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ASSOCIATION BETWEEN BREAST CANCER, BREAST DENSITY, AND BODY ADIPOSITY EVALUATED BY MRI

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Abstract

Objective—Despite the lack of reliable methods with which to measure breast density from 2D mammograms, numerous studies have demonstrated a positive association between breast cancer and breast density. The goal of this study was to study the association between breast cancer and body adiposity, as well as breast density quantitatively assessed from 3D MRI breast images.

Methods—Breast density was calculated from 3D T1-weighted MRI images. The thickness of the upper abdominal adipose layer was used as a surrogate marker for body adiposity. We evaluated the correlation between breast density, age, body adiposity, and breast cancer.

Results—Breast density was calculated for 410 patients with unilateral invasive breast cancer, 73 patients with DCIS, and 361 controls without breast cancer. Breast density was inversely related to age and the thickness of the upper abdominal adipose layer. Breast cancer was only positively associated with body adiposity and age.

Conclusion—Age and body adiposity are predictive of breast density. Breast cancer was not associated with breast density; however, it was associated with the thickness of the upper abdominal adipose layer, a surrogate marker for body adiposity. Our results based on a limited number of patients warrant further investigations.

Keywords

Magnetic resonance imaging; Breast Cancer; Breast Density; Adiposity; Age

Introduction

The breast is composed of fatty and dense glandular and fibrous tissues. Breast density (BD), also referred to as percent BD, is expressed as the fraction of a mammogram occupied by dense tissues. Although studies performed in the last forty years have demonstrated that women with mammographically dense breasts have an increased risk of developing breast cancer [1; 2], there is still a paradoxical lack of reproducible and accurate BD measurement methods [3; 4].

The only clinical classification of mammographic density in the U.S. is BI-RADS® (Breast Imaging Reporting and Data System), which was developed by the American College of Radiology to communicate how likely a tumour is obscured by dense breast tissue [5]. The fifth edition of BI-RADS® reports breast composition in four categories only without a reference to the numeric percentage ranges of dense tissue, since the estimates of BD based on 2D mammograms are imprecise [6; 7]. It was urged that all investigators stop drawing breast cancer risk conclusions based on 2D BD [7]. Others also voiced concerns that mammographically dense breasts were not a reliable cancer risk factor [8]. No significant association was found between breast cancer and MRI BD in women at high genetic risk for breast cancer, although it was augured that the number of breast cancer patients (56 patients) in the study was too small to detect an association [9]. Nevertheless, continued epidemiologic studies identified the strongest associations between breast cancer and the percentage mammographic BD [2], but the official BI-RADS® density category was considered the least reliable variable with which to predict breast cancer risk [4].

Automated BD measurement methods have been developed for full-field digital mammography [3], but it remains to be tested whether these methods can mitigate the intrinsic flaws associated with using 2D mammographic projection images to assess the density of the entire 3D breast [4; 7]. Quantra [10] and Volpara [11], two FDA-approved software packages designed to estimate volumetric BD, have produced inconsistent density measurements [12]. Digital tomosynthesis [13], a new 3D mammographic technology, may allow BD calculations directly from volumetric data sets.

There has been an increased interest in the estimation of BD using 3D T1-weighted MRI images [9; 12; 14-16], which provide excellent contrast between the bright fatty tissues and dark, dense fibroglandular tissues with high water content at high spatial resolution. The percent BD is calculated as the volume fraction occupied by the dark signals in the entire breast from 3D T1-weighted MRI images without fat saturation. A relative good correlation between MRI and mammographic BD measurements has been reported [9; 12; 14; 16]. These studies demonstrated the feasibility of using MRI to quantitatively measure BD. Notably, 3D MRI provides reproducible and compression-free quantitative volumetric BD assessment [17] and eliminates the guessing work to segment the overlapping adipose and dense breast tissues in 2D mammographic BD estimation [4; 7].

