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Improving Performance of Computer-Aided Detection of Masses by Incorporating Bilateral Mammographic Density Asymmetry: An Assessment

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Abstract

Rationale and Objectives—Bilateral mammographic density asymmetry is a promising indicator in assessing risk of having or developing breast cancer. This study aims to assess the performance improvement of a computer-aided detection (CAD) scheme in detecting masses by incorporating bilateral mammographic density asymmetrical information.

Materials and Methods—A testing dataset containing 2400 full-field digital mammograms (FFDM) acquired from 600 examination cases was established. Among them, 300 are positive cases with verified cancer associated with malignant masses and 300 are negative cases. Two computerized schemes were applied to process images of each case. The first single-image based CAD scheme detected suspicious mass regions and the second scheme computed average and difference of mammographic tissue density depicted between the left and right breast. A fusion method based on rotation of the CAD scoring projection reference axis was then applied to combine CAD-generated mass detection scores and either the computed average or difference (asymmetry) of bilateral mammographic density scores. The CAD performance levels with and without incorporating mammographic density information were evaluated and compared using a free-response receiver operating characteristic (FROC) type data analysis method.

Results—CAD achieved a case-based mass detection sensitivity of 0.74 and a region-based sensitivity of 0.56 at a false-positive rate of 0.25 per image. By fusing the CAD and bilateral mammographic density asymmetry scores, the case-based and region-based sensitivity levels of the CAD scheme were increased to 0.84 and 0.69, respectively, at the same false-positive rate. Fusion with average mammographic density only slightly increased CAD sensitivity to 0.75 (case-based) and 0.57 (region-based).

Conclusions—This study indicated that (1) bilateral mammographic density asymmetry was a stronger indicator of the case depicting suspicious masses than the average density computed from two breasts and (2) fusion between the conventional CAD scores and bilateral mammographic density asymmetry information could substantially increase CAD performance in mass detection.

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Keywords

Breast cancer; computer-aided detection of mammograms; mammographic density

I. INTRODUCTION

Breast cancer is one of the leading cancers in women over the age of 40 years old worldwide [1] and scientific evidence has shown the breast cancer screening resulted in the early cancer detection and reduced patients' mortality and morbidity rates [2]. Although mammography is a most cost-effective and widely used imaging modality for breast cancer screening for the last several decades, interpreting mammograms to achieve high accuracy in terms of cancer detection and recall rates is a difficult and time-consuming task due to the large variability of breast abnormalities, overlapping dense fibro-glandular tissue, and low cancer prevalence in the screening environment [3, 4]. As a result, a large number of computer-aided detection (CAD) schemes of mammograms have been developed to detect micro-calcification clusters and masses in the last two decades and the commercialized CAD systems have also been routinely used to assist radiologists in interpreting mammograms in the clinical practice to date [5]. Although there is no universal agreement of whether using current CAD systems as "a second reader" actually helped improve radiologists' performance in the screening environment [6–8], improving CAD performance alone is important and has scientific merit [9]. Current CAD schemes are able to detect micro-calcification clusters with high sensitivity and low false-positive detection rates, which helps improve radiologists' efficiency in interpreting mammograms and detect more cancers that are associated with micro-calcifications [10]. However, current CAD schemes have relatively lower performance in mass detection [11], which may reduce the overall performance level of radiologists as measured by the areas under receiver operating characteristic (ROC) curves [7]. Previous studies have also found high correlation of mass detection results between radiologists and CAD schemes [11, 12], which could substantially reduce the clinical utility of using CAD as "the second reader." Hence, improving CAD sensitivity while maintaining or reducing the false positive rates remains a challenge in developing CAD schemes of mammographic masses.

Since mammographic tissue density is one of the strongest known breast cancer risk indicator to date [13, 14], several research groups have attempted to improve CAD performance in mass detection by taking mammographic density information into account in CAD decision making [15, 16]. Due to considerable inter- and intra-observer variability, subjectively rating mammographic density using Breast Imaging Reporting and Data System (BIRADS) is often unreliable [17]. Hence, a number of computerized schemes have been developed and tested to segment fibro-glandular tissue and compute mammographic density. The results were proved to highly correlate to radiologists' subjective assessment [18–20]. As a result, one recent study reported that incorporating automatically computed mammographic density information into CAD schemes enabled CAD to achieve higher performance than incorporating CAD with manually (subjectively) assessed mammographic density [21]. In our previous studies, we have pursued a new approach to extract and utilize mammographic density information. Based on the scientific evidence of that bilateral breast tissue pattern asymmetry is an important phenotype related to the abnormal biological processes that may increase the risk of developing breast cancer [22] and our observation that radiologists routinely examined regional breast tissue density asymmetry depicted on bilateral mammograms of the left and right breast when identifying and/or classifying suspicious lesions, we demonstrated in our previous studies that computerized bilateral mammographic tissue density asymmetry was also an useful indicator in assessing the risk of developing breast cancer [23, 24]. Hence, in this study we investigated the feasibility of

improving CAD performance in mass detection by incorporating bilateral mammographic density asymmetry information, in particular enabling CAD scheme detecting more subtle masses without increasing false-positive rates. The details of our experimental procedures and results are presented in the following sections.

