Breast density and parenchymal texture measures as potential risk factors for Estrogen-Receptor positive breast cancer

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Abstract

Accurate assessment of a woman's risk to develop specific subtypes of breast cancer is critical for appropriate utilization of chemopreventative measures, such as with tamoxifen in preventing estrogen-receptor positive breast cancer. In this context, we investigate quantitative measures of breast density and parenchymal texture, measures of glandular tissue content and tissue structure, as risk factors for estrogen-receptor positive (ER+) breast cancer. Mediolateral oblique (MLO) view digital mammograms of the contralateral breast from 106 women with unilateral invasive breast cancer were retrospectively analyzed. Breast density and parenchymal texture were analyzed via fully-automated software. Logistic regression with feature selection and was performed to predict ER+ versus ER− cancer status. A combined model considering all imaging measures extracted was compared to baseline models consisting of density-alone and texture-alone features. Area under the curve (AUC) of the receiver operating characteristic (ROC) and Delong's test were used to compare the models' discriminatory capacity for receptor status. The density-alone model had a discriminatory capacity of 0.62 AUC (p=0.05). The texture-alone model had a higher discriminatory capacity of 0.70 AUC (p=0.001), which was not significantly different compared to the density-alone model (p=0.37). In contrast the combined density-texture logistic regression model had a discriminatory capacity of 0.82 AUC (p<0.001), which was statistically significantly higher than both the density-alone (p<0.001) and texture-alone regression models (p=0.04). The combination of breast density and texture measures may have the potential to identify women specifically at risk for estrogen-receptor positive breast cancer and could be useful in triaging women into appropriate risk-reduction strategies.

Keywords

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1. INTRODUCTION

The personalization of breast cancer screening recommendations based on an individual woman's risk for breast cancer is becoming increasingly important for clinical practice and patient care[1, 2]. The National Cancer Institute's (NCI's) risk assessment tool, often referred to as the Gail model[3], is one of the most commonly utilized breast cancer risk assessment tools and has been used to establish guidelines for offering customized breast cancer screening recommendations for women at an elevated risk of developing breast cancer[4]. For example, the American Cancer Society (ACS) recommends that women with more than 20%–25% lifetime risk of breast cancer also be screened with breast magnetic resonance imaging, which has been shown to detect mammographically occult breast cancers with higher sensitivity than with screening mammography[5]. Furthermore, such models have also been utilized in preventive, risk-reduction strategies for woman at risk of developing specific sub-types of breast cancer, such as an estrogen-receptor positive (ER+) breast cancer[6]. As a result, tamoxifen, a selective estrogen receptor modulator (SERM) chemoprevention agent shown to reduce the risk of breast cancer by up to 48%[7], has been recommended for use in women with more than 1.67% 5-year Gail risk[6]. However, while well calibrated at the general-population level, the Gail model has been shown to only have a modest discriminatory accuracy at the individual level[8], therefore being limited for individualized clinical decision making. As such, it is estimated that of the 10 million US women eligible for SERM chemoprevention only about 25% would actually benefit[9], exposing a considerable fraction of the population to substantial side effects.

Previous studies have identified several image-derived biomarkers associated with a woman's individual risk of developing breast cancer. Specifically, breast percent density (PD%), the relative amount of mammographically-opaque fibroglandular tissue, has been consistently shown to be a strong risk factor for breast cancer[10]. In addition, parenchymal texture descriptors which describe localized properties of the parenchymal tissue patterns as seen mammographically have also been shown to be associated with breast cancer, and may contain complementary information about cancer risk (Figure 1)[11]. However, while most studies have focused on the relationship between breast density and texture and a woman's overall risk for developing cancer, few have investigated the discriminatory capacity of these features in determining a woman's risk for developing specific sub-types of breast cancer. Therefore, in the context of identifying sub-type specific biomarkers, the purpose of this study is to investigate whether fully-automated measures of breast density and whole-breast parenchymal texture are associated with estrogen-receptor positive (ER+) breast cancer. Ultimately, sub-type specific risk assessment could help better guide chemopreventative interventions for breast cancer.

2. METHODS

2.1 Study population and image dataset

In this IRB-approved, HIPAA-compliant retrospective study, we identified a cohort of 106 women over 40 years of age with unilateral primary invasive breast cancer with known estrogen receptor (ER) status from a previously completed multimodality breast imaging trial at our institution (National Institutes of Health P01 CA85484; PI: M. Schnall). For each

woman, we obtained their raw (i.e., "For Processing") full-field digital mammograms (Senographe 2000D and DS; GE Healthcare, Chalfont St Giles, UK) for analysis. In this study, we analyzed the mediolateral-oblique (MLO) view mammogram of the contralateral (i.e., cancer-unaffected) breast as a surrogate of inherent tissue properties predisposing women to have a higher risk for developing ER sub-type specific breast cancer[12].