High BD as a risk factor, however, is in direct contradiction to other risk factors, such as aging and obesity [18-21], which are associated with lower BD [22]. There is no reliable evidence with which to predict whether a slim woman with dense breasts faces a higher

breast cancer risk than an overweight woman with fatty breasts under otherwise identical familial and health conditions. The biological basis for the association of BD and breast cancer risk is unclear [4; 23]. Despite the relative lack of evidence and standardization, many states in the U.S. have passed laws mandating that the presence of dense breast tissue and its potential to obscure cancer on mammography be communicated to the patient, as well as its association with breast cancer risk [24-26].

In this retrospective study, we aimed to verify and validate the status of BD as an independent risk factor of breast cancer, using values obtained from MRI images. We evaluated the correlation between MRI BD and patient age, as well as body adiposity, using the thickness of the upper abdominal adipose layer as a surrogate marker. Breast cancer occurrence was assessed in association with age, body adiposity, and MRI BD.

Materials and Methods

Patient Selection

This retrospective study was approved by our Institutional Review Board under the Health Insurance Portability and Accountability Act. Consent was waived. Only patients older than 20 years were included in the study.

Breast MRI images and reports acquired on patients with high breast cancer risk, suspicious mass/nodules, and known malignancy to evaluate the extent of the disease from 2007 to 2014 at our institution were reviewed using the picture archiving and communication system (PACS) database. The indications for high risk breast MRI screening included family history, a genetic mutation such as BRCA1/2, and/or benign lesions. The corresponding electronic medical records were subsequently reviewed to confirm the presence or absence of a primary diagnosis of breast cancer. Case breast cancer patients were selected as those diagnosed with unilateral invasive breast cancer (IC) and ductal carcinoma in situ (DCIS) who had breast MRI performed before the start of any cancer drug treatments. Controls (NoCA) were those patients who had breast MRI performed, and at least three years of medical records, either before or/and after the MRI, which showed no breast cancer diagnosis. Women with a prior history of breast surgery and/or cancer of any organs were excluded from both cases and controls.

Breast MRI Acquisition Protocol

Three-dimensional axial T1-weighted images that covered the entire breasts were acquired without fat saturation, prior to the administration of contrast, on one of the 1.5-T Achieva (Philips Medical System, Andover, MA), 3-T Intera (Philips Medical System, Andover, MA), 3-T TrioTim (Siemens, Erlangen, Germany), or 3-T Skyra (Siemens, Erlangen, Germany) MRI scanners, using bilateral phased-array breast coils with patients lying in a prone position. The axial in-plane field of view ranged from 300×300 mm to 350×350 mm and the in-plane resolution was $0.33 \text{ mm} \times 0.33 \text{ mm}$ to $0.67 \text{ mm} \times 0.67 \text{ mm}$. Slice thickness across subjects ranged from 1 mm to 5 mm and the covered depth was 120 to 170 mm. A total of 67 sets of T1-weighted images were acquired using a spin echo sequence, with a TE = 8-9 ms, and a TR = 550 ms (1.5-T and 3-T), or a TR = 367 ms (3-T) prior to

early 2008. The rest of the T1-weighted images were acquired using a gradient echo sequence with a TE = 2.3 – 2.5 ms, a TR = 5.27 – 5.32 ms, and a flip angle of 10 – 20 degrees. We used the same BD analysis methods for all types of T1-weighted images in this study.

Thickness of Upper Abdominal Adipose Layer Measurement

We were not able to determine the body mass index (BMI) since patient heights were not uniformly available and some of the patient weights were self-reported at the time of imaging. No other body adiposity measurements, such as waist circumference, waist-to-hip ratio, or skinfold thickness, were available in this retrospective study. An earlier study indicated that breast adipose tissue volume correlates with body weight, BMI, and subcutaneous adipose tissues of the trunk and arms [27]. One study demonstrated a stronger correlation between body fat percentage and breast cancer risk than BMI [28]. Another report demonstrated a strong correlation between BMI and abdominal subcutaneous fat [29]. There was a good correlation between the body density and the subcutaneous fat thickness measured by the caliper technique [30]. Thus, we measured the thickness of the upper abdominal adipose layer (UAAL) immediately below the breasts on 3D axial MRI T1-weighted breast images without fat saturation, as shown in Figure 1. This thickness was used as a surrogate marker for body adiposity.