II. MATERIALS AND METHODS

2.1. Testing Image Dataset

Under our internal review board (IRB) approved data collection protocol we established an image testing dataset used in this study. The dataset involves 600 full-field digital mammography (FFDM) examination cases and each case contains four FFDM images representing both craniocaudal (CC) and mediolateral oblique (MLO) view images acquired from the left and right breast of a woman. Thus, there are total 2400 FFDM images in this testing dataset. All examinations were acquired using Hologic Selenia (Hologic Inc., Bedford, MA, USA) FFDM systems between 2006 and 2008 in our medical center. In this dataset, 300 are positive cases with cancer detected and verified by biopsy and pathology examinations and 300 are randomly selected negative cases acquired in the screening examinations. All negative cases contain no detectable masses in the retrospective review by the radiologists. A total of 314 malignant masses were detected in 300 positive cases including one mass detected in each of 287 cases, two detected in each of 12 cases, and three detected in one case. Among these 314 masses, 297 are visually detectable on both CC and MLO view images and 15 are only detectable on one view image, which makes the dataset include total 609 regions associated with malignant masses. The locations of all mass regions were marked by the radiologists and recorded in a “truth file” that provides a reference standard to assess CAD performance.

The groups of positive and negative cases have similar distribution of subjectively rated mammographic density (BIRADS) as shown in Figure 1. The majority of cases namely 35.2% and 57.3% were rated by radiologists as scattered fibro-glandular densities (BIRADS II) and heterogeneously dense (BIRADS III), respectively. In the total 314 verified malignant masses, majority of them (57.0% and 25.5%) were classified as irregular and spiculated masses by the radiologists in the original image interpretation (Table 1).

2.2. CAD scheme of mass detection

A pre-developed CAD scheme to detect mass regions depicted on FFDM images [25] was applied (“as is”) to detect suspicious mass regions depicted on each of 2400 FFDM images in the testing dataset. In brief, this scheme includes three steps. The first step applies a difference-of-Gaussian filtering method to search for and identify suspicious regions. This step typically identifies between 10 and 50 suspicious regions per image depending on breast tissue density and pattern distribution, which determines the upper level of CAD sensitivity. The second step applies a multilayer topographic region growth and active contour algorithm to segment suspicious regions. In each initially detected suspicious region, the algorithm searches for a growth seed (pixel) with local minimum value. A growth threshold for each topographic growth layer is adaptively determined by the computed region’s local contrast. A set of classification rules related to the region size, shape, and inter-layer growth ratio is applied to delete false-positive regions. After passing through three growth layers, an active contour algorithm is applied to determine the final boundary contour of the growth region. This step typically eliminates over 80% of initially identified suspicious regions and reduces the number of growth regions to ≤ 5 per image. The third step computes a set of image features from each segmented region and applies an artificial neural network to classify this region by generating a detection score (in the range of 0 to 1) indicating the likelihood of the region associating with a positive mass. Applying a

pre-determined operating threshold (i.e., >0.55 [26]), CAD cues the detected mass regions (with detection scores greater than the CAD operating threshold) on the FFDM images. Figure 2 shows an example including a set of CC and MLO view FFDM images acquired from one woman with and without CAD cued regions associated with a malignant mass.

2.3. Computing mammographic tissue density and its bilateral asymmetry

In this study we used two CC view images of both left and right breasts to compute mammographic tissue density. First, we applied a pre-developed computer scheme to segment breast tissue area by iteratively searching for a transition curve with the smoothest curvature between breast tissue and air background [27]. After breast area segmentation, two methods were applied. First, we computed the average pixel value or intensity (I_k , $k = 1, 2, \dots, N$) of the segmented breast area, $\bar{I} = \frac{1}{N} \sum_{k=1}^N I_k$. Since a dark pixel in FFDM image (Figure 2) has a greater digital value than a “white” pixel, the dense breast has lower $\bar{I}$ value due to the dominated “white” tissue areas. We then computed (1) average pixel intensity of the left ($\bar{I}_L$) and right ($\bar{I}_R$) breasts, $(\bar{I}_T) = (\bar{I}_L + \bar{I}_R)/2$, to represent the computed mammographic density and (2) the absolute difference between $\bar{I}_L$ and $\bar{I}_R$, $\Delta\bar{I} = |\bar{I}_L - \bar{I}_R|$, to represent bilateral mammographic density asymmetry.

