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PRINCIPAL INVESTIGATOR: Maureen Sanderson, Ph.D.

CONTRACTING ORGANIZATION: Meharry Medical College
Nashville, TN 37208

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| 14. ABSTRACT The purpose of this HBCU/MI Partnership Training Award is to train Meharry Medical College faculty to conduct independent breast cancer research by collaborating with faculty from Vanderbilt University Medical Center. Year 1 was a training year and during Years 2 through 4 a case-control study of obesity, insulin resistance and mammographic breast density is being conducted. Specific aims include: 1) to assess mammographic breast density through digital mammograms; for a sample of women we will also assess mammographic breast density through film mammograms to determine the diagnostic accuracy of digital versus film mammogram, 2) to obtain information on breast cancer risk factors including health literacy, and to collect anthropometric measurements and fasting blood, 3) to assay blood for select hormones and growth factors, 4) to perform statistical analyses to determine the associations between obesity and insulin resistance and mammographic breast density, and 5) to evaluate patients' ability to understand their mammogram findings as they are explained by their medical provider. Drs. Sanderson, O'Hara and Khoder attended/presented at conferences and published a manuscript. Continuing institutional review board approval was obtained for the Mammographic Breast Density Project. Subject recruitment, data collection and processing, auditing quality assurance, and performing interim analyses were completed on 476 women. | | | | |
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Table of Contents

| | <u>Page</u> |
|--|-------------|
| Introduction..... | 4 |
| Body..... | 4 |
| Key Research Accomplishments..... | 5 |
| Reportable Outcomes..... | 5 |
| Conclusions..... | 5 |
| References..... | 6 |
| Appendices..... | 7 |

Introduction

The purpose of this HBCU/MI Partnership Training Award is to train Meharry Medical College (MMC) faculty to conduct independent breast cancer research by collaborating with faculty from Vanderbilt University Medical Center (VUMC). Three MMC faculty will undergo intensive training supervised by three VUMC faculty during year 1 with additional training taking place in subsequent years. To reinforce training, faculty from MMC and VUMC will conduct a case-control study of mammographic breast density to investigate its' association with obesity and insulin resistance in years 2 through 4. Cases (n=150) whose breasts are in the upper quartile of breast density and controls (n=850) whose breast are in the lowest three quartiles of breast density, will be recruited from the MMC Center for Women's Health Research which serves a medically underserved population. Specific aims are: 1) to assess mammographic breast density through digital mammograms; for a sample of women we will also assess mammographic breast density through film mammograms to determine the diagnostic accuracy of digital versus film mammogram, 2) to obtain information on breast cancer risk factors including health literacy, and to collect anthropometric measurements and fasting blood, 3) to assay blood for select hormones and growth factors, 4) to perform statistical analyses to determine the associations between obesity and insulin resistance and mammographic breast density, and 5) to evaluate patients' ability to understand their mammogram findings as they are explained by their medical provider.

Body

As indicated in the Statement of Work (Appendix), this project is occurring in two phases, the training phase (year 1) and the investigation phase (years 2 through 4). We completed all training tasks during the first year of the project; however, ongoing training tasks include the attendance and presentation of MMC investigators at workshops and conferences, the publication of manuscripts utilizing existing data, and Institutional Review Board (IRB) approval of the Mammographic Breast Density Project. Dr. Waseem Khoder an MMC co-investigator began a fellowship in urologic gynecology and was replaced by Dr. Nia Foderingham, a Preventive Medicine physician with a Master's of Science in Public Health, effective October 21, 2013. Dr. Maureen Sanderson attended the Society for Epidemiologic Research conference, and Drs. Heather O'Hara and Nia Foderingham attended the American College of Preventive Medicine conference. The MMC (Drs. Sanderson, O'Hara, Foderingham) and VUMC (Drs. Dupont, Shu, Peterson) investigators presented a poster at the Society for Epidemiologic Research conference and submitted a manuscript for publication (Appendix includes the abstract and manuscript). We obtained continuing IRB approval for the project from MMC on 9/8/2014, VUMC on 1/27/2014, and the Department of Defense (DOD) on 9/11/2014.

During the fourth year of the project we continued in the investigation phase. The study team has met on a monthly basis and the investigative team (Drs. Sanderson, O'Hara, and Foderingham from MMC and Drs. Dupont, Shu and Peterson from VUMC) has met on a quarterly basis. Between October 12, 2013 and March 31, 2014 we completed subject recruitment and data collection of 62 participants for a total of 476 participants of the 480 participants we had proposed (Appendix includes the methods manuscript). We fully completed investigation tasks 2 through 5 by quantitating mammographic breast density measurement; recruiting subjects and collecting data; assessing health literacy; and processing blood samples, taking body measurements and performing assays. We fully completed investigation tasks 7 and

8 by conducting ongoing quality assurance audits to ensure patient safety and integrity, and conducting interim analyses.

