Research Article

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Comparison of Mammographic Density Assessed as Volumes and Areas among Women Undergoing Diagnostic Image-Guided Breast Biopsy

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Abstract

Background: Mammographic density (MD), the area of non–fatty-appearing tissue divided by total breast area, is a strong breast cancer risk factor. Most MD analyses have used visual categorizations or computer-assisted quantification, which ignore breast thickness. We explored MD volume and area, using a volumetric approach previously validated as predictive of breast cancer risk, in relation to risk factors among women undergoing breast biopsy.

Methods: Among 413 primarily white women, ages 40 to 65 years, undergoing diagnostic breast biopsies between 2007 and 2010 at an academic facility in Vermont, MD volume (cm^3) was quantified in craniocaudal views of the breast contralateral to the biopsy target using a density phantom, whereas MD area (cm^2) was measured on the same digital mammograms using thresholding software. Risk factor associations with continuous MD measurements were evaluated using linear regression.

Results: Percent MD volume and area were correlated ($r = 0.81$) and strongly and inversely associated with age, body mass index (BMI), and menopause. Both measures were inversely associated with smoking and positively associated with breast biopsy history. Absolute MD measures were correlated ($r = 0.46$) and inversely related to age and menopause. Whereas absolute dense area was inversely associated with BMI, absolute dense volume was positively associated.

Conclusions: Volume and area MD measures exhibit some overlap in risk factor associations, but divergence as well, particularly for BMI.

Impact: Findings suggest that volume and area density measures differ in subsets of women; notably, among obese women, absolute density was higher with volumetric methods, suggesting that breast cancer risk assessments may vary for these techniques. *Cancer Epidemiol Biomarkers Prev; 23(11); 2338–48. ©2014 AACR.*

Introduction

Epidemiologic studies have consistently demonstrated that elevated mammographic density, a reflection of the fibroglandular tissue content of the breast, is a strong, independent breast cancer risk factor (1, 2). Mammographic density has typically been rated visually in broad categories [e.g., the Breast Imaging Reporting and Data System (BI-RADS) density classification (3)] or quantified as a percentage of the total breast area by computer-assisted thresholding software (4). These methods are reproducible in trained hands but are subjective and do not account for variation in breast thickness (4).

Methods for measuring mammographic density are rapidly evolving, and advanced methods permit measurement of density as a volume using digitized screen film mammograms (5–7) or full-field digital mammography (FFDM; refs. 8–11), where calibration data are more reliable and readily available. Applying volumetric density techniques to FFDM to account for breast thickness may further improve the reproducibility and accuracy of density measurements; however, comparisons of area and volume measures of mammographic density within women are limited.

Percent dense area (PD) is known to decrease with increasing age, body mass index (BMI), parity, and

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menopause (12) and to increase with menopausal hormone therapy (MHT) use (13). Most prior reports have found similar relationships for these factors with percent fibroglandular volume (% FGV), and to a lesser extent, for absolute FGV (14–18). A notable exception is BMI, which has been reported to be inversely associated with absolute dense area (DA) but positively associated with absolute FGV in studies using volumetric density technologies based on digitized film screen images (14, 16, 18) and FFDM (17). Given that obesity is related to both breast cancer risk (19) and prognosis (20), understanding the etiologic associations of BMI, density, and breast cancer risk is important. In several studies, volumetric density measures have not improved breast cancer risk prediction models as compared with area-based measures (14, 15, 21, 22), with the notable exception of an investigation using a fully automated technique called Single X-ray Absorptiometry (SXA; ref. 23). Clarifying determinants of SXA measures of volumetric density, especially with regard to the influence of BMI, may enhance its utility in risk assessment, which is important given the limitations of currently available models and the desirability of tailoring screening and prevention to individual levels of risk (24).

Accordingly, we prospectively collected FFDM with SXA density phantoms (10) and assessed volumetric and area density measures in a cross-sectional study of women referred for image-guided breast biopsy. Here, we aimed to explore the relation between volumetric and area measures of mammographic density with epidemiologic risk factors.

Materials and Methods

Study population

The NCI Breast Radiology Evaluation and Study of Tissues (BREAST) Stamp Project is a cross-sectional molecular epidemiologic study of mammographic density undertaken at the University of Vermont College of Medicine and its affiliated academic hospital, Fletcher Allen Health Care (FAHC). FAHC is the largest radiologic facility in the Vermont Breast Cancer Surveillance System (VBCSS), which is part of the NCI's Breast Cancer Surveillance Consortium (25). As part of this effort, patients were asked to complete a standard VBCSS health history questionnaire at the time of mammography.

The current investigation focused on patients who were referred for a diagnostic image-guided breast biopsy between October 2007 and June 2010. When a breast imaging study was indeterminate for cancer, indicating the need for a biopsy, patients were asked whether the study research coordinator could contact them. These potentially eligible participants were contacted by the research coordinator to determine eligibility, obtain verbal consent, and administer an approximately 20-minute telephone interview, collecting additional health information. Eligible women were 40 to 65 years of age, had not had breast cancer or received any cancer treatment, had not undergone breast surgery within 1 year, did not have breast implants, were not taking breast cancer chemoprevention, and were scheduled to have an image-guided breast biopsy.

Height and weight were measured on the day of the breast biopsy, and patients were asked to provide written informed consent (in accordance with Institutional Review Boards at the University of Vermont and the NCI), which included providing access to existing medical records and mammographic images collected within the prior 2 years and for the next 10 years and to breast pathology specimens not needed for clinical care. Compensation of $50 was provided to participants who opted to donate blood and/or mouthwash samples.

