A comparative study of volumetric breast density estimation in digital mammography and magnetic resonance imaging: Results from a high-risk population

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ABSTRACT

We performed a study to compare methods for volumetric breast density estimation in digital mammography (DM) and magnetic resonance imaging (MRI) for a high-risk population of women. DM and MRI images of the unaffected breast from 32 women with recently detected abnormalities and/or previously diagnosed breast cancer (age range 31-78 yrs, mean 50.3 yrs) were retrospectively analyzed. DM images were analyzed using *Quantra*^{TM} (*Hologic Inc*). The MRI images were analyzed using a fuzzy-C-means segmentation algorithm on the T_1 map. Both methods were compared to *Cumulus* (Univ. Toronto). Volumetric breast density estimates from DM and MRI are highly correlated (r=0.90, $p\leq$0.001). The correlation between the volumetric and the area-based density measures is lower and depends on the training background of the *Cumulus* software user (r=0.73-84, $p\leq$0.001). In terms of absolute values, MRI provides the lowest volumetric estimates (mean=14.63%), followed by the DM volumetric (mean=22.72%) and area-based measures (mean=29.35%). The MRI estimates of the fibroglandular volume are statistically significantly lower than the DM estimates for women with very low-density breasts ($p\leq$0.001). We attribute these differences to potential partial volume effects in MRI and differences in the computational aspects of the image analysis methods in MRI and DM. The good correlation between the volumetric and the area-based measures, shown to correlate with breast cancer risk, suggests that both DM and MRI volumetric breast density measures can aid in breast cancer risk assessment. Further work is underway to fully-investigate the association between volumetric breast density measures and breast cancer risk.

Keywords: Digital mammography, magnetic resonance imaging, volumetric breast density, breast cancer risk.

1. INTRODUCTION

Growing evidence suggests that breast density is an independent risk factor for breast cancer[1]. Currently, the most widely used methods to quantify breast density rely on measures derived from mammograms using semi-automated image thresholding techniques to segment the area of the dense tissue[2]. Percent density is then calculated as the ratio of the dense tissue area divided by the total area of the breast[1, 2]. Although useful for breast cancer risk assessment, these methods are highly subjective and difficult to standardize[1-4]. In addition, they do not estimate true volumetric breast density but a rather rough area-based measure from the projection image of the breast. To overcome this limitation, methods have been developed that can estimate volumetric breast density from digital mammograms by incorporating breast thickness and imaging physics information[2, 5]. Emerging breast imaging modalities such as breast MRI and whole breast ultrasound provide additional means for multimodality volumetric breast density estimation[6, 7]. Knowing that the risk of breast cancer is associated with the amount of fibroglandular tissue in the breast (where breast cancer generally originates), volumetric measures of density hold the promise to also provide more accurate measures of risk [8].

We performed a study to compare volumetric breast density measures obtained from digital mammography (DM) and magnetic resonance imaging (MRI) for a population of high-risk women. The validated image-thresholding *Cumulus* software (Ver. 4.0, Univ. Toronto)[2] was used to compare the obtained volumetric breast density measures to the commonly used area-based mammographic percent density estimates, shown to correlate with breast cancer risk[1]. If proven viable, volumetric breast density measures could provide an imaging biomarker for breast cancer risk estimation.

Medical Imaging 2010: Computer-Aided Diagnosis, edited by Nico Karssemeijer, Ronald M. Summers,
Proc. of SPIE Vol. 7624, 762409 · © 2010 SPIE · CCC code: 1605-7422/10/$18 · doi: 10.1117/12.845568

2. METHODS

2.1. Dataset

DM and MRI images from 32 women with recently detected abnormalities and/or previously diagnosed breast cancer (age 31-78 yrs, mean 50.3 yrs) were analyzed. All images were collected under HIPAA and IRB approval from a multimodality breast imaging clinical trial in our department[†]. Only images from the unaffected (*i.e.,* contralateral) breasts were analyzed. DM acquisition was performed with a GE Senographe 2000D FFDM system (GE Healthcare, Chalfont St. Giles, UK) at 0.1 mm/pixel resolution. Image post-processing was performed with the GE *PremiumView*™ algorithm[9]. The MRI images were acquired the same day with DM using a 3D inversion-recovery spoiled gradient-echo sequence (IR-SPRG, Siemens)[10]. For each breast, five series of 3D images were acquired by using five different sets of inversion time T_I and repetition time T_R, *i.e.*, $\{(T_I^m, T_R^m), m=1,\ldots,5\}=\{(1600, 280), (800, 280), (400, 280), (200, 280), (140, 280)\}$ in a unit of *ms*. The observation flip angle was fixed to $\alpha=20^0$.

