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Comparison of breast density measured by dual energy x-ray Absorptiometry (DXA) with mammographic density among adult women in Hawaii

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Abstract

While use of mammography is limited, due to concerns related to radiation exposure, Dual Energy X-ray Absorptiometry (DXA), commonly available in medical care settings, is characterized by low radiation exposure. In the current paper, we compared breast density measured by DXA with mammographic density in 101 adult women who had a screening mammogram during the last 2 years. DXA scans of both breasts were taken using a clinical DXA system calibrated to measure breast density. The total projected breast area was manually delineated on each image and percent fibroglandular volume density (%FGV), absolute fibroglandular volume, total breast area and volume were computed. After digitizing mammographic films, total breast area, dense area, and percent density (PD) were estimated using computer-assisted mammographic density assessment. Both DXA and mammographic measures showed high correlations between left and right breasts ranging from 0.85 to 0.98 (p <0.0001). Mean %FGV was 38.8±14.3%, and mean percent density was 31.9±18.2% for craniocaudal views and 28.3±16.2% for mediolateral views. The correlation between the two measures was 0.76 for both views (p <0.0001). Associations with common risk factors showed similar patterns for DXA and mammographic densities; in particular, the inverse associations with BMI and age at menarche were evident for both methods. Multilinear regression with stepwise selection indicated an explained variance of 0.56 for %FGV alone and of 0.58 for %FGV plus number of children. Despite some differences in methodology, the current comparison suggests that DXA may provide a low-radiation option in evaluating breast density.

Keywords

DXA; mammographic density; mammogram; breast; adult; risk factors

Mammographic density, the distribution of fat, connective, and epithelial tissues in the female breast, is strongly associated with breast cancer and has been used as a biomarker for breast cancer risk among adult women [1,2]. However, use of X-ray based mammography is limited due to concerns related to radiation exposure. In contrast, Dual Energy X-ray

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Absorptiometry (DXA) is characterized by low radiation exposure and commonly available in medical care settings. As shown among 17 women, a commercial DXA device, when it is calibrated to measure breast density, provides a precise measure of breast composition in comparison with mammography [3]. This suggests that DXA may provide an additional tool for evaluating breast cancer risk with minimal radiation exposure. For now, DXA breast imaging serves as a research tool to investigate breast development in girls and young women. However, in the future it may play a role in individualized risk prediction [4]. In the current paper, we compared breast density measured by DXA and by regular mammography in women who took part in a study that included mothers and their adolescent daughters 10-16 years of age. An additional objective of this report was to explore a prediction model for mammographic density using the DXA measure in combination with demographic, anthropometric, and reproductive information.

Materials and Methods

Study design and procedure

The current analysis was conducted as part of a study that measured breast density and body-fat composition in adult women and their daughters using DXA. The project was approved by the Committee on Human Studies at the University of Hawaii and the Institutional Review Board of Kaiser Permanente (KP) Hawaii. We recruited women aged 30 years and older who had received a normal mammogram (defined as BIRADS categories 1 through 3) during the last 2 years and their daughters aged 10-16 years through KP Hawaii, a large health maintenance organization. We mailed 3,915 invitation letters to women and to girls in the respective age ranges over the course of 11 months. Potential participants were selected from the membership data base according to the age and mammographic criteria. From the 304 respondents, we excluded mothers who had no mammograms, a previous history of breast cancer or surgery, an abnormal mammogram, a previous biopsy, breast implants, or chronic health conditions that interfered with study participation. We excluded girls without breast development and mother-daughter pairs who were not biologically related or did not reside on Oahu. A few daughters were recruited though KP whose biological mother was not a KP member.

Of the 138 eligible mother-daughter pairs, 102 pairs completed the study visit. Prior to DXA scans, all mothers signed informed consent, answered a demographic questionnaire, and completed height and weight measurements in duplicate. The six women whose screening mammograms were not performed at KP signed a mammogram release authorization form for the respective clinics. In the questionnaire, participants reported ethnicity and reproductive factors, i.e., age at menarche, age at first live birth, number of children, menopausal hormone use, and the most recent menstrual period. Women whose last menstrual period was >1 year ago were classified as postmenopausal. Body mass index (BMI) was calculated using the height and weight and classified as normal (18.5 - <25), overweight (25 - <30) and obese (≥30 kg/m^2).

