of Diorio et al., and others [4,5,29-31] which showed a benefit of these nutrients with breast density in pre-menopausal women only. Similarly, Bertone-Johnson et al.,[7, 32] found evidence of protective association with supplemental vitamin D in analyses restricted to younger women with high mammography breast density, or those at higher risk of developing breast cancer. Our failure to find associations in postmenopausal women is in agreement with Bertone-Johnson et al.,[7] and Vachon et al.,[8] for vitamin D intake and with several authors [8-11,13,33] for circulating levels of vitamin D. The outcomes of our study should be considered preliminary because of the following limitations; the sample size, cross-sectional nature of the study and limited generalizability due to recruitment from a single mammography center. Additionally, a single serum measure of vitamin D might not accurately classify subjects with respect to their usual vitamin D status.

1 The association of vitamin D and breast density remains unclear perhaps due to
2 misclassification of dietary intake, and the varying ability of some persons to absorb vitamin D
3 through sunlight[4]. Confirmation of our findings in larger longitudinal studies may assist in
4 clarifying the role of vitamin D in breast density over a longer duration of time.

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Figure

Figure1. Methods to recruit and deliver research study to participants for Vitamin D and mammographic breast density study.

Table 1. Demographic characteristics and breast cancer risk factors of participants by menopausal status ^a

Characteristic	Premenopausal (n=57)		Postmenopausal (n=106) ^b	
	n	%	n	%
Mean age (years)	57	46.2 ± 3.8	106	55.6 ± 7.0
Race				
White	30	52.6	50	47.2
Black	27	47.4	56	52.8
Educational level				
≤ High school	21	36.8	48	45.7
≥ Some college	36	63.2	57	54.3
Missing	0		1	
Marital status				
Married	18	31.6	30	29.9
Single/living with a partner	20	35.1	52	44.5
Divorced/widowed/separated	19	33.3	23	25.6
Missing	0		1	
Household income				
≤ \$19,999	26	47.3	55	53.4
\$20,000-\$39,999	12	21.8	26	25.2
\$40,000-\$59,999	8	14.5	10	9.7
≥ \$60,000	9	16.4	12	11.7
Missing	2		3	
Age at menarche (years)				
≤ 12	31	54.4	56	52.8
13	9	15.8	24	22.7
> 13	17	29.8	26	24.5
Number of full-term pregnancies				
0	16	28.1	23	21.7
1	7	12.3	21	19.8
2	16	28.1	28	26.4
≥ 3	18	31.5	34	32.1
Age at first pregnancy (years) ^c				
< 30	39	95.1	79	95.2
≥ 30	2	4.9	4	4.8
Oral contraceptive use				
No	12	21.1	26	24.5
Yes	45	78.9	80	75.5
Diabetes				
No	50	87.7	95	89.6
Yes	7	12.3	11	10.4
Type 1	1	1.8	3	2.8
Type 2	5	8.7	8	7.6
Don't know	1	1.8	0	0.0
Smoking				
No	22	39.3	41	38.7
Yes	34	60.7	65	61.3
Missing	1		0	

Table 1. Demographic characteristics and breast cancer risk factors of participants by menopausal status (continued)

Characteristic	Premenopausal (n=57)		Postmenopausal (n=106) ^a	
	n	%	n	%
Alcohol intake (grams) ^d				
None	24	42.1	46	43.4
<4.63	21	36.8	30	28.3
≥4.63	12	21.1	30	28.3
Body mass index (kg/m ²)				
<25	11	19.3	22	20.8
25-29.9	13	22.8	32	30.2
30-34.9	13	22.8	21	19.8
≥35	20	35.1	31	29.2
Waist-hip ratio				
<0.77	17	29.8	33	31.1
0.77-0.81	20	35.1	22	20.8
0.82-0.85	5	8.8	29	27.4
≥0.86	15	26.3	22	20.8
Melanin index				
<0.99	20	39.4	33	32.0
0.99-1.78	16	29.1	36	35.0
≥1.79	19	34.5	34	33.0
Missing	2		3	
Season of blood draw				
Summer	26	45.6	39	36.8
Spring	17	29.8	33	31.1
Fall	10	17.6	25	23.6
Winter	4	7.0	9	8.5
Age at menopause (years) ^e				
<50			78	73.6
50-54			24	22.6
≥55			4	3.8
Hormone replacement therapy use ^e				
No			63	59.4
Yes			43	40.6

^aFor continuous variables means ± SD are presented , for categorical variables percentages are presented.
For pre and post menopausal groups

^bInformation on menopausal status was missing for 2 women.

^cAmong parous.

^dFrom food frequency questionnaire.

^eAmong postmenopausal.

Table 2. Levels of breast density associated with dietary vitamin D and calcium by menopausal status^a

Characteristic	Premenopausal (n=57)			Postmenopausal (n=106)		
	n	% density ^b	95% CI	n	% density ^b	95% CI
Total vitamin D intake, IU/d						
<191.56	12	33.0	23.9-42.1	36	20.8	15.8-25.8
191.55-568.8	24	30.9	24.4-37.4	36	20.0	14.8-25.1
≥568.9	21	23.9	17.1-30.7	34	16.5	10.8-22.2
P for trend			0.03			0.67
Vitamin D from food sources, IU/d						
<124.57	16	32.7	24.5-40.8	32	20.2	15.0-25.5
124.57-243.86	21	31.0	24.2-37.8	36	16.9	11.6-22.1
≥243.86	20	23.4	16.3-30.4	38	20.6	15.5-25.7
P for trend			0.02			0.33
Total calcium intake, IU/d						
<730.1	13	30.2	21.1-32.2	33	20.4	15.2-25.7
730.1-1405.69	22	31.0	24.0-38.0	37	21.1	16.0-26.1
≥1405.69	22	25.7	19.0-32.5	36	16.1	10.8-21.4
P for trend			0.003			0.51

^aValues are means expressed as percentages and 95% confidence intervals^bAnalysis performed using linear regression adjusted for age, race, and BMI

Table 3. Percent breast density associated with serum vitamin D levels and vitamin D deficiency by menopausal status^a

Characteristic	Premenopausal (n=57)			Postmenopausal (n=106)		
	n	% density ^b	95% CI	n	% density ^b	95% CI
Serum vitamin D levels, ng/mL						
<17.55	20	29.7	21.3-38.0	35	19.4	13.5-25.4
17.56-28.6	16	26.4	17.7-35.2	38	23.4	17.5-29.3
≥28.7	21	25.0	16.3-33.6	33	20.2	14.1-26.3
P for trend			0.69			0.20
Vitamin D deficiency (<20 ng/mL)						
No	32	24.6	17.1-32.0	61	22.4	17.6-27.2
Yes	25	29.9	22.5-37.2	45	18.9	13.5-24.2
P-value			0.31			0.31

^aValues are means expressed as percentages and 95% confidence intervals.

^b Analysis performed using linear regression adjusted for age, race, BMI and season of blood draw.