2.2 Breast density and parenchymal texture feature extraction

Absolute area density, non-dense area, and PD% were estimated using fully-automated, validated software previously developed by our group[13]. The algorithm first segments the breast region of a mammogram via an automated thresholding technique to remove the air-region followed by a straight-line Hough transform to delineate and remove the region of the mammogram containing pectoral muscle. The algorithm then clusters the pixels within the breast region into groups of similar intensity via an adaptive, multi-class fuzzy c-means clustering algorithm. Lastly, these sub-regions of the breast are classified as being either dense or non-dense (i.e., fatty), with the dense clusters being merged into a final dense-tissue segmentation. The absolute dense tissue area of the segmentation can be then be used to obtain PD%:

$$PD\% = \frac{|M_D|}{|M_B|} \cdot 100\%; \quad (1)$$

where $|M_D|$ and $|M_B|$ are the area of the breast segmentation and dense tissue segmentation. Example breast density segmentations for two women with approximately equal PD% estimates are provided in figures 1A and 1C.

Whole breast parenchymal texture analysis was performed using our validated lattice-based approach[14]. Briefly, using the breast mask generated by the density segmentation algorithm above, a lattice of sampling points is overlaid on the breast region. At each lattice-point, a 63-pixel-square window is analyzed to extract a series of 19 first-order histogram[15], run-length[16], gray-level co-occurrence[17], fractal[18] and structure[19] features (previously also shown to be robust to image-detector effects[20]). The average of value of each texture feature within the breast tissue region of a given mammogram was used as the aggregate score of that texture descriptor within the breast. The texture features, as well as their individual correlations to area breast density estimates, are provided in Table 1. Sample texture maps of the co-occurrence matrix entropy texture measure are shown for two women in figures 1B and 1D.

2.3 Statistical analysis

The association between the 19 texture measures and the 3 breast density estimates, namely absolute dense area, absolute non-dense (i.e., area adipose) and area percent density, was assessed using Pearson's correlation. To estimate the joint discriminatory capacity of the breast density and texture features to distinguish between women with ER+ and ER− breast cancer, logistic regression analysis with backward stepwise feature selection using standard entry ($p<0.05$) and exit ($p>0.10$) criterion was performed. A model considering of all the image-derived measures was compared to a baseline model consisting of only the three area

density measures and a second model consisting of only the texture measures. In this analysis, all area density measures were log-transformed and all texture measures were z-scored. Area under the curve (AUC) of the receiver operating characteristic (ROC) and Delong's test were used to compare model performance in distinguishing between women with ER+ versus ER− cancer.

3. RESULTS

The texture and breast density measures have different strengths of associations between them. Non-dense area and skewness have the strongest association with a Pearson correlation of r=−0.88 (p<0.001). In contrast, the kurtosis, energy and local binary pattern texture features are not significantly correlated with any of the three breast density measures. The complete list of correlations between the breast density and parenchymal texture measures are provided in Table 1. In terms of the performance of the imaging measures to distinguish between women with ER+ versus ER− cancer, the density-alone model had a discriminatory capacity of 0.62 AUC (p=0.05). The texture-alone model had a higher discriminatory capacity of 0.70 AUC (p=0.001), which was not statistically different compared to the density- alone model (p=0.37). In contrast the combined density-texture logistic regression model had a discriminatory capacity of 0.82 AUC (p<0.001), which was statistically significantly higher than both the density-alone (p<0.001) and texture-alone models (p<0.04). In the combined model, the absolute dense, non-dense, and PD% density measures were retained after feature-selection (p<0.05), as were also the energy, local skewness, local standard deviation, local binary pattern, edge radius, inverse difference moment, entropy, cluster-shade and inertia texture features (p<0.05) (i.e., a total of 12 out of the 22 density and texture features combined). The ROC curves of the three models are provided in figure 2.

4. DISCUSSION

Our study demonstrates a novel application of parenchymal texture analysis, showing that subtype-specific breast cancer risk assessment may be feasible using fully-automated measures of parenchymal texture combined with breast density. We found that certain measures of the parenchymal texture pattern, namely the kurtosis, energy and local binary pattern features, have no correlation with area breast density measures, thus indicating that they may be capturing different properties of the breast parenchymal tissue. Specifically in the context of sub-type specific breast cancer risk assessment, texture measures may be useful in capturing differences of underlying endogenous hormonal tissue exposure[21] and other biological factors which may be potentially related to a woman's risk of developing different sub-types of cancer as well as her risk to develop cancer in general. Furthermore, we also found that breast density and texture measures may independently contribute to measuring a woman's risk to develop sub-type specific breast cancers. Future larger studies will be focused on investigating the capacity of these imaging features to distinguish between sub-type specific risk in the general population using independent sample validation.

5. CONCLUSION

In this work, we demonstrate that the combination of breast density and parenchymal texture measures may have the potential to identify women specifically at risk for estrogen-receptor positive breast cancer. Ultimately, sub-type specific breast cancer risk assessment models may help to better guide chemoprevention for women at high-risk of breast cancer.

