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Journal

Academic Radiology, 24(7)

ISSN

1076-6332

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Publication Date

2017-07-01

DOI

10.1016/j.acra.2016.12.016

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Peer reviewed

3D MRI for Quantitative Analysis of Quadrant Percent Breast Density: Correlation with Quadrant Location of Breast Cancer

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Rationale and Objectives: Breast cancer occurs more frequently in the upper outer (UO) quadrant, but whether this higher cancer incidence is related to the greater amount of dense tissue is not known. Magnetic resonance imaging acquires three-dimensional volumetric images and is the most suitable among all breast imaging modalities for regional quantification of density. This study applied a magnetic resonance imaging-based method to measure quadrant percent density (QPD), and evaluated its association with the quadrant location of the developed breast cancer.

Materials and Methods: A total of 126 cases with pathologically confirmed breast cancer were reviewed. Only women who had unilateral breast cancer located in a clear quadrant were selected for analysis. A total of 84 women, including 47 Asian women and 37 western women, were included. An established computer-aided method was used to segment the diseased breast and the contralateral normal breast, and to separate the dense and fatty tissues. Then, a breast was further separated into four quadrants using the nipple and the centroid as anatomic landmarks. The tumor was segmented using a computer-aided method to determine its quadrant location. The distribution of cancer quadrant location, the quadrant with the highest QPD, and the proportion of cancers occurring in the highest QPD were analyzed.

Results: The highest incidence of cancer occurred in the UO quadrant (36 out of 84, 42.9%). The highest QPD was also noted most frequently in the UO quadrant (31 out of 84, 36.9%). When correlating the highest QPD with the quadrant location of breast cancer, only 17 women out of 84 (20.2%) had breast cancer occurring in the quadrant with the highest QPD.

Conclusions: The results showed that the development of breast cancer in a specific quadrant could not be explained by the density in that quadrant, and further studies are needed to find the biological reasons accounting for the higher breast cancer incidence in the UO quadrant.

Key Words: Breast cancer; magnetic resonance imaging; dense tissue; quadrant percent density.

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INTRODUCTION

Mammographic density (MD) is an independent risk factor for development of breast cancer (1,2). The biological basis for the association between increased breast cancer risk and higher MD is not fully understood. Studies of mammographically dense tissues suggest that density may represent increased epithelial cellular

concentration, stromal fibrosis, and epithelial hyperplasia (3). A fundamental question that has yet to be answered is whether cancers tend to arise in mammographically dense tissue. Among several studies exploring the question, two studies showed that tumors occur overwhelmingly in the mammographically dense areas, suggesting that some aspects of glandular or stromal tissue comprising the dense tissue directly influence the carcinogenic process (4,5). Another study, however, found that after accounting for overall density, the regional density was not a significant risk factor for subsequently developed cancer (2).

Many studies have shown the quadrant disparity of cancer risk and noted that the upper outer (UO) quadrant was the most frequent site of carcinoma (6–8). A study consisting of 746 consecutive breast core biopsies found that 217 of 349 (62%) malignant lesions (95% confidence interval: 57%–67%) occurred in the UO quadrant (7). An adequate explanation for this asymmetric occurrence of breast cancer has never been established. Is the disparity of breast cancer

Acad Radiol 2017; 24:811–817

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<http://dx.doi.org/10.1016/j.acra.2016.12.016>

in different quadrants related to the amount of breast density? As the first step to answer this question, it is necessary to develop a reliable quantification method to measure quadrant breast density. Most published studies analyzed the cancer risk related to the whole breast density, which did not consider the spatial variation of the dense tissue in the breast.