DXA data collection

At the exam, a urine test excluded pregnancy in all participants. We performed DXA scans of both breast, as well as of the whole body, using the research scan protocol and software version 10.1 on a GE Lunar Prodigy Bone Densitometer (GE Healthcare). Prodigy utilizes an ultra low radiation and cadmium-zinc-telluride detector to convert X-rays into an electronic signal without the intermediate conversion to light. We used a custom thickness-step phantom made of reference materials to recalibrate the DXA device. Details of this phantom and mathematical equations to compute breast density and thickness were described elsewhere [5,6]. After changing into a hospital gown, breast scans were taken on

both breasts in the decubitus mediolateral position with the nipple positioned in a true lateral profile. A duplicate breast scan of the left breast was performed on a random 10% of subjects for quality control.

A low energy and high energy attenuation image was saved for each scan using the options available from GE Lunar for the research scan mode. These images were analyzed by the University of California at San Francisco using a Breast Density Workstation. The total projected breast area was manually delineated on each image by the same operator (Figure 1). From the bottom of the breast, the delineation followed the thoracic cage, then the pectoral muscle to continuously reach the exterior of the breast. Finally the external line was delineated. To calculate DXA density, a two-compartment model of adipose and fibroglandular tissue was used [7]. Scans of a calibrated phantom with known composition and thicknesses allowed the calculation of calibration curves. We computed total breast area, breast volume, absolute fibroglandular volume (FGV), and percent FGV (%FGV).

For quality control, a calibrated phantom was scanned over 8 months, once every day if participants were scheduled, and once a week if no participant was scheduled. The phantom varied in thickness (2, 10, and 20 cm) and contained three %FGV values of 28%, 65%, and 100%. The phantom precision values ranged from 1.9% (10 cm in thickness and 65% composition) to 5.4% (2 cm in thickness and 65% composition). For the repeated breast scans, a root mean square standard deviation of 2.5 and a correlation of 0.975 were achieved.

Mammographic data

Craniocaudal (CC) and mediolateral (ML) views of screening mammograms taken within the last 2 years were scanned with a Kodak LS85 Film Digitizer for 101 women; one film could not be located. Ninety-five women had film mammography at KP, and 6 women had digital mammography at non-KP clinics and hospitals. All personal identifiers were removed from the scanned images. One of the authors (GM) performed computer-assisted density assessment using the Cumulus package [8,9]; all mammograms for one woman were assessed during the same session. Using this interactive method, the reader selects a threshold value (gray scale on the screen) that best distinguishes the breast from the dark background and another threshold value, the gray value that best identifies the edges of the mammographically dense areas within the breast outline. The number of pixels in the two areas is then measured by the computer. The mammographic measures for our analysis included the total breast area and the dense area of the breast; percent density (PD) was calculated as the ratio of the two. In a sample of 49 duplicate mammographic readings, the correlations were 0.997 for the size of the total breast area and 0.959 for the dense breast area resulting in a coefficient of 0.955 for PD.

Statistical Analysis

All statistical analyses were performed using the SAS statistical software package version 9.2 (SAS Institute, Inc., Cary, NC). Correlations between right and left breasts measures were computed for both DXA and mammographic measures. The correlation between the two methods was evaluated using their corresponding measures, i.e., total area (cm^2) by DXA and total area (cm^2) by mammography, FGV (cm^3) and dense area (cm^2), and %FGV and PD. Because of the small sample size, subjects were grouped into 3 major ethnic categories: Caucasian, Asian (Japanese, Chinese, Filipino, Korean, and Other Asian), and Other (Hawaiian and other Pacific Islanders, Black, Native American, Hispanic, and Other). Correlation coefficients and analysis of variance were used to detect statistically significant differences in demographic characteristics by ethnic category. Mean DXA and mammographic measures were calculated by ethnicity and relevant risk factors, i.e., age,

BMI, age at menarche, age at first live birth, number of children, menopausal status, and menopausal hormone use. To develop a prediction formula, we performed multilinear regression using the stepwise selection method with PD as dependent variable and %FGV and all covariates as independent variables. An α-level of 0.15 was used to select independent predictors for inclusion in the final model.

