Published in final edited form as:

Cancer Causes Control. 2015 February ; 26(2): 303–309. doi:10.1007/s10552-014-0502-3.

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, and Anthony C. Disher, MD¹

¹Meharry Medical College, Nashville, TN 37208, USA

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

Abstract

Purpose—We conducted a study of women recruited at Meharry Medical College, 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 by self-report.

Results—After adjustment for confounding variables, the mean percent breast density among premenopausal women with type 2 diabetes (μ 13.8%, 95% confidence interval [CI] 11.6–15.9) was non-significantly lower than that of women without type 2 diabetes (μ 15.9%, 95% CI 15.0–16.8) ($p=0.07$); however, there was no association among postmenopausal women. The effect of type 2 diabetes in severely obese women (BMI ≥ 35) appeared to differ by menopausal status with a reduction in mean percent breast density in premenopausal women, but an increase in mean percent breast density in postmenopausal women which could have been due to chance.

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

Keywords

mammographic breast density; type 2 diabetes; cross-sectional study; underserved

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; msanderson@mmc.edu.

Conflict of Interest

The authors declare that they have no conflict of interest.

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, consisting primarily of cohort studies, 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 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 parity, menopause, hormone replacement therapy, body mass index, and hormone levels, are also associated with mammographic breast density [7, 9–10]. 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 [11–13], breasts of similar density [14–15] or less dense breasts [16], while Hispanic women have been reported to have breasts of similar density [11, 16]. 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 [17], very few studies have investigated the association between diabetes and mammographic breast density. Diabetes may play a role in mammographic breast density through the insulin signaling pathway given that insulin has been linked with low breast density in premenopausal women [18–19]. We conducted a study of women recruited at Meharry Medical College, a Historically Black Medical School, to investigate the relationship between diabetes and mammographic breast density.

Materials and Methods

Study Design

We conducted a clinic-based cross-sectional study of underserved women aged 40 to 79 years recruited at Meharry Medical College, a Historically Black Medical School, between December 2011 and February 2014 to investigate mammographic breast density and its

relation with potential breast cancer pathways including insulin [18–19], insulin-like growth factor [10, 20] and adipocytokine [19, 21]. The present study focuses on the insulin signaling pathway by investigating the association between Type 2 diabetes and mammographic breast density. Subjects were eligible if they were underserved meaning their primary place of health care was a safety net clinic. 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. 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. Body mass index (BMI) (kg/m^2) and waist-to-hip ratio (WHR) were calculated from body measurements and percent body fat was estimated from a body fat monitor scale.

Study Population

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. Of the 479 women recruited, exclusions due to incomplete interviews ($n=4$), type 1 diabetes ($n=11$), and unknown age at diabetes diagnosis ($n=1$) resulted in 175 premenopausal women and 288 postmenopausal women for analysis.

Assessment of Breast Density

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 and assigned Breast Imaging Reporting and Data System (BI-RADS) categories of 0 through 4 represented by increasing density [22]. Subjects with abnormal mammograms (BI-RADS=0: additional imaging evaluation, $n=45$; BI-RADS=3: probably benign finding, $n=3$; BI-RADS=4: suspicious abnormality, $n=2$) were notified immediately by certified mail, while subjects with normal mammograms were notified of their results within 30 days.

Assessment of Type 2 Diabetes Status

To define diabetes, we used self-reported diabetes from the questionnaire. Women were considered diabetic if 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 and were excluded from analysis [23]. For the medication analysis, women who used pills and then switched to insulin to control diabetes were classified as having used insulin.

We conducted a validation study of self-reported diabetes using c-peptide (a biomarker of insulin secretion) which 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 2.2%, 3.4% and 3.0%, respectively, within the range of acceptable sensitivity and CVs [24]. The inter-assay CVs were not available because the sera were batch analyzed in two assays. For the validation study, women were considered to have diabetes if their fasting serum c-peptide was >2.0 ng/mL [25].

