A Pilot Study of Compositional Analysis of the Breast and Estimation of Breast Mammographic Density Using Three-Dimensional T1-Weighted Magnetic Resonance Imaging

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Abstract

Purpose: A method and computer tool to estimate percentage magnetic resonance (MR) imaging (MRI) breast density using three-dimensional T1-weighted MRI is introduced, and compared with mammographic percentage density [X-ray mammography (XRM)].

Materials and Methods: Ethical approval and informed consent were obtained. A method to assess MRI breast density as percentage volume occupied by water-containing tissue on three-dimensional T1-weighted MR images is described and applied in a pilot study to 138 subjects who were imaged by both MRI and XRM during the Magnetic Resonance Imaging in Breast Screening study. For comparison, percentage mammographic density was measured from matching XRM images as a ratio of dense to total projection areas scored visually using a 21-point score and measured by applying a two-dimensional interactive computer program (CUMULUS). The MRI and XRM percent methods were compared, including assessment of left-right and interreader consistency.

Results: Percent MRI density correlated strongly (r = 0.78; P < 0.0001) with percent mammographic density estimated using Cumulus. Comparison with visual assessment also showed a strong correlation. The mammographic methods overestimate density compared with MRI volumetric assessment by a factor approaching 2.

Discussion: MRI provides direct three-dimensional measurement of the proportion of water-based tissue in the breast. It correlates well with visual and computerized percent mammographic density measurements. This method may have direct application in women having breast cancer screening by breast MRI and may aid in determination of risk. (Cancer Epidemiol Biomarkers Prev 2008;17(9):2268–74)

Introduction

Percentage mammographic density is a major risk factor for breast cancer. Individuals with dense breasts have 4- to 6-fold greater chance of developing breast cancer than those with fatty breasts (1). There is however no standard, accurate method for measuring mammographic density. A two-dimensional interactive computer program (CUMULUS) has been widely used, giving percentage mammographic density and dense breast area (2). This method and other similar interactive computer and visual estimates analyze a three-dimensional organ by two-dimensional techniques, so are inevitably limited. Magnetic resonance imaging (MRI) has been explored as a method of estimating the water content of a breast via slices or slabs of breast tissue (3, 4). More recently, MRI techniques for measuring MRI density based on segmentation of three-dimensional images have been reported (5-7).

The Magnetic Resonance Imaging in Breast Screening study (MARIBS; ref. 8) was a United Kingdom national MRI screening study of women at genetic risk of breast cancer. MRI provides radiation-free MRI density measurements suitable for young women and TP53 carriers, who may be susceptible to cancer initiation by radiation (9). Such screening may provide density measures that can be used in the risk models applied to high-risk women (10). A method of assessing MRI density using three-dimensional data have been developed and, in a pilot study, is compared with existing methods of percentage mammographic density measurement.
Materials and Methods

The method was applied to patients who participated in the MARIBS study (8, 11). All participants had given informed consent to a protocol approved by the Research Ethics Committee.

MARIBS Study Design. Subjects were chosen from participants in the MARIBS study, in which 649 women ages 35 to 49 y with a very strong family history of breast cancer (estimated annual risk of breast cancer was at least 0.9%) attended for MRI and X-ray mammography (XRM) annually. A sample population of 138 subjects without pathologically confirmed findings of benign or malignant lesions, but with date-matched MRI and mammography, was chosen. The age distribution was similar to the main study population.

MR Imaging Protocol. The MRI imaging technique has been described in detail elsewhere (11) and is detailed in Web Appendix 1. In brief, a three-dimensional T1-weighted high resolution scan was done before the dynamic contrast enhanced measurements and used for MRI density measurements, together with a proton density image, which was used for uniformity correction. All acquisitions used for MRI density measurements used a dedicated double breast coil with scanning in the prone position without compression.