We received a no cost extension on June 17, 2014 to extend the period of performance through June 31, 2015. During the fifth year of the project, we will fully complete investigation task 9 by conducting final analyses and disseminating data. We will not complete investigation task 6 by comparing analog and digital mammograms because it is beyond the scope of the study.

Key Research Accomplishments

- Completed ongoing training task by Drs. Sanderson, O'Hara and Khoder attending conferences, presenting a poster at a conference, and publishing a manuscript.
- Completed ongoing training task by obtaining continuing IRB approval from three entities.
- Fully completed investigation tasks 2 through 5 by recruiting subjects and collecting and processing data (digital mammograms, blood, body measurements, questionnaires including health literacy).
- Fully completed investigation tasks 7 and 8 by conducting quality assurance audits and interim analyses.
- Partially completed investigation task 9 by conducting final analyses and disseminating data.

Reportable Outcomes

1) Manuscripts

Sanderson M, O'Hara H, Foderingham N, Dupont WD, Shu X-O, Peterson N, Fair AM, Disher AC. Type 2 diabetes and mammographic breast density among underserved women. Cancer Causes Control (under review).

2) Abstracts

Sanderson M, O'Hara H, Foderingham N, Dupont WD, Shu X-O, Peterson N, Fair AM, Fadden MK. Diabetes and mammographic breast density among white and black women. Am J Epidemiol 2014;179:L02.

3) Grants

Not applicable

Conclusions

The overall goal of this proposed HBCU/MI Partnership Training Award is to strengthen the existing collaborative relationship between the minority institution, MMC, and the collaborating institution, VUMC. The investigators from MMC and VUMC have mutual interests in studying the interplay of lifestyle and molecular factors on breast cancer risk as measured by its precursor, mammographic breast density. High mammographic breast density is

comparable in its predictive magnitude of risk to historically well-established breast cancer risk factors. The biological basis for the association between higher percentage of density and risk of breast cancer is not clear but may be related to increased stroma and glandular tissue in dense breasts through estrogen exposures or production of certain growth factors including insulin-like growth factor-I (IGF-I) or adipokines such as leptin. Very few studies have focused on obesity and insulin resistance as they relate to mammographic breast density. We hypothesize that: 1) obesity and insulin resistance, defined as high levels of C-peptide, will be positively associated with high mammographic breast density, and 2) these associations will be more pronounced among women with high levels of IGF-I and high levels of leptin.

This project will establish associations between some lifestyle and molecular factors and mammographic breast density; known to be linked to subsequent breast cancer, especially in minority and medically underserved women. By identifying biomarkers that influence mammographic breast density in minority women, this project may provide therapeutic targets for new prevention strategies in this population. While faculty from VUMC has expertise in breast cancer research, faculty from MMC has strong ties with minority communities in Nashville and Davidson County. To date, limited breast cancer research has been conducted at MMC. By partnering together, MMC and VUMC hope to build infrastructure to conduct population-based case-control studies of breast cancer at MMC, and to establish an outstanding collaborative breast cancer research program.

References

Sanderson M, O'Hara H, Foderingham N, Dupont WD, Shu X-O, Peterson N, Fair AM, Disher AC. Type 2 diabetes and mammographic breast density among underserved women. Cancer Causes Control (under review).

Statement of WorkPhase 1: Training Phase (Year 1)

Task 1: (Drs. Sanderson, Khoder, Jones, Richard-Davis, Disher, Sanderson, Dupont, Peterson and Shu) (Jones replaced by O’Hara and Khoder replaced by Foderingham)

- 1a. Drs. Sanderson, Khoder and Jones audit courses at Summer Research program at University of Michigan (months 6-7).
- 1b. Dr. Jones begins the Meharry Medical College, Master’s of Science in Clinical Investigation Program (months 1-30).
- 1c. Consult with advisory board and health providers in the Center for Women’s Health Research (CWHR) to design a cross-sectional study for measurement of mammographic breast density, related hormones and health literacy (months 1-3).
- 1d. Develop and finalize study protocol for recruitment of participants (months 1-6).
- 1e. Develop and finalize study protocol for obtaining analog screening mammograms and digital mammograms (months 1-3).
- 1f. Finalize advertisements for contacting participants, questionnaires, and other data collection forms (months 1-3).
- 1g. Order supplies for blood collection and processing, order supplies for performing assays (months 5-6).
- 1h. Create and finalize quality assurance audit forms to ensure safety of participants and integrity of all data (months 4-6).
- 1i. Update IRB protocols, informed consent documents, and HIPAA waivers for IRB submission (months 4-6).
- 1j. Generate standard operating procedures manual to reflect all aspects of study procedures (months 4-6).
- 1k. Work with Dr. Dupont to modify accrual database to include scripts and screening forms, and allow accrual and productivity reports to be generated (months 7-12).
- 1l. Work with the project coordinator to create REDCAP database for entry of study data (months 7-12).