2.2. Volumetric breast density estimation

DM images were analyzed using *Quantra*™ (*Hologic Inc.*) an FDA approved and commercially available fully-automated software for volumetric breast density estimation, which is based on an extension of the Highnam & Brady method[5, 11]. *Quantra*™ estimates the thickness of fibroglandular breast tissue above each pixel in the image and aggregates these values to compute the total volume of fibroglandular tissue in the breast (Fig. 1). Through a similar process, *Quantra*™ considers the entire imaged breast outline, compensating for those portions of the breast that were not uniformly compressed, to estimate the entire breast volume. The estimated fibroglandular tissue volume is then divided by the total breast volume to calculate the volumetric percentage of fibroglandular tissue in the breast [12].

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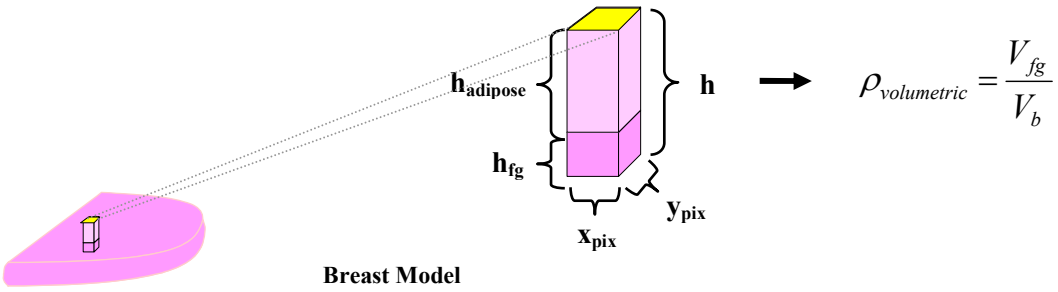

Figure 1. The *Quantra*™ method for estimating pixel-wise breast thickness and deriving a volumetric density measure.

The MR data were analyzed using a custom segmentation method[13, 14], in which the breast boundary is semi-automatically outlined using an active contour algorithm. The fibroglandular parenchyma (FP) is then segmented using a fuzzy-C-means (FCM) algorithm based on the T_1 map, which is estimated by fitting the IR-SPRG data to the Bloch equation[13]. FCM provides a continuous voxel-wise probabilistic membership value ranging from 0 (*i.e.*, pure fat) to 1 (*i.e.*, pure parenchyma), which is important for dealing with the partial volume effect in the breast MR images. Notice that the partial volume effect is common in breast MR imaging, and it is the result of to the contribution of both fat and fibroglandular parenchyma into the intensity of the same voxel. Thus, by using FCM, the estimated probabilities of fat and parenchyma in a voxel directly represent the percentages of fat and parenchyma within this voxel. The MRI dense tissue is segmented by thresholding the FCM probability map at the 0.50 probability level and the corresponding volumetric breast density measure is derived by dividing the estimated FP with the total MRI breast volume[14] (Fig 2).

2.3. Area-based breast density estimation

To compare to the commonly-used area-based breast percent density measures, the *PremiumView*™ post-processed DM images were also analyzed using *Cumulus* (Ver. 4.0, Univ. Toronto), the widely-validated image-thresholding software for mammographic percent density estimation[2]. To investigate the effect of the *Cumulus* user in estimating density when comparing to the automated volumetric methods, two experienced readers were considered, one with clinical training (*i.e.*, breast imaging radiologist, 20 yrs of experience) and one with non-clinical training (*i.e.*, medical physicist, 14 yrs of experience). Both readers received the training outlined in the manual of the *Cumulus* software.