MRI-Density Measurement. The detail of the method can be found in Web Appendix 2. In brief, an MRI density measurement tool (Fig. 1) was developed that calculated the percentage MRI volumetric content of water-based (dense) tissue in the breast. Water-containing tissues were identified by interactive segmentation of tissues anterior to the pectoral muscle on the basis of signal intensity in the precontrast T1-weighted images. A coil uniformity correction based on the proton density image was applied before segmentation of water-based and fat-based tissues. Percentage MRI Density was calculated as the ratio of the volume occupied by MRI water-containing tissue to the total volume of breast tissue. EB and SR had trained to obtain consistent

Figure 1. General view of the mammographic density analysis tool.
readings using this experimental method. EB read the images for all 138 cases reported here. SR read a subset for repeatability analysis (52 images from 26 women). Due to team changes, intrareader repeatability estimates cannot be obtained for EB’s MRI readings.

**Mammographic Density Measurement.** Original mammograms retrieved from the centers were digitized using an Array 2905 DICOM ScanPro Plus Laser Film Digitiser Version 1.3E (Array Corp.) at absorbance of 4.7. Medial-Lateral Oblique XRM images were used for mammographic density assessment by the two-dimensional interactive method developed by the University of Toronto (CUMULUS V3.1; refs. 2, 12). This method estimates dense breast area and whole breast area from scanned mammograms and yields a percentage value for density. The pectoral muscle is excluded from the image before measuring. CUMULUS analyses were undertaken by two experienced observers. RW read all the images and a subset were read also by IW (59 images from 30 women), and RW independently second read 30 images from 30 women for repeatability studies. All readings were read as individual images blinded to all patient information and all other readings.

**Visual Assessment of Mammographic Density.** Mammographic density was assessed by experienced radiologists (CB & RW). The digitized images were viewed individually on a standard PC, and a percentage estimate of density to 5% was made by the radiologist using a 21-point scale. This method is designed to detect differences smaller than one Boyd category (13). CB read all the images. RW undertook repeat readings of 10% of the images, and CB read the same 10% a second time for repeatability studies.

**Statistical Analysis.** First, we assessed the relationship between the paired MRI percent density (volumetric) and projection-based (Cumulus) mammographic percent density measurements, using correlation and regression analysis. The analysis included the right and left breasts of each woman where available (264 breasts from 137 women), using the sandwich variance estimator to allow for the nonindependence of the two sides. The relationship between MRI density and visually scored percent density on a 21-point scale was similarly assessed, based on the 210 breasts from 108 women for whom this information was available.

Second, we tested left to right side density correlation for each of the modalities, to inform on the consistency of each approach. MRI density estimates for both breasts were available for 137 women (132 women for the CUMULUS-based estimates). Systematic and absolute differences between the left and right breasts were tested using t tests, and the difference in density estimates between sides was plotted against the average density estimate i.e., a Bland-Altman plot.

The images from a random sample of 30 women were analyzed by a second reader to assess the interreader agreement of each method (26 women for the MRI method) using t tests and Bland-Altman plots, as above.

**Results**

The percent MRI and CUMULUS mammographic density findings showed a positive linear correlation, based on the images of 264 breasts from 133 women (correlation factor r = 0.78; Fig. 2). Linear regression analysis, allowing for the nonindependence of the two images from each woman, gave the following regression equation:

\[
\frac{\text{MRI dense volume}}{\text{MRI total volume}} = 0.02 + 0.56 \times \frac{\text{Cumulus dense area}}{\text{Cumulus total area}}
\]

The 95% confidence interval (95% CI) for the slope was 0.48 to 0.63, \( P < 0.001 \), i.e., the MRI measure of the
millar different (percent density (Fig. 3A and B), which were not significant for the less-dense breasts; the slope was 0.25 for the 54 breasts with CUMULUS density of <20% (95% CI, 0.07-0.43; P = 0.007) and 0.62 (95% CI, 0.50-0.73; P < 0.001) for the 210 breasts with a CUMULUS density above this level (P = 0.001 for the difference). There was also evidence of a strong positive linear relationship between the MRI density and the percentage area mammographic density estimated visually using the 21-point scale, with a very similar overall slope (slope, 0.56; 95% CI, 0.47-0.64; P < 0.001).