Statistical Analysis

Statistical analyses were performed in SAS version 9.2. Linear regression was used to estimate mean percent breast density by type 2 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]. Interaction terms, the product of diabetes and race/ethnicity (White, Black, Hispanic) and BMI (<35 , ≥ 35), were added to linear regression models and likelihood ratio tests were performed to test for effect measure modification. 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. Confounders were examined as categorized in Table 1 with the exception of age, BMI, WHR and percent body fat which were examined continuously.

Variables were considered confounders if their addition to the model changed the unadjusted mean percent breast density by 10 percent or more. There was no evidence of statistical interaction for race/ethnicity or BMI; however, we present results for type 2 diabetes stratified by BMI since the effect of diabetes on mean percent breast density appears to be most pronounced among severely obese women. In addition, we stratified by menopausal status and adjusted for race/ethnicity, age and BMI (as needed), 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. For our validation study of self-reported diabetes, we used serum c-peptide as the gold standard and calculated sensitivities and specificities and their respective confidence intervals as measures of validity. Lastly, 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. In both premenopausal and postmenopausal groups, we observed a high prevalence of 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 by menopausal status. After adjustment for confounding variables, the mean percent breast density among premenopausal women with type 2 diabetes (μ 13.8%, 95% confidence interval [CI] 11.6–15.9) was non-significantly lower than that of women without type 2 diabetes (μ 15.9%, 95% CI 15.0–16.8) ($p=0.07$); however, there was no association among postmenopausal women. Among severely obese (BMI ≥ 35) premenopausal women, the mean percent breast density was non-significantly lower in women with diabetes (μ 10.8%, 95% CI 8.3–13.2) than in women without diabetes (μ 13.1%, 95% CI 11.9–14.4) ($p=0.07$). However, the opposite was true in severely obese postmenopausal women with a significantly higher mean percent breast density in women with diabetes (μ 12.8%, 95% CI 11.8–13.8) than in women without diabetes (μ 11.1%, 95% CI 10.1–12.0) ($p=0.01$). 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.

To ascertain misclassification of self-reported diabetes we conducted a validation study using fasting serum c-peptide available for 95% of subjects as the gold standard. Results 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. [28], but may be due to the high rates of obesity (BMI 30–34.9; 25%) and severe obesity (BMI ≥ 35 ; 29%) in our study population.

Discussion

We found a non-significantly lower mean percent density associated with self-reported diabetes among premenopausal women, but no association in postmenopausal women after continuous adjustment for BMI. This finding is in agreement with two studies of self-reported diabetes and mammographic breast density. Robidoux et al. [18], in a study of Southwestern Native-American women, classified breast density using BI-RADS categories 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. [29], in a study of primarily postmenopausal White women in Minnesota, found no association between self-reported type 2 diabetes and breast density based on a computer-assisted thresholding program (Cumulus) [30] of analog mammograms in premenopausal or postmenopausal women. However, these investigators did identify a positive association between diabetes and breast cancer.

This finding is in partial agreement with two other studies that investigated c-peptide levels and breast density which found overall or within strata of menopausal status [31–32]. Diorio et al. [31], in a study of primarily White women in Quebec City, found no association between non-fasting c-peptide levels and breast density based on the Cumulus thresholding program after adjustment for BMI and WHR ($p=0.41$), and after stratification by menopausal status ($p=0.94$). Ahern et al. [32], in a case-control study nested within the Nurses' Health Study cohorts, found no association between fasting c-peptide levels and breast density measured using Cumulus after adjustment for BMI and WHR in premenopausal and postmenopausal women combined and within strata of menopausal status. As was the case with Sellers et al. [29], these investigators did identify a positive association between diabetes and breast cancer.

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 may have been due to limited statistical power, but was unexpected given the recent interest in utilizing metformin, one of the most common oral diabetes medications, as a breast cancer chemopreventive agent [33], particularly in postmenopausal women [34]. 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 [35].

Our study was potentially limited by selection bias since our sample was one of convenience. In addition, statistical power was limited, especially when we stratified by both menopausal status and BMI, so these results should be interpreted with caution. 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. To date, the validity of Quantra has yet to be established. In comparing Quantra with magnetic resonance imaging (MRI), Wang et al. [36] 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 [37] reported systematically lower percent breast density with Quantra compared with visual classification using BI-RADS by eleven experienced radiologists, but the authors maintained that its reproducibility makes it preferable to visual classification. Engelken et al. [38] 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 [39] 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. [40] 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 chance or due to the high prevalence of obesity, and therefore less dense breasts, in our population.