Calculation of Percent Breast Density on MRI

The BD of cancer patients was calculated from the contralateral breast without a tumour. Control BD was calculated from the right breast, unless there was an ipsilateral benign lesion present. In those cases, the left breast was assessed. The density calculation was performed with 3D T1-weighted axial breast MRI images without fat saturation, using the NIH Fiji (ImageJ) image processing software, with the following steps as shown in Figure 2: 1) Image intensity bias field artefacts were corrected [31], using a 3D Gaussian filter approach to compensate for the low-frequency spatial intensity variation due to magnetic field heterogeneity prior to the segmentation process [32]; 2) Chest regions were removed from the image using a mask drawn along the pectoral muscle; 3) The breast area was cropped; 4) The entire breast was segmented using the Fiji (ImageJ) minimum/auto threshold method interactively; and 5) The bright fatty tissue was segmented using the Fiji moment/auto threshold method interactively. All the above calculations were performed throughout the entire stack of 3D breast MRI images using automated macros. Percent fatty tissue density was calculated as the percentage of total voxel counts occupied by the fatty tissues over that of the entire breast. The MRI percent BD was calculated as the remaining percentage of the fatty tissue. It was estimated that the inter- and intra-operator variation of our procedure was less than 10%.

Statistical Analysis

Each patient in our cohort was characterized by three numerical variables (age, thickness of the UAAL, and MRI BD) and one categorical variable for breast cancer type (NoCA, DCIS, and IC). The Kruskal-Wallis test was performed in JMP 11 to compare the BD and the thickness of the UAAL of different subgroups of patients stratified by age groups. Spearman partial correlation analysis was used to investigate the pairwise correlation between the

thickness of the UAAL, age, and BD while eliminating the effects of the remaining variable. Logistic regression was performed to estimate the association between of the thickness of the UAAL (TU), age, as well as BD; and DCIS and IC individually; using the controls as a reference. Both Spearman correlation and logistic regression were performed using MATLAB.

Results

Distribution of Breast Density by Age

We identified the MRI images of 410 patients with a first-time diagnosis of primary invasive breast cancer (age 23 to 89, average 52.5), 73 with DCIS (age 30 to 76, average 55.3), and 361 controls (age 20 to 91, average 48.7). One DCIS and 5 IC cases were diagnosed during the routine high risk MRI screening. All but 5 DCIS and 18 IC patients had a positive breast cancer diagnosis prior to the breast MRI procedures. Patient distribution by age groups is listed in Table 1. A majority of breast cancer occurred in women older than 40 years, at 84.6% for invasive cancer and 90.4% for DCIS. Those with invasive breast cancer had a breast density ranging from 3.2% to 80.3%, those with DCIS 4.1% to 60.4%, and controls 3.1% to 79.1%. Despite a great variation in BD at the individual level at each age, a general trend toward decreasing BD was observed as women aged, Figure 3a. Figure 3a also demonstrated that breast cancer afflicted women of all breast densities, from very fatty to extremely dense. No clusters were observed of breast cancer patients with high MRI BD with respect to the controls.

Distribution of Thickness of the Upper Abdominal Adipose Layer by Age

There was a great variation in the thickness of the UAAL at the individual level at each age, Figure 3b. The thickness of the UAAL in invasive breast cancer patients was 1 to 39 mm, in DCIS, 1 to 40 mm, and in controls, 1 to 38 mm. Notably, there was a high occurrence of a thick UAAL (> 25 mm) in invasive cancer patients in the 50 – 60 age group, Figure 3b.

