The Association of Breast Density with Tumor Subtypes: Evaluation with 3D MRI

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Background and Purpose: Breast stromal tissue is reflected as dense areas in mammography. Breast stroma has a profound influence on the phenotype of various carcinomas. There was a great research effort devoted to investigate the association between clinical risk factors and the development of subtype cancers based on the molecular biomarker, including estrogen receptor (ER), progesterone receptor (PR) and the Her-2 status. Characterizing the association between breast density and risk of tumor subtypes may enhance our understanding of how breast density influences breast cancer risk, as well as our understanding of how breast cancer subtypes differ in etiology. Studies evaluating the association between breast density and breast cancer risk by expression of biomarkers in the tumor were controversial. Some reported no difference in the magnitude of the association between breast density and risk for ER-positive vs. ER-negative breast cancer [1], while others [2] reported higher mean percent density associated with ER-positive disease than ER-negative disease. Results from the Nurses' Health Study [3] found that breast density has a stronger association with ER-negative than ER-positive tumors. The results presented in this study [3] suggest that breast density is an important risk factor for a range of biologically diverse subtypes of breast cancer, including tumors exhibiting characteristics indicative of poorer prognosis. It is plausible that tumors that arise in dense breasts may be more aggressive because of the interaction of increased numbers of stromal and epithelial cells [4]. High breast density has been positively associated with breast tumor characteristics that are predictive of worse prognosis [3]. The goal of this study was to use 3D MR-based density method to investigate the association of breast density with the development of different subtypes of breast cancer. The results may potentially provide very helpful information for each individual woman to choose the optimal chemoprevention strategies based on the type of cancer that she is at risk of developing.

Materials and Methods: In total 114 women (mean age 49, range 28-82) diagnosed with unilateral breast cancer were included in this study. Of these women, 80 were ER positive, 14 were ER negative, and 20 were triple negative cancers. Twenty-nine were Her-2 positive, 83 were Her-2 negative cancers, and 2 had no Her-2 information. To measure the breast density, the contralateral normal breast was analyzed. The MR density measurement was based on our well-established template-based automatic segmentation method [5]. With the method, the chest body region on a middle slice was used as the template. Within the chest template, an initial V-shape cut using three body landmarks (thoracic spine and bilateral boundary of the pectoralis muscle) was performed 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 a 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 was based on N3+FCM algorithm [5]. Percent breast density (PD) was defined as the ratio of the fibroglandular tissue volume over the breast volume. The overall distribution of measured density was correlated with age. The PD was also compared among different tumor subtypes.

Results: The mean±STD PD for the whole cohort was 14.7±11.8%. **Figure 1a** showed the correlation of PD with age. It was noted there was a negative correlation (r=-0.49), with older women tended to have lower PD. **Figure 1b** showed the PD distribution among ER positive, ER negative, and triple negative cancers. **Figure 1c** showed the PD distribution between Her-2 positive and Her-2 negative cancers. Overall, ER negative cancer and triple negative cancer had higher PD (16.7±12.5% and 15.6±13.8% respectively) than other tumor subtypes (ER positive cancer 14.1±11.2%, Her-2 positive cancer 13.5±11.2%, and Her-2 negative cancer 15.0±12.2%), but no statistically significant difference was noted for all the comparisons (all p>0.05). **Figure 2** showed three represented cases of different tumor subtypes: ER negative cancer (upper panel, 45 y/o), triple negative cancer (44 y/o, middle panel), and ER positive cancer (45 y/o, lower panel). The MR measured PD was 47.6%, 17.2%, and 12.7% respectively.

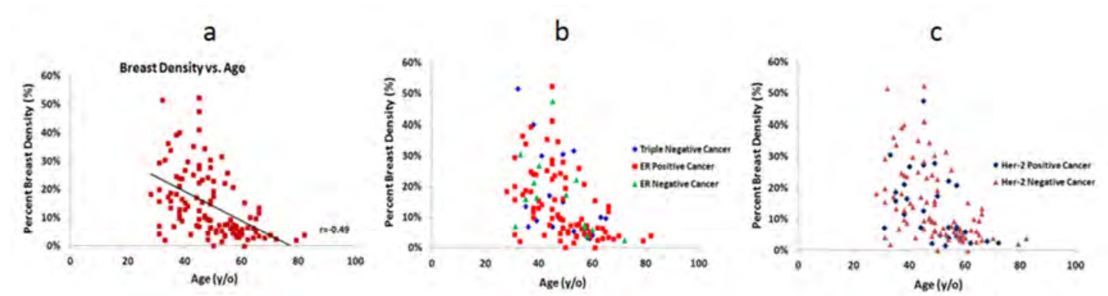

Figure 1.

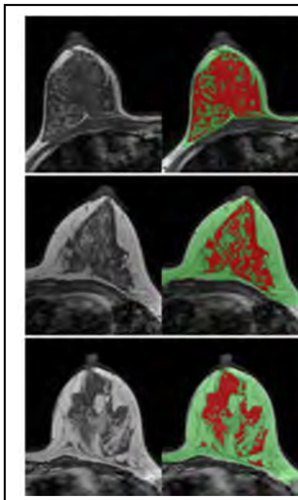

Figure 2.

Conclusion: The results from our study based on 3D MR measurement were consistent with the mammographic density findings that older women tended to have lower PD than younger women. ER negative cancer and triple negative cancer had higher PD than other tumor subtypes, a finding consistent with the large series of Nurses' Health Study [3]. Nevertheless, due to small number of subjects in this study, the statistically significant difference could not be identified. Our results deserved further studies based on large series of subjects, because, unlike 2D mammographic density, 3D MRI can provide true volumetric information which is believed to be more reliable. Our current fully automatic segmentation algorithm can remarkably reduce imaging procession time, enabling its potential application for large epidemiological studies.

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