Journal of Primary Care & Community Health
Volume 12: 1–5

DOI: 10.1177/21501327211017792
journals.sagepub.com/home/jpc
SAGE

Assessing Biomarkers of Breast Cancer Risk in Underserved Women in a Midwestern County

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Abstract

Objective: The primary aim of this study was to evaluate the feasibility of collecting risk factor information and accessing digitized mammographic data in a medically marginalized population. A secondary aim was to examine the association between vitamin D status and mammographic density. **Methods:** Breast-screening examinations were provided for age-appropriate patients, and a referral for no-cost screening mammography was offered. Study participants were asked to undergo 25-hydroxyvitamin D testing at mammography and 1-year follow-up. **Results:** Of 62 women approached, 35 (56%) consented to participate. Of 32 participants who had baseline mammography, the median mammographic density measured by VolparaDensity (Volpara Solutions Limited) was 5.7%. After 1 year, 9 women obtained follow-up mammograms, with a median density of 5.7%. Vitamin D status was measured for 31 participants at baseline and 13 participants in the following year. Insufficient vitamin D status (<30 ng/mL) was noted in 77% at each time point. Mammographic density was not significantly correlated with vitamin D status ($P = .06$). **Conclusions:** On the basis of this small pilot study, vitamin D insufficiency is common in this study population. Owing to the small sample size, an association between vitamin D insufficiency and breast density was not clear. Additional unexpected findings included substantial barriers in initial access to care and longitudinal follow-up in this population. Further study of these issues is needed.

Keywords

breast cancer, mammographic breast density, mammography, patients, underserved, vitamin D, 25-hydroxyvitamin D

Dates received: 1 April 2021; revised: 11 May 2021; accepted: 22 April 2021

Introduction

Although the lifetime risk of any cancer in the US population is 1 in 3, breast cancer remains one of the most predominant cancers in the United States, with a 1-in-8 lifetime prevalence among women.[1] Indeed, the incidence of breast cancer has been increasing at a rate of 0.4% per year since 2004.[2]

Breast cancer affects people in all racial and socioeconomic categories, but breast cancer outcomes differ significantly across these groups. Medically marginalized populations have disproportionately lower rates of screening and bear an undue burden of disease complications and death related to breast cancer. Among women, breast cancer is the most common cancer across all racial and ethnic groups, but the highest rates of breast cancer–related death are seen in Black women.[3] Specifically, in non-Hispanic Blacks, the rate of hormone receptor–negative/HER2-negative breast cancer is higher, which has a less-favorable prognosis.[1]

Various factors have been examined for potential correlations with breast cancer, including mammographic breast density and vitamin D status. Potentially, finding easily identifiable risk factors could help all women (especially in marginalized populations) to determine whether they have a higher risk status and potentially access screening earlier.

Mammographic breast density, the proportion of fibroglandular tissue seen on mammography, is strongly associated with risk of breast cancer. Women with mammographically dense

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breasts have 4 to 6 times the risk of breast cancer as women with low mammographic density.[4] Breast density generally decreases with age, especially after menopause.

Mammographic breast density can be assessed and reported in various ways. The Breast Imaging Reporting and Data System (BI-RADS) score is the most ubiquitous and requires a visual assessment of breast density by a radiologist for classification. It classifies breast density into 4 categories from A (least dense) to D (most dense). Computerized quantification methods are also available and remove the component of subjective interpretation. Of these, the VolparaDensity (Volpara Solutions Limited) breast density assessment method has more consistency between measurements than some other methods.[5]

There appears to be a link between mammographic breast density and plasma 25-hydroxyvitamin D [25(OH)D] status, but demonstration of that link in the literature has varied. In general, high vitamin D intake (via dietary sources or supplements) correlates with lower breast density.[6] Vitamin D deficiency is common in the general population, with 5% of the US population older than 1 year having deficiency or insufficiency.[7] Suboptimal levels of 25(OH)D are particularly prevalent in minority populations. In one study,[8] non-Hispanic Blacks were up to 6 times more likely to be deficient in vitamin D than non-Hispanic Whites.

