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Short Communication

Quantification of Breast Density Using Three-Dimensional Magnetic Resonance Imaging

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Abstract

Breast density has been proven as an independent risk factor of breast cancer. Due to the limitation of two dimensional mammographic density, various alternative imaging modalities have been investigated to provide more quantitative measurement of breast density. Among these potential imaging tools, three dimensional (3D) magnetic resonance imaging (MRI) based density method is mostly studied. Our research group has been focusing on this topic for years. Here we present our experience of developing 3D MRI density method and briefly review several studies we have published related to the consistency of the 3D MR method. The results have suggested that 3D MRI can be a reliable tool for the measurement of breast density.

ABBREVIATIONS

MD: Mammographic Density; LVI: Lympho-Vascular Invasion; SMF: Standard Mammogram Form; 2D: Two Dimensional; 3D: Three Dimensional; MRI: Magnetic Resonance Imaging; FCM: Fuzzy C-Means; N3: Nonparametric Nonuniform Intensity Normalization; CV: Coefficient of Variation; BV: Breast Volume; FV: Fibroglandular Tissue Volume; PD: Percent Breast Density; T: Tesla

INTRODUCTION

Association of mammographic density with breast cancer risk

The breast mainly consists of two tissue components: fibroglandular tissue and fat. Fibroglandular tissue is a mixture of fibrous stroma and epithelial cells that line the ducts of the breast. Breast density, most commonly measured as mammographic density (MD), is associated with the amount of fibroglandular tissue. Evidence from many large screening mammography studies has established the role of mammographic density as an independent risk factor for breast cancer [1-9]. Most of these studies used the typical case-control study design based on large cohorts of women enrolled into screening mammography studies. The women were followed longitudinally to find out who developed cancer as "cases" and the matching "controls" selected from women who did not develop cancer. It was consistently found that the cases had, on average, 20% higher mammographic density compared to controls [10-12]. Mammographic density was reported to be associated with age and race [13-15], higher in pre-menopausal than in post-menopausal women [4,8], and higher in Asians than Caucasians [14]. Women with dense tissue visible on a mammogram have a cancer risk 1.8 to 6.0 times that of women with little density [8]. Studies have also shown that BC arising within areas of high MD is more commonly associated with factors indicative of a poor prognosis, including large tumour size, high histological grade, lympho-vascular invasion (LVI) and advanced stage, compared to those arising within low MD tissue [16-18]. Increasing evidence has also suggested the role of peritumoral adipose tissue and secreted steroids and adipokine in breast cancer [19-22]. Several studies have analyzed the morphological distribution pattern of the projected dense tissue (texture) on mammograms [23-25], and shown differences between women with invasive cancer and women without cancer [25]. There were also differences between high-risk women carrying the BRCA-1 and BRCA-2 gene and low-risk women [23,24].

Measurement of breast density with mammography and its drawbacks

Quantitative mammographic density uses computer-aided calculation of percent dense tissue area on mammograms, and most of early studies were performed using a Cumulus thresholding segmentation method [3,12,13,26,27]. Although Cumulus and similar mammographic density estimator programs were widely applied in earlier studies, they are based on a user-defined thresholding method. This method is subjective and the measured density is known to be highly dependent on the observer, with substantial inter- and intra-observer variability. Other quantitative measurement approaches, including the use of a lateral phantom [28], the standard mammogram form (SMF)

analysis program [29, 30], volumetric assessment methods [31-33], and automated volumetric density quantification tool using **Quantra™** (http://www.hologic.com/wh/news-101107.htm) and Volpara™ (http://www.volparadensity.com) were developed. Overall, two dimensional (2D) mammography suffers from tissue-overlapping problem, not revealing genuine three dimensional (3D) morphological information, thus is unable to accurately differentiate between fatty and fibroglandular tissues. Nonetheless, since the cohorts of screening mammography studies are very large, thus statistically, many studies have sufficient power to demonstrate that there is a strong association between the mammographic density and the cancer risk, and provide strong evidence supporting the role of mammographic density as a strong independent risk factor. The accuracy of breast density determined by mammography has been seriously questioned. It was concluded that studies showing small percentage differences between groups are likely to be inaccurate [34].

