Automated assessment of bilateral breast volume asymmetry as a breast cancer biomarker during mammographic screening

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ABSTRACT

The biological concept of bilateral symmetry as a marker of developmental stability and good health is well established. Although most individuals deviate slightly from perfect symmetry, humans are essentially considered bilaterally symmetrical. Consequently, increased fluctuating asymmetry of paired structures could be an indicator of disease. There are several published studies linking bilateral breast size asymmetry with increased breast cancer risk. These studies were based on radiologists' manual measurements of breast size from mammographic images. We aim to develop a computerized technique to assess fluctuating breast volume asymmetry in screening mammograms and investigate whether it correlates with the presence of breast cancer. Using a large database of screening mammograms with known ground truth we applied automated breast region segmentation and automated breast size measurements in CC and MLO views using three well established methods. All three methods confirmed that indeed patients with breast cancer have statistically significantly higher fluctuating asymmetry of their breast volumes. However, statistically significant difference between patients with cancer and benign lesions was observed only for the MLO views. The study suggests that automated assessment of global bilateral asymmetry could serve as a breast cancer risk biomarker for women undergoing mammographic screening. Such biomarker could be used to alert radiologists or computer-assisted detection (CAD) systems to exercise increased vigilance if higher than normal cancer risk is suspected.

Keywords: mammography, breast cancer, diagnosis, fluctuating asymmetry, imaging biomarker

1. INTRODUCTION

Bilateral symmetry of paired structures (i.e., hands, ears, or breasts) is well established as an important marker of developmental stability and good health in humans [1]. Although small deviations from perfect symmetry is normal, several studies have linked high fluctuating asymmetry to a variety of genetic and mental disorders. Many of these studies are reviewed in Ref [1]. Fluctuating asymmetry (FA) is the scientific term that describes the random deviations from perfect bilateral symmetry. Sexually selected traits are more susceptible to high FA [2-4]. Thus, any developmental or health disturbance could be potentially revealed in higher asymmetries of sexually selected traits.

Visually apparent bilateral differences in breast shape and size are relatively common in women although we have not found any reported statistics on their prevalence. Typically, these differences manifestate during puberty when estrogen hormone stimulates breast growth. In some women, the breasts simply grow differentially with respect to starting and stopping. In these young women, breast size asymmetry is considered a sign of developmental instability.

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Breast size asymmetry as an indicator for breast cancer susceptibility has been explored before. In 1997, bilateral breast asymmetry was linked to the presence of breast cancer [5]. The study showed significantly higher fluctuating asymmetry of the breasts in breast cancer patients than in an age-matched control group. Since the study found no correlation between tumor size and amount of breast size asymmetry, the authors argued that their finding could be more than merely the effect of cancer. It could be a predictor of future breast cancer risk. A 2006 study by the same authors showed that indeed breast size asymmetry is linked to predisposition to breast cancer [6]. The study was based on 504 age-matched asymptomatic women who had normal mammograms. One half of those women later developed breast cancer. The study showed larger breast volume bilateral asymmetry in those women than the control group (i.e., women with normal mammograms during the study period). For the post-menopausal subgroup, breast volume asymmetry assessed in the craniocaudal (CC) view was found to be a significant predictor of breast cancer. Both studies were based on breast size measurements made manually on film mammograms by expert radiologists using a ruler.

A study, published in 2000, linked ipsilateral decrease in breast size to infiltrating lobular carcinoma (ILC) [7]. A similar finding was reported for clinically advanced ILC cases in 1991 [8]. The study showed that a similar trend existed for ILC cases that were not advanced cancers. Although the breast size decrease was mammographically measurable, it was not physically apparent. These studies provide further evidence that the presence of breast cancer (or at least some types of breast cancer) causes changes in breast size that are measurable in mammography. Ipsilateral breast size changes would translate to higher bilateral breast asymmetry.