Phase 2: Investigation Phase (Years 1 through 5)

Specific Aim 1) to assess mammographic breast density through digital mammograms; for a sample of women we will also assess mammographic breast density through analog mammograms to determine the efficacy of digital versus analog mammogram;

Specific Aim 2) to obtain information on breast cancer risk factors including health literacy, and to collect anthropometric measurements and fasting blood;

Specific Aim 3) to assay blood for select hormones and growth factors;

Specific Aim 4) to perform statistical analyses to determine the association between obesity and insulin resistance and mammographic breast density;

Specific Aim 5) to evaluate patients’ ability to understand their mammogram findings as they are explained by their medical provider.

Task 2: (Drs. Sanderson, Dupont, Disher, Khoder) (Khoder replaced by Foderingham)

Quantitate mammographic breast density measurement, Months 1-42.

- 2a. Work with Dr. Disher to refine protocols for mammographic density analyses (months 1-12).
- 2b. Work with Dr. Disher to observe Cumulus computer program to quantify breast density (months 7-12).
- 2c. Coordinate flow of digital mammography data from the Center of Women's Health Research to Dr. Disher for quantitation (months 7-42).
- 2d. Assess breast density of mammograms using digital quantitative analysis to obtain the percentage of the breast occupied by breast tissue (months 7-42).

Task 3: (Drs. Sanderson, Jones, Disher) (Jones replaced by O'Hara)

Recruit subjects and collect data, Months 7-42.

- 3a. Screen and recruit potentially eligible women for digital mammography study at the Center for Women's Health Research (1,000 patients total) (months 7-42).
- 3b. Administer questionnaire (months 7-42).
- 3c. Perform standardized body measures; weight, height, skinfold thickness, and waist and hip circumference (months 7-42).
- 3d. Collect blood samples and transport to Vanderbilt molecular epidemiology laboratory for storage and processing (months 7-42).
- 3e. Order additional supplies as needed (months 7-42).

Task 4: (Drs. Jones, Khoder and Peterson) (Jones replaced by O'Hara and Khoder replaced by Foderingham) Months 7-42.

- 4a. Administer Short Test of Functional Literacy in Adults (S-TOFHLA) to study participants (months 7-42).
- 4b. Score S-TOFHLA instruments and categorize levels of patient's health literacy (months 7-42).

Task 5: (Drs. Sanderson, Jones, Khoder and Shu) (Jones replaced by O'Hara and Khoder replaced by Foderingham)

Process blood samples, measurements and perform stated assays, Months 7-42.

- 5a. Supervise research staff in acquisition and analysis of data (months 7-42).
- 5b. Separate serum, plasma and clot in blood sample and store at -80°C (months 7-42).
- 5c. Transport biospecimens to the Vanderbilt University molecular epidemiology laboratory for processing and analysis (months 7-42).

Task 6: (Drs. Khoder, Disher and Dupont) (Khoder replaced by Foderingham) Months 7-42.

- 6a. Obtain analog mammography films and digital mammography films for each participating patient for rating of quantitative breast density by interpretation (months 7-42).
- 6b. Calculate the sensitivity and specificity of each modality for detecting mammographic breast density (months 7-42).
- 6c. Perform statistical analyses to account for multiple comparisons in breast density subgroups (months 40-42).

Task 7: (Drs. Sanderson, Jones, Khoder , Dupont) (Jones replaced by O’Hara and Khoder replaced by Foderingham)

Conduct ongoing quality assurance audits to ensure patient safety and data integrity, Months 7-48. Twice monthly monitoring of activities (number of screening phone calls logged, number and type of contacts with potential or actual participants, progress with data entry, etc.).

- 7a. Twice monthly monitoring of study accrual (months 7-42).
- 7b. Continuous monitoring/reporting of potential adverse events (months 7-48).
- 7c. Monthly audits to verify study staff adherence to standard operating procedures (months 7-48).

Task 8: (Drs. Sanderson, Jones, Khoder, Shu, Dupont, Peterson) (Jones replaced by O’Hara and Khoder replaced by Foderingham)

Conduct interim analyses, Months 12-48.

- 8a. Perform interim statistical analysis (months 12-18, months 24-30, months 36-42).
- 8b. Preparation and submission of abstracts reflecting findings to date (months 36-48).
- 8c. Creation and submission of annual reports to funding agency (months 12, 24, 36).

Task 9: (Drs. Sanderson, O’Hara, Khoder, Shu, Dupont, Peterson)

Final analyses and dissemination of data, Months 40-58.

- 9a. Begin final statistical analyses (months 40-58).
- 9b. Preparation and submission of final report to funding agency (months 58).
- 9c. Preparation and submission of abstracts and manuscripts reflecting final results (months 40-58).

Diabetes and mammographic breast density among white and black women. *M. Sanderson, H. O'Hara, N. Foderingham, W. Dupont, X.O. Shu, N. Peterson, A.M. Fair, M.K. Fadden. (Meharry Medical College, Nashville, USA).