Strengths of our study included the high rates of diabetes in our population, a priori stratification by menopausal status, adjustment for known confounders, the validation study of self-reported diabetes, and the examination of findings with and without women who had abnormal mammograms. To our knowledge, our study is the first to identify a suggested association between type 2 diabetes and mammographic breast density in severely obese women that appeared to operate in opposite directions in premenopausal and postmenopausal women which could have been due to chance. Most studies of diabetes and breast density have only identified weak associations in premenopausal women suggesting that the link between diabetes and breast cancer is not mediated through breast density. Confirmation of our findings in larger studies may assist in clarifying the role of the insulin signaling breast cancer pathway in women with high breast density and ultimately target those women who will benefit most from primary and secondary prevention.

Acknowledgements

This research was supported in part by grant number W81XWH 10 1 0993 from the Department of Defense, U.S. Army Medical Research and Materiel Command. The c-peptide assay was conducted in the Endocrine Core Laboratory of Meharry Medical College, funded in part by the National Institutes of Health via the grant numbers P20RR011792 and U54RR019192.

The authors wish to thank the subjects and study staff (Mary Kay Fadden, Raquel Mack, Cynthia Harris, Jacqueline Favours, Asia Jones, Tierra Dennis, Melanie Velazquez, Lauren Cooper, Saima Faisal, Whitney Lovett, Helen Howse Cunningham, Merlicia Harden, Veronica Johnson, Kimberly Vaughn, Mechelle Tuck, and Nancy Harker) for their invaluable assistance with the project.

References

1. Wolf I, Sadetzki S, Catane R, Karasik A, Kaufman B. Diabetes mellitus and breast cancer. *Lancet Oncol.* 2005; 6:103–111. [PubMed: 15683819]
2. Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. *Int J Cancer.* 2007; 121:856–862. [PubMed: 17397032]
3. Xue F, Michels KB. Diabetes, metabolic syndrome, and breast cancer: a review of the current evidence. *Am J Clin Nutr.* 2007; 86:s823–s835. [PubMed: 18265476]
4. Liao S, Li J, Wei W, Wang L, Zhang Y, Li J, Wang C, Sun S. Association between diabetes mellitus and breast cancer risk: a meta-analysis of the literature. *Asian Pac J Cancer Prev.* 2011; 12:1061–1065. [PubMed: 21790252]
5. Lambe M, Wigertz A, Garmo H, Walldius G, Jungner I, Hammar N. Impaired glucose metabolism and diabetes and the risk of breast, endometrial, and ovarian cancer. *Cancer Causes Control.* 2011; 22:1163–1171. [PubMed: 21688131]