The above studies were based on radiologists' ruler-based measurements of breast size from mammograms. The purpose of our study was to apply an automated way of measuring fluctuating breast volume asymmetry from mammograms and investigate whether the automated measurements correlate with the presence of breast cancer using a large dataset of screening mammograms with known ground truth. The issue of bilateral breast differences has been investigated only in the context of regional matching for localized detection of breast abnormalities [e.g., 9-14]. Typically, a mammographic region of interest is identified and then compared to its matched location in the bilateral breast to determine if it is different enough to qualify as a detected abnormality. Reference 15 provides a recent survey of studies of algorithms for alignment of the left and right breasts as well as methods for comparing the morphology, texture, and directionality of the left and right breast parenchyma. Unlike those studies, we aim to explore automated assessment of global bilateral breast asymmetry in size and volume as a diagnostic indicator of breast cancer.

2. MATERIALS AND METHODS

2.1 Breast Size Measurements

Breast region segmentation is a critical step for automated assessment of breast size. Numerous algorithms have been proposed for the task, utilizing thresholding, gradients, polynomial modeling, active contours, and many others [16]. For this study we implemented the algorithm proposed by Mirzaalian et al [17] for segmenting the breast region in both the craniocaudal (CC) and medio-lateral oblique (MLO) views of a screening mammogram. The algorithm includes low-level preprocessing such as histogram equalization, convolution with a low-pass mask, thresholding, connected-component analysis, as well as a non-linear diffusion algorithm for segmenting the pectoral muscle in the MLO views. The software was developed in openCV.

The height and width of each segmented breast were determined automatically in each view. Figure 1 illustrates these breast size measurements in each view. Then, the volume of each breast was calculated according to well-established, published methods, which have been shown to be highly reliable. Namely, the Katariya method was used in CC views [18], the Hoe method for MLO views [19], and the Fung method was applied to assess breast volume size by fusing breast size measurements from both the CC and MLO views [20].

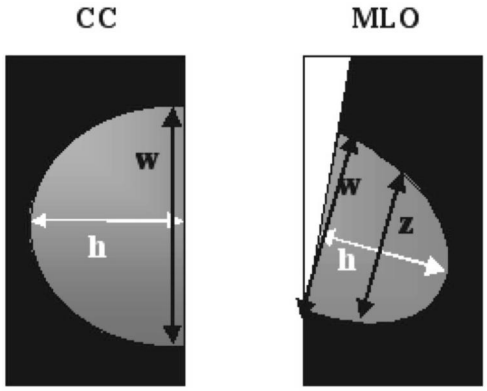

Figure 1: Illustration of breast size measurements in CC and MLO views

Katariya Method [18]: This method focuses on the craniocaudal (CC) view and essentially aims to automate the manual measurement process followed in [5]. Specifically, breast height (h) is measured as the maximum perpendicular distance from the distal edge of the breast outline to the proximal edge of the film. Breast width (w) is measured as the maximum breast width across the proximal edge of the film. Finally, the breast volume is calculated assuming a circular cone shape for the breast:

$$\text{CC:} \quad Volume = \pi \times w_{CC}^{\,2} \times h_{CC} \Big/ 12 \tag{1}$$

Hoe Method [19]: This method focuses on the mediolateral oblique (MLO) view and essentially automates the manual measurement process followed in [20]. Specifically, breast height (h) is measured as the maximum perpendicular distance from the distal edge of the breast outline to the pectoral muscle. Breast width is measured as the superolateral-to-inferomedial perpendicular distance at full (w) and half height (z).

$$\text{MLO:} \quad Volume = h_{MLO} \times z_{MLO} \tag{2}$$

Fung Method [21]: Recently Fung et al proposed a modified version of the Katariya algorithm, treating the breast as an elliptical (instead of circular) cone on both CC and MLO views (instead of CC only). Using the height measurement from the MLO view aimed to eliminate a potential error introduced in the CC view which may miss the base of the breast and underestimate the breast volume.

$$\text{CC+MLO:} \quad Volume = \pi \times w_{CC}^{\,2} \times h_{MLO} \Big/ 12 \tag{3}$$

The above methods do not take into account the breast compression factor during the image acquisition process. Although volume calculations that include the compression factor are slightly more accurate, studies have shown that the formulas given above correlate highly with true breast measurements made on mastectomy specimens [22].