After applying the scheme to process and compute average and asymmetry of bilateral mammographic tissue density for all cases in our database, 600 output scores are generated, which are likely to span over a wide range (in terms of mean, standard deviation, and distribution shape), all scores need to be normalized into [0, 1] range in order to combine with CAD-generated mass detection scores. In this study, we applied a data normalization approach that uses a standard ROC-type data analysis method based on grouping the data before fitting the latent binormal ROC model [28]. Thus, exchangeability of the original data will be maintained under this transformation. Specifically, in this rank order data transformation, 600 score data was first sorted from minimum to maximum. These 600 scores were then equally divided into 10 bins with 60 scores distributed inside each bin. Inside each bin the scores were linearly expanded to cover the limited data range (e.g., between 0.5 and 0.6). In this way all mammographic density related scores were normalized between 0 and 1 with their rank order preserved.

2.4. Fusion of CAD scores and mammographic density information

Based on the underlying assumption that women with higher dense breast tissue and/or larger bilateral breast tissue density asymmetry have higher risk of having or developing breast abnormalities and cancer, we applied and tested a fusion method that weights more on CAD-detected mass regions depicting on the images involving either dense breasts (e.g., BIRADS 3 or 4) or larger bilateral mammographic density asymmetry. For example (as shown in Figure 3), assuming S represents CAD-generated likelihood score of a detected region being positive (the horizontal axis) and D represents the computed bilateral mammographic density asymmetrical score of the image where the detected region locates (the vertical axis), we gradually rotate the reference (or CAD scoring projection) axis from the horizontal direction with increased angles (or slopes). Specifically, the CAD operating (or cueing) threshold changes from S to S' based on following axis rotation function, $S' = S + (D - S \times \tan(\alpha)) \times \sin(\alpha)$, where α is the rotation angle of the reference axis and $k = \tan(\alpha)$ is the slope of the rotated reference axis. Thus, the new CAD cuing threshold is adaptively changed and it forces CAD cues more suspicious regions in the images with greater D values and fewer regions in the images with smaller D values. By gradually rotating the reference axis (e.g., from $k = 0.1$ to $k = 1.0$), we investigated the impact of this fusion method on the change of CAD performance.

To evaluate CAD performance levels in mass detection, we used a FROC type data analysis method that has been tested and verified in our previous studies [29, 30]. In addition to the comparison of entire FROC curves with and without incorporating mammographic density information in CAD cueing decision making, we focused on the analysis and comparison of CAD sensitivity level variations at a fixed false-positive rate of 0.25 per image, which is smaller or comparable to the false-positive rates of the commercial CAD systems used in the clinical practice to date [26]. Both case-based and region-based FROC performance curves and detection sensitivity levels at a rate of 0.25 false-positive per image were analyzed. In case-based analysis, a positive case is counted as detected as long as at least one mass region depicted on one of FFDM images is detected, while in region-based analysis all mass regions are counted independently. We analyzed the trend of CAD performance change as the increase of rotation slope of the CAD projection scoring axis and compared the different impact by incorporating the average and asymmetry of bilateral mammographic density into CAD cueing process.

III. RESULTS

Figure 4 shows two histograms representing the distribution of normalized average and asymmetry scores of bilateral mammographic density between 300 positive and 300 negative cases in our testing dataset. Similar to the subjective breast density BIRADS rating (Figure 1), the distribution difference of the computed average bilateral mammographic density levels between the positive and negative cases is also small. The computed areas under ROC curves are 0.522 ± 0.017 and 0.745 ± 0.013 when using the normalized average and asymmetry scores of bilateral mammographic density to classify between two groups of the 300 positive and 300 negative cases, respectively. The results indicated that the bilateral mammographic density asymmetry was a significantly stronger risk indicator than the average mammographic density ($p < 0.01$).

When applying our CAD scheme to detect suspicious mass regions depicted on all 2400 FFDM images in our dataset, CAD initially detected 517 of 609 mass regions that are distributed on 297 of 300 positive cases, which makes the maximum 99% case-based sensitivity and 85% region-based sensitivity. CAD also detected a total of 8396 false-positive regions distributed on 2400 images (making the maximum false-positive rate of 3.5 per image). After applying a multi-feature based ANN classifier to assign a likelihood score of being a true-positive mass region to each of initially detected region, CAD only cued the regions with detection scores greater than the operating threshold and discarded all other regions. By setting up the threshold = 0.64 to achieve a false-positive rate of 0.25 per image, CAD scheme detected (cued) 341 true-positive mass regions distributed on 222 positive cases making the case-based sensitivity of 0.74 and region-based sensitivity of 0.56.