6. Bowker SL, Marra CA, Richardson K, Johnson JA. Risk of breast cancer after onset of type 2 diabetes. *Diabetes Care*. 2011; 34:2542–2544. [PubMed: 21972408]
7. Boyd NF, Lockwood GA, Byng JW, Tritchler DL, Yaffe MJ. Mammographic densities and breast cancer risk. *Cancer Epidemiol Biomarkers Prev*. 1998; 7:1133–1144. [PubMed: 9865433]
8. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2006; 15:1159–1169. [PubMed: 16775176]
9. Vachon CM, Kuni CC, Anderson K, Anderson VE, Sellers TA. Association of mammographically defined percent breast density with epidemiologic risk factors for breast cancer (United States). *Cancer Causes Control*. 2000; 11:653–662. [PubMed: 10977110]
10. Berube S, Diorio C, Masse B, Hebert-Croteau N, Byrne C, Cote G, Pollak M, Yaffe M, Brisson J. Vitamin D and calcium intakes from food or supplements and mammographic breast density. *Cancer Epidemiol Biomarkers Prev*. 2005; 14:1653–1659. [PubMed: 16030097]
11. El-Bastawissi AY, White E, Mandelson MT, Taplin S. Variation in mammographic breast density by race. *Ann Epidemiol*. 2001; 11:257–263. [PubMed: 11306344]
12. Chen Z, Wu AH, Gauderman WJ, Bernstein L, Ma H, Pike MC, Ursin G. Does mammographic density reflect ethnic differences in breast cancer incidence rates? *Am J Epidemiol*. 2004; 59:140–147. [PubMed: 14718215]
13. Habel LA, Capra AM, Oestreicher N, et al. Mammographic density in a multiethnic cohort. *Menopause*. 2007; 14:891–899. [PubMed: 17414171]
14. del Carmen MG, Halpern EF, Kopans DB, Moy B, Moore RH, Goss PE, Hughes KS. Mammographic breast density and race. *AJR Am J Roentgenol*. 2007; 188:1147–1150. [PubMed: 17377060]
15. Tehranifar P, Reynolds D, Flom J, Fulton L, Liao Y, Kudadjie-Gyamfi E, Terry MB. Reproductive and menstrual factors and mammographic density in African American, Caribbean, and white women. *Cancer Causes Control*. 2011; 22:599–610. [PubMed: 21327938]
16. del Carmen MG, Hughes KS, Halpern E, Rafferty E, Kopans D, Parisky YR, Sardi A, Esserman L, Rust S, Michaelson J. Racial differences in mammographic breast density. *Cancer*. 2003; 98:590–596. [PubMed: 12879477]
17. Boyd NF, Rommens JM, Vogt K, Lee V, Hopper JL, Yaffe MJ, Paterson AD. Mammographic breast density as an intermediate phenotype for breast cancer. *Lancet Oncol*. 2005; 6:798–808. [PubMed: 16198986]
18. Roubidoux MA, Kuar JS, Griffith KA, Sloan J, Wilson C, Novotny P, Lobell M. Correlates of mammogram density in Southwestern Native-American women. *Cancer Epidemiol Biomarkers Prev*. 2003; 12:552–558. [PubMed: 12815002]
19. Furberg A-S, Jasienska G, Bjurstam N, Torjesen PA, Emaus A, Lipson SF, Ellison PT, Thune I. Metabolic and hormonal profiles: HDL cholesterol as a plausible biomarker of breast cancer risk. The Norwegian EBBA Study. *Cancer Epidemiol Biomarkers Prev*. 2005; 14:33–40. [PubMed: 15668473]
20. Diorio C, Pollak M, Byrne C, Masse B, Hebert-Croteau N, Yaffe M, Cote G, Berube S, Morin C, Brisson J. Insulin-like growth factor-I, IGF-binding protein-3, and mammographic breast density. *Cancer Epidemiol Biomarkers Prev*. 2005; 14:1065–1073. [PubMed: 15894654]
21. Maskarinec G, Woolcott C, Steude JS, Franke AA, Cooney RV. The relation of leptin and adiponectin with breast density among premenopausal women. *Eur J Cancer Prev*. 2010; 19:55–60. [PubMed: 19927000]
22. Sickles, EA.; D'Orsi, CJ.; Bassett, LW., et al. ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. Reston, VA: American College of Radiology; 2013. ACR BI-RADS® Mammography.
23. Michels KB, Solomon CG, Hu FB, Rosner BA, Hankinson SE, Colditz G, Manson JE. Type 2 diabetes and subsequent incidence of breast cancer in the Nurses' Health Study. *Diabetes Care*. 2003; 26:1752–1758. [PubMed: 12766105]
24. Bal, TA. C-peptide: roles in diabetes, insulinoma, and hypoglycemia. *Siemens Perspectives*. 2009. Available from: www.siemens.com/diagnostics