Diabetes, independent of obesity, has been identified as a weak risk factor for breast cancer (relative risk [RR]~1.2), while high mammographic breast density has been identified as a strong risk factor (RR~4-6). The very few studies of the association between diabetes and high breast density, defined here as the percentage of fibroglandular tissue in the breast, have been mixed. We conducted a study of women recruited at a historically black medical school to investigate the relationship between diabetes and mammographic breast density. A total of 479 women completed in-person interviews, body measurements and full-field digital mammograms on a Hologic™ workstation from December 2011 through February 2014. Average percent breast density for the left and right breasts combined was estimated using Quantra™, an automated algorithm for volumetric assessment of breast tissue. After adjustment for race, age, and body mass index, premenopausal women without a self-reported history of diabetes had a greater mean (μ) percent breast density (μ 17.0, standard error [SE] 1.80) than diabetic women (μ 15.0, SE 1.83) ($p=0.06$); however, there was no association among postmenopausal women. When we stratified by race, the diabetes and percent breast density relation was present in white women (non-diabetic μ 16.4, SE 2.05; diabetic μ 13.3, SE 2.16; $p=0.05$), but not in black women (non-diabetic μ 16.6, SE 0.84; diabetic μ 15.8, SE 1.34; $p=0.55$). We were unable to examine a potential effect of metformin on decreasing breast density due to its low use. Confirmation of our findings in larger studies may assist in clarifying the role of the insulin signaling pathway in high breast density.

Type 2 Diabetes and Mammographic Breast Density among Underserved Women

Maureen Sanderson, PhD¹, Heather O'Hara, MD, MSPH¹, Nia Foderingham, MD, MSPH¹,

William D. Dupont, PhD², Xiao-Ou Shu, PhD², Neeraja Peterson, MD²,

Alecia M. Fair, DrPH², Anthony C. Disher, MD¹

¹ Meharry Medical College, Nashville, TN 37208, USA

² Vanderbilt University Medical Center, Nashville, TN 37203; USA

Running title: Diabetes and breast density

Correspondence: Dr. Maureen Sanderson, Department of Family and Community Medicine,
Meharry Medical College, 1005 Dr. D.B. Todd Jr. Blvd., Nashville, TN 37208, USA; telephone:
615-321-2977; fax: 615-327-6296; e-mail: msanderson@mmc.edu

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Abstract

Purpose: High mammographic breast density has been identified as a strong risk factor for breast cancer (relative risk [RR]~4-6), while type 2 diabetes has been identified as a weak risk factor (RR~1.2). The very few studies of the association between diabetes and high mammographic breast density, defined here as the percentage of fibroglandular tissue volume in the breast, have been mixed. We conducted a study of women recruited at a Historically Black Medical School to investigate the relationship between diabetes and mammographic breast density.

Methods: A total of 476 women completed in-person interviews, body measurements and full-field digital mammograms on a Hologic mammography unit from December 2011 through February 2014. Average percent breast density for the left and right breasts combined was estimated using Quantra, an automated algorithm for volumetric assessment of breast tissue. The prevalence of type 2 diabetes was determined primarily by fasting c-peptide levels.

Results: Premenopausal women with and without type 2 diabetes had similar mean percent breast density after adjustment for confounding variables. This finding was also true for postmenopausal women.

Conclusions: There was no association in premenopausal or postmenopausal women between type 2 diabetes based on c-peptide levels and breast density. Confirmation of our findings in larger studies may assist in clarifying the role of the insulin signaling pathway in women with high breast density.

Keywords: mammographic breast density, type 2 diabetes, cross-sectional study, underserved

Introduction

Type 2 diabetes has been identified as a weak risk factor for breast cancer, independent of obesity. Meta-analyses of the association between diabetes and breast cancer have reported summary relative risks (RR) of approximately 1.20, with 95% confidence intervals (CI) ranging from 1.12 to 1.30 [1-4]. Three of the four meta-analyses stratified by menopausal status at breast cancer diagnosis reported an increased risk of postmenopausal breast cancer associated with diabetes among women, but not among premenopausal women [2-4]. The increase in postmenopausal breast cancer risk associated with diabetes was also reported in a recent large cohort study conducted since these meta-analyses [5]. In another more recent large cohort study, Bowker and colleagues [6] reported that risk for breast cancer diagnosed among women at age 55 years or older, and presumably postmenopausal, was non-significantly increased for 0 to 3 months following diabetes diagnosis (hazard ratio [HR] 1.31, 95% CI 0.92-1.86), but then returned to baseline from 3 months to 10 years following diabetes diagnosis (HR 1.00, 95% CI 0.90-1.11). The authors concluded that the initially elevated postmenopausal breast cancer risk may have been due to detection bias.