[†] Evaluation of Multimodality Breast Imaging, NIH P01 CA85484, PI: M.D. Schnall

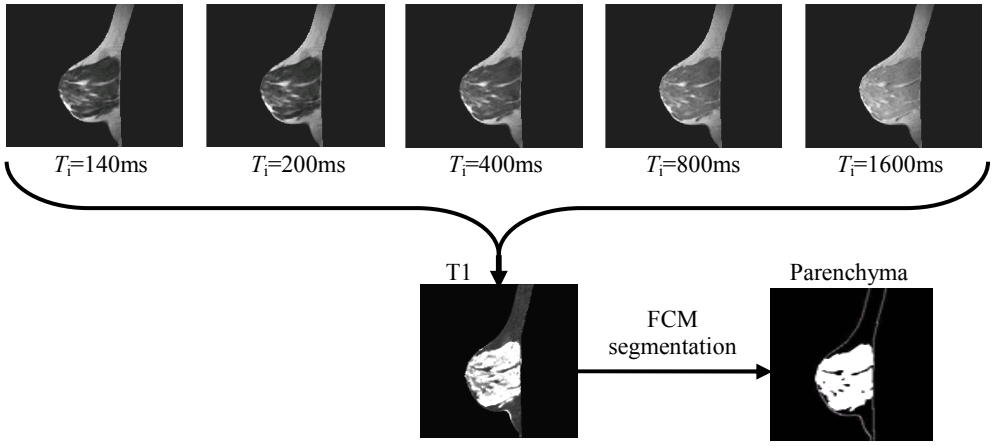

Figure 2. The main idea of the fuzzy-C-means (FCM) parenchyma segmentation algorithm for the MRI T1 map**.**

2.4. Data analysis

The Pearson correlation coefficient (*r*) was computed and linear regression analysis was performed to determine the degree of association between the breast density measures obtained using the different methods and the different breast imaging modalities. Comparison was performed both in terms of the percentage density estimates and the absolute measures of fibroglandular and breast tissue volume, from which the corresponding percentages are derived. Pairwise Student's t-test was also applied to directly compare the means of the distributions for all measured variables.

3. RESULTS

Correlation and linear regression analysis indicates a strong association between the volumetric breast density (VD%) estimates obtained from DM and from the MRI T1-map (r=0.90, R^2=0.80, $p\leq0.001$). In terms of absolute values, the DM VD% estimates are higher (mean=22.72%) than the MRI estimates (mean=14.63%) ($p\leq0.001$) (Fig. 3).

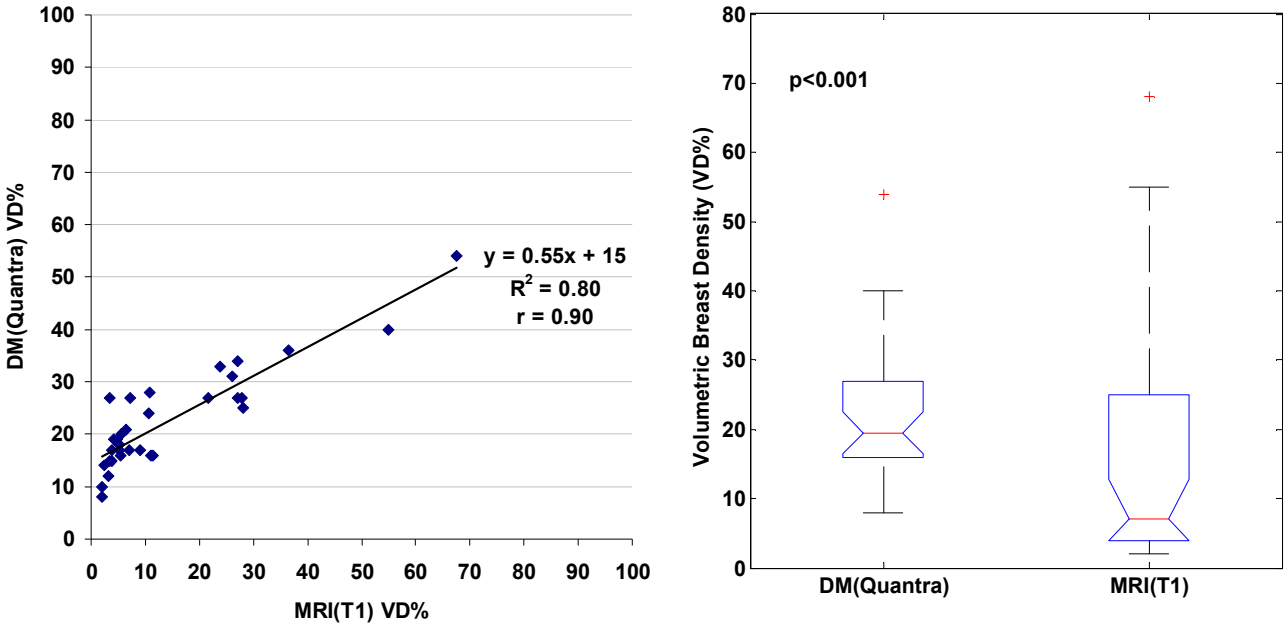

Figure 3. Linear regression and box-plots for volumetric breast density (VD%) estimates obtained from DM and MRI.

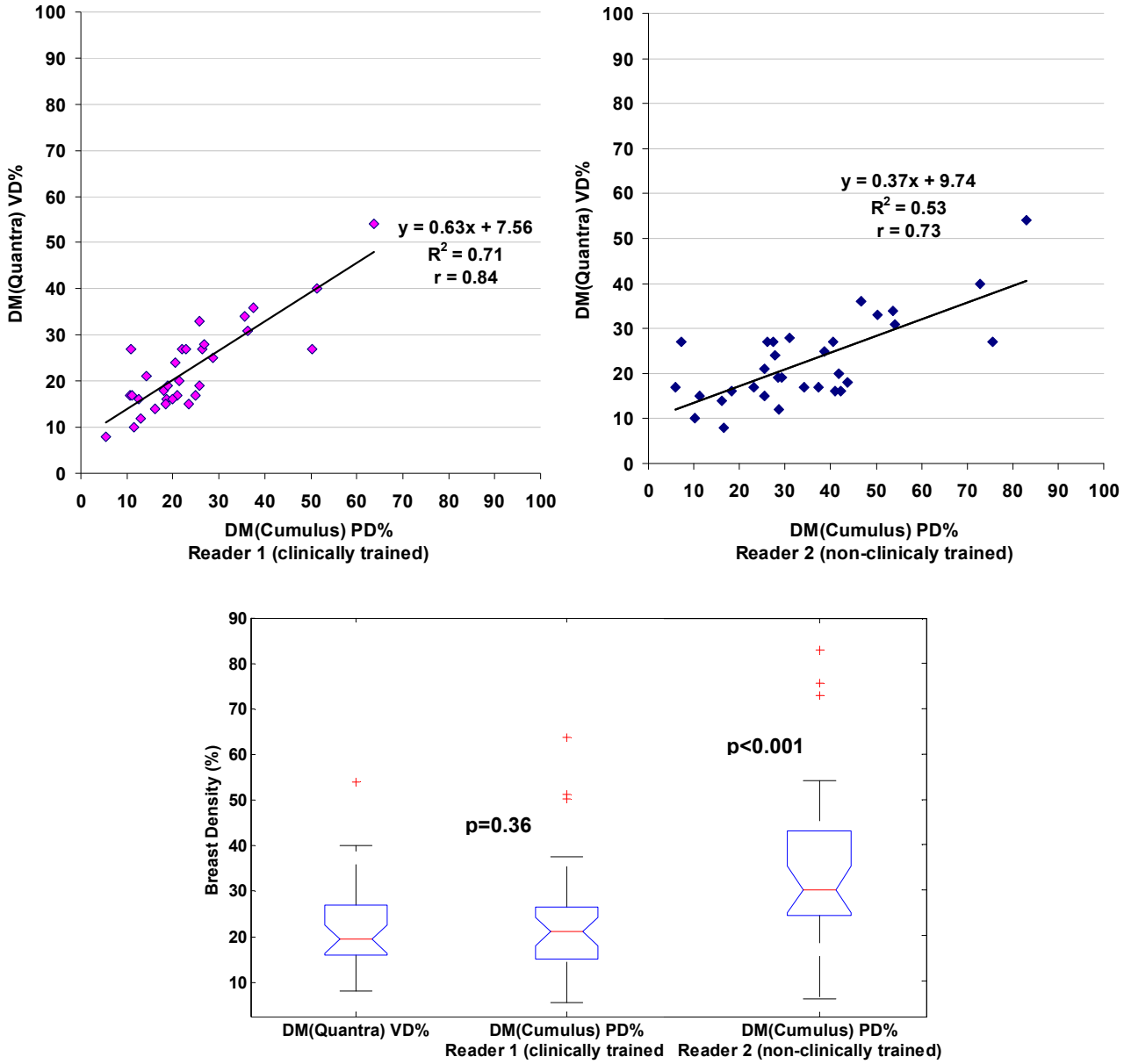

Figure 4. Linear regression fits and box-plots for the DM volumetric (VD%) and area-based (PD%) breast density measures obtained by the clinically-trained (*i.e.,* breast imaging radiologist) and the non-clinically trained (*i.e.,* medical physicist) *Cumulus* readers.

The VD% measures from DM are significantly correlated to the corresponding area-based PD% measures ($p<0.001$). This correlation is lower than the one observed between the VD% estimates from DM and MRI and its strength depends on the training background of the *Cumulus* software user (Fig. 4). The PD% estimates of the clinically-trained reader (*i.e.,* breast imaging radiologist) have a higher correlation to VD% ($r=0.84$, $R^2=0.7$, $p\leq0.001$) and the means of the corresponding distributions are not statistically significantly different ($mean_{VD\%}=22.72\%$, $mean_{PD\%}=23.88\%$, $p=0.36$). The PD% estimates of the non-clinically trained reader (*i.e.,* medical physicist) have a lower correlation to the VD% measures ($r=0.73$, $R^2=0.53$, $p\leq0.001$) and are statistically significantly higher ($mean_{PD\%}= 34.83\%$, $p<0.001$).

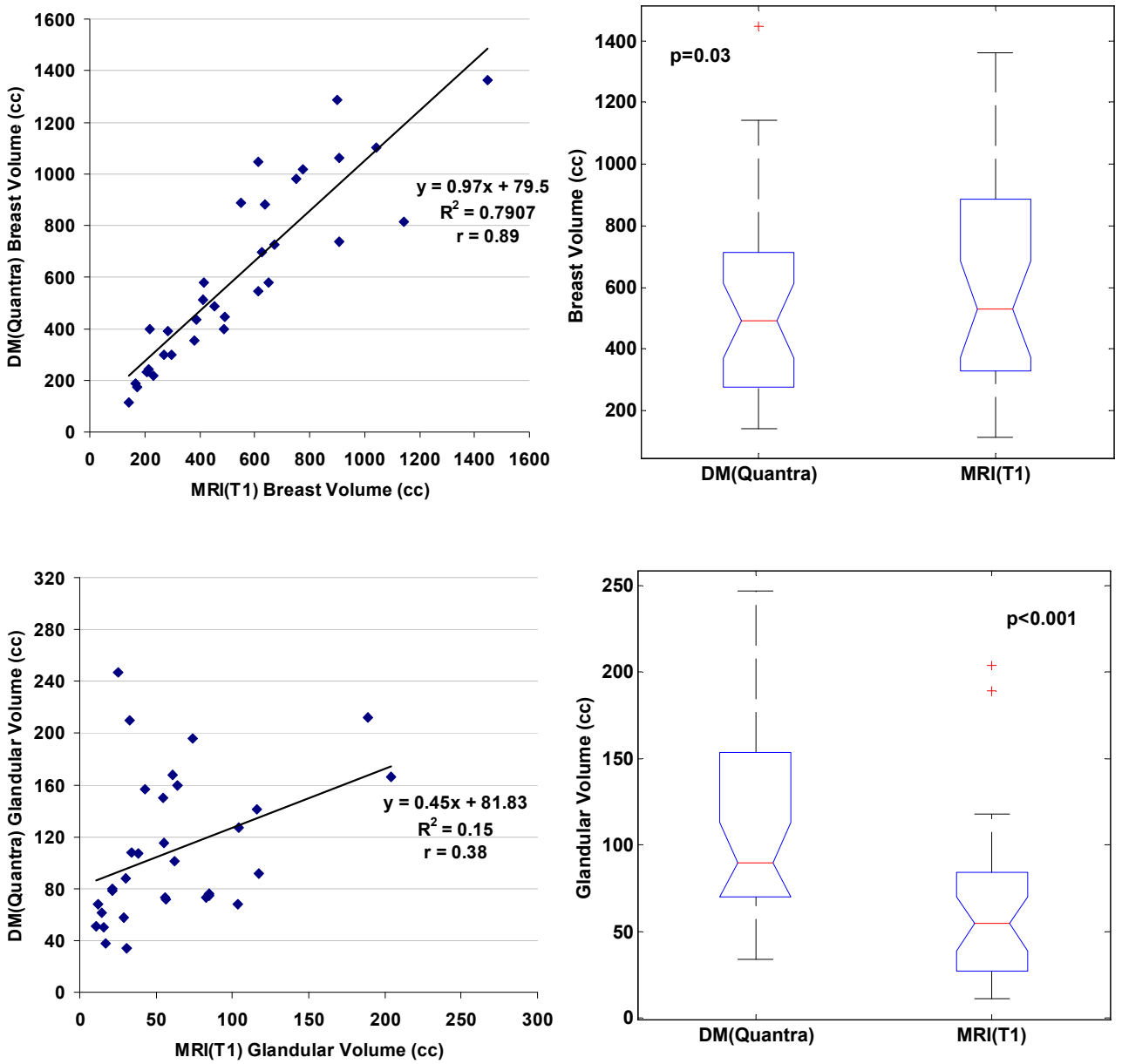

Figure 5. Linear regression and box-plots for the DM and MRI estimates of the total breast volume and the fibroglandular volume.

Comparison of the absolute measures of the total breast tissue volume and the fibroglandular volume, from which VD% estimates are derived, show a significant agreement between DM and MRI in the estimate of the total breast tissue volume and a lower agreement in the estimated fibroglandular volume, particularly for the low-density breasts (Fig. 5). More specifically, correlation and linear regression analysis indicates a strong association between the estimates of the total breast volume from DM and MRI (r=0.89, R^2=0.79, $p\leq$0.001). The means of the corresponding distributions are not statistically significantly different ($mean_{DM}$=546cc, $mean_{MRI}$=609cc, p=0.36) (Fig. 5). The degree of association between the fibroglandular volume estimates from DM and MRI was lower overall (r=0.38, R^2=0.15, $p\leq$0.001). The means of the corresponding distributions are statistically significantly different, with MRI providing lower estimates for the fibroglandular tissue volume ($mean_{DM}$=110cc, $mean_{MRI}$=61cc, p=0.36).

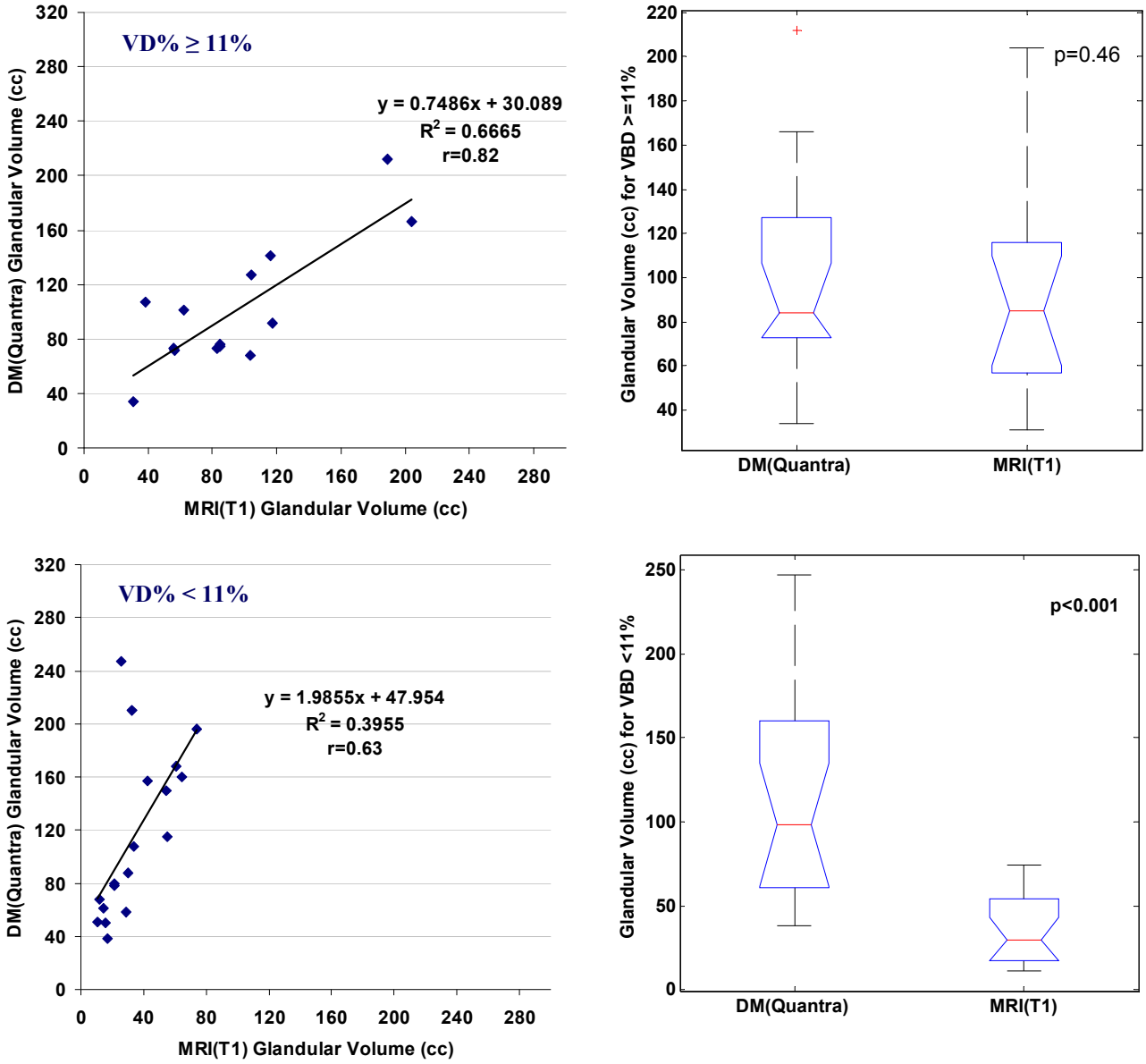

Figure 6. Linear regression fits and corresponding box-plots for the DM and MRI estimates of the fibroglandular tissue volume for women with ≥11% volumetric density (VD%) and < 11% VD%.

To further investigate these differences we performed subgroup analysis (Fig. 6). The linear regression fit shown in figure 3 suggests a difference in the degree of association for the DM and MRI VD% estimates for the very low-density breasts, as indicated by a curvature (*i.e.,* "hook") in the plotted data points below 11% MRI VD%. Therefore, we also compared the DM and MRI fibroglandular volumes separately for cases below and above 11% MRI VD%. Correlation and linear regression analysis indicates a strong association between the fibroglandular volume estimated from DM and MRI for women with equal or higher than 11% MRI VD% (r=0.82, R^2=0.67, $p \leq 0.001$). The means of the corresponding distributions are not statistically significantly different ($mean_{DM}$=101cc, $mean_{MRI}$=95cc, p=0.46) (Fig. 6). The degree of association for the fibroglandular volume was lower for women with less than 11% VD% (r=0.63, R^2=0.40, $p \leq 0.001$). The means of the corresponding distributions are statistically significantly different, with MRI providing lower estimates for the fibroglandular tissue volume ($mean_{DM}$=116cc, $mean_{MRI}$=34cc, p<0.001).

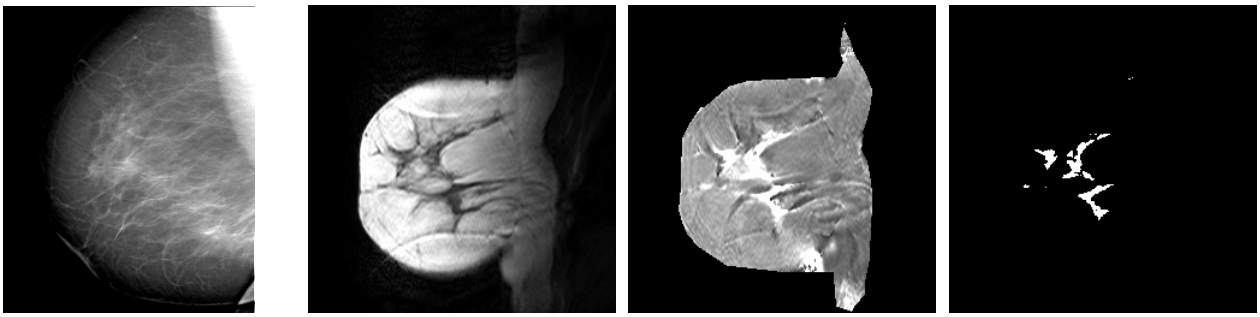

Figure 7. A DM image (*Cumulus Reader*$_1$ PD =16.10%, *Cumulus Reader*$_2$ PD =16.14% , *Quantra*^{TM} VD=14%) and a tomographic slice of the corresponding MRI $T_{i=400}$, the estimated T1 map, and the fuzzy-C-means parenchyma segmentation (MRI VD%=2%).

4. DISCUSSION

The good correlation observed in our study between the volumetric (VD%) and the area-based percent density measures (PD%), shown in studies with mammograms to correlate with breast cancer risk[1], suggests that volumetric density measures from both DM and MRI can have a role in breast cancer risk assessment. To date, most studies in breast density estimation and breast cancer risk assessment have been performed using digitized screen-film mammograms[1, 15]. New-generation breast imaging modalities provide the opportunity for multimodality breast density estimation, including the ability to measure volumetric breast density[16, 17]. Digital imaging, in particular, allows the implementation of fully-automated computerized methods that can provide objective quantitative measures [5, 13]. Such automated methods can alleviate the subjectivity of the currently used semi-automated methods (Fig. 3) and ultimately accelerate the translation of breast density estimation in clinical breast cancer risk assessment for the general population.

The statistically significant difference observed in the corresponding estimates of the fibroglandular tissue volume for women with very low-density (*i.e.,* fatty) breasts may be attributed to the fact that each of the breast imaging modalities and image quantitation techniques capture different breast tissue properties and different imaging features respectively. Figure 7 illustrates an example of the DM and breast MRI images of such a low-density case. The DM image captures the x-ray attenuation of the compressed breast tissues with high spatial resolution (0.1x0.1 mm/pixel). The MR images capture the corresponding fat and glandular tissue content in a lower resolution (0.78x0.78x3.0 mm/voxel). The latter may have implications for density quantitation due to partial volume effects. The fuzzy-C-means (FCM) algorithm used in our study for MR breast density estimation calculates voxel-wise probabilities that are interpreted as the percent of fibroglandular tissue content for the corresponding voxel. Based on these probabilities, a threshold is applied at the 0.5 probability level to segment the fibroglandular parenchyma. In the very low-density breasts, it is highly likely that the corresponding voxel-wise parenchyma content will be relatively low and therefore potentially not accounted for in the calculations of the MRI quantitation algorithm, resulting in the observed lower fibroglandular volume estimates. This potential effect is illustrated in the FCM segmentation output of the breast MRI volume in figure 7. On the other hand, due to the relatively large breast size observed for some of these very low-density cases, certain parts of the breast tissue may not be fully-visualized in the DM and MRI images. This may result in inconsistent breast density estimates, both by the area-based and the volumetric methods, especially because accurate breast boundary delineation and breast thickness estimation is essential for the accurate calibration of the automated volumetric density estimation algorithm[12].

A major limitation impacting the development of quantitative imaging methods to measure breast density is the lack of knowledge of ground-truth. With the exception of studies that have used mastectomy specimens [18, 19] and breast cadavers [20], most breast density studies are restricted in performing multimodality comparisons and correlative investigations, which can mainly inform on the relative performance but not on the actual accuracy of the obtained measures. Ideally, the obtained density estimates should pass the "Turing Test" in that the resulting measures should be indistinguishable from ground-truth and all tests performed and statistics calculated on these measures should be equivalent to what would result if the actual ground-truth measures of density were used. Such equivalence is unlikely, but as discussed by Kleijnen [21, 22], a measure which allows correlation with reality can be useful even if it does not measure reality with perfect fidelity. Therefore, while we will keep striving for accuracy, it is still possible to investigate the advantage of the various breast imaging modalities in breast cancer risk estimation, provided that the association between the obtained density measures and breast cancer risk can be validated with prospective clinical trials.

5. CONCLUSION

We performed a study to compare volumetric breast density measures obtained from DM and MRI for a population of high-risk women. Our results demonstrate that volumetric breast percent density measures (VD%) from DM and MRI are highly correlated and statistically significantly different from the corresponding area-based mammographic breast percent density (PD%) estimates. The good correlation observed between the volumetric and the area-based measures, shown by several studies to correlate with breast cancer risk[1], suggests that both DM and MRI volumetric breast density measures can aid in breast cancer risk assessment. Further work is underway to extend this study in larger clinical datasets and investigate the association between volumetric breast density measures and breast cancer risk. Our long-term hypothesis is that quantitative imaging measures of volumetric breast density can result in more realistic measures of breast density and ultimately result in more accurate measures of breast cancer risk.

ACKNOWLEDGEMENT

This work was funded by the Susan G. Komen for the Cure Foundation Postdoctoral Fellowship (KG080756), by a DOD Concept Award (BC086591), and by a National Institutes of Health/National Cancer Institute Program Project Grant (P01-CA85484). We would also like to thank Dr. Ann-Katherine Carton for facilitating image acquisition and Dr. Johnny Kuo for developing and maintaining the RSNA Medical Imaging Resource Center (MIRC) image archive.

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