Breast Density and the Thickness of the Upper Abdominal Adipose Layer

Figure 4 shows a general downward trend in MRI BD as the thickness of the UAAL increased in all patients. Figure 4 demonstrated that extremely dense breasts (such as > 60% density) were associated only with women with a thin UAAL. Just over 1% (5/457) of our patients older than age 50 had MRI BD over 50%. All of these five women had a UAAL less than 5 mm thick; four of them were in the control group and one in the invasive cancer group. Figures 3 and 4 all suggest that there were such significant overlaps in age, thickness of the UAAL, and BD among the control, DCIS, and IC groups that it was difficult to visually identify factors to separate them.

Breast MRI (Figure 5) showed that a thick UAAL was consistently accompanied by a thick layer of breast periphery fat, which inevitably reduced the BD. The distribution of the breast fat varied. It remained in the outer breast in some women and diffused into almost the entire breast in others. Figure 5 also shows that, regardless of the UAAL thickness, the lower and upper breast regions were mostly occupied by adipose tissue. This explains why the highest MRI BD we observed was around 80%.

Breast Cancer Association

Our results indicated that age might be predictive of the thickness of the UAAL, and both age and the thickness of the UAAL might be predictive of MRI BD. To control the confounding effects of age on the UAAL and BD, we compared the thickness of the UAAL and MRI BD of patients among three breast cancer types (NoCA, DCIS, and IC) stratified by age groups using the Kruskal-Wallis test. Both median and mean values are listed in Table 1 due to a lack of normality in data distribution, although the non-parametric Kruskal-Wallis test is not a direct evaluation of either group medians or means. Table 1 demonstrate a consistent trend toward increasing thickness of the UAAL in invasive breast cancer patients, with respect to the controls, in women older than 30; although the difference was only significant in the 51 - 60 age group. There was also a consistent trend toward higher MRI BD in the controls than in the invasive breast cancer patients of all age groups older than 30, although the differences were not statistically significant in our cohort of patients. The number of patients diagnosed with DCIS in our cohort was relatively small for statistically significant conclusions in most age groups.

The results of the Spearman partial correlation are shown in Table 2, which indicated that age was negatively associated ($\rho = -0.364$) with BD. The thickness of the UAAL was negatively associated with BD ($\rho = -0.636$). Both associations were statistically significant, as demonstrated by p values less than 0.001.

Logistic regression results are shown in Table 3 and Table 4. These results demonstrated that, while both age and the thickness of the UAAL were associated with IC, only age was associated with DCIS in our cohort of patients. An increase in the thickness of the UAAL from 10 mm to 30 mm was associated with a 70% increase of the invasive cancer probability based on these regression results. Similarly, there was a 70% increase in invasive cancer probability from age 40 to 80. However, no significant association between BD and IC or DCIS was identified in our cohorts of patients.

Discussion

Our retrospective investigation provided a quantitative correlation between MRI BD and age, as well as the thickness of the UAAL, a surrogate marker of body adiposity. This study of 483 breast cancer patients (410 invasive and 73 DCIS) and 375 controls did not identify any clusters of breast cancer patients with a high MRI BD. High BD was associated with younger ages and the lack of a large upper abdominal adipose layer, while low BD was associated with an older age and a thick upper abdominal fat layer. Both age-stratified analysis of the UAAL thickness and BD and the logistic regression analysis indicated a strong association of invasive breast cancer with the thickness of the UAAL, a surrogate marker for body adiposity. The association between breast cancer and BD was weak and not statistically significant.

Mammographic breast BD decreased with increased age and BMI [9; 22; 33; 34]. Moreover, BD has been negatively associated with BMI as early as puberty [35]. A report from Boyd's group showed that body weight was positively associated with total breast fat and inversely associated with MRI percent density in a group of women in their late teens or early

twenties [16]. Physical exercises resulted in increased BD due to the loss of fat [36]. Consistent with these findings, our study shows that the thickness of the UAAL had a strong impact on MRI BD. Extremely dense breasts were observed only in those women with a very thin layer of UAAL.