Measurements of breast density and breast morphology using 3D MRI

Because of the limitations of mammographic density, in the breast densitometry community, there is a strong urgency to develop quantitative density measurement methods that are reliable, thus can be used to predict each individual patient's risk. Among the various emerging 3D imaging modalities, such as 3D ultrasonography [35], computed tomography [36], and magnetic resonance imaging (MRI), 3D MRI-based analysis has received a great attention. MRI provides detailed 3D distribution of fibroglandular tissue, not subject to the tissue-overlapping problem as in mammography. Also, it allows the slice-by-slice segmentation of fibroglandular and fatty tissues for analysis of morphological pattern. The American Cancer Society recommended screening breast MRI for high-risk women (with lifetime risk greater than 20%) in March 2007; to date there is still no large screening MRI cohort with a high number of cases available in the United States for a traditional case-control study. With the maturity and increasing popularity of this imaging modality and its high sensitivity for breast cancer detection, it is anticipated that the number of women receiving diagnostic and screening breast MRI study will be increased. When large MRI datasets from multiple sites are available, the role and value of 3D MRI-based breast density for improving the prediction of cancer risk and/or aiding in clinical management will be further studied and clarified.

Our group has been working on MRI-based density analysis for more than 10 years, starting from the development of a novel computer-aided segmentation method for quantitative analysis of whole breast volume and breast density on 3D MRI [37,38], then based on that to develop further refined methods for evaluating the density morphological distribution pattern [39]. The method has been applied to study the age- and race-related differences [40], as well as the change in patients receiving chemotherapy [41] and tamoxifen [42]. Although several groups also have publications on MRI-based density [43-51], we are the only group that has the method to characterize the morphological distribution pattern of the fibroglandular tissues for exploring the additional value that the 3D information can provide [39].

To become an accurate and reliable modality for the quantitative measurement of breast density, and further can be used as an imaging biomarker, 3D MRI has to go through several steps of test to prove its robustness. These challenges include the robustness of the methodology itself and its high consistency in different situations, including MR scanner, pulse sequences, physiology, and operator factor. In the past years we have spent tremendous effort focusing on these issues [37,38,40,52-55] and proved the value of 3D MRI for the quantification of breast density.

To use 3D MRI for quantitative analysis of breast density, since there is no clear boundary between the body and the breast, the first step is to define a reliable anatomic landmark to segment the breast tissue. Because of no ground truth to be compared with, this is more an issue of consistency than accuracy. Among all the published studies, two landmarks are commonly used, a V-shaped landmark of each individual woman [37], or a horizontal line drawn manually along the ventral surface of the pectoralis major muscle [44,51] or immediately posterior and parallel to the sternum [53]. Whatever the landmark is used, it should be made sure that no fibroglandular tissue is chopped off. The next step is to segment the fibroglandular tissue. In our early methodology development paper [37], we used fuzzy C-means (FCM) algorithm, which worked well for most cases but could not handle women with obvious imaging in homogeneity due to bias field issue. We thus further improved the segmentation algorithm using FCM plus nonparametric nonuniform intensity normalization (N3) [52]. The new algorithm works very well for women with different breast morphology and can deal with imaging inhomogeneity issue much better than using FCM alone (Figure 1).

Our developed MR method has shown high intra- and inter-operator consistency, and high consistency due to positional change [37]. The average standard deviation for breast volume and percent density measurements was in the range of 3%-4% among three trials of one operator or among three different operators. The body position dependence was also investigated by performing scans of two healthy volunteers, each at five different positions, and found the variation in the range of 3%-4%. We further tested the impact of pulse sequences and imaging resolution on the segmentation results [53]. It was noted that breast volume, fibroglandular volume, and percent density between fat-suppressed and nonfat-suppressed sequences were highly correlated. The fibroglandular tissue volume measured on down sampled images only showed a small (<5%) difference. Breast density may fluctuate in a menstrual cycle due to the effect of endogenous hormone on the breast tissue. To clarify the impact of menstrual cycle on measuring breast density, we studied thirty healthy female subjects, 24 premenopausal and six postmenopausal [54]. All subjects underwent MR imaging examination each week for 4 consecutive weeks. The fluctuation of each parameter measured over the course of the four examinations was evaluated on the basis of the coefficient of variation (CV). The mean CV was 5.0% and 5.6% for breast volume (BV), 7.6% and 4.2% for fibroglandular tissue volume (FV), and 7.1% and 6.0% for percent breast density (PD), in the respective premenopausal and postmenopausal groups. The difference between premenopausal and postmenopausal groups