During the study enrollment period, VBCSS registry data indicated that 1,227 patients were eligible for the study, of whom 673 (55%) were referred to the study by the radiology facility at the time of biopsy scheduling upon giving permission to be contacted by the study research coordinator. Of the 673 women referred for the study, 465 women (69%) agreed to participate, 90 (13%) refused, and 118 (18%) could not be contacted before breast biopsy. The phone interview was completed an average of two days before the scheduled biopsy. Information supplied by the radiology facility included the reason for the mammogram and its final assessment, in BI-RADS diagnostic categories: 3, "probably benign finding"; 4, "suspicious abnormality"; and 5, "highly suggestive of malignancy" (3). The radiologists tried, when possible, to perform biopsies immediately following the diagnostic evaluation for BI-RADS diagnostic category 5 cases; as there was less time available between assessment and biopsy, these patients were less likely to be enrolled. Compared with women who were eligible but not enrolled, study participants were less likely to have assessments highly suggestive of malignancy (BI-RADS diagnostic category 5: enrolled, 5.6%; not enrolled, 13.8%) and to be subsequently diagnosed with invasive breast carcinoma (invasive diagnosis: enrolled, 8.5%; not enrolled, 19.3%). Study participants were comparable with eligible patients who did not enroll with respect to race (% white: enrolled, 93%; not enrolled: 90%, $P = 0.19$) and age [mean (SD) age: enrolled, 50.8 (6.6); not enrolled, 50.9 (7.2), $P = 0.99$].

Assessment of breast cancer risk factors and covariates

BMI (kg/m^2) was computed from measured height and weight for 456 (98%) women and from self-reported data for the remainder. The following factors were obtained from the VBCSS health history collected on the acquisition date of the image selected for mammographic density analysis: race/ethnicity, education, age at menarche, age at first live birth, presence of a lump at the time of mammography, and history of breast biopsy (see sample questionnaire at http://breastscreening.cancer.gov/; ref. 26). When possible, questionnaire data for missing factors that were unlikely to change over time were obtained from mammography visits within the 2 years

before or after the mammogram date. The supplementary interview captured information related to parity, exogenous hormone use (duration of use of oral contraceptives and MHT), menopausal status, and smoking status. A combination of data collected from the VBCSS and the interview was used to assess family history of breast cancer in first-degree female relatives. A woman was considered postmenopausal if menstrual periods had permanently stopped more than 12 months before interview, she had undergone bilateral oophorectomy, or she had reported having undergone a hysterectomy (or gynecologic surgery associated with cessation of menses) and was 55 years of age or older; otherwise, a woman was considered premenopausal.

Assessment of pathologic diagnosis

To assign a final pathologic diagnosis, breast biopsy and surgical pathology reports were reviewed for all study participants. Diagnoses were classified as benign (i.e., normal lobules or ducts defined as sclerotic/atrophied; nonproliferative fibrocystic change; discrete entities), proliferative (i.e., ductal hyperplasia; sclerosing adenosis), proliferative with atypia (atypical ductal or lobular hyperplasia), *in-situ*, and invasive breast carcinoma. Information about biopsy type and laterality was obtained from breast biopsy reports.

Assessment of mammographic density

Mammograms were acquired on one of six FFDM systems at FAHC. For the initial 3 months of the study, mammograms were acquired on GE Senographe 2000D FFDM systems; the remaining (97%) images were obtained on Hologic Selenia FFDM systems. For storage, raw ("For Processing") mammographic images were bidimensionally reduced by 50%, resulting in an image resolution of 140 μm × 140 μm averaged pixels. Images were encrypted and transferred to the University of California at San Francisco (UCSF) for quantitative volume and area density assessment. This analysis was restricted to prebiopsy craniocaudal views of the contralateral breast. If more than one mammogram was available, the mammogram taken closest in time within the year before the breast biopsy date was selected.

SXA was used to measure FGV (cm^3) and % FGV as described previously (10). An SXA breast density phantom was affixed to the top of the compression paddle and included in the X-ray field during mammography examinations (Fig. 1). The grayscale values for the pixels in the breast image were calibrated by comparing with the grayscale values in the SXA phantom with a known FGV composition and thickness (10). In this way, volumetric measures were achieved using a planar image. Previous estimates of reproducibility for the SXA test phantoms demonstrated a repeatability SD of 2%, with a ±2% accuracy for the entire thickness and density ranges (10). To evaluate stability of SXA measures over time, initial calibration images were taken on each machine and serial scans of a quality control phantom were acquired; no systematic changes over time were observed.

For the same FFDM images that were selected for SXA analyses, area measures of density were estimated as described previously (23, 27), using the UCSF Mammographic Density Program, which is interactive, computer-assisted thresholding software comparable with other validated methods (28). The software automatically detects and delineates the skin edge to define the total breast area (cm^2). Any pectoralis muscle within the field of view was excluded manually. One trained experienced reader (Bo Fan; refs. 23, 27) measured DA (cm^2) by setting a pixel threshold for dense tissue on the images. PD was calculated by dividing DA by the total breast area and multiplying by 100. Distributions of density measures were examined, and images with extreme values were reviewed visually for validation.

The American College of Radiology's BI-RADS breast density assessment (reported on the same images used for quantitative analysis) was analyzed as (I) almost entirely fat; (II) scattered fibroglandular densities; (III) heterogeneously dense; and (IV) extremely dense (3).