Obesity is a well-recognized breast cancer risk factor in postmenopausal women. Consistent with this risk factor, we found a trend toward increased thickness of the UAAL in invasive breast cancer patients older than 30. We also found that invasive breast cancer patients in the 51 – 60 age range had a significantly thicker overall UAAL. These results support the previous observation that obesity poses a particularly high risk for women in early menopause [37].

There are few limitations in this study. Insurance and the American Cancer Society [38] guidelines dictate that only patients at high risk of developing breast cancer are eligible to be screened by MRI in addition to mammograms. It is difficult to determine whether these high-risk women who received MRI screening in our study are a good representation of the general population in terms of body adiposity and BD. This study focused on age, BD, and body adiposity only. Other known breast cancer risk factors, such as smoking history, hormone usage, menarche/menopause age, and gravidity and parity history were not included. The patient size of this study was not sufficient to investigate whether the BD morphology (such as packed or diffused) affected the breast cancer occurrence. This was a retrospective study; however, prospective BD MRI studies that involve healthy women would be time-consuming and prohibitively expensive. It is also worth noting that, although women who have first-degree relatives with a history of breast cancer are at increased risk for the disease, most will never develop breast cancer [39].

Other experimental factors that may affect the accuracy of MRI BD of this retrospective investigation include the variation in the image acquisition parameters, such as field strength, slice thickness, and pulse sequences. However, it was possible to obtain sufficient adipose/dense tissue contrast at our experimental conditions due to the large T1 difference between these two types of tissue at both 1.5-T and 3-T [40]. Early study demonstrated that a 10 mm gap between the slices had resulted in only a small increase in the uncertainty in MRI body fat percentage estimation [41]. Thus we expected very small change in uncertainty in MRI BD calculation when slice thickness varied from 1 mm to 5 mm. We also reviewed the images for signs of tissue compression due to the body weight for patients scanned in prone position, which may introduce errors in the UAAL thickness measurement. No discernable variation in the UAAL thickness from the front to the sides of patients was observed. We concluded that compression had a negligible effect in the thickness of the UAAL measurements. Other studies have indicated a high consistency in MRI BD measured at different field strength, image resolution, and patient positions [42].

While the results of our study diminish the strength of the association between dense breasts and increased breast cancer risk, they support the increased breast cancer risk in obese postmenopausal women, especially those in early menopause [37]. Given the current role of breast density in determining breast cancer screening protocols, public health policy, and

future research directions; it is important to validate our findings in a larger scale investigation.

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Abbreviations

BI-RADS	Breast Imaging Reporting and Data System
2D	two-dimensional
3D	three-dimensional
BD	breast density
IC	invasive breast cancer
DCIS	ductal carcinoma in situ
NoCA	no breast cancer diagnosed
UAAL	upper abdominal adipose layer
TU	the thickness of the upper abdominal adipose layer
BMI	body mass index

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Key Points

MRI breast density is negatively associated with body adiposity.

MRI breast density is negatively associated with age.

Breast cancer is positively associated with body adiposity.

Breast Cancer is not associated with MRI breast density.

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Figure 0001

Figure 0002

Figure 0003

Figure 1.

T1-weighted breast image without fat saturation. Adipose tissues appear bright and fibroglandular breast tissues, with a high water content, appear dark. (a) A sagittal central slice from a breast image. The arrow indicates the position where the thickness of the upper abdominal adipose layer was measured in relation to the breast. (b) and (c) Axial breast images. Arrows indicate where the thickness was actually measured.

Figure 2.

Segmentation of the breast adipose and fibroglandular tissues, and density calculation steps.

1) Correct the image intensity bias artefacts due to magnetic field heterogeneity; 2) Remove the chest regions using a mask drawn along the chest curvature; 3) Crop the breast area; 4) Segment the entire breast; and 5) Segment the bright fatty tissue.

Figure 0005 **Figure 0006****Figure 3.**

Scatterplot of breast density and age (a), and scatterplot of the thickness of the upper abdominal adipose layer and age (b).

Figure 4.
Scatterplot of breast density and the thickness of the upper abdominal adipose layer.