Results

The ethnic background of the study population was 31% Caucasian, 46% Asian, and 23% Other (Table 1). With one exception (age of 64 years), the ages ranged between 39 and 58 years. The three ethnic groups differed in BMI, age at menarche, and age at first live birth. The mean BMI was highest in the Other group ($p = 0.01$), while the mean age at menarche was lowest among Asians and highest among Others ($p < 0.001$). Age at first live birth was higher in Asian and Caucasian than in Other women ($p = 0.01$). Mammographic density, DXA measures, menopausal status, number of children, and menopausal hormone use did not differ significantly by ethnicity although PD for the CC view was marginally significant ($p = 0.08$).

When comparing left and right breasts, both DXA and mammographic measures showed high correlations (Table 2) ranging from 0.85 to 0.98 ($p < 0.0001$) with a stronger association for CC than ML views. In addition, correlation coefficients were higher for DXA measures (0.96 to 0.98) than mammographic measures (0.85 to 0.95).

For the overall population, mean %FGV was 38.8±14.3, and mean PD was 31.9±18.2 for CC and 28.3±16.2 for ML views. PD in CC and ML views were strongly correlated with %FGV (Figure 2). The associations between DXA and mammographic measures were >0.80 for the total area and 0.76 for PD ($p < 0.0001$ for both). However, the correlation coefficients between DXA FGV (cm^3) and dense area (cm^2), which possessed different dimensional characteristics, were 0.30 to 0.36 for CC and ML views ($p < 0.01$ and < 0.001, respectively).

In evaluating the relation of DXA and mammographic measures with characteristics that have previously been found to be associated with breast density, we observed highly significant inverse associations of BMI with %FGV and PD (Table 3). The respective differences between normal weight and obese women were 22% and 25% ($p < 0.001$ for both). As to reproductive characteristics, we observed non-significant, higher %FGV and PD in menopausal hormone users than non-users and significantly higher %FGV and PD among pre- than postmenopausal women. Age at menarche was positively associated with %FGV and PD ($p < 0.0001$ and 0.04, respectively). Age and ethnicity did not show significant associations. DXA and mammographic density were non-significantly lower with more children ($p = 0.47$ and 0.09, respectively).

Multilinear regression with stepwise selection indicated an adjusted r^2 of 0.56 for %FGV to PD both for the CC and the MLO views, and an adjusted r^2 of 0.58 when the number of children was added. Other demographic and reproductive variables including menopausal hormone use did not contribute to the model. We also included a time variable describing the number of days between mammography and DXA. The mean time difference was 5.6 ± 4.2 months and inclusion of the time variable did not modify the regression estimates.

Discussion

The current study compared the breast density of adult women calculated from DXA images with mammographic density from screening mammograms. We observed moderate to high correlations between the two methods: 0.83-0.89 for total area, 0.30-0.36 for FGV and dense area and 0.76 for %FGV and PD. Moreover, the associations with demographic, BMI, and

reproductive characteristics showed very similar patterns for DXA and mammographic density, in particular, the strong inverse association of PD with BMI was evident for both methods. In comparison with a previous report that computed a correlation of 0.52 between PD and %FGV [3], the current analysis evaluated DXA in a larger sample of women and found a stronger association between DXA and mammographic measures. Correlations between left and right measures were comparable in both DXA and mammography, and the linear association between DXA and mammographic measures were also strong. The correlation between FGV and dense area was considerably lower. This may be in part due to the breast compression used for mammography but not for DXA, but primarily it is due to the 3-dimensonial nature of FGV in contrast to the 2-dimensional mammograms. Other volumetric density methods suggest that percent density may be lower when assessed as a volumetric measure than as the 2-dimensional percentage of the breast area [10,11]. As apparent from Figure 2, the lowest DXA density was approximately 20% while several women had mammographic density values below 20%. The reason for this is that DXA measures the breast as compartments of fibroglandular tissue and fat. In DXA, fat is used as a reference since the water content of adipose tissue changes and is not a stable reference. Thus, the breast does not get leaner than about 20%FGV, the fraction of water in adipose tissue. A similar result was presented by a report using magnetic resonance images (MRI) volume of fat and water to measure breast density [12].