Three studies have previously analyzed quadrant density based on mammography (2,4,5). With mammography, the craniocaudal (CC) and mediolateral oblique (MLO) images could be divided into two regions: the CC image was divided into a lateral and medial part (CC-L and CC-M), whereas the MLO image was divided into a superior and inferior part (MLO-S and MLO-I) (2,4). The quadrant breast density was estimated as the average of the density assessments of two mammographic areas. For example, the UO quadrant density is the average density of the CC-L and MLO-S areas. Because mammography acquires two-dimensional (2D) projection images, this method could only provide a reasonable estimate, not a true measure, of density in four quadrants. Furthermore, traditional mammography is not able to provide quantitative volumetric measures.

Breast magnetic resonance imaging (MRI) acquires three-dimensional (3D) volumetric images that show a good contrast between fibroglandular (dense) and fatty tissues, and well-developed segmentation methods capable of measuring breast volume (BV) and fibroglandular tissue volume (FV) quantitatively have been reported (9,10). In this work, we applied an MR-based quadrant separation method to measure quadrant percent density (QPD), and evaluated its association with the quadrant location of the developed breast cancer (11). Bilateral breasts in a healthy woman can be assumed to be symmetrical (12–14). Because the density in the diseased breast has been altered with the presence of tumor, we analyzed the QPD in the normal contralateral breast to simulate the density in the diseased breast before the cancer occurred.

MATERIALS AND METHODS

Subjects

This study was approved by the institutional review board and complied with the Health Insurance Portability and Accountability Act. A total of 126 cases with pathologically confirmed breast cancer were reviewed. Women with bilateral breast cancer and women with unilateral breast cancer but with the cancer occupying more than two quadrants or located in the subareolar area were excluded from the study. Only those women who had unilateral breast cancer located in a clear dominant quadrant location were selected for analysis. In total, 84 women (mean age: 49, range: 28–70) were included. Thirty seven of these subjects were western women from one institution. These women had advanced invasive breast cancer and received baseline and several follow-up breast MRI studies following neoadjuvant chemotherapy. In this study, only the baseline breast MR images were used for density analysis. The tumor size of these 37 women measured on baseline breast

MRI ranged from 1.7 cm to 8.8 cm (mean \pm standard deviation (STD) = 4.1 ± 1.8 cm). Forty-seven subjects were Asian women from a diagnostic setting in another institution. These subjects received diagnostic breast MRI studies due to various clinical reasons, such as palpable breast lumps or suspicious breast lesions detected by mammography or breast ultrasonographic studies, and were found to have unilateral breast cancer. Of these 47 women, 29 were found to have invasive cancer and 18 had ductal carcinoma in situ. The tumor size of these 47 women measured on preoperative diagnostic breast MRI ranged from 0.3 cm to 4.2 cm (mean \pm STD = 1.7 ± 1.0 cm). All subjects gave written informed consent to participate in the MRI study.

MR Imaging Acquisition

In this study, only the non-contrast, T1-weighted (T1W) images without fat suppression were used to measure breast density. For the western women, the MR images were acquired on a 3.0 Tesla MR scanner (Philips Achieva, Philips Medical Systems, Best, Netherlands) with a dedicated, sensitivity encoding (SENSE)-enabled, bilateral four-channel breast coil. The precontrast, non-fat-suppressed T1W imaging sequence used for density analysis was 2D turbo spin echo, with repetition time (TR) = 800 ms, echo time (TE) = 8.6 ms, flip angle = 90° , matrix size = 480×480 , field of view = $31\text{--}38$ cm, and slice thickness = 2 mm.

The Asian subjects were examined using a 3.0 Tesla MR scanner (Magnetom Skyra, Siemens Medical Solutions, Erlangen, Germany), with a 16-channel Sentinelle breast coil. The precontrast, non-fat-suppressed T1W imaging sequence used for density analysis was a three-dimensional, fast low-angle shot (3D-FLASH) sequence, with TR/TE = 4.36/1.58 ms, flip angle = 10° , number of signal average = 1, matrix size = 384×288 , field of view = 30 cm, and slice thickness = 1.0 mm.

Breast and Fibroglandular Tissue Segmentation

The MR density measurement was done using an established template-based automatic segmentation method (10). With this method, the chest body region on a middle slice was used as the template. Within the chest template, three body landmarks (thoracic spine and bilateral boundary of the pectoralis muscle) were identified for performing the initial V-shaped cut to determine the posterior lateral boundary of the breast. The chest template was mapped to each subject's image space to obtain a subject-specific chest model for exclusion. The chest and muscle boundaries determined on the middle slice were used as the reference for the segmentation of adjacent slices, and the process continued until all 3D slices were segmented. The segmentation of fibroglandular tissue and fatty tissue used non-parametric, non-uniformity normalization (N3) + fuzzy c means algorithm (15). The segmented breast and fibroglandular tissue from all slices were used to calculate the BV and FV, and then the percent density (PD)

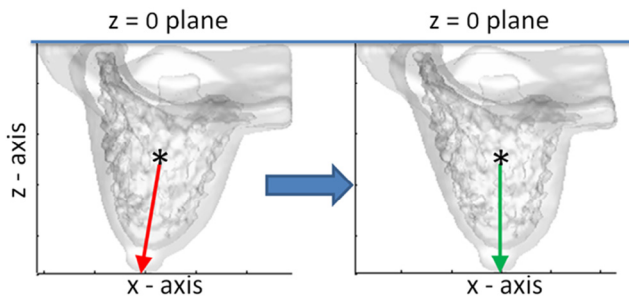


Figure 1. Correction of the breast orientation based on the centroid-nipple line.

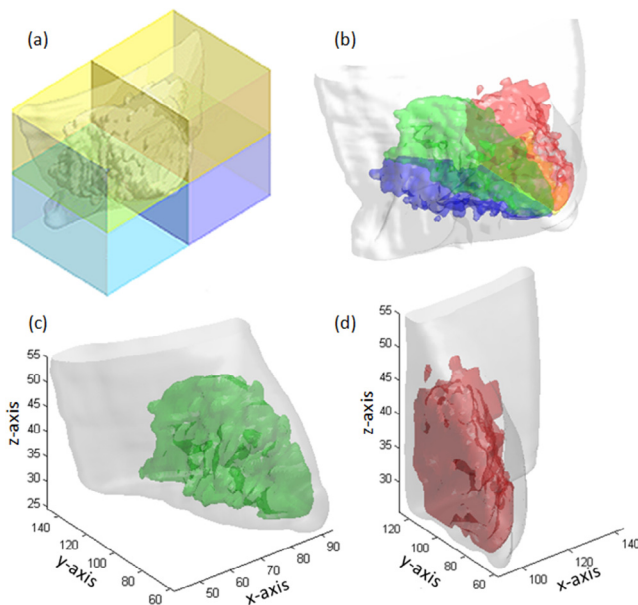


Figure 2. Division of breast tissue and fibroglandular tissue into four quadrants, and the separated upper outer and upper inner quadrants.

as $FV/BV \times 100\%$. Detailed procedures for the density quantification have been reported before (10).

Quadrant Breast Density Assessment

The quadrant separation was done using a recently reported method (16). The nipple and the centroid of the segmented breast were used as anatomic landmarks to divide the breast into four quadrants—upper outer (UO), upper inner (UI), lower outer (LO), and lower inner (LI)—by one horizontal plane and one vertical plane intersecting along the aligning nipple-centroid line (Fig 1). Figure 2 illustrates how the breast tissue and fibroglandular tissue were divided into four quadrants. After the four quadrants were separated, the BV and FV were measured to calculate the QPD. Detailed methods for the quantification of QPD have been reported before (16).

Determination of Tumor Quadrant Location

The quadrant location of the breast cancer in the diseased breast was determined using a computer-aided method based on the

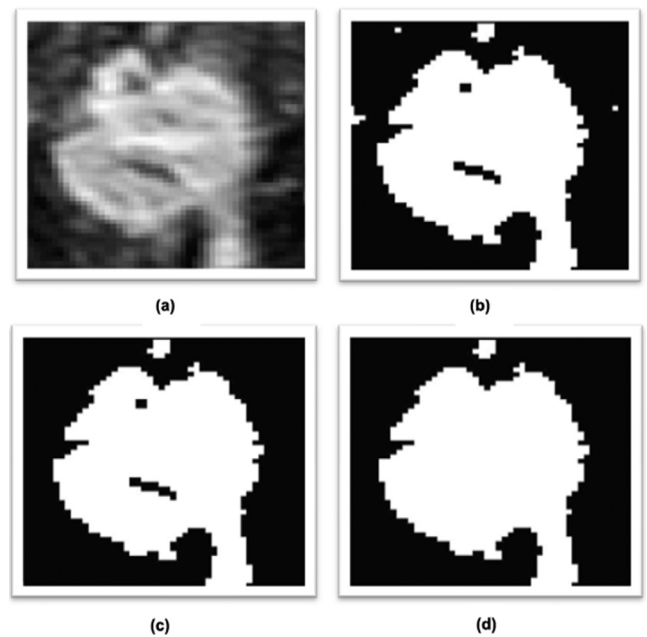


Figure 3. Illustration of the tumor segmentation process on one image slice. (a) contrast enhancement map; (b) tumor voxels determined after FCM clustering segmentation; (c) tumor mask after removing scattered voxels; and (d) tumor mask after hole filling. FCM, fuzzy c means.

DCE-MRI sequence. The tumor was segmented on the contrast enhancement maps obtained 2 minutes after contrast injection, as reported before (17). The operator placed a rectangle box to cover the whole lesion on the maximum intensity projection, and then the outline of the tumor was obtained by the fuzzy c means algorithm based on signal intensity. Scattered voxels not connecting to the tumor were removed, and then the hole-filling algorithm was applied to outline the whole tumor. An example is shown in Figure 3. The tumor volume was measured. The separation of the diseased breast into four quadrants was done using the same methods described earlier for the contralateral normal breast. After the breast quadrants and the tumor were segmented, the location of the tumor could be determined. If more than 50% of the tumor was in a specific quadrant, that quadrant was determined as the dominant quadrant. In this study, only cases with a clear dominant quadrant for the tumor that occurred were analyzed.

Statistics

The mean BV, FV, and PD in the four quadrants were calculated. For each case, the quadrant of tumor location and the quadrant with the highest QPD were determined for descriptive analysis. The proportion of cases whose tumor occurred in the quadrant with the highest QPD was calculated.

RESULTS

Quadrant BV, FV, and PD

Table 1 shows the mean and standard deviation of the BV, FV, and PD in the four quadrants in Asian and western women.

TABLE 1. Breast Volume, Fibroglandular Tissue Volume, and Percent Density in the Four Quadrants in Asian and Western Women

		Upper Outer	Upper Inner	Lower Outer	Lower Inner
Breast volume (cm³)					
Asian women (<i>n</i> = 47)	Mean	201.8	120.9	199.1	119.2
	STD	119.4	66.4	121.1	68.0
	Median	170.9	108.7	171.9	109.3
Western women (<i>n</i> = 37)	Mean	308.8	269.4	287.5	279.4
	STD	135.6	119.0	123.2	123.3
	Median	287.1	256.9	281.3	260.5
Fibroglandular tissue volume (cm³)					
Asian women (<i>n</i> = 47)	Mean	29.5	17.0	33.1	16.3
	STD	19.1	13.3	22.3	14.9
	Median	27.2	12.0	28.8	11.2
Western women (<i>n</i> = 37)	Mean	44.2	31.4	34.2	27.9
	STD	29.6	22.8	20.8	19.4
	Median	33.2	26.2	38.8	24.0
Percent density (%)					
Asian women (<i>n</i> = 47)	Mean	17.5	15.9	19.6	14.5
	STD	12.5	11.5	13.8	11.8
	Median	15.3	13.0	15.8	10.0
Western women (<i>n</i> = 37)	Mean	14.4	12.2	11.4	10.2
	STD	9.3	8.9	6.8	7.7
	Median	12.0	9.5	9.6	8.3

STD, standard deviation. The bold value in each row of the Mean indicates the highest measured value among the four quadrants.

TABLE 2. Distribution of Breast Cancer in the Different Quadrants of the Breast

	Upper Outer	Upper Inner	Lower Outer	Lower Inner
All subjects (<i>N</i> = 84)	36 (42.9%)	20 (23.8%)	17 (20.2%)	11 (13.1%)
Asian women (<i>n</i> = 47)	21 (44.7%)	9 (19.1%)	7 (14.9%)	10 (21.3%)
Western women (<i>n</i> = 37)	15 (40.6%)	11 (29.7%)	10 (27.0%)	1 (2.7%)

TABLE 3. Distribution of Highest QPD and the Lesions Occurring in the Highest QPD Quadrant

	Upper Outer	Upper Inner	Lower Outer	Lower Inner
Asian women (<i>n</i> = 47)				
Highest QPD	11 (23.4%)	8 (17.0%)	19 (40.4%)	9 (19.2%)
Lesions in highest QPD	5 (45.5%)	0 (0%)	2 (10.5%)	1 (11.1%)
Western women (<i>n</i> = 37)				
Highest QPD	20 (54.1%)	7 (18.9%)	8 (21.6%)	2 (5.4%)
Lesions in highest QPD	6 (30.0%)	2 (28.6%)	1 (12.5%)	0 (0%)

QPD, quadrant percent density.

It was noted that the mean BV was highest in the UO quadrant for both western and Asian women (BV: 308.8 cm³ and 201.8 cm³, respectively). The mean FV was highest in the UO for the western women (44.2 cm³) and highest in the LO for the Asian women (33.1 cm³). The mean QPD for western women was highest in the UO quadrant (14.4%) and highest in the LO quadrant (19.6%) for Asian women.

Quadrant Location of Tumor and Highest QPD

Table 2 shows the distribution of breast cancer in different quadrants. The most frequent tumor site was the UO quadrant

(36 out of 84, 42.9%), followed by the UI quadrant (20 out of 84, 23.8%), the same for both Asian and western women. Table 3 shows the distribution of the highest QPD and cancers occurring in the highest QPD quadrant. The UO quadrant was the most likely to have the highest QPD (31 out of 84, 36.9%), followed by the LO quadrant (27 out of 84, 32.1%). The LI quadrant was the least likely to have the highest QPD (11 out of 84, 13.1%). Overall, only 17 women (out of 84, 20.2%) had breast cancer that occurred in the quadrant with the highest QPD, with 11 in the UO quadrant. Three examples are shown. Figure 4 shows a 65-year-old woman with a 2.5 cm invasive cancer in the UO quadrant of the left breast.

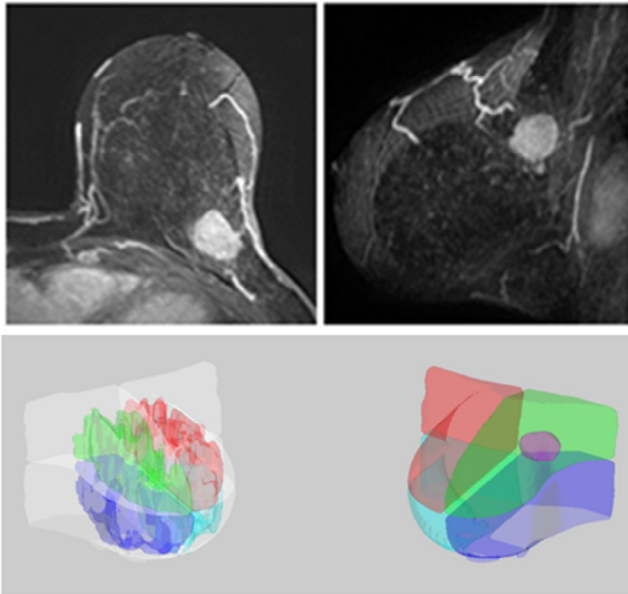


Figure 4. A 65-year-old woman with a 2.5 cm invasive cancer in the UO quadrant of the left breast. The quadrant density in the right normal breast is highest in the UO quadrant (16.7%) and lowest in the LI quadrant (9.3%). LI, lower inner; UO, upper outer.

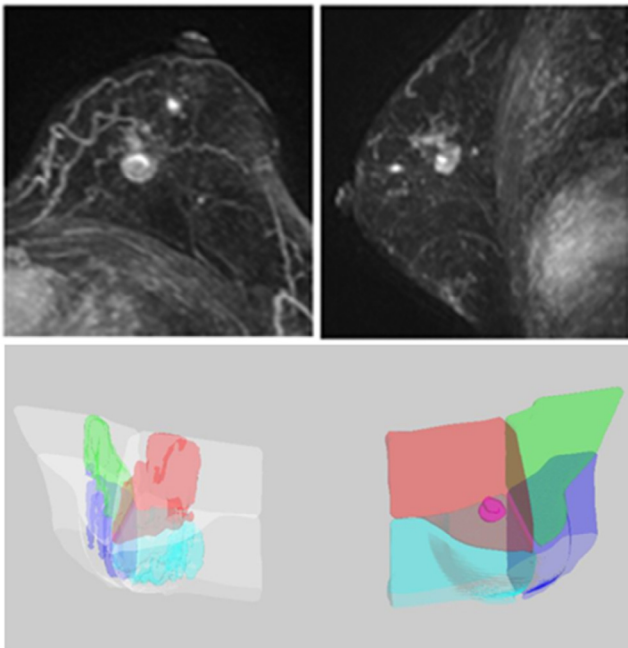


Figure 5. A 56-year-old woman with a 1.3 cm invasive cancer in the UI quadrant of the left breast. The quadrant density in the right normal breast is highest in the UI quadrant (12.0%) and the lowest in the LO quadrant (1.4%). LO, lower outer; UI, upper inner.

Figure 5 shows a 56-year-old woman with a 1.3 cm invasive cancer in the UI quadrant of the left breast. Figure 6 shows a 38-year-old woman with a 2.9 cm invasive cancer in the LO quadrant of the right breast.

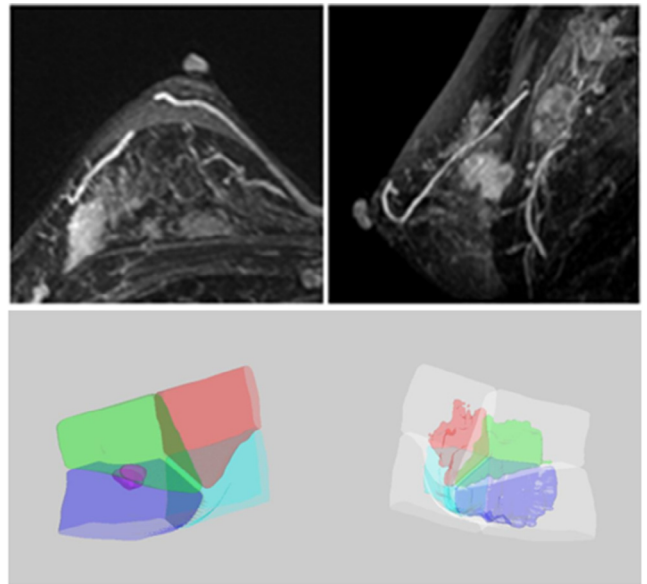


Figure 6. A 38-year-old woman with a 2.9 cm invasive cancer predominantly in the LO quadrant of the right breast. The LO quadrant contained 69.1% of the total tumor volume, whereas the remaining tumor (30.9%) was in the UO quadrant. The quadrant breast density in the left normal breast was highest in the UI quadrant (21.9%) and lowest in the LI and LO quadrant (7.2% and 7.2%). The quadrant breast density in the UO quadrant was 14.0%. LI, lower inner; LO, lower outer; UI, upper inner; UO, upper outer.

DISCUSSION

Although MD is associated with breast cancer risk, it is not known whether MD is directly related to cancer occurrence, ie, tumors arising within the dense tissue (2). Clarification of whether MD is directly related to risk will enhance our understanding of the pathogenesis of breast cancer and will provide information on the value of using localized MD as a predictor of subsequent tumor location, possibly opening up new avenues for the clinical management of high-risk women (2). The density assessment using MD is, however, fundamentally limited by the fact that mammography is a 2D projection imaging method, and natural distortions between breasts are likely to occur during the course of breast compression used in mammography. As such, the density measures can be confounded by the nature of the imaging procedure itself (13). Breast MRI allows a 3D quantitative measurement of BV and FV without suffering from the problem of tissue overlapping. The goal of this study is to measure QPD in the normal breast and evaluate its association with the tumor location in the diseased breast.

The quantitative analysis of QPD required two computer-aided procedures: first to segment the whole breast and the dense tissue, and second to separate a breast into four quadrants. The 3D MR-based density quantification method was done using a well-developed automatic segmentation algorithm to measure BV, FV, and PD (10). Then within the segmented breast, the nipple and the centroid were used as references to divide a breast into four quadrants to measure

QPD (15). In most women, the bilateral breasts were generally symmetrical (12–14). In this study, all the 84 patients had unilateral breast cancer. The tumor size ranged from 0.3 cm to 8.8 cm. With tumor in one breast, it thus was not possible to evaluate breast symmetry. However, in an analysis based on a separate dataset of mammograms in 67 healthy women (unpublished data, Jeon-Hor Chen, University of California Irvine, 2015), we noted that the right and left symmetry of percent breast density is pretty high ($r = 0.84$). Despite the high symmetry, the assessment of symmetry in mammography is potentially limited by the fact that natural distortions between breasts are likely to occur during the course of breast compression routinely used in mammography. As such, symmetry measures can be confounded by the nature of the imaging procedure itself (13). In our recently published results using 3D MRI in the study of breast density in 58 normal women, 47 premenopausal and 11 postmenopausal women (16), we found that bilateral breasts in women without cancer are highly symmetrical ($r = 0.97$ for BV, $r = 0.97$ for FV, and $r = 0.98$ for percent breast density). Another study using MRI showed small differences in the bilateral breast tissue composition, ie, fat and water content, in young women and adults (18).

A study to investigate the spatial distribution of density within the breast using 493 mammographic images from a sample of 165 premenopausal women showed that the degree of the spatial clustering of density was similar between a woman's two breasts and did not change with aging (12). Therefore, in this study, we analyzed the contralateral normal breast to simulate the density in the diseased breast without the presence of the tumor. Two different cohorts, Asian women from diagnostic MRI setting and western women from more advanced neoadjuvant chemotherapy setting, were studied.

The results showed that breast cancer was most likely to occur in the UO quadrant in both cohorts. The finding was consistent with most of the literature reports on studies of western women (6–8), eastern women (19), and Asian women (20,21). A study of Taiwanese women (21) showed that more than half (52.3%) of the primary breast tumors occurred in the UO quadrant. In the MR study, the woman was examined in a prone position, and the separation of four quadrants in a different breast shape will be different from the traditional assessment if the woman was in a standing position for mammography or a spine position for ultrasound. Our frequency of UO tumor in this MR study was lower than the reports from mammographic studies (6–8,19–21). The UO quadrant is also the most frequent location for benign lesions, including fibroadenoma and breast cysts (22) and phyllodes tumor (23). The reasons why breast cancer grows more frequently in the UO quadrant are not clear. The results from a study (7) noted that the high proportion of UO quadrant carcinomas of the breasts is a reflection of the greater amount of breast tissue in this quadrant. In that study, the numbers of core biopsies reported as normal, benign, and malignant in each quadrant were used as measures of the frequency of normal tissue, benign disease, and malignant disease, respectively, in the different quadrants. It was noted that the

proportion of core biopsies from the UO quadrant reported as normal (67%), benign (57%), or malignant (62%) was similar. However, this study did not measure the MD, thus did not provide sufficient evidence to support the relationship with density. The results from another study (8) did not support that the higher frequency of UO quadrant cancer was due solely to a greater amount of target epithelial tissue in that region. It was postulated that the increasing use of cosmetics applied to the adjacent underarm and upper breast area might account for the findings. The underarm cosmetics are known to contain both DNA-damaging chemicals and chemicals that can mimic estrogen action (24), and greater use of these cosmetics can reduce the age of breast cancer diagnosis (25).

Higher MD has, histologically, a greater cellular concentration or proliferation of the stroma or epithelium (3). It was thus postulated that areas of increased density may be more susceptible to the initiation and promotion of breast cancers than areas of lower densities (2). To clarify the question, several mammographic studies (2,4) had been conducted to correlate quadrant breast density with the occurrence of breast cancer, but the findings were inconsistent. A study investigated whether tumors arise specifically within dense tissue by generating a virtual 1 cm² grid overlaid on a mammogram and estimating the odds of a tumor arising in a square in relation to its prediagnostic square-specific MD (5). The results showed that tumors arise predominantly within the radiodense breast tissue, but this method of analysis could not explain the relationship between density and the high cancer incidence in the UO quadrant. Overall, 2D mammographic method cannot truly measure volumetric regional density. Our study based on the analysis of 3D MR images noted that only 20.2% of women had breast cancer occurring in the breast quadrant with the highest QPD. The results agreed with the mammographic study (2) that quadrant breast density was not a significant risk factor for the subsequent development of breast cancer, and that a greater amount of breast tissue in a specific quadrant cannot solely explain the high breast cancer incidence in the UO quadrant (8). A more recent study of genomic patterns of loss of heterozygosity and allelic imbalance in breast quadrants from 21 breast cancer patients showed increased levels of genomic instability in the outer breast quadrants, suggesting that increased levels of breast cancer in the UO quadrant might result from the development of genetic alterations in that region of the breast rather than from only a greater tissue volume (26).

In our study, we noted that among the four breast quadrants, the UO quadrant had the highest mean BV in both Asian and western women. But Asian women tended to have the highest mean FV in the LO quadrant, different from the western women noted in the UO quadrant. This was a finding that has never been reported before, and large series of studies are needed before any conclusion can be drawn. Other limitations included the small subject number and the two patient groups that came from different settings, one from neoadjuvant chemotherapy study and the other from screening and diagnostic study.

In conclusion, we used a recently developed method to quantify the QPD based on MR images, and to investigate whether the PD in a specific breast quadrant was associated with the occurrence of breast cancer. We found a higher proportion of women with breast cancer in the UO quadrant, true for both Asian and western women. The UO quadrant was the most likely to have the highest QPD among the four quadrants in the western women but not in the Asian women. Only 20% of women had breast cancer growing in the quadrant with the highest QPD. The results suggested that fibroglandular tissue quantity and density did not explain the asymmetry of tumor distribution among quadrants in women undergoing neoadjuvant chemotherapy, and in women with cancer detected during routine diagnostic breast MRI studies. Therefore, the larger amount of breast tissue alone in a specific quadrant cannot fully explain the disproportional occurrence of breast cancer in different quadrants.

ACKNOWLEDGMENTS

This work was supported in part by NIH/NCI Grant Nos. R01 CA127927, R21 CA170955, and R03 CA136071.

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