In addition to vitamin D, multiple other lifestyle and reproductive factors influence breast cancer risk to some degree, including body mass index (BMI), smoking status, pregnancy history, lifetime cumulative duration of lactation/breastfeeding, age of menarche/menopause, and many others.[9]

The aim of this pilot study was to establish the feasibility of a large academic center interfacing with existing community resources to broaden access to basic health care screening and to engage populations that might not otherwise be screened. An additional goal was to evaluate the relationship between 25(OH)D status and mammographic density in a medically underserved population and to correlate other breast cancer risk factors, including reproductive, family, and hormonal history, with breast density in the study population. We hypothesized that breast density would be lower with higher levels of 25(OH)D.

Methods

Study Overview

This study was an open-label clinical trial in which participants received a free mammogram and measurement of 25(OH)D levels. This study was approved by our institutional review board (ID 16-004817), and written informed consent was obtained for all study participants.

Setting

Currently, our institution's Breast Clinic provides screening services for a community adult and family literacy program by way of breast examinations and annual mammography screening. The Breast Clinic follows our state's Department of Health cancer screening program guidelines, which enables underserved women to receive mammograms and clinical breast examinations at no charge to the patient, beginning at age 40 years, annually. Women younger than 40 years with breast concerns were also eligible for diagnostic breast imaging, covered also by the cancer screening program. Interpreter services were available for all clinical encounters for patients with a primary language other than English. The screening mammograms and diagnostic breast imaging procedures were completed at our institution.

All procedures were in accordance with the ethical standards of our institutional review board and with the Declaration of Helsinki 1975, as revised in 2000. Potential participants were recruited from the local community between October 10, 2013, and November 16, 2016. This report is based on all participants who went on to be treated in the study. The study adhered to the CONSORT guidelines for reporting of clinical trials.[10]

Participants

Eligible participants were at least 18 years old attending the free breast-screening clinic and understood and signed the study informed consent. After consenting to participation, they signed a written informed consent and were screened for study eligibility. If they accepted the invitation to participate in the study, participants were asked to have their blood drawn either before or after their free mammogram while at our institution. A study coordinator met patients when they arrived to escort them to their mammogram and to the blood draw. This was repeated 1 year later.

Outcomes and Safety Measures

For each participant, we (1) measured height and weight (with BMI calculated); (2) asked about hormone therapy use, history of breastfeeding, menopausal status, and vitamin/supplement use; and (3) measured serum 25(OH)D levels. Blood draws occurred at baseline/study initiation and after 1 year and involved less than 15 mL of blood per sample. All 25(OH)D tests were performed at our institution's laboratory using isotope-dilution liquid chromatography tandem mass spectrometry. Levels of 25(OH)D were quantified from serum samples, and mammographic density (VolparaDensity and BI-RADS score) was quantified from mammograms obtained at the time of the blood draw.

Statistical Analysis

Breast density percentage and serum 25(OH)D levels were compared with selected categorical participant characteristic categories (vitamin D supplementation, reproductive, hormonal, and family history risk factors) with Wilcoxon rank

sum or Kruskal–Wallis tests, as appropriate. Nonparametric (rank-based) Spearman correlation coefficients were computed to quantify the strength of the associations of 25(OH)D levels and breast density with age and BMI. The partial Spearman correlation was computed to quantify the association between 25(OH)D status and breast density, adjusting for age, BMI, and vitamin D supplementation. *P* values less than .05 were considered statistically significant.

Study data were collected with both paper-based case report forms and either paper or emailed surveys (per participant preferences). Data were managed using the REDCap tool hosted at our institution.[11] Data analyses were conducted using SAS statistical software (SAS Institute Inc).

This study was initially designed around the assumption that approximately 40% of the study participants would be vitamin D deficient and that the average mammographic density would be BI-RADS class B (approximately 30% glandular tissue) for perimenopausal women. Assuming an SD of 20% for mammographic density, with a sample size of 70 participants, we would have 80% power to detect an average difference of 14 percentage points in density between those who are deficient versus not deficient in vitamin D (effect size, 0.69). As the study progressed, this sample size was not achievable due to relatively few patients each month, and this will now serve as a pilot study to provide important preliminary information to enable the development of future related studies.

Results

Of 62 women approached during the study period, 35 (56%) consented to the study, 32 completed the baseline mammogram, and 31 also completed a blood draw for assessing 25(OH)D status. For the 32 women with a baseline mammogram, mean (SD) age at enrollment was 53.1 (8.0) years, 21 (66%) were postmenopausal, and mean (SD) BMI was 28.7 (6.0) (n = 26), with 11 (42%) overweight and 9 (35%) obese (Table 1). Half the women reported at least some level of vitamin D supplementation (either alone, or as part of a multivitamin).