Similar to DXA, a number of different methods are currently under investigation to examine breast density without radiation. Boyd et al [12] evaluated the use of MRI in 400 mother-daughter pairs and found a strong correlation ($r = 0.85$, $p < 0.0001$) between percent breast water (as surrogate for fibroglandular-tissue level) calculated from MRI and mammographic density among 100 mothers. The same study also evaluated the use in young women 15-30 years and compared the results with density measures of their mothers. Investigators in Minnesota evaluated the use of ultrasound tomography images to assess breast density and found positive associations with mammographic density [13,14]. Both MRI and ultrasound tomography are non-radiation methods and require no breast compression. One major advantage of DXA as compared to the other methods, both mammography and other novel approaches, is that it is widely available in clinics and hospitals, more than 30,000 systems worldwide, and relatively inexpensive. Unlike mammography, it provides three-dimensional data for density calculation, does not require a subjective interpretation of results [7], and has been explored as a research tool among young girls during pubertal development [6]. Furthermore, DXA provides additional information on whole body composition that may be useful in assessing additional breast cancer risk factors.

Some of the limitations of our analysis include the narrow age range of subjects, the exclusion of nulliparous women, and the lack of data in breast cancer cases. The combination of the restricted age range, the inclusion of only parous women, the high proportion of women who reported more than one ethnic background, and the small sample size are probably responsible for a lack of association of age and ethnicity with breast density in this study. Thus, our results need to be replicated in broader populations and should be interpreted with caution. Despite the great stability of mammographic density over time [15], breast density may change, especially during the menopausal transition or due to menopausal hormone therapy [16,17]. Therefore, it was not ideal that we compared DXA and mammogram images taken at different times, but the time difference was not a significant predictor of PD in a multiple regression model with %FGV as an independent variable. Based on our previous study among premenopausal women [18], the mean annual change in PD is less than 2%; for 94 out of 101 women in the current analysis the time difference was less than one year. Thus, the differences should be very small. A strength of our study is the excellent quality control result. Duplicate readings of a subset of mammograms showed high reproducibility with a coefficient of 0.955 for PD. The

calibration data and the repeated breast scans indicated high precision of the DXA data. Our multiethnic population strengthens the generalization of our results.

Our findings suggest that DXA has potential to provide a low-radiation option for evaluating breast density and may be useful as part of breast cancer risk prediction although it is unlikely to play a role in the detection of abnormalities [4,19]. Its current use is restricted to being a research tool, but in the future, DXA imaging may allow the identification of high-risk girls and young women and make it possible to offer them early detection approaches and/or interventions to reduce breast cancer risk. The method has advantages of relative low cost, broad availability, and simultaneous provision body composition data. However, we need more imaging information from younger women and from breast cancer cases to evaluate the method.