Figure 5.

Sample axial breast T1-weighted images without fat saturation. All images are from control patients without breast cancer. Images at the upper abdominal, lower breasts, central breasts, and upper breasts are shown from left to right. Top: 37-year-old, thickness of the UAAL 2 mm, breast density 65%; Middle: 50-year-old, thickness of the UAAL 22 mm, breast density 31.4%; and Bottom: 50-year-old, thickness of UAAL 7 mm, breast density 8.4%.

Table 1

Patient counts, median and mean age, median and mean UAAL, and median and mean breast density stratified by age and breast cancer type.

Age Groups		20 -30	31 -40	41 -50	51 -60	61 -70	>70
Patient Counts, %	NoCA	28, 7.8%	55, 15.2%	121, 33.5%	99, 27.4%	46, 12.7%	12, 3.3%
	DCIS	1, 1.3%	6, 8.2%	16, 21.9%	29, 39.7%	15, 20.5%	6, 8.2%
	IC	9, 2.2%	54, 13.2%	115, 28.0%	134, 32.7%	68, 16.7%	30, 7.3%
Median, Mean Age	NoCA	26.5, 26.3	37.0, 36.2	45.0, 45.6	54.0, 54.9	63.0, 64.2	74.5, 77.0
	DCIS	30.0, 30.0	37.5, 37.3	47.0, 46.9	56.0, 56.0	63.0, 63.6	74.0, 74.0
	IC	27.0, 27.4	36.0, 35.9	46.0, 45.9	55.0, 55.2	65.0, 64.9	73.5, 74.7
Median, Mean UAAL	NoCA	9.0, 10.2	7.0, 9.5	10.0, 11.5	13.0 [*] , 13.1 [*]	14.0, 14.9	14.5, 14.7
	DCIS	5.0, 5.0	6.5, 7.3	9.0, 9.1	14.0 [*] , 14.2 [*]	15.0, 14.7	21.5, 21.5
	IC	3.0, 5.3	10.0, 10.8	11.0, 12.8	17.0 [*] , 17.3 [*]	15.0, 15.6	16.0, 15.3
Median, Mean Breast Density	NoCA	27.4, 36.2	30.0, 33.3	19.8, 23.9	13.8, 17.6	10.6, 14.2	15.5, 16.2
	DCIS	24.0, 24.0	38.7, 37.2	31.9, 29.8	12.9, 16.6	11.6, 15.1	13.1, 15.0
	IC	49.6, 47.3	26.3, 29.8	19.7, 22.8	11.7, 15.3	10.3, 12.7	9.4, 14.2

* A indicates that the *p*-value from the Kruskal-Wallis test was less than 0.05

Table 2

Spearman partial correlation coefficient ρ of the UAAL thickness, age, and breast density.

	UAAL Thickness (ρ, p value)	Age (ρ, p value)	Breast Density (ρ, p value)
UAAL Thickness	1, 0		
Age	-0.0124, 0.720	1, 0	
Breast Density	-0.636, 1e-96	-0.364, 8e-28	1, 0

Table 3

Logistic regression results for the relative risk of DCIS; TU = thickness of the UAAL, and BD = breast density.

	Coefficient	p	95 % Confidence level	
β_0 , intercept	-4.67	1e-7	-6.39	-2.94
β_1 , slope for TU	0.0109	0.609	-0.0308	0.0525
β_2 , slope for Age	0.0517	2e-5	0.0278	0.0756
β_3 , slope for BD	0.0117	0.303	-0.0106	0.034

Table 4

Logistic regression results for the relative risk of IC; TU = thickness of the UAAL, and BD = breast density.

	Coefficient	p	95 % Confidence level	
β_0 , intercept	-1.67	0.0007	-2.64	-0.7087
β_1 , slope for TU	0.0370	0.0022	0.0133	0.0607
β_2 , slope for Age	0.0240	0.0008	0.01	0.038
β_3 , slope for BD	0.0045	0.4886	-0.0082	0.0172