When incorporating the normalized scores of bilateral mammographic density asymmetry into CAD-cueing decision making process, the results showed that as rotation slope of the CAD scoring projection (reference) axis (Figure 3) gradually increased from 0.1 to 1.0, the mass detection sensitivity produced by the transformed (fused) new CAD scoring system was monotonously increased (by detecting more true-positive masses and mass regions at the same false-positive rate) at initial stage and then decreased after reaching a peak point. For example as shown in Figure 5, at a fixed false-positive rate of 0.25 per image, the case-based CAD sensitivity levels were increased from the original 0.74 (222/300) to the maximum of 0.84 (253/300) at rotation slope = 0.6 and then decreased to 0.73 (219/300) at the slope = 1.0. Figures 6 and 7 show and compare two sets of FROC curves generated by the original CAD scheme and the new CAD cueing method after fusion of CAD scores with the bilateral mammographic density asymmetrical scores at rotation slope = 0.6. The results demonstrated that incorporating bilateral mammographic density asymmetry information

into CAD-cueing process substantially improved overall CAD performance particularly in the lower false-positive range (<1.0 per image).

Similar to Figure 5, Figure 8 demonstrates an example of incorporating the normalized average mammographic density scores into CAD-cueing process. As the rotation slope of CAD scoring projection axis gradually increased from 0.1 to 1.0, the case-based CAD sensitivity at the false-positive rate of 0.25 per image was only slightly increased at slope = 0.1 from 0.74 (222/300) to 0.75 (225/300) representing the detection of three more malignant masses and then CAD sensitivity levels monotonously decreased as the rotation slope increased from 0.2 to 1.0.

IV. DISCUSSION

In this study we investigated whether incorporating two breast cancer risk factors (namely the average and asymmetry of bilateral mammographic density) into CAD-cueing decision making process could improve overall CAD performance in mass detection. Although except women's age mammographic density has been recognized as the strongest risk factor of developing breast cancer in many epidemiology-based risk models [14], it has quite low positive predictive value to predict the breast cancer risk at the individual level [31]. This study also showed that incorporating mammographic density information into CAD-cueing decision making process had little positive impact on CAD performance (Figure 8). This is likely due to the two facts: (1) Mammographic density distributions between positive and negative case groups in our testing dataset are quite similar. (2) Although higher breast density typically indicates higher probability of having or developing breast cancer, current CAD schemes actually also detect more false-positive regions in the images of dense breasts than the images depicting lower breast tissue density [11]. Hence, when we put more detection (sensitivity) weights on the dense breasts by reducing CAD cueing threshold on the corresponding images, the benefit of increasing CAD sensitivity on dense breasts is overturned by the higher false-positive detection rates generated from the same images with dense breasts.

However, the bilateral mammographic density asymmetry does not depend on the mammographic density level. When using this new risk factor, a lower dense case with larger bilateral breast tissue density asymmetry is considered or classified as a higher risk case of having or developing breast cancer than the cases with highly symmetrical dense breasts. Due to the fact that the bilateral breast density asymmetry has a significant higher positive predictive value than the average mammographic density in predicting the likelihood of the cases depicting abnormalities and/or masses, the results of this study indicated that incorporating bilateral mammographic asymmetry information into CAD-cueing decision making process was able to substantially improve CAD performance (Figures 6 and 7). At a false-positive rate of 0.25 per image the case-based sensitivity could increase by as much as 10% from 0.74 to 0.84. The increase of the sensitivity is probably due to the fact that as increasing rotation slope of CAD-cueing scoring projection axis, CAD gradually reduces its operating (cueing) threshold on the cases with greater bilateral mammographic density asymmetry and increases the threshold on the cases with smaller bilateral density asymmetry. Thus, CAD cues more suspicious mass regions in the cases with greater bilateral mammographic density asymmetry (increasing both sensitivity and false-positive rate) and less number of regions in the cases with smaller density asymmetry level (reducing both sensitivity and false-positive rate). Due to the different density asymmetry distribution between the positive and negative cases (as shown in Figure 4(b)), CAD is able to detect more true-positive masses with lower detection scores on the positive cases while maintaining the same false-positive rates (by discarding more false-positives on the cases with lower level of density asymmetry).