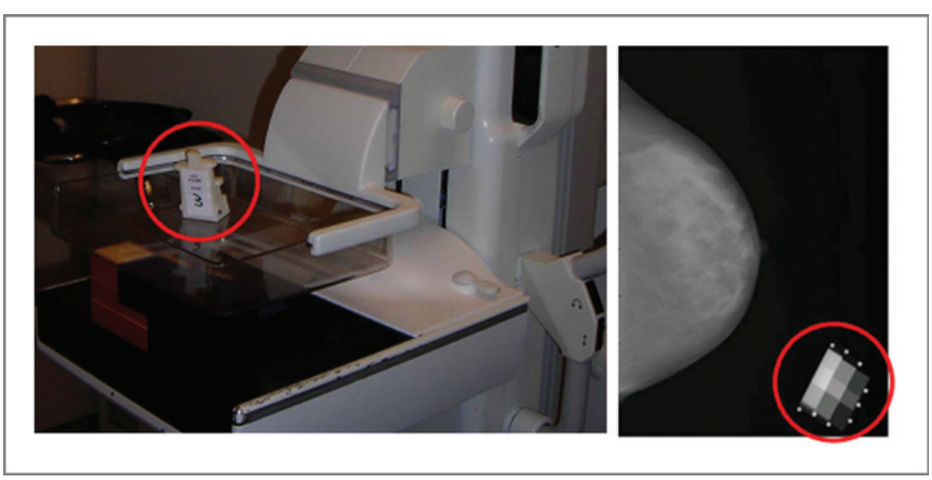

Figure 1. The SXA volumetric density method. Left, the density phantom is affixed to the top compression paddle on an FFDM machine at the University of Vermont Fletcher Allen Health Care Medical Center; Right, the digital mammogram is acquired with the phantom in the corner of the image to allow for automated computation of volumetric mammographic density.

Analytic population

Of the 465 women who consented to the telephone interview, 12 were not subsequently biopsied, 13 were missing SXA density data, and nine women lacked pre-biopsy SXA results for the contralateral breast within 1 year of breast biopsy and were excluded. We also excluded 18 participants who underwent bilateral breast biopsies (preventing assessment of a contralateral breast), resulting in a final analytic population of 413 women.

Statistical analysis

Descriptive statistics for mammographic density measures were calculated, and Spearman rank correlation coefficients were estimated for quantitative volume versus area density measures. We examined correlations between volume and area density measures adjusted for and stratified by age (39–49, 50–54, 55+ years) and BMI (<25, 25–<30, 30+ kg/m^2), which are known to be strongly associated with mammographic density. On the basis of a Box–Cox transformation analysis (29), we square-root transformed all quantitative, raw density measures to optimally approximate normal distributions. Mean quantitative density measures were compared across BI-RADS density categories using analysis of variance.

Linear regression models were used to examine age- and BMI-adjusted associations of participant characteristics with each density measure. Age at mammogram was coded as an ordered categorical variable (39–44, 45–49, 50–54, 55–59, and 60–65 years) and BMI was coded in categories (<25, 25–<30, 30+ kg/m^2). Additional adjustment for pathologic diagnosis and exclusion of 12 participants who were imaged on the GE machine had minimal effects (data not shown). We also used stepwise linear regression models without prior adjustment for age and BMI to identify associated factors. Both approaches yielded similar results; thus, only results from the age- and BMI-adjusted analyses are shown. Results from linear regression models in which β coefficients were standardized per SD change in each density measure were also similar (Supplementary Table S1).

Because volume and area density measures are correlated, we sought to assess whether there is explanatory value in volumetric mammographic density after accounting for the covariate associations with area density by using a residual regression approach. First, we fit linear regression models with PD as the outcome and included factors shown to be associated with mammographic density in the present analysis and in prior work (age: 39–44, 45–49, 50–54, 55–59, 60–65 years; education level: ≤high school, some college+; BMI: <25, 25–<30, 30+ kg/m^2; age at menarche: ≤12, 13, ≥14 years; age at first live birth: <30, ≥30 years/nulliparous; age at menopause: premenopausal, ≤45, 46–49, 50–52, 53+ years, missing; MHT use: never, former, current, missing; cigarette smoking: never, ever; history of breast biopsy before enrollment: never, ever, missing; family history of breast cancer in a first-degree female relative: no, yes; and pathologic diagnosis: benign, proliferative, proliferative with atypia, *in-situ*, and invasive breast carcinoma), to minimize the effects of residual confounding. We then regressed the residuals from the linear model on % FGV and evaluated its association. Analyses were repeated for absolute DA and FGV. When more than 3% of the data were missing for a particular covariate, missing values for covariates were modeled as a separate category (i.e., age at menopause, MHT use, and history of breast biopsy).

Probability values of <0.05 were considered statistically significant. All tests of statistical significance were two-tailed. Analyses were performed using SAS software (SAS Institute Inc.).

Results

Participant characteristics

The median (range) age of participants at enrollment was 51 (40–65) years and the median (range) BMI was 25.4 (17.4–51.3) kg/m^2. Most participants were non-Hispanic white (92.7%), college graduates (84.6%), parous (76.2%), and premenopausal (60.5%). MHT use was infrequent (current 5.0%; former 19.3%). Most initial mammograms were screening examinations (79.9%), and most were subsequently categorized after work-up as suspicious abnormality (BI-RADS diagnostic category 4: 88.1%). The remainder were categorized as probably benign (BI-RADS diagnostic category 3: 6.3%) or highly suggestive of malignancy (BI-RADS diagnostic category 5: 5.6%). Half of participants underwent a stereotactic-guided breast biopsy, and 47.2% underwent an ultrasound-guided biopsy; 1.7% had both stereotactic- and ultrasound-guided biopsies, 0.2% underwent magnetic resonance imaging (MRI)-guided biopsy, and 0.5% had surgical excision without prior core biopsy. Laterality of breast biopsy was distributed evenly such that 49.2% of women had left breast biopsies and 50.8% had right biopsies. The distribution of pathologic diagnosis was as follows: benign (34.1%), proliferative (41.4%), proliferative with atypia (7.7%), *in-situ* (8.2%), and invasive breast cancer (8.5%).