The intramodality left/right side correlation coefficients were 0.95 for MRI density and 0.84 for XRM percent density (Fig. 3A and B), which were not significantly different (P = 0.16). There were no systematic differences between left and right breast percent densities as measured by either MRI (P = 0.51) or XRM (P = 0.85). The mean absolute difference in estimated percentage density between sides was larger for the XRM-based method (7.9 percentage point difference; 95% CI, 6.5-9.2) than for the MRI method (3.6 percentage point difference; 95% CI, 3.1-4.1; P < 0.001 comparing MRI with XRM), with the XRM method showing a greater range of values, including some substantial differences between sides. However, when the estimates from the mammographic method were scaled according to the linear regression coefficients (estimated above), the mean absolute difference between sides was closer to that observed using MRI, with overlapping confidence intervals (4.4 percentage points; 95% CI, 3.6-5.2).

Figure 3C and D show the MRI density measurements to have a higher interreader consistency than the XRM CUMULUS measurements for the 30 samples whose images were analyzed by a second observer. The mean absolute difference between MRI readers was 4.3 percentage points (SD, 3.1; 95% CI, 3.4-5.2), but one MRI reader did not give estimates that were consistently higher than the other (P = 0.13). The linear relationship between the density estimates from the two XRM readers was not quite as strong, although the difference was not significant (intraclass correlation coefficient, 0.079 for XRM; r = 0.90 for MRI; P = 0.16 for the interaction term in a linear regression model). The mean absolute difference in estimated density between observers was larger than for MRI (7.2 percentage points; SD, 5.5; 95% CI, 5.8-8.6; P = 0.001 comparing MRI with XRM) but was almost identical to the difference between MRI readers once the XRM-based estimates had been scaled according to the MRI/XRM regression coefficients (4.3 percentage points difference; 95% CI, 3.4-5.2). The differences between XRM observers were not consistent in direction (P = 0.30).

Thirty images were independently reanalyzed by the original XRM reader, with a mean absolute difference in estimated density between reads of 5.2 percentage points (95% CI, 3.9-6.4).

Discussion

Mammographic breast density has been identified as an independent risk factor for breast cancer (1). Women with density in >75% of the mammogram have a risk of breast cancer 4.7 times those with density in 10% or less of the mammogram (14). Genetic differences may affect density, which may further modulate the risk of breast cancer (15).

High mammographic density increases the chances of missing cancer on XRM. MRI screening is included in recent recommendations for women at high risk of familial breast cancer (16) or who have received supra-diaphragmatic irradiation for lymphoma (17), and breast density may guide this use in high-risk groups (18).

Mammographic density evaluates the X-ray attenuation of different tissues in a two-dimensional projection of a three-dimensional volume. In most studies, these are not calibrated directly for compression, X-ray exposure, and film response. Percent mammographic density does not reliably measure the true proportion of parenchymal tissue in the breast but correlates well with risk in many studies (1).

The MRI estimates of breast density described here provide a direct three-dimensional method of assessing the proportion of water-based tissues (presumed parenchyma) in a volume of breast tissue, which may more accurately assess the proportion of parenchyma in the breast. However, it is intrinsically a different (although related) estimate of breast density to that provided by mammography. It has not yet been validated in a case-control setting to determine whether it is predictive of breast cancer risk. It is an accessible technique for women where there is concern about radiation sensitivity due to genetic defect (e.g., TP53) or young age. Neither technique truly measures the entire breast, due to anatomical issues in sampling of, for example, the axilla.

Figure 2 shows a good correlation between volume breast percent density measured by MRI and mammographic area percent density estimated using CUMULUS, although the slope of the regression line implies that projection-based mammographic assessment overestimates the actual breast percentage density by a factor approaching two. This can be explained by the two-dimensional representation of the breast on which the threshold readings are made. The fat above and below the breast plate is not included in the fat measurement. A well-accepted 21-point visual assessment scheme (13) similar to the Boyd score (19) also showed a good correlation with MRI breast density. Lee et al. (5) found a similar correlation (r = 0.63) in their study and similarly found differences in relative accuracy when compared with percent mammographic density between the measures in dense and fatty breasts.

The techniques used in this study sample the breast tissue in different ways, and none of them can encompass all of the breast tissue, due to limitations in the field of view, superposition of other tissues, and areas of motion. Two-dimensional XRM techniques are limited by the need to assess projections of X-ray attenuation, nonlinearity and variability in breast thickness and compression, X-ray exposure, and film processing of the data. Despite these limitations mammographic density has been shown to predict breast cancer risk well. The MRI assessment of density is affected by coil uniformity, addressed by a correction method. Partial volume effects may contribute some error to the analysis, although this is expected to be small. Currently assessment of breast density is restricted to volumes (for the prone patient) lying below the pectoral muscle.

Our results can be compared with previous MRI measures of breast density, none of which have been established into analytic studies beyond their first experimental description. The method of Lee required...
manual mapping of the individual slices of the three-dimensional MRI study (5). Wei et al. (7) used a semiautomated method of segmentation with good repeatability (0.99), which exceeded the mammographic density measure (0.91 and 0.89 for CC and Medial-Lateral Oblique views). Klifa et al. (6) applied fuzzy $c$-means clustering and manual segmentation to obtain a breast tissue index that correlated with mammographic density ($r = 0.75$ and 0.78, respectively). Graham et al. (4) used relative water content ($r = 0.79; P < 0.0001$) and mean T2 relaxation time ($r = -0.61; P < 0.0001$). This team also showed that their measure of density was associated with the same sociodemographic and anthropometric risk factors for breast cancer as are found with percent mammographic density. Because many of the mammographic methods are operator dependent and time consuming, the MRI measure has the potential to give an equally reliable method with full automation. Our present method uses interactive thresholding and takes significant operator time to apply. However, our team is attempting to introduce automation to the computer procedure. Our present pilot project of 138 women is larger than those presented in the literature [the projects involved were as follows: Klifa, 10 cases (6); Lee, 40 cases (5); Graham, 42 cases (4); Poon, 23 cases (3); Wei 67 cases (7)], and form the first stage in the plan to analyze MRI density in the high-risk group of the MARIBS multicenter highrisk screening study.
A limitation of the study is that no validation with biological phantoms was undertaken for MRI. Although mammographic density is widely used, the amount of such biological validation is extremely limited because the experiments are difficult to devise.

Conclusion

Our pilot study shows that breast MRI assessment of percent density correlates well with mammographic measures of percent density. Our study is based on the supposition that they measure the same tissue, for which we do not at present have pathologic evidence. Where MRI screening is undertaken in high-risk young women, it may have potential to provide a useful measure of MRI density. This may then support the application of surveillance, risk assessment, and preventative strategies. This will only be true if better comparisons can be made to large epidemiologic studies on cases and controls, and the histologic validation can be established. This is the pilot to a larger study in high-risk women.

Figure 3 Continued. Interreader agreement of MRI-based estimates (C; 26 women), and interreader agreement of XRM CUMULUS estimates (D; 30 women).
Disclosure of Potential Conflicts of Interest

R. Eeles: support from VISTA diagnostics and Tepnel & Illumina genotyping services for a screening conference Royal Marsden Hospital, London, United Kingdom, Feb 2008. Support from Astra Zeneca for zoladex prevention pilot in high risk women; M. Leach: Specialty Scanners plc, Director of a company developing a dedicated breast imaging system; share options in Specialty Scanners plc; patent application for fat suppression methodology. The other authors disclosed no potential conflicts of interest.

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It uses data collected as part of the MARIBS study—a UK-wide collaboration of 22 genetics centers and their associated MRI and mammography departments. The key clinical contributors are listed in Web Appendix 3. We thank radiographers, nurses, clerical staff, physicists, engineers—whose contribution is important but who have not been named—and to the women and their surgeons and oncologists who referred them without whom the study would not have been possible.

References

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