We recognized that using mammographic tissue pattern asymmetry or difference depicted in the matched regions between two bilateral mammograms to develop CAD schemes of mass detection has been extensively investigated during the early stage of CAD development (e.g., before 1990s) [32]. Previous efforts aimed to search for and detect suspicious mass regions and it has been proved to be very difficult and unreliable due to the difficulty in bilateral image registration [33]. However, our approach presented in this study is different. It avoids bilateral image registration and the computed bilateral mammographic density asymmetry information is not used as an additional image feature combining with other available features to classify suspicious mass regions in CAD schemes. In our approach, the bilateral mammographic density asymmetry is independently computed from the CAD scheme and the result is then fused with CAD-generated scores of all detected suspicious regions in a specific case in question. This approach is not unique to our CAD scheme. It can also be easily integrated into any of other existing CAD schemes requiring neither change of schemes' internal structures nor the complicated re-optimization process.

Although, to the best of our knowledge, this is the first study that investigated and demonstrated the feasibility of improving CAD performance by incorporating bilateral mammographic density asymmetry information into CAD-cueing process, this study has a number of limitations. First, we applied and tested a unique fusion method to combine the original CAD-generated detection scores and the normalized bilateral mammographic density asymmetry scores. As a result, CAD enabled to detect more "difficult" malignant masses with lower CAD-generated detection scores (as shown in Figure 5) in the cases with greater bilateral mammographic density asymmetry, but CAD also discarded a fraction of "easy" masses with higher CAD-generated detection scores in the cases with more symmetrical breasts. Since CAD is used as "a second reader" in the clinical practice, whether and how such a new transformed CAD-cueing (scoring) method affects radiologists' performance (in particular to help radiologists detect more cancers associated with subtle masses) has not been investigated. Second, our testing dataset includes equal number of 300 positive and 300 negative cases, which does not represent the actual cancer prevalence rates in the real screening environments. The difference distribution of bilateral mammographic density asymmetry between positive and negative cases needs to be verified using large and more diverse databases acquired from the prospective studies. Third, we used a simple pixel intensity based method to compute mammographic density in this study. Previous studies have indicated that more sophisticated statistical features or textures might yield more accurate results in assessing mammographic tissue density patterns [18–20]. Thus, the results reported in this study are very preliminary and may not be optimal. Despite these limitations, we demonstrated that the bilateral mammographic density asymmetry was a promising risk indicator that may also be used to help significantly improve CAD performance in mass detection. To fully identify and understand its advantages and limitations in CAD development, more studies are needed in this field.

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Figure 1.
Distribution of breast density BIRADS ratings in the testing dataset.

Figure 2.
An example of applying our CAD scheme to both CC and MLO view images of a testing case in which a true-positive mass is cued on both CC and MLO view images.

Figure 3.

Illustration of fusion between CAD scores and bilateral mammographic density asymmetry scores by rotating the CAD scoring projection (reference) axis. In the figure 300 true-positive mass regions (o) and 300 CAD-detected false-positive regions (Δ) are presented, which represent one region with the maximum CAD-generated detection score per case. For the cases without a detected suspicious region, a sign (Δ or o) is added in the position of CAD score = 0. The dash line represents the original CAD scoring axis and the solid line represents the rotated new CAD scoring projection axis.

Figure 4. Comparison of two histograms of normalized average (a) and asymmetry (b) of bilateral mammographic density scores between 300 positive and 300 negative cases.

Figure 5.

The trend of CAD cueing sensitivity and minimum CAD cueing score (threshold) as the increase of CAD scoring projection (reference) axis rotation slopes when fusion of CAD scores and the bilateral mammographic density asymmetry scores. The false-positive rate is 0.25 per image.

Figure 6. Comparison of two case-based FROC curves representing the original CAD performance ($S = 0.0$) and CAD performance after incorporating the bilateral mammographic density asymmetry information with a rotation slope of $S = 0.6$.

Figure 7.
Comparison of two region-based FROC curves representing the original CAD performance ($S = 0.0$) and CAD performance after incorporating the bilateral mammographic density asymmetry information with a rotation slope of $S = 0.6$.

Figure 8.

The trend of CAD cueing sensitivity and minimum CAD cueing score (threshold) as the increase of CAD scoring projection (reference) axis rotation slopes when fusion of CAD scores and the average mammographic density scores. The false-positive rate is 0.25 per image

Table 1

Distribution of 314 verified malignant masses in the testing dataset.

Mass Type	Not-specified	Smoothed	Irregular	Spiculated	Focal asymmetry
Mass Number	26	7	179	80	22
Percentage	8.3%	2.2%	57.0%	25.5%	7.0%