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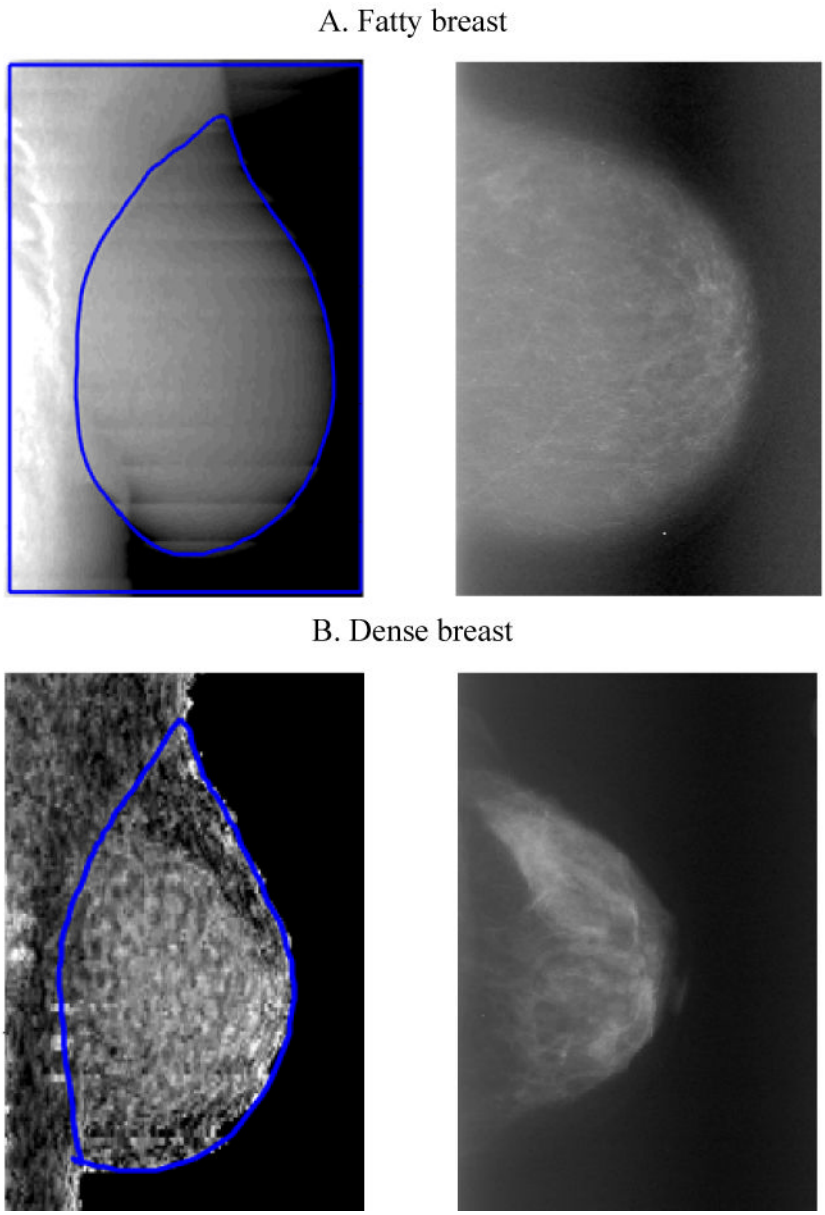

Figure 1. Breast images by DXA (left) and mammography (right)

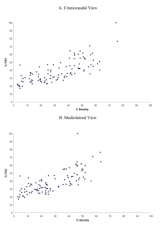

Figure 2. Correlation of breast densities measured by DXA and mammography

Table 1

Characteristics of study participants by ethnicity

Ethnic category	Caucasian	Asian	Other	All	*p* value[a]
N	32	47	23	102	--
Age (years)	48.0±4.4	48.3±5.3	46.2±3.8	47.7±4.8	0.19
BMI (kg/m^2)	26.6±5.8	26.5±5.6	31.1±5.8	27.5±5.9	<0.01
Age at menarche (years)	12.9±1.6	11.9±1.2	13.3±1.9	12.5±1.6	<0.001
Age at first live birth (years)	30.0±5.4	30.1±5.8	26.0±5.4	29.1±5.8	0.01
Number of children (N)	2.5±1.0	2.3±0.8	2.9±1.3	2.5±1.0	0.07
Postmenopausal status (N)[b]	9	12	7	28	0.89
Menopausal hormone use (N)	5	13	4	21	0.38
Overweight/Obese (N)[c]	9/8	17/8	7/12	33/28	0.02
DXA total volume (cm^3)	819.5±521.0	746.6±448.2	1005.7±535.5	827.9±497.6	0.12
total area (cm^2)	95.6±43.4	85.2±35.5	103.3±38.2	92.5±39.0	0.16
FGV (cm^3)	275.9±103.7	259.9±112.8	298.6±102.3	273.7±107.7	0.37
%FGV	40.4±14.0	40.1±15.3	33.9±11.8	38.8±14.3	0.18
Mammographic PD CC view	30.9±19.6	35.8±17.4[d]	25.5±16.2	31.9±18.2	0.08
ML view	29.8±18.4	29.9±15.6[d]	23.3±13.5	28.3±16.2	0.23

[a] *p* value based on analysis of variance or chi-square test

[b] Last menstrual period more than one year ago; one woman had missing data.