High mammographic breast density is a well-established risk factor for breast cancer. Depending on how high mammographic breast density is defined, the range of RRs for breast cancer is around 4 to 6 [7]. In a meta-analysis of 42 studies, the group of women whose fibroglandular tissue comprised $\geq 75\%$ of breast tissue had a summary RR for breast cancer of 4.64 (95% CI 3.64-5.91) relative to women with $< 5\%$ [8]. Several breast cancer risk factors that affect the growth (proliferation and apoptosis) and/or differentiation of breast tissue, such as pregnancy, menopause, hormone replacement therapy, and hormone levels, are also associated with mammographic breast density [9-11]. Few studies have assessed breast density among

Black or Hispanic women. In comparison to White women, Black women have been reported to have denser breasts [12-14], breasts of similar density [15-16] or less dense breasts [17], while Hispanic women have been reported to have breasts of similar density [12, 17]. These studies varied in regard to the age of the study subjects and the methods used to assess breast density.

Although mammographic breast density is thought to be an intermediate phenotype of breast cancer [18], very few studies have investigated the association between diabetes and mammographic breast density. Robideaux et al. [19], in a study of Southwestern Native-American women, classified breast density using Breast Imaging Reporting and Data System (BI-RADS) categories of 1 (fat) through 4 (dense) [20] of analog mammograms, and found that self-reported diabetes was associated with lower breast density (moving up from one BI-RADS category to the next) in premenopausal ($p=0.0032$) but not in postmenopausal women ($p=0.3178$). Sellers et al. [21], in a study of primarily White women in Minnesota, found no association between self-reported type 2 diabetes and breast density based on a computer-assisted thresholding program (Cumulus) [22] of analog mammograms in premenopausal or postmenopausal women. However, these investigators did identify a positive association between diabetes and breast cancer. Diorio et al. [23], in a study of primarily White women in Quebec City, found a significant negative association ($r_s=-0.210$, $p<0.0001$) between non-fasting c-peptide levels and breast density based on the Cumulus thresholding program in premenopausal and postmenopausal women combined. This association disappeared after adjustment for body mass index (BMI) and waist-to-hip ratio (WHR) ($r_s=-0.022$, $p=0.41$), and after stratification by menopausal status (premenopausal $r_s=-0.034$, $p=0.37$; postmenopausal $r_s=-0.003$, $p=0.94$).

In an attempt to isolate the effect type 2 diabetes has on breast cancer in a racially and ethnically diverse population we conducted a clinic-based cross-sectional study of diabetes and mammographic breast density.

Materials and Methods

We conducted a clinic-based cross-sectional study of underserved women aged 40 to 79 years recruited at a Historically Black Medical School between December 2011 and February 2014 to investigate mammographic breast density. Women were recruited by placing flyers around the campus, and at health fairs and local community agencies. The flyer described the study and asked women to provide contact information if they were interested in participating. Project staff telephoned each woman to evaluate eligibility and to schedule a study appointment. Women who were pregnant, unable to comprehend study materials, or had a history of cancer, breast augmentation or reduction, symptoms of a breast disorder, or a focal dominant lump were ineligible. Premenopausal women were asked the date of their last menstrual period so their appointment could be scheduled during the follicular phase (1-14 days) of their menstrual cycle when their breast tissue is less dense. The day prior to their appointment women were telephoned and reminded to observe a 10-hour fast for their blood draw the following morning. For the present study, c-peptide (a biomarker of insulin secretion) was measured in fasting serum samples using chemiluminescence technology- based assay kits on a proprietary automated moderate complexity endocrine panel (Immulite 1000) according to the manufacturer's instructions (Siemens, Dallas, TX). The calculated sensitivity of the assay (N = 6) was 0.03 ng/tube and the intra--assay coefficients of variation (CVs) for levels 1, 2 and 3 controls (N = 10/level of control) were 2.24, 3.42 and 2.99%, respectively. The inter-assay CVs are not available because the sera were batch analyzed in two assays.

The Institutional Review Boards of Meharry Medical College and Vanderbilt University approved this study's protocol. After informed consent was obtained, women provided a fasting blood sample, underwent body measurements (height, weight, waist, hips, percent body fat) and a digital screening mammogram, and completed an in-person interview on demographics, lifestyle factors, personal health history, family history of cancer and other chronic diseases, adult weight history, diet, and health literacy. A trained radiologic technician completed full-field digital screening mammograms on a Hologic mammography unit that uses selenium direct capture technology to eliminate light diffusion completely for perfect clarity and image quality. Our study radiologist (ACD) estimated average percent breast density, defined as the ratio of estimated fibroglandular tissue volume to total breast volume, for the left and right breast combined using Quantra software. Quantra, an automated algorithm for volumetric assessment of breast tissue, assigns BI-RADS categories allowing for the identification of abnormal mammograms (BI-RADS=0: additional imaging evaluation, BI-RADS=3: probably benign finding or BI-RADS=4: suspicious abnormality). Subjects with abnormal mammograms (BI-RADS=0, n=45; BI-RADS=3, n=3; BI-RADS=4, n= 2) were notified immediately by certified mail, while subjects with normal mammograms were notified of their results within 30 days.