25. Buse, JB.; Polonsky, KS.; Burant, CF. Type 2 diabetes mellitus. In: Melmed, S.; Polonsky, KS.; Larsen, PR.; Kronenberg, HM., editors. *Williams Textbook of Endocrinology*. 12th ed.. Philadelphia: Elsevier Saunders; 2011. p. 1371-1435.
26. Dupont, WD. *Statistical modeling for biomedical researchers: a simple introduction to the analysis of complex data*, 2nd edition. Cambridge: Cambridge University Press; 2009. p. 97-155.
27. Vachon CM, Pankratz VS, Scott CG, et al. Longitudinal trends in mammographic percent density and breast cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2007; 16:921–928. [PubMed: 17507617]
28. Centers for Disease Control and Prevention. *National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014*. Atlanta: U.S. Department of Health and Human Services; 2014.
29. Sellers TA, Jensen LE, Vierkant RA, Fredricksen ZS, Brandt KR, Giuliano AR, Pamkrantz VS, Cerhan JR, Vachon CM. Association of diabetes with mammographic breast density and breast cancer in the Minnesota breast cancer family study. *Cancer Causes Control*. 2007; 18:505–515. [PubMed: 17437179]
30. Byng JW, Boyd NF, Fishell E, Jong RA, Yaffe MJ. The quantitative analysis of mammographic densities. *Phys Med Biol*. 1994; 39:1629–1638. [PubMed: 15551535]
31. Diorio C, Pollak M, Byrne C, Masse B, Hebert-Croteau N, Yaffe M, Cote G, Berube S, Brisson J. Levels of C-peptide and mammographic breast density. *Cancer Epidemiol Biomarkers Prev*. 2005; 14:2661–2664. [PubMed: 16284393]
32. Ahern TP, Hankinson SE, Willett WC, Pollak MN, Eliassen AH, Tamimi RM. Plasma c-peptide, mammographic breast density, and risk of invasive breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2013; 22:1786–1796. [PubMed: 24097198]
33. Goodwin PJ, Thompson AM, Stambolic V. Diabetes, metformin, and breast cancer: lilac time? *J Clin Oncol*. 2012; 30:2812–2814. [PubMed: 22689806]
34. Chlebowski RT, McTiernan A, Wactawski-Wende J, et al. Diabetes, metformin, and breast cancer in postmenopausal women. *J Clin Oncol*. 2012; 30:2844–2852. [PubMed: 22689798]
35. Bershtein LM, Vasil'ev DA, Kovalenko IG, Poroshina TE, Kisel'nikov KS, Boiarkina MP, Zaitsev AN. The influence of metformin and N-acetylcysteine on mammographic density in postmenopausal women [Russian]. *Voprosy Onkologii*. 2012; 58:45–49. [PubMed: 22629827]
36. Wang J, Azziz A, Fan B, et al. Agreement of mammographic measures of volumetric breast density to MRI. *PLOS ONE*. 8:e81653. [PubMed: 24324712]
37. Ciatto S, Bernardi D, Calabrese M, et al. A first evaluation of breast radiological density assessment by QUANTRA software as compared to visual classification. *Breast*. 2012; 21:503–506. [PubMed: 22285387]
38. Engelken F, Singh JM, Fallenberg EM, Bick U, Bottcher J, Renz DM. Volumetric breast composition analysis: reproducibility of breast percent density and fibroglandular tissue volume measurements in serial mammograms. *Acta Radiol*. 2014; 55:32–38. [PubMed: 23878356]
39. Skippage P, Wilkinson L, Allen S, Roche N, Dowsett M, a'Hern R. Correlation of age and HRT use with breast density as assessed by Quantra™. *Breast J*. 2012; 19:79–86. [PubMed: 23230974]
40. Hammann-Kloss JS, Bick U, Fallenberg E, Engelken F. Volumetric quantification of the effect of aging and hormone replacement therapy on breast composition from digital mammograms. *Eur J Radiol*. 2014; 83:1092–1097. [PubMed: 24788077]

Table 1

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

Characteristic	Premenopausal (n=175)		Postmenopausal (n=288)	
	n	%	n	%
Race				
White	36	20.6	74	25.7
Black	79	45.1	172	59.7
Hispanic	60	34.3	42	14.6
Age (years)				
40–49	157	89.7	59	20.5
50–64	18	10.3	178	61.8
65–79	0	0.0	51	17.7
Education				
< High school	49	28.3	65	22.6
High school graduate	41	23.7	74	25.7
Some college	55	31.8	91	31.6
College graduate	28	16.2	58	20.1
Missing	2		0	
Family history of breast cancer				
No	116	66.3	184	64.8
Yes	50	28.5	91	32.0
Adopted	8	4.6	8	2.8
Don't know	1	0.6	1	0.4
Missing	0		4	
Family history of diabetes				
No	58	33.1	77	26.9
Yes	109	62.3	200	69.9
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	143	49.7
13	35	20.0	68	23.6
>13	55	31.4	77	26.7
Number of full-term pregnancies				
0	23	13.2	23	8.0
1–2	43	24.7	90	31.4
3–4	72	41.4	109	38.0
5	36	20.7	65	22.6
Missing	1		1	
Age at first pregnancy (years) ^a				
<30	134	89.3	247	95.0

Characteristic	Premenopausal (n=175)		Postmenopausal (n=288)	
	n	%	n	%
30	16	10.7	13	5.0
Missing	1		4	
Oral contraceptive use				
No	50	28.9	77	26.7
Yes	123	71.1	211	73.3
Missing	2		0	
Smoking				
No	104	59.4	116	40.4
Yes	71	40.6	171	59.6
Missing	0		1	
Alcohol intake				
No	99	56.9	135	47.2
Yes	75	43.1	151	52.8
Missing	1		2	
Physical activity				
None	54	30.9	97	33.8
Moderate	63	36.0	116	40.4
Strenuous	58	33.1	74	25.8
Missing	0		1	
Body mass index				
<25	25	14.4	52	18.1
25–29.9	56	32.4	77	26.8
30–34.9	41	23.7	75	26.2
35	51	29.5	83	28.9
Missing	2		1	
Waist-to-hip ratio				
<0.84	49	28.3	66	23.0
0.84–0.88	40	23.1	75	26.1
0.89–0.92	51	29.5	64	22.3
0.93	33	19.1	82	28.6
Missing	2		1	
% Body fat				
<37.9	45	26.5	64	22.6
37.9–43.0	51	30.0	67	23.7
43.1–47.2	34	20.0	78	27.6
47.3	40	23.5	74	26.1
Missing	5		5	
Age at menopause (years) ^b				
<50			218	75.7
50–54			54	18.7

Characteristic	Premenopausal (n=175)		Postmenopausal (n=288)	
	n	%	n	%
55			12	4.2
Don't know			4	1.4
Hormone replacement therapy use ^b				
No			199	69.3
Yes			88	30.7
Missing			1	

^a Among parous.

^b Among postmenopausal.

Table 2

Mean percent breast density associated with type 2 diabetes by menopausal status

Characteristic	Premenopausal				Postmenopausal			
	n	Mean % density ^a	95% CI	P-value	n	Mean % density ^b	95% CI	P-value
Type 2 diabetes								
Overall								
No	151	15.9	15.0–16.8		221	13.0	12.3–13.6	
Yes	24	13.8	11.6–15.9	0.07	67	13.1	12.1–14.2	0.78
BMI <35								
No	108	17.0	15.8–18.2		167	13.5	12.7–14.3	
Yes	14	15.1	11.9–18.2	0.25	37	13.0	11.5–14.5	0.49
BMI ≥35								
No	41	13.1	11.9–14.4		54	11.1	10.1–12.0	
Yes	10	10.8	8.3–13.2	0.07	29	12.8	11.8–13.8	0.01
Times since diabetes diagnosis (years) ^b								
<5	16	14.2	12.4–16.0	Referent	31	12.3	10.9–13.8	Referent
5–9	4	10.5	6.7–14.3	0.07	17	11.7	9.8–13.6	0.55
10	4	10.2	6.4–14.0	0.05	19	14.8	13.0–16.5	0.03
Diabetes medications ^b								
None	6	13.9	11.0–16.9	Referent	12	13.4	11.2–15.6	Referent
Insulin	11	13.7	11.2–16.2	0.90	30	12.3	10.8–13.9	0.42
Pills	7	10.9	7.6–14.2	0.16	25	13.3	11.5–15.1	0.94

^a Adjusted for race/ethnicity, age, and BMI (as needed).^b Adjusted for race/ethnicity, age, BMI (as needed) and HRT use.^c Among self-reported diabetics.