[c] Overweight: BMI 25-30 kg/m^2; Obese: BMI ≥30 kg/m^2

[d] N=46; one film could not be located.

Table 2

Summary of DXA and mammographic measures for left and right breasts

		Left[a]	Right[a]	r[b]	p
DXA (N=102)	Total volume (cm^3)	834.6±508.3	821.2±490.5	0.98	<0.0001
	Total area (cm^2)	93.2±39.0	91.8±39.7	0.97	<0.0001
	FGV (cm^3)	275.0±109.8	272.3±108.1	0.96	<0.0001
	%FGV	38.7±14.3	38.8±14.5	0.97	<0.0001
Mammography (N=101)	Total area (cm^2) CC view	122.7±57.6	112.8±52.7	0.90	<0.0001
	ML view	130.8±53.6	125.8±54.1	0.95	<0.0001
	Dense area (cm^2) CC view	34.2±22.3	31.1±18.1	0.88	<0.0001
	ML view	32.3±20.2	32.7±21.7	0.85	<0.0001
	PD (%) CC view	31.7±18.4	32.2±18.8	0.90	<0.0001
	ML view	28.1±16.9	28.6±16.7	0.87	<0.0001
DXA and mammography	Total area (CC view)			0.83	<0.0001
	Total area (ML view)			0.89	<0.0001
	FGV and dense area (CC view)			0.30	<0.01
	FGV and dense area (ML view)			0.36	<0.001
	%FGV and mammographic PD (CC view)			0.76	<0.0001
	%FGV and mammographic PD (ML view)			0.76	<0.0001

[a] Mean and standard deviations

[b] Spearman rank order correlation coefficient.

Table 3

DXA and mammographic measures by breast cancer risk factors

Risk factor	Category	N	FGV (%)[a]	p[b]	N	PD (%)[a]	p[b]
Age (years)	<45	34	41.1±16.7		33	32.0±18.0	
	45-49	37	36.9±11.7		37	33.9±17.5	
	≥50	31	38.5±14.3	0.45	31	29.5±19.4	0.59
Ethnicity	Caucasian	32	40.4±14.0		32	30.9±19.6	
	Asian	47	40.1±15.3		46	35.8±17.4	
	Other	23	33.9±11.8	0.18	23	25.5±16.2	0.08
Body mass index (kg/m^2)	18.5-<25	41	48.8±15.0		41	42.7±15.8	
	25-<30	33	36.3±8.1		33	30.0±16.8	
	≥30	28	27.1±7.0	<0.0001	27	17.8±12.0	<0.0001
Age at menarche (years)	<13	60	34.5±10.5		59	28.8±16.7	
	≥13	42	44.9±16.6	<0.001	42	36.2±19.4	0.04
Age at first live birth (years)	<30	60	38.4±15.2		59	29.2±18.2	
	≥30	42	39.2±13.3	0.76	42	34.9±17.9	0.11
Number of children (N)	1-2	59	39.7±15.8		59	34.5±18.7	
	≥3	43	37.6±11.8	0.47	42	28.3±17.0	0.09
Menopausal status[c]	Pre	73	40.5±14.7		72	34.6±17.2	
	Post	28	34.3±12.5	0.05	28	25.8±19.3	0.03
Menopausal hormone use	Yes	22	38.6±13.4		22	29.9±18.2	
	No	80	38.8±14.6	0.95	79	32.5±18.2	0.56

[a] Mean and standard deviations of left and right breast measures (CC view for mammographic density)

[b] Calculated by ANOVA as the trend across categories

[c] One women had missing data; N=101