Distributions of mammographic density measures

The median (range) number of days between the contralateral mammogram selected for analysis and subsequent breast biopsy was 14 (1–294) days. Overall distributions and Spearman rank correlation coefficients for volume and area density measures are shown in Fig. 2. The distributions of all density measures were positively skewed. Mean values were higher for % FGV (38.6%) versus PD (27.5%) measures, and % FGV ranged from 0% to 100% compared with a narrower range for PD of 0% to 86.5%. The correlation between % FGV and PD was moderately strong ($r = 0.81$), reflecting the modest correlation between FGV and DA ($r = 0.46$). Total breast volume and area were highly correlated ($r = 0.97$). Age adjustment did little to alter the correlations between volume and area density measures (Supplementary Table S2). Adjustment for BMI did not alter the correlation between total breast volume and area; however, BMI

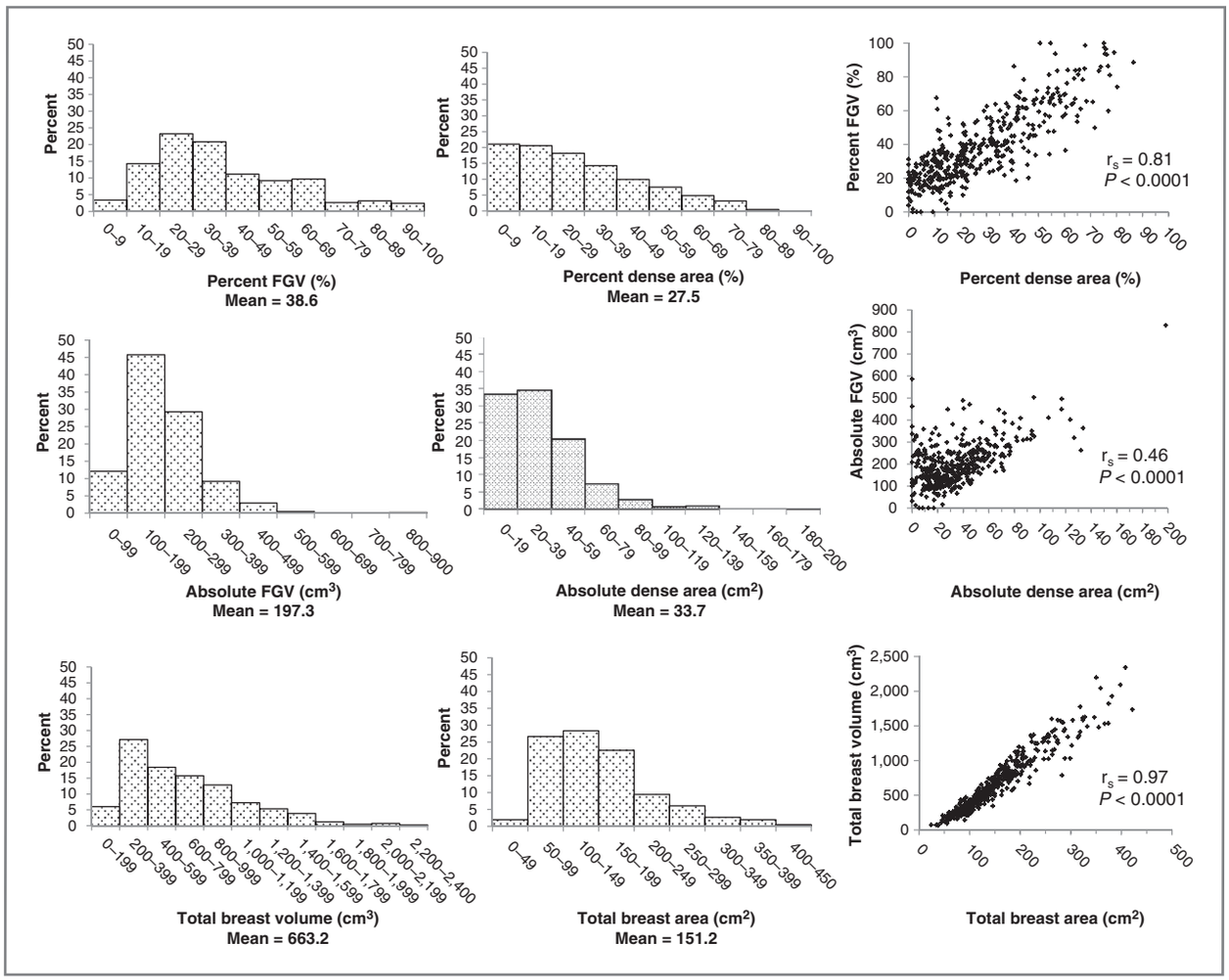

Figure 2. Distributions and Spearman rank correlation coefficients (r_S) for volume and area density measures, The BREAST Stamp Project, 2007–2010 (n = 413). FGV, fibroglandular volume.

adjustment attenuated the correlation between % FGV and PD (r = 0.67) and strengthened the correlation between FGV and DA (r = 0.58; Supplementary Table S2). Stratification by age and BMI revealed that correlations between % FGV and PD, and between FGV and DA, were strongest among the youngest and leanest women and progressively decreased with increasing age (Supplementary Fig. S1) and BMI (Fig. 3).

Mean quantitative density measures were compared across BI-RADS density categories, and associations were in expected directions: with increasing BI-RADS breast density, volume and area measures of percent and absolute density increased, whereas measures of total breast volume and area decreased (P value <0.0001 for all density measures, except FGV where P = 0.08; Table 1).

Associations between mammographic density measures and participant characteristics

Both % FGV and PD were strongly and inversely associated with age, weight, BMI, and menopause (Table 2). Percent density according to both methods was reduced among non-white women and those who reported ever smoking and was elevated among those who reported a breast biopsy before study enrollment. The strong and positive association between percent density and BI-RADS breast density persisted after age and BMI adjustment.