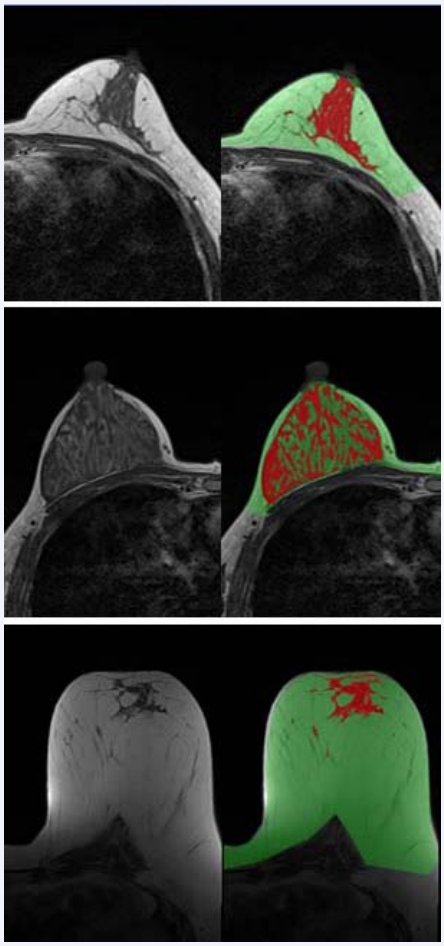

Figure 1 Breast (green color) and fibroglandular tissue segmentation (red color) in three women with different breast size, morphology, and imaging quality. Note the fibroglandular tissue can be accurately segmented (red color).

was not significant (all P values > .05). Overall, the fluctuation of breast density measured at MR imaging during a menstrual cycle was around 7%.

Lastly, we investigated how the breast density would change when a woman was scanned in different MR scanner [55]. This is a very challenging topic yet very important issue to be answered, especially for multi-center combination of MR data. We recruited 34 healthy Asian women to have breast MRI study using four different MR systems from three vendors, including two 1.5 Tesla (T) (GE and Siemens) and two 3T (GE and Philips) MR scanners. All the four MR studies were completed in half day to avoid any physiological effect on the measured breast density. The measured parameters between each pair of MR scanners were highly correlated, with $R^2 \geq 0.95$ for BV, $R^2 \geq 0.99$ for FV, and $R^2 \geq 0.97$ for PD in all comparisons. The mean percent differences between each pair of scanners were 5.9%-7.8% for BV, 5.3%-6.5% for FV, 4.3%-7.3% for PD; with the overall CV of 5.8% for BV, 4.8% for FV, and 4.9% for PD. The results showed that the variation of FV and PD measured from four different MR scanners is around 5%, suggesting the parameters measured using different scanners can be used for a combined analysis in a multicenter study.

Despite of the merit of 3D MR density method, there are two issues which may hinder its clinical application. First, MRI is costly compared to 2D MD. Second, the procession time of multi-slices 3D MR data is generally time consuming. To gain popularity for this new density method, there is a need to make technical breakthrough. Most of the reported MR density methods in the literature are based on semi-automated methods that require some operator interventions, which are subject to variations from an operator's personal judgment. To overcome the problems, model-based segmentation methods, using the whole breast as the template, have been developed [56-58]. However, simply using one universal template may not be accurate enough to segment all types of breasts. To improve the robustness, we have developed a new automatic template-based method using the chest body model for breast segmentation [59]. In this method, the chest template was mapped to each subject's image space to obtain a subject-specific chest model for exclusion. The automatic method can provide an efficient tool for processing large clinical datasets for quantifying the fibroglandular tissue content in breast MRI [60].

CONCLUSIONS

Breast MRI has emerged as a new imaging tool for assessing breast density, which provides 3D true volumetric information without tissue overlapping issue. Efforts have been made to improve the technique and segmentation algorithm. Its high measurement consistency has been proven in different situations related to scanners, sequences, operators, and physiology. Current fully automatic methods have tremendously solved the time-consuming issue and human intervention. Studies have also been performed and others are still undergoing to investigate its role in improving cancer risk assessment and aid in treatment response.

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