All but 1 woman (97%) had at least 1 pregnancy, and the mean (SD) number of live births per study participant was 2.8 (1.8) (Table 1). Fifty-two percent of participants reported at least 1 year of breastfeeding in their lifetime. Regarding self-reported descriptors of ethnicity, 47% of the participants identified as Hispanic or Latino, 19% described their race as Asian, and 34% self-described as White.

On analysis of mammograms with BI-RADS density scoring, 14 participants (44%) had a density score of C or D at baseline. Using VolparaDensity analysis (available for 30 participants), the median percentage volumetric density was 5.7%. For the 31 women who had an initial vitamin D measurement, the mean (SD) serum total 25(OH)D was 24.4 (12.8) ng/mL, and 24 participants (77%) had levels less than 30 ng/mL (deficient or insufficient).

Table 1. Participant Characteristics.

Characteristic	Value (N = 32)[a]
Age, years	53.1 (8.0)
Race/ethnicity	
Hispanic	15 (47)
Non-hispanic white	11 (34)
Non-hispanic Asian	6 (19)
BMI value	28.7 (6.0) (n = 26)
Normal weight	6 (23)
Overweight	11 (42)
Obese	9 (35)
Live births	2.8 (1.8) (n = 31)
0	1 (3)
1-2	15 (48)
3-4	10 (32)
5-7	5 (16)
Breastfeeding history	n = 25
Never	4 (16)
< 1 year	8 (32)
≥ 1 year	13 (52)
Any vitamin D supplementation[b]	16 (50)
Mammographic density result, BI-RADS scoring	
1	2 (6)
2	16 (50)
3	12 (38)
4	2 (6)
Mammogram density result, 1-year follow-up	n = 9[c]
2	7 (78)
3	2 (22)

Abbreviations: BI-RADS, breast imaging reporting and data system; BMI, body mass index.
[a]Values are mean (SD) or No. (%).
[b]Medications, vitamins, and supplements were recorded at baseline.
[c]Among the 9 women with baseline and follow-up mammograms: 6 women had a result of 2 at both time points; 2 women had a result of 3 at both time points; and 1 woman changed results from 3 at baseline to 2 at follow-up.

After 1 year, repeat mammography was obtained at our institution in 9 participants. Using BI-RADS density scoring, 22% of this group (n = 2) had a density score of C. Among these 9 participants, 8 had the same BI-RADS result as baseline (score of B [n = 6], score of C [n = 2]), and 1 participant's score decreased from C to B. For the 6 participants with available VolparaDensity data at both time points, the median volumetric density was 5.7% at follow-up (vs 5.3% at baseline).

For 13 participants with levels of 25(OH)D obtained at 1-year follow-up, the mean (SD) value was 25.0 (12.2) ng/mL (vs 21.8 [11.3] ng/mL at baseline), and 10 participants (77%) had a 25(OH)D level in the deficient range. Two participants had a normal level at both time points, 9 were

deficient at both time points, 1 changed from normal to deficient, and 1 changed from deficient to normal.

A moderate difference in breast density percentage was noted by race/ethnicity. The median percentage density was highest among Asian participants (10.8%) as compared with Hispanic and White participants (6.3% and 4.8%, respectively; $P = .01$). Although 25(OH)D levels were slightly higher among Asian participants (median, 28.5 ng/mL) than among Hispanic (21.5 ng/mL) and White participants (19.0 ng/mL), this was not significant ($P = .06$).

Baseline volumetric breast density was moderately negatively correlated with age (Spearman correlation = −0.40) but not with BMI (−0.06). Baseline breast density was not significantly associated with vitamin D supplementation (median, 5.3% vs 6.2% for those with vs without supplementation; $P = .33$). Serum 25(OH)D level was positively correlated with age (0.53) and negatively correlated with BMI (−0.50). Mean 25(OH)D value was higher among women reporting at least some vitamin D supplementation (30.5 vs 18.8 ng/mL; $P = .003$). Adjusting for age, BMI, and vitamin D supplementation, a low correlation between breast density percentage and 25(OH)D level was detected (partial Spearman correlation = 0.14). Baseline breast density was not correlated with number of live births (Spearman correlation = −0.09, adjusted for age, BMI, and vitamin D supplementation).