FGV and DA decreased with increasing age and with menopause, though associations were weaker than those observed for the percent density measures. Whereas DA was inversely associated with weight and BMI, FGV was positively associated with weight and BMI. Absolute density measures were positively associated with education and history of breast biopsy, but findings were only statistically significant for DA. On the other hand, elevated FGV (but not DA) of the contralateral breast was associated with having a left breast biopsy at study enrollment. FGV and DA increased with increasing BI-RADS breast density categories. Statistically significant trends were not observed with any of the density measures for height, age at menarche, parity, age at first birth, final

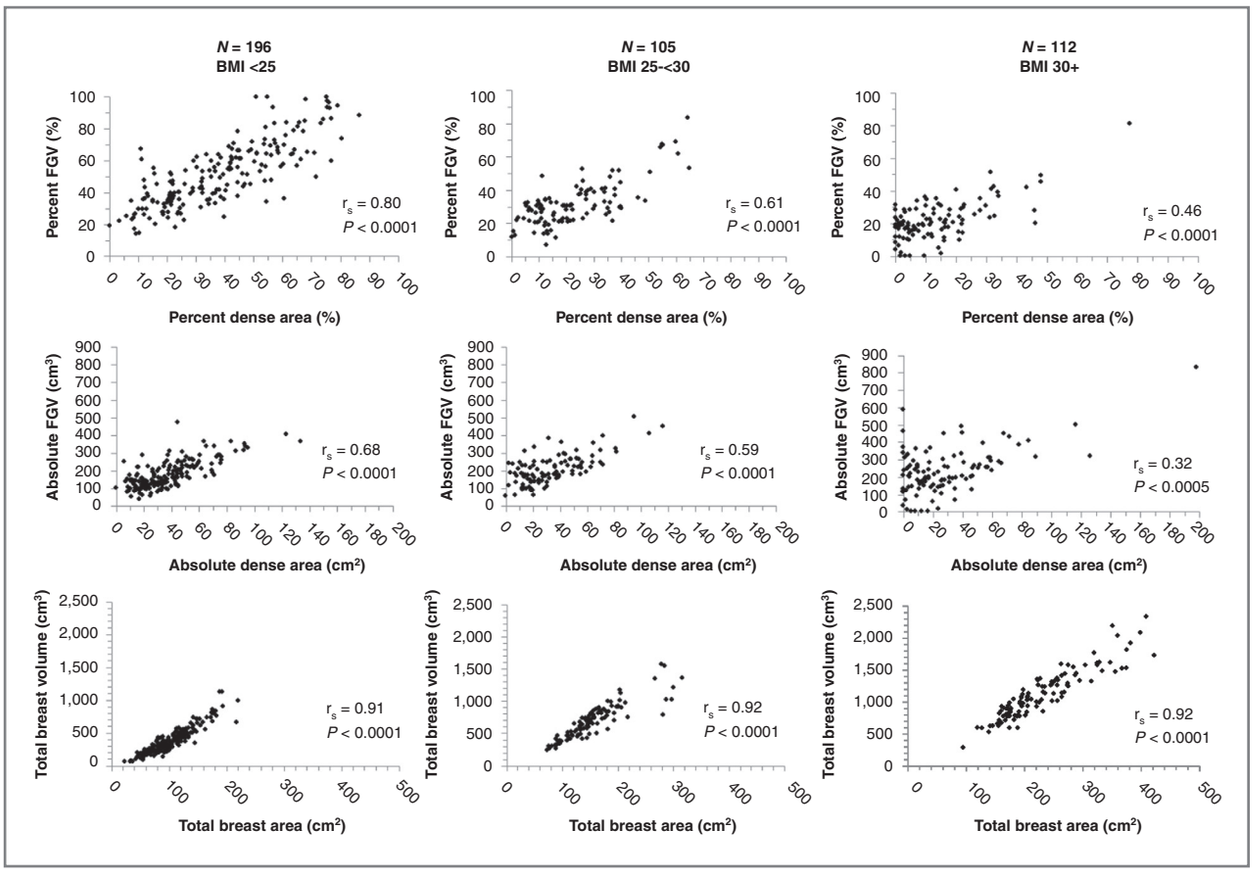

Figure 3. Spearman rank correlation coefficients (r_s) for volume and area density measures, stratified by BMI, The BREAST Stamp Project, 2007–2010 ($n = 413$). FGV, fibroglandular volume.

BI-RADS diagnostic mammography assessment, and pathologic diagnosis; use of oral contraceptives and MHT, and family history of breast cancer were also not associated with any of the density measures.

Results from linear models in which we regressed the residuals from a fully adjusted model for PD (in which BMI, breast biopsy before enrollment, age at menarche, proliferative atypia pathologic diagnosis, and ever smoking were associated with PD) on % FGV revealed that % FGV was still strongly associated with PD ($P < 0.0001$, data not shown). Likewise, regression of residuals from a fully adjusted model for DA (in which BMI and breast biopsy before enrollment were associated with DA) on FGV yielded statistically significant results ($P < 0.0001$).

Discussion

This analysis of women referred for clinically indicated breast biopsies demonstrates associations between a reproducible, valid, and automated volumetric density methodology—SXA—with some well-known density correlates, providing further support for the broad comparability of this measurement technique in FFDM. Although volume and area density measures were correlated with each other and shared important risk factor associations with several epidemiologic factors, our data revealed some differences. In particular, higher absolute dense volume, but not area, was associated with elevated BMI.

The inverse associations we observed for % FGV with age, BMI, and menopause are consistent with prior studies using different volumetric density approaches, including the Standard Mammogram Form tool, which uses imaging acquisition parameters to determine breast thickness and compute volumetric density for digitized films (14, 16, 18), a density phantom on digitized images (15), and a FFDM method which incorporates imaging acquisition parameters and internal calibration to estimate volume (17). We found elevated % FGV among never smokers and those with a history of breast biopsy, observations that are consistent with prior studies of PD (30–33). However, we did not observe associations with some reproductive factors that have been previously reported to be inversely associated with % FGV and breast cancer risk, such as parity (15, 17, 18) and early age at first birth (15, 17). With each birth, PD is thought to decrease by approximately 2% (12). The prior studies that observed associations for parity and age at first birth reported similar relationships for both % FGV and PD (15, 17, 18). Parity and age at first birth were not associated

with % FGV or PD in our study; this may reflect unique characteristics and potentially limited generalizability of our study population, which consisted primarily of white, highly educated women, who were referred for a breast biopsy from breast imaging.

With respect to absolute density, we found significant inverse associations between age and FGV and DA. Although our findings are consistent with prior work on DA (14, 17, 30), age has not been related to FGV in prior studies using different volumetric density methodologies (14, 17, 18). Similarly, we observed inverse associations between menopause and FGV, a finding consistent with one FFDM study (17) but not two other studies that evaluated the relation in digitized mammograms (14, 16). The varying results for absolute density and these established breast cancer risk factors could be due to differences in volumetric density assessment across studies. Indeed, SXA is the only volumetric methodology that has been shown to provide stronger risk associations than area measures for both % FGV and FGV (23). As absolute density is thought to reflect the breast tissue at risk, it is possible that SXA captures a potentially more biologically relevant measure of absolute dense tissue as compared with other density methods.

Volume and area density measures were positively correlated with one another, but not perfectly so, suggesting that volumetric density measurements do provide some different information. The divergent findings we observed for BMI—its positive association with FGV but inverse association with DA—have been reported previously in studies using different volumetric density methods (14, 16–18, 23), including SXA in digitized films (23). We delved further into the relation between volume and area density, stratifying by BMI, and found that the correlations between FGV and DA were strongest among the leanest women and decreased with increasing BMI. One explanation for the contrasting BMI associations is that FGV and DA likely capture different variations in breast tissue composition. For SXA, water contained in adipose tissue contributes to the FGV measure (23), which translates into higher % FGV than PD, and potentially contributes to the accuracy of % and absolute FGV in risk prediction (23). Indeed, it is thought that both the fibroglandular and adipose tissue components, which are reflected radiographically in mammographic breast density, play a role in breast carcinogenesis (12).

We had the unique opportunity to evaluate density associations with characteristics associated with biopsy and subsequent pathologic diagnosis. We found that neither volume nor area density measures were associated with lesion severity, although our study population was limited in that patients with breast imaging assessments highly suggestive of malignancy were less likely to be enrolled. Nevertheless, our null finding is not necessarily surprising; prior work in the VBCSS has shown that risk factors that traditionally predict the future development of breast cancer, including BI-RADS density (34), do not necessarily predict biopsy outcome at the time of biopsy (35). We observed that elevated FGV in the breast contralateral to the area of suspicion was related to an increased likelihood of undergoing a biopsy in the left breast. This finding could be related to chance, although prior studies have consistently demonstrated that breast cancer is more frequently diagnosed in the left breast (36–38).

SXA requires the installation of density phantoms and prospective collection of data, as compared with other volumetric methods (39, 40), which can be retrospectively applied. Although SXA has been previously shown to be associated with breast cancer risk in

Table 1. Quantitative mammographic density measurements by BI-RADS breast density categories, The BREAST Stamp Project, 2007–2010 ($n = 413$)

		BI-RADS density categories								
		I: entirely fat ($n = 56$)		II: scattered densities ($n = 183$)		III: heterogeneously dense ($n = 131$)		IV: extremely dense ($n = 33$)		ANOVA
Variable	Abbreviation	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*P* value[a]
Volume measures										
Percent fibroglandular volume (%)	% FGV	18.3	9.0	31.7	14.1	48.7	18.3	72.9	19.0	**<0.0001**
Absolute fibroglandular volume (cm^3)	FGV	202.6	118.1	185.5	81.6	200.7	86.1	241.3	155.8	**0.08**
Total breast volume (cm^3)		1,148.6	420.9	690.4	372.0	485.1	307.5	363.5	258.0	**<0.0001**
Area measures										
Percent dense area (%)	PD	4.3	4.3	19.3	11.3	40.4	14.8	62.3	11.7	**<0.0001**
Absolute dense area (cm^2)	DA	10.2	11.5	27.8	17.2	45.9	24.3	59.2	33.6	**<0.0001**
Total breast area (cm^2)		239.0	76.0	156.2	63.2	118.9	56.4	95.7	48.9	**<0.0001**

NOTE: *P* values <0.05 are presented in bold font.

[a]ANOVA tests were performed using square-root–transformed mammographic density measures.

Table 2. Age- and BMI-adjusted linear regression results for the association between participant characteristics and volume and area mammographic density measures[a], The BREAST Stamp Project, 2007–2010 ($n = 413$)

		Percent mammographic density measures						Absolute mammographic density measures					
		% FGV			PD			FGV (cm^3)			DA (cm^2)		
Characteristic	***N***	β	**SE**	***P***	β	**SE**	***P***	β	**SE**	***P***	β	**SE**	***P***
Age at mammogram (years)													
39–44	81	Ref.			Ref.			Ref.			Ref.		
45–49	109	−0.04	0.19	0.84	0.03	0.25	0.90	0.21	0.50	0.68	0.14	0.31	0.64
50–54	102	−0.36	0.19	0.06	−0.14	0.25	0.59	−0.24	0.51	0.63	0.14	0.31	0.65
55–59	68	**−1.14**	**0.21**	**<0.0001**	**−0.86**	**0.28**	**0.002**	**−1.55**	**0.56**	**0.006**	−0.64	0.34	0.07
60–65	53	**−0.91**	**0.23**	**<0.0001**	**−1.06**	**0.30**	**0.0005**	−0.66	0.61	0.28	**−0.76**	**0.37**	**0.04**
P value for trend		***<0.0001***			***<0.0001***			***0.01***			***0.0065***		
Race													
White, non-Hispanic	383	Ref.			Ref.			Ref.			Ref.		
Other	30	**0.50**	**0.25**	**0.04**	**0.80**	**0.32**	**0.01**	−0.05	0.65	0.94	0.56	0.40	0.16
Education level													
<High school or high school grad	63	Ref.			Ref.			Ref.			Ref.		
College/graduate school degree	347	0.19	0.18	0.28	0.44	0.23	0.06	0.56	0.47	0.23	**0.56**	**0.28**	**0.048**
Height (inches)[b]													
51–62	113	Ref.			Ref.			Ref.			Ref.		
63–65	168	0.04	0.20	0.85	0.20	0.25	0.41	**−0.87**	**0.43**	**0.04**	−0.04	0.26	0.88
66–72.5	132	0.11	0.22	0.62	0.43	0.26	0.10	−0.79	0.45	0.08	0.09	0.27	0.74
P value for trend		*0.62*			*0.09*			*0.09*			*0.72*		
Weight (pounds)[b]													
90–136	134	Ref.			Ref.			Ref.			Ref.		
137–166	141	**−1.10**	**0.16**	**<0.0001**	**−1.07**	**0.21**	**<0.0001**	**1.25**	**0.42**	**0.003**	−0.17	0.25	0.50
167–338.5	138	**−2.61**	**0.16**	**<0.0001**	**−2.62**	**0.21**	**<0.0001**	**1.62**	**0.42**	**0.0001**	**−1.02**	**0.25**	**<0.0001**
P value for trend		***<0.0001***			***<0.0001***			***0.0001***			***<0.0001***		
BMI, kg/m^2													
<25	196	Ref.			Ref.			Ref.			Ref.		
25–<30	105	**−1.40**	**0.16**	**<0.0001**	**−1.31**	**0.21**	**<0.0001**	**1.32**	**0.42**	**0.002**	−0.21	0.25	0.41
30+	112	**−2.52**	**0.15**	**<0.0001**	**−2.67**	**0.20**	**<0.0001**	**1.79**	**0.41**	**<0.0001**	**−1.07**	**0.25**	**<0.0001**
P value for trend		***<0.0001***			***<0.0001***			***<0.0001***			***<0.0001***		
Age at menarche (years)													
≤12	153	Ref.			Ref.			Ref.			Ref.		
13	150	0.28	0.15	0.06	**0.47**	**0.19**	**0.02**	0.28	0.39	0.47	0.43	0.24	0.08
≥14	104	0.21	0.16	0.19	0.24	0.21	0.25	0.01	0.44	0.97	0.08	0.27	0.75
P value for trend		*0.15*			*0.17*			*0.95*			*0.65*		
Parity													
Nulliparous	98	Ref.			Ref.			Ref.			Ref.		
1	58	0.10	0.22	0.66	0.20	0.28	0.48	0.54	0.57	0.35	0.55	0.35	0.11
2	164	0.11	0.17	0.52	−0.17	0.22	0.43	0.04	0.43	0.93	−0.03	0.27	0.92
3+	92	0.08	0.19	0.66	−0.13	0.25	0.60	−0.62	0.50	0.21	−0.16	0.30	0.61
P value for trend		*0.59*			*0.37*			*0.23*			*0.39*		
Age at first birth (years)													
<30	217	Ref.			Ref.			Ref.			Ref.		
Nulliparous or 30+	195	0.14	0.13	0.30	0.20	0.17	0.24	0.41	0.34	0.23	0.13	0.21	0.53
P value for trend		*0.13*			*0.87*			*0.44*			*0.54*		
Oral contraceptives													
Never	58	Ref.			Ref.			Ref.			Ref.		
Former	335	−0.11	0.18	0.55	−0.02	0.23	0.92	−0.32	0.47	0.49	−0.17	0.29	0.55
Current	14	0.28	0.39	0.46	0.36	0.50	0.48	0.79	1.02	0.44	0.39	0.62	0.53
Menopausal status													
Premenopausal	250	Ref.			Ref.			Ref.			Ref.		
Postmenopausal	163	**−0.84**	**0.20**	**<0.0001**	**−0.79**	**0.27**	**0.004**	**−1.47**	**0.55**	**0.007**	**−0.80**	**0.33**	**0.02**
Age at menopause (years)													
Premenopausal	250	**0.89**	**0.32**	**0.006**	0.35	0.42	0.40	**1.71**	**0.85**	**0.04**	0.32	0.52	0.53
≤45	32	0.23	0.35	0.51	−0.15	0.46	0.74	0.37	0.93	0.69	−0.28	0.57	0.62
46–49	34	0.11	0.34	0.75	−0.62	0.45	0.17	0.12	0.92	0.89	−0.86	0.56	0.13
50–52	23	Ref.			Ref.			Ref.			Ref.		
53+	21	0.11	0.39	0.77	−0.46	0.51	0.37	0.53	1.04	0.61	−0.49	0.63	0.44
Postmenopausal, age unknown	53	−0.08	0.32	0.81	−0.61	0.42	0.15	0.34	0.85	0.69	−0.51	0.52	0.32

(Continued on the following page)

Table 2. Age- and BMI-adjusted linear regression results for the association between participant characteristics and volume and area mammographic density measures[a], The BREAST Stamp Project, 2007–2010 ($n = 413$) (Cont'd)

		Percent mammographic density measures						Absolute mammographic density measures					
		% FGV			PD			FGV (cm^3)			DA (cm^2)		
Characteristic	***N***	β	**SE**	***P***	β	**SE**	***P***	β	**SE**	***P***	β	**SE**	***P***
Menopausal hormone therapy													
Never	303	Ref.			Ref.			Ref.			Ref.		
Former	77	0.05	0.18	0.79	−0.05	0.23	0.83	−0.78	0.46	0.10	−0.27	0.28	0.34
Current	20	0.38	0.31	0.23	0.004	0.41	0.99	−0.56	0.82	0.49	−0.43	0.50	0.39
Missing/unknown	13	0.39	0.37	0.29	0.67	0.48	0.16	1.16	0.97	0.23	0.85	0.59	0.15
Cigarette smoking, 100+ cigarettes/lifetime													
Never	203	Ref.			Ref.			Ref.			Ref.		
Ever	201	**−0.30**	**0.13**	**0.02**	**−0.45**	**0.17**	**0.008**	0.22	0.34	0.52	−0.21	0.21	0.31
Breast biopsy before enrollment													
Never	269	Ref.			Ref.			Ref.			Ref.		
Ever	140	**0.32**	**0.14**	**0.02**	**0.62**	**0.18**	**0.0004**	0.55	0.36	0.12	**0.71**	**0.22**	**0.001**
Family history of breast cancer in a first-degree female relative													
0	305	Ref.			Ref.			Ref.			Ref.		
1+	103	0.18	0.15	0.23	0.08	0.19	0.69	0.56	0.39	0.15	0.11	0.24	0.65
Lump at the time of mammography													
No	357	Ref.			Ref.			Ref.			Ref.		
Yes	52	0.23	0.19	0.24	**0.64**	**0.25**	**0.01**	−0.76	0.51	0.14	0.49	0.31	0.12
Reason for mammography													
Screening	326	Ref.			Ref.			Ref.			Ref.		
Short-interval follow-up	21	−0.05	0.29	0.87	0.61	0.38	0.11	−0.42	0.77	0.58	0.61	0.47	0.20
Evaluation of breast problem	61	0.13	0.18	0.46	**0.51**	**0.24**	**0.03**	−0.61	0.48	0.20	0.45	0.29	0.12
BI-RADS breast density													
I (entirely fat)	56	Ref.			Ref.			Ref.			Ref.		
II (scattered densities)	183	**0.51**	**0.17**	**0.002**	**1.60**	**0.18**	**<0.0001**	0.64	0.51	0.21	**2.15**	**0.26**	**<0.0001**
III (heterogeneously dense)	131	**1.47**	**0.18**	**<0.0001**	**3.35**	**0.20**	**<0.0001**	**1.56**	**0.56**	**0.01**	**3.72**	**0.29**	**<0.0001**
IV (extremely dense)	33	**2.81**	**0.25**	**<0.0001**	**4.79**	**0.27**	**<0.0001**	**2.85**	**0.78**	**0.0003**	**4.67**	**0.39**	**<0.0001**
P value for trend		***<0.0001***			***<0.0001***			***<0.0001***			***<0.0001***		
Final BI-RADS mammography assessment													
3 (probably benign finding)	26	Ref.			Ref.			Ref.			Ref.		
4 (suspicious abnormality)	363	0.29	0.26	0.27	0.23	0.34	0.51	0.73	0.68	0.29	0.35	0.42	0.40
5 (highly suggestive of malignancy)	23	−0.03	0.37	0.93	0.27	0.48	0.58	0.26	0.98	0.79	0.33	0.60	0.58
P value for trend		*0.96*			*0.53*			*0.68*			*0.50*		
Biopsy type													
Ultrasound-guided	195	Ref.			Ref.			Ref.			Ref.		
Stereotactic-guided	208	0.16	0.13	0.23	0.13	0.17	0.46	0.36	0.34	0.29	0.15	0.21	0.49
Both	7	0.41	0.50	0.41	0.20	0.66	0.76	**2.63**	**1.32**	**0.047**	0.88	0.81	0.28
Biopsy laterality													
Left	203	Ref.			Ref.			Ref.			Ref.		
Right	210	−0.25	0.13	0.05	0.21	0.17	0.20	**−1.42**	**0.33**	**<0.0001**	0.12	0.21	0.55
Pathologic diagnosis													
Benign	141	Ref.			Ref.			Ref.			Ref.		
Proliferative	171	0.10	0.15	0.51	−0.06	0.19	0.75	0.28	0.39	0.47	−0.01	0.24	0.96
Proliferative with atypia	32	**0.55**	**0.26**	**0.03**	**0.81**	**0.33**	**0.02**	0.81	0.68	0.24	0.71	0.41	0.09
In-situ	34	−0.09	0.25	0.73	0.21	0.33	0.53	0.13	0.67	0.85	0.20	0.41	0.63
Invasive breast cancer	35	0.06	0.25	0.81	0.06	0.32	0.86	0.60	0.65	0.36	0.23	0.40	0.56
P value for trend		*0.71*			*0.35*			*0.35*			*0.32*		

NOTE: Beta coefficients with *P* values <0.05 are presented in bold font. *P* values for trend are presented in italics.

[a]Mammographic density measures were square-root transformed.

[b]Tertiles of height and weight are presented.

digitized mammograms (23), its definitive relationship with risk in FFDM remains to be established. Nevertheless, the demonstrated associations between SXA density measures with established density correlates in expected directions, combined with the strong associations between SXA with quantitative area and BI-RADS density measures, lend support to its validity in FFDM. Though volumetric in its conceptual design, SXA still represents a volumetric measure that is derived from a 2-dimensional mammography system. The distribution

of fibroglandular tissue may be assessed by true 3-dimensional breast imaging modalities (e.g., MRI, ultrasound tomography; ref. 41), but the added utility of these methods has not been established. However, a recent study showed that SXA from FFDM corresponds well to MRI measures of fibroglandular volume, suggesting that SXA may indeed be an accurate and valid representation of breast tissue volumes (42).

Strengths of our study include the use of an automated volumetric density method that precludes the need for operator training. Volumetric measures were calibrated to permit estimation of dense volume using a reference standard. Evaluation of the contralateral breast mitigated concerns that density estimates were influenced by so-called "field effects" related to the suspicious lesions. On the other hand, these field effects—if apparent in the mammogram—may serve as a useful clinical indicator of underlying pathology (43). Prior studies have reported that high-risk lesions tend to occur in regions of the breast that are mammographically dense (44, 45), suggesting that localized density measures may prove to be informative with respect to risk prediction. Research relating perilesional dense volumes surrounding the biopsy target to pathologic diagnosis in this study population is ongoing.

In conclusion, our findings suggest that risk factor associations with volumetric density, estimated with the SXA method, differ from those with area density, particularly for BMI. Future comparisons of volume and area density measures stratified by BMI may clarify whether differences between these measures translate into differences in breast cancer risk, particularly among obese women.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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