2.2 Fluctuating Asymmetry

The above size parameters are calculated separately for each breast and from each mammographic view. Since the study focuses on bilateral breast differences, we calculate the absolute volume difference between the left (L) and right (R) breasts. The absolute difference can be utilized as a measurement of fluctuating asymmetry (FA). It has been recommended to normalize the absolute volume differences and express FA as a percentage of the average breast size [6]. This is known as relative fluctuating asymmetry:

Relative Fluctuating Asymmetry: $$_{relative}FA = \frac{\left|VOLUME_L - VOLUME_R\right|}{2 \times \left(VOLUME_L + VOLUME_R\right)} \quad (4)$$

2.3 Image Database

800 screening mammograms from the Digital Database of Screening Mammography (DDSM) were used for this study: 394 cancer cases, 324 benign cases, and 82 normal cases [23]. The normal cases were deemed normal based on 2-yr cancer-free follow-up. The benign and cancer cases were biopsy-proven and they contained all possible types of lesions (calcifications, masses, architectural distortions, asymmetries, etc.). Of those, 25 cancer, 74 benign, and 13 normal cases were excluded from further analysis because, upon visual inspection, the breast segmentation step was deemed unsuccessful in at least one view. A total of 688 mammograms were used to measure the FA. The average relative FA was compared among the 3 groups of cases (cancer, benign, normal) and across the 3 FA estimation methods (CC only, MLO only, CC+MLO).

3. RESULTS

Table 1 reports the average breast volume fluctuating asymmetry for each pathology and estimation method.

Table 1. Average breast volume fluctuating asymmetry for each group of cases (cancer, benign, normal) and for each estimation method implemented in this study.

METHOD	CANCER	BENIGN	NORMAL
CC	0.045±0.030	0.045±0.036	0.034±0.020
MLO	0.047±0.030	0.041±0.025	0.028±0.019
CC+MLO	0.054±0.036	0.055±0.037	0.034±0.023

Overall, the results support that the average breast volume fluctuating asymmetry is significantly larger in patients with breast lesions than those without. However, fluctuating breast volume asymmetry was statistically significant between cancer and benign cases only based on MLO estimates. Table 2 summarizes the two-tailed p-values of the FA comparisons among the various groups of patients. In addition, fluctuating breast volume asymmetry measurements had substantially lower variability in normal patients than cancer and benign patients (see Table 1). In other words, even though some breast volume asymmetry is expected in women, the presence of a benign or cancerous growth appears to contribute further.

4. DISCUSSION

Evolutionary studies have established asymmetry of paired structures as a strong indicator of developmental stability and good health. It is known that if an individual has harmful mutations, then the homeostatic mechanisms that maintain symmetry tend to break down. Our study was inspired by this basic principle of evolutionary and developmental biology. Since sexually selected traits (such as breasts) are more revealing of genetic or environmental stresses, we hypothesized that the presence of breast cancer may be manifested in higher breast asymmetry measured in a screening mammogram. Specifically, we hypothesized that mammographic analysis of bilateral breast asymmetry will provide us with a set of quantitative imaging biomarkers that correlate highly with the presence of breast cancer. The hypothesis does not contradict breast cancer etiology theories (genetic disease vs. the result of environmental causes).

Preliminary analysis on a large set of screening mammograms supports that computer-based assessment of bilateral breast volume asymmetry could be exploited as an additional breast cancer risk biomarker during mammographic screening. Such biomarker can be used to alert accordingly the radiologist before mammographic interpretation. Further investigation with larger datasets is necessary to determine whether certain patient subgroups (e.g., unilateral/bilateral findings, masses vs. calcifications, etc.) present a stronger trend of bilateral breast size asymmetry as a diagnostic indicator of breast cancer.

There were some important limitations with this pilot study. First, the quantitative biomarker depended on a single breast region segmentation algorithm. The study must be repeated with other breast segmentation techniques to determine the robustness of the discovered trends. Furthermore, the proposed measurements of fluctuating asