# MRI-based Measurements of Breast Density and Morphologic Features for Prediction of Cancer Risk: A Case-Control Study

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**Background and Purpose:** Mammography separates tissues based on their differential absorption of the X-ray beam. Mammographic density (MD) is a measure of the dense (or non-fatty) tissue on the mammogram image, which is based on a single 2-D projection of the breast. In contrast, MRI acquires a set of 3D images. It can distinguish between fatty and fibroglandular tissues thus can be used for segmentation to enable detailed volumetric and morphologic analysis of breast density. The rationale for MRI measures of breast cancer risk include: 1), volumetric density measures derived from full-field digital mammography (FFDM) show similar risk estimate as area-based measures from digitized film- which were only fair; there is a need for improvement in risk prediction. MRI measures have potential to improve risk discrimination among highest risk women; 2), ACS guidelines since 2007 recommends women with > 20% lifetime risk to have screening MRI in addition to mammography, and a relatively large sample of women receiving screening MRI is available; 3), So far there has been no comparisons to determine whether MRI-based density measures are more informative than mammographic measures for association with breast cancer. In a previous study of 38 cancer cases, the preliminary results showed that there was no association between cancer risk with MD. It is known that MD and MRI-density was correlated, but not strongly [1]; 4), MRI has been shown to effectively measure density changes in women on tamoxifen and chemotherapy [2]. The goals of this study were to examine whether breast density and morphological pattern characterized by MRI can differentiate patients with and without cancer, and further to compare their associations with cancer risk based on MRI-density, MD (using qualitative BI-RADS or the percent density based on raw data or processed images), or combined variables.

**Methods:** We conducted a matched case-control study of incident breast cancer cases diagnosed from 2007-2011 at the Mayo Clinic who had an MRI and digital mammogram at or prior to diagnosis. Two controls were matched to each case on date of diagnosis (or exam date), indication (screening vs. diagnostic), menopausal status at exam, and age at diagnosis. Women with prior breast cancer, bilateral mastectomy prior to MRI, bilateral breast cancer, or implants were excluded. The contralateral normal breast of the cases and matched breast of the controls were examined and compared. Non-contrast-enhanced T1-weighed MRI images were used for the analysis of MR breast density. The measurements of mammographic and MRI density parameters were performed in blinded fashion. After the retrieval of digital mammograms and MRI on cases and controls, de-identification of all the images was done before the imaging analysis. Categorical BI-RADS density was evaluated on mammogram, and the mammographic percent density (MPD) was measured from both raw and processed FFDM images. The MRI percent density and morphologic parameters were measured from non-fat saturated T1WI sequences, based on the segmented dense tissue using our previously developed method [3]. A novel method based on nonparametric nonuniformity normalization (N3) and adaptive FCM algorithm was used to remove the strong intensity non-uniformity and correct the bias field for segmentation of fibroglandular tissue and fatty tissue. The standard FCM algorithm is applied to classify all pixels on the image. The default setting is to use a total of 6 clusters, 3 for fibroglandular tissue and 3 for fatty tissues. MR morphological parameters, including "circularity", "convexity", and "irregularity", were also analyzed. Conditional logistic regression with adjustment for BMI and age, was used to examine the associations between MRI-based and MD measures and breast cancer risk. C-statistics were used to assess ability to discriminate case and control status.