Acknowledgments

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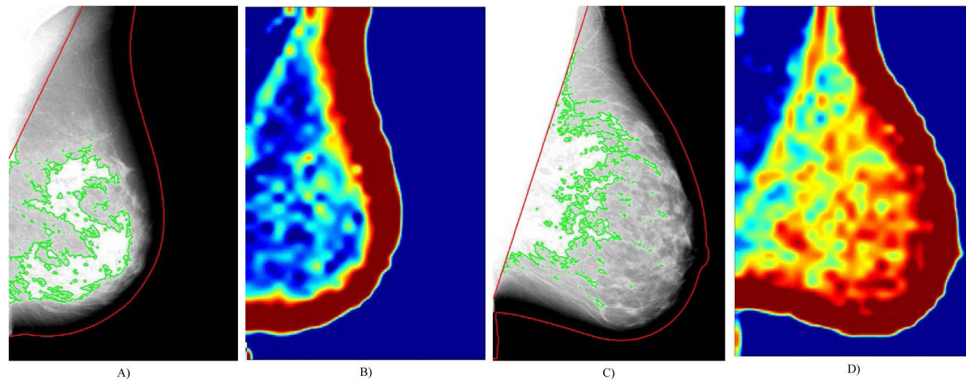
Fig. 1.
Breast density segmentations (A, C) and entropy texture maps (B, D) from raw (i.e., "For Processing"), contralateral mammograms of women diagnosed with ER+ (A–B) and ER− breast cancer (C–D). These women have approximately equal breast percent density scores (PD=23%) but different parenchymal patterns of the entropy texture measure (B and D).
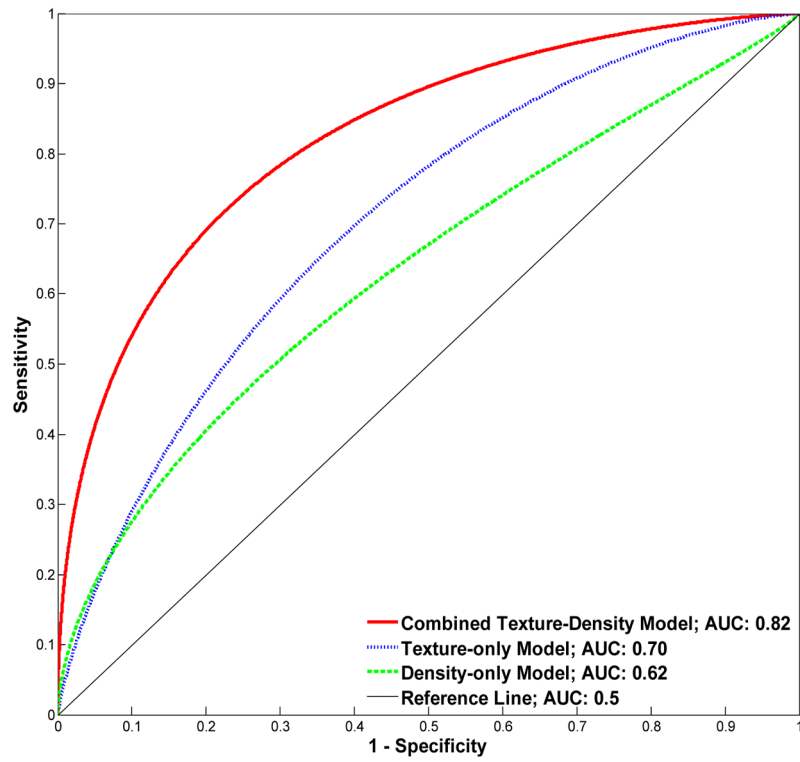
Fig. 2.
Receiver operating characteristic performance of the logistic regression models compared to classify ER cancer status.

Table 1

Pearson correlations between the parenchymal texture and breast density measures. Correlation values marked with an '*' indicate statistically significant associations at the α=0.05 level.

Texture Measure	Dense Area	Non-dense Area	Area Percent Density
5th Percentile	0.07	0.23*	−0.13
95th Percentile	−0.44*	−0.63*	0.21*
Cluster Shade	−0.20*	−0.31*	0.10
Correlation	0.24*	−0.04	0.14
Edge Radius	−0.16	−0.31*	0.16
Energy	−0.04	−0.09	0.00
Entropy	−0.28*	−0.41*	0.18
Fractal Dimension	0.17	0.59*	−0.38*
Grey Level Non-uniformity	0.00	0.20*	−0.22*
Haralick Correlation	−0.23*	−0.50*	0.23*
High Gray Level Run Emphasis	−0.36*	−0.54*	0.21*
Inertia	−0.48*	−0.67*	0.22*
Inverse Difference Moment	0.22*	0.24*	−0.09
Kurtosis	−0.16	−0.16	0.02
Local Binary Pattern	−0.08	0.14	−0.19
Maximum Value	−0.45*	−0.64*	0.21*
Minimum Value	0.17	0.35*	−0.15
Skewness	−0.26*	−0.88*	0.49*
Standard Deviation	−0.45*	−0.67*	0.24*