To define diabetes, we used serum c-peptide (available for 454 women) followed by information from the questionnaire (for the remaining 25 women for whom c-peptide was unavailable). Women were considered diabetic if they had a fasting serum c-peptide >2.0 ng/mL [24] or for those women missing c-peptide information they responded "Yes" to the question "Did a doctor or other health care provider ever tell you that you had diabetes, or high sugar in your blood or urine?" on the questionnaire. Women who indicated they had diabetes "Only during pregnancy" on the questionnaire were categorized as non-diabetic. On the questionnaire, women who reported they had diabetes were then asked how old they were when they were first

told they had diabetes and whether they used pills or insulin injections to control their diabetes.

Women who indicated their age at diabetes diagnosis was ≤ 30 years were considered to have type 1 diabetes regardless of their c-peptide level [25]. For the medication analysis, women who used pills and then switched to insulin to control diabetes were classified as having used insulin. BMI (kg/m^2) and WHR were calculated from body measurements and percent body fat was estimated from a body fat monitor scale. Of the 479 women recruited, exclusions due to incomplete interviews ($n=3$), type 1 diabetes ($n=11$), and unknown age at diabetes diagnosis ($n=1$) resulted in 175 premenopausal women and 289 postmenopausal women for analysis.

Statistical analyses were performed in SAS version 9.2. Linear regression was used to estimate mean percent breast density by diabetes status, while adjusting for confounding variables [26]. We stratified by menopausal status a priori, since fibroglandular breast tissue decreases during the menopausal transition [27]. Covariates examined as potential confounders of the relationship between diabetes and mean percent breast density included race/ethnicity, age, education, family history of breast cancer, family history of diabetes, age at menarche, parity, age at first pregnancy, oral contraceptive use, smoking, alcohol intake, physical activity, BMI, WHR, percent body fat, age at menopause and hormone replacement therapy (HRT) use as categorized in Table 1. Variables were considered confounders if their addition to the model changed the unadjusted mean percent breast density by 10 percent or more. We stratified by menopausal status and adjusted for race/ethnicity, age and BMI, and additionally for HRT use among postmenopausal women which met our criteria for model inclusion. Adjustment for WHR and percent body fat did not meet our criteria for confounding. We performed a validation study of self-report of diabetes using serum C-peptide as the gold standard. Sensitivity and specificity and their respective confidence intervals were calculated as measures of validity. In addition, we

performed a sensitivity analysis by examining our findings with and without the inclusion of 50 women with abnormal mammograms and our results were similar.

Results

Table 1 presents the demographic characteristics and breast cancer risk factors of participants by menopausal status. A high prevalence of women in both groups possessed several breast cancer risk factors including family history of breast cancer, younger age at menarche, alcohol intake, no physical activity and high body measurements. The percentage of all women reporting a family history of diabetes was extremely high (premenopausal 62.3%; postmenopausal 69.9%).

Table 2 presents mean percent breast density associated with type 2 diabetes as determined primarily by fasting c-peptide and self-reported diabetes by menopausal status. After adjustment for confounding variables, premenopausal and postmenopausal women with and without type 2 diabetes based on c-peptide levels had similar mean percent breast density. Premenopausal women without a self-reported history of diabetes had greater mean $\hat{\mu}$ percent breast density ($\hat{\mu}$ 15.3%, 95% confidence interval [CI] 14.0%-16.7%) than diabetic women ($\hat{\mu}$ 13.1%, 95% CI 10.7%-15.5%) ($p=0.05$); however, there was no association among postmenopausal women. While premenopausal women whose diabetes was diagnosed at least 10 years ago had lower mean percent breast density than women diagnosed less than 5 years ago, the opposite was true for postmenopausal women. There was no effect of the use of insulin or pills among diabetics on mean percent breast density. When we stratified by race/ethnicity, mean percent breast density was similar among White, Black and Hispanic diabetics and non-diabetics within menopausal status (data not shown).

Discussion

We found no association in premenopausal or postmenopausal women between type 2 diabetes based on c-peptide levels and breast density. This finding is in agreement with the only other study to investigate c-peptide levels and breast density which found a negative association that disappeared once they adjusted for BMI and WHR overall and within menopausal status [23]. When basing diabetes status on self-report, we did find that mean breast density appeared to be higher among non-diabetics than diabetics who were premenopausal, but not among those who were postmenopausal. While this finding agrees with one study which found that self-reported diabetes was associated with lower breast density in premenopausal but not postmenopausal women [19], it differs from another study which found no association in women regardless of menopausal status [21].

Among self-reported diabetics in our study, premenopausal women whose diabetes was longer standing had lower mean percent breast density than women diagnosed more recently. To our knowledge, no other study has investigated breast density as it relates to the time since diabetes diagnosis. Our failure to find an effect of diabetes treatment on breast density was unexpected given the recent interest in utilizing metformin, one of the most common oral diabetes medications, as a breast cancer chemopreventive agent [28], particularly in postmenopausal women [29]. To date, one study has investigated the effect of metformin and breast density in postmenopausal women and reported a decrease in 7 of 14 women after 10.5 months of use that was more pronounced in women with no signs of metabolic syndrome [30].

Our study was potentially limited by selection bias since our sample was one of convenience. Also misclassification of breast density could have affected our results since we used Quantra, a fairly new automated algorithm for volumetric assessment of breast tissue, rather

than the standard computer-assisted Cumulus thresholding program. Both the validity and reliability of Quantra have been examined. In comparing Quantra with magnetic resonance imaging (MRI), Wang et al. [31] reported lower median percent breast density with Quantra (22.0%, interquartile range [IQR] 14.0%) than with MRI (24.0%, IQR 36.0%). Ciatto et al [32] reported systematically lower percent breast density with Quantra compared with visual classification (BI-RADS) by eleven experienced radiologists, but the authors maintained that its reproducibility makes it preferable to visual classification. Engelken et al. [33] reported a Pearson correlation coefficient of 0.920 ($p < 0.05$) for serial digital mammograms using Quantra software on the same unit within a 24-month period.

Very few epidemiologic studies of breast density have utilized full-field digital mammograms with Quantra software for comparison with our study. The mean breast density (19.7%, range 8.5%-48.5%) and age (59 years, range 49-81 years) of an English study of premenopausal and postmenopausal women combined [34] were higher than that of our study (breast density 14.1%, range 6.5%-34.0%; age 51 years, range 40-76 years). In a German study, Hammann-Kloss et al. [35] reported median breast densities for women of <46 years (28%, IQR 15.0%), 46-55 years (23.0%, IQR 15.3%) and >55 years (16.0%, IQR 10.0%) that were higher than those of our study (<46 years 15.0%, IQR 8.25%; 46-55 years 12.5%, IQR 5.5%; >55 years 11.5%, IQR 3.75%). Both of these findings may have been due to the high prevalence of obesity, and therefore less dense breasts, in our population.

To minimize misclassification of diabetes we used fasting serum c-peptide available for 95% of subjects followed by self-report available for the remaining 5% of subjects. Results of our validation study indicated very low sensitivity (22.8, 95% CI 18.0-28.3) and high specificity (83.2, 95% CI 77.2-87.9) of self-report of diabetes in comparison with serum c-peptide. The total percentage of women whose c-peptide level indicated diabetes (58.0%) was 37.8% higher than

the percentage of women who self-reported diabetes (20.2%). This percentage is higher than the estimated 27.8% of undiagnosed diabetes in the U.S. [36], but may be due to the high rates of obesity (BMI 30-34.9; 25%) and severe obesity (BMI \geq 35; 29%) in our study population.

Additional strengths of our study included the extremely high rates of diabetes in our population, a priori stratification by menopausal status, adjustment for known confounders, and a the examination of findings with and without women who had abnormal mammograms.

Confirmation of our findings in larger studies may assist in clarifying the role of the insulin signaling pathway in women with high breast density.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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

| Characteristic | Premenopausal (n=175) | | Postmenopausal (n=289) | |
|---|-----------------------|------|------------------------|------|
| | n | % | n | % |
| Race | | | | |
| White | 36 | 20.6 | 75 | 26.0 |
| Black | 79 | 45.1 | 172 | 59.5 |
| Hispanic | 60 | 34.3 | 42 | 14.5 |
| Age (years) | | | | |
| 40-49 | 157 | 89.7 | 59 | 20.4 |
| 50-64 | 18 | 10.3 | 179 | 61.9 |
| 65-79 | 0 | 0.0 | 51 | 17.7 |
| Education | | | | |
| < High school | 49 | 28.3 | 65 | 22.7 |
| High school graduate | 41 | 23.7 | 74 | 25.8 |
| Some college | 55 | 31.8 | 89 | 31.0 |
| College graduate | 28 | 16.2 | 59 | 20.5 |
| Missing | 2 | | 2 | |
| Family history of breast cancer | | | | |
| No | 116 | 66.3 | 184 | 64.6 |
| Yes | 50 | 28.5 | 92 | 32.3 |
| Adopted | 8 | 4.6 | 8 | 2.8 |
| Don't know | 1 | 0.6 | 1 | 0.3 |
| Missing | 0 | | 4 | |
| Family history of diabetes | | | | |
| No | 58 | 33.1 | 77 | 26.8 |
| Yes | 109 | 62.3 | 201 | 70.0 |
| Adopted | 8 | 4.6 | 8 | 2.8 |
| Don't know | 0 | 0.0 | 1 | 0.4 |
| Missing | 0 | | 2 | |
| Age at menarche (years) | | | | |
| ≤12 | 85 | 48.6 | 144 | 49.8 |
| 13 | 35 | 20.0 | 68 | 23.6 |
| >13 | 55 | 31.4 | 77 | 26.6 |
| Number of full-term pregnancies | | | | |
| 0 | 23 | 13.2 | 23 | 8.0 |
| 1-2 | 43 | 24.7 | 90 | 31.2 |
| 3-4 | 72 | 41.4 | 110 | 38.2 |
| ≥5 | 36 | 20.7 | 65 | 22.6 |
| Missing | 1 | | 1 | |
| Age at first pregnancy (years) ^a | | | | |
| <30 | 134 | 89.3 | 248 | 95.0 |
| ≥30 | 16 | 10.7 | 13 | 5.0 |
| Missing | 1 | | 4 | |
| Oral contraceptive use | | | | |
| No | 50 | 28.9 | 78 | 27.0 |
| Yes | 123 | 71.1 | 211 | 73.0 |
| Missing | 2 | | 0 | |