**Results:** Images of 97 cases and 166 controls were analyzed for current study. Figure 1 shows four case examples with different breast shape, dense tissue volume and the distribution morphologies from one selected image in the mid-section of the breast. The fibroglandular tissue volume, MR percent density, and three morphological parameters were calculated based on the segmentation results from all imaging slices. The BMI was higher in the cases relative to controls (29.1 vs. 26.8) p=0.003, but age (mean 52.7 vs. 51.5), post-menopausal status (55% vs. 51%), and percent mammographic density (median 27.6% vs. 27.9%) were not significantly different between these two groups. The mean MR % density was 11.9% for the cases and 11.8% for the controls. The median values of the three morphological parameters were the same in the two groups (0.4, 0.3, and 0.8 for circularity, convexity, and irregularity respectively). Among controls, the correlation co-efficient (r) of MR % density with PD analyzed on processed images was 0.8, and 0.82 for raw PD. As previously seen, when compared to MR % density, the mammographic percent density over-estimated breast density by a factor of about 2.5-3. The AUC of models with BI-RADS, Mammographic raw PD, MR-fibro-volume, MR-%density, and MR morphology - circularity, convexity, and irregularity, for differentiating cases and controls were 0.7, 0.7, 0.66, 0.7, 0.7, 0.73, and 0.67 respectively. Compared to BI-RADS and mammographic measurement, MR-%density showed slightly higher odd ratios (Table 1). Models with combined mammographic BI-RADS and MR density did not substantially improve the ability to discriminate case-control status (Table 2). Similarly, MR morphology parameters did not increase the discrimination in models with MR % density or BI-RADS mammographic density (Table 2). The AUC was 0.73 for all 3 models in Table2.

Figure 1: MRI segmentation in four women

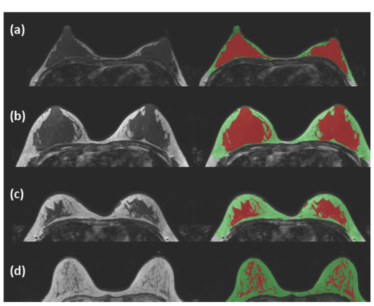


Table 1: OR and AUC to differentiate cases vs. controls

| Density Parameters (per SD) | Odds Ratio (95% CI) | AUC |
|---|---|---|
| MR Fibroglandular Volume | 1.05 (0.78-1.41) | 0.66 |
| MR % Density | 1.51 (1.03-2.2) | 0.70 |
| BI-RADS MD (per category) | 1.46 (0.92-2.2) | 0.70 |
| Mammographic PD-Raw | 1.15 (0.80-1.65) | 0.70 |
| Mammographic PD-Processed | 0.98 (0.67-1.43) | 0.66 |

Table2: OR and AUC based on combined parameters

| Parameters | Odds Ratio (95% CI) | AUC |
|---|---|---|
| BI-RADS MD<br>MR % Density | 1.14 (0.74, 1.74)<br>1.57 (1.02, 2.42) | 0.73 |
| MR % Density<br>Circularity<br>Convexity<br>Irregularity | 1.40 (0.90-2.18)<br>1.24 (0.73-2.10)<br>0.95 (0.61-1.76)<br>0.97 (0.62-1.53) | 0.73 |
| BI-RADS MD<br>MR % Density<br>Circularity<br>Convexity<br>Irregularity | 1.12 (0.72-1.75)<br>1.50 (0.92-2.4)<br>1.15 (0.67-1.98)<br>0.93 (0.49-1.75)<br>0.94 (0.59-1.59) | 0.73 |

**Discussion:** Early results from this small cohort suggest mammographic density measures are not strongly associated with breast cancer in this symptomatic population. MRI density remains a strong risk factor for breast cancer, which is consistent with results from a prior screening study (only 38 cancers). Other morphologic parameters appear to add minimally to the MRI density and breast cancer association. The subjects included in this analysis included both diagnostic and screening patients. Based on the strict matching process we can evaluate the role of density in risk prediction by comparing between cases and controls, but the data are not optimal for building a risk prediction model. The next steps of work include additional analyses of data with composite morphologic measure, continuous study to confirm findings in larger sample, and translation to the screening setting.

**References: [1]** Thompson DJ. Breast Cancer Res. 2009; 11(6):R80. [**2**] Chen JH. Magn Reson Imaging. 2011;29(1):91-8. [**3**] Lin M. Medical Physics. 2011, 38(1):5-14.
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