Discussion

Extensive, existing evidence indicates that the rates of breast cancer screening are lower in medically marginalized populations.[2,3] There are multiple barriers to both initial access and follow-up in these populations, including lack of insurance coverage and transportation, incomplete education and knowledge about health care screening guidelines, and language and cultural barriers.[12] Many of these barriers are not easily addressed at the level of health care delivery and will require changes in health care policy. However, removing as many barriers as possible at the level of the patient's initial interface with the health care system is crucial to promoting access for vulnerable populations. This study showed that we were able to engage with an at-risk population and successfully offer age-appropriate screenings, with all participants completing baseline screening mammography and all but 1 completing baseline vitamin D measurement.

There are multiple challenges to maintaining longitudinal participation of underserved and minority populations in research studies.[13] In our study, participation in 1-year follow-up decreased substantially, with only 13 of the 31 patients with baseline vitamin D measurement (42%) returning for follow-up mammography and vitamin D measurement. Capitalizing on community partnerships, and delivering these educational interventions in friendly, community-centered health clinics, churches or other places where the community gathers, may help build trust in the medical community.[14]

The positive response offered anecdotally by the study participants to the services offered during this study suggests that lack of interest by medically underserved populations is not a primary barrier to obtaining cancer screening or accessing preventive health services. The relationship between health care access, screening completion, disease management, and overall health care outcomes in vulnerable populations is complex, but the need for these services is great and much appreciated by the populations involved.

This project offered an opportunity to provide community outreach, mammographic screening, and clinical breast examinations to a medically underserved population. In the process of fostering a dialog about breast health and screenings, more detailed discussions about risk factors related to breast cancer were able to occur. Although logistical barriers hampered sequential follow-up measurements of serum vitamin D after 1 year, the vast majority of our study population was willing to obtain a baseline vitamin D measurement at the time of their initial mammogram. Similar to other studies,[15] this finding demonstrates a willingness of the study population to explore other potential risk factors for cancer and participate in clinical research.

Our initial study population was heterogeneous, with a large range in age, ethnicity, education level, BMI, and pregnancy history. We observed a high level of vitamin D inadequacy that was persistent over the study period. Overall breast density was fairly static over the course of our study and was not obviously correlated with serum 25(OH)D status in the small subgroup that completed both breast density evaluation and vitamin D measurements at baseline and follow-up testing. Given the small sample size and heterogeneous study population, our study did not have adequate power to detect a significant correlation between breast density and 25(OH)D levels. Our study also did not control for the time of year during which vitamin D levels were obtained, which may also present a confounding factor in seeking correlations with breast density. There is a need for further investigation of the complex relationship between serum 25(OH)D levels, mammographic breast density, and overall breast cancer risk in all populations, but especially in groups who are less likely (for various reasons) to access standard and age-appropriate screenings.

Conclusion

On the basis of this small pilot study, the incidence of vitamin D insufficiency appears to be high in the study population. Because of the small number of participants, a clear association between vitamin D insufficiency and breast density was more difficult to detect. Although we saw success in partnering with existing community resources and interest from populations in need of screening, there appear to be

significant barriers in initial access to care as well as longitudinal follow-up in this population. Further study on these issues is needed.

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To expedite proof approval, send proof via email to scipubs@mayo.edu.

Authors' Contributions

All the authors participated in the study concept and design, analysis and interpretation of data, drafting and revising the paper, and have seen and approved the final version of the manuscript.

Acknowledgments and Compliance with Ethical Standards

We thank Thomas E. Witzig, MD, for the endless support and advice during the study process. Special thanks to the exceptional research staff of the Clinical Research, Department of Medicine at Mayo Clinic for their patience and persistence in helping to collect, compile, and organize these data. Special thanks to Katrina A. Croghan, CCRP, Shawn C. Fokken, CCRP, and Fang Fang Wu for their hard work and dedication to this study. Finally, we also thank the study participants who participated in this clinical trial, without whom this project would not have been possible.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported in part by the Department of Medicine Clinical Research Office. The data entry system used was REDCap, supported in part by the Center for Clinical and Translational Science award (UL1 TR000135) from the National Center for Advancing Translational Sciences (NCATS).

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Availability of Data and Materials

All data supporting the study findings are contained within this manuscript.

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