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

| Characteristic | Premenopausal (n=175) | | Postmenopausal (n=289) | |
|--|-----------------------|------|------------------------|------|
| | n | % | n | % |
| Smoking | | | | |
| No | 104 | 59.4 | 116 | 40.3 |
| Yes | 71 | 40.6 | 172 | 59.7 |
| Missing | 0 | | 1 | |
| Alcohol intake | | | | |
| No | 99 | 56.9 | 136 | 47.4 |
| Yes | 75 | 43.1 | 151 | 52.6 |
| Missing | 1 | | 2 | |
| Physical activity | | | | |
| None | 54 | 30.9 | 97 | 33.7 |
| Moderate | 63 | 36.0 | 117 | 40.6 |
| Strenuous | 58 | 33.1 | 74 | 25.7 |
| Missing | 0 | | 1 | |
| Body mass index | | | | |
| <25 | 25 | 14.4 | 52 | 18.1 |
| 25-29.9 | 56 | 32.4 | 77 | 26.7 |
| 30-34.9 | 41 | 23.7 | 75 | 26.0 |
| ≥35 | 51 | 29.5 | 84 | 29.2 |
| Missing | 2 | | 1 | |
| Waist-to-hip ratio | | | | |
| <0.84 | 49 | 28.3 | 66 | 22.9 |
| 0.84-0.88 | 40 | 23.1 | 76 | 26.4 |
| 0.89-0.92 | 51 | 29.5 | 64 | 22.2 |
| ≥0.93 | 33 | 19.1 | 82 | 28.5 |
| Missing | 2 | | 1 | |
| % Body fat | | | | |
| <37.9 | 45 | 26.5 | 64 | 22.5 |
| 37.9-43.0 | 51 | 30.0 | 67 | 23.6 |
| 43.1-47.2 | 34 | 20.0 | 79 | 27.8 |
| ≥47.3 | 40 | 23.5 | 74 | 26.1 |
| Missing | 5 | | 5 | |
| Age at menopause (years) ^b | | | | |
| <50 | | | 219 | 75.8 |
| 50-54 | | | 54 | 18.7 |
| ≥55 | | | 12 | 4.1 |
| Don't know | | | 4 | 1.4 |
| Hormone replacement therapy use ^b | | | | |
| No | | | 200 | 69.4 |
| Yes | | | 88 | 30.6 |
| Missing | | | 1 | |

^aAmong parous.^bAmong postmenopausal.

Table 2. Mean percent breast density associated with diabetes by menopausal status

| Characteristic | Premenopausal (n=175) | | | | Postmenopausal (n=288) | | | |
|---|-----------------------|-----------------------------|-----------|----------|------------------------|-----------------------------|-----------|----------|
| | n | Mean % density ^a | 95% CI | P-value | n | Mean % density ^b | 95% CI | P-value |
| Type 2 diabetes | | | | | | | | |
| No | 99 | 14.8 | 12.4-17.3 | | 104 | 13.4 | 12.5-14.4 | |
| Yes | 76 | 14.6 | 12.1-17.1 | 0.77 | 184 | 12.9 | 12.1-13.6 | 0.27 |
| Self-reported diabetes | | | | | | | | |
| No | 151 | 15.3 | 14.0-16.7 | | 221 | 13.0 | 12.3-13.7 | |
| Yes | 24 | 13.1 | 10.7-15.5 | 0.05 | 67 | 13.2 | 12.1-14.2 | 0.78 |
| Times since diabetes diagnosis (years) ^b | | | | | | | | |
| <5 | 16 | 16.1 | 13.5-18.7 | Referent | 31 | 12.9 | 11.4-14.4 | Referent |
| 5-9 | 4 | 13.1 | 8.7-17.5 | 0.11 | 17 | 12.3 | 10.4-14.3 | 0.61 |
| ≥10 | 4 | 12.4 | 8.2-16.7 | 0.05 | 19 | 15.0 | 13.2-16.8 | 0.05 |
| Diabetes medications ^b | | | | | | | | |
| None | 6 | 16.2 | 12.5-19.8 | Referent | 12 | 13.6 | 11.4-15.8 | Referent |
| Insulin | 11 | 15.5 | 12.4-18.6 | 0.70 | 30 | 12.9 | 11.2-14.6 | 0.63 |
| Pills | 7 | 13.5 | 9.3-17.8 | 0.20 | 25 | 14.0 | 12.1-16.0 | 0.74 |

^aAdjusted for race/ethnicity, age, and BMI.

^bAdjusted for race/ethnicity, age, BMI and HRT use.

^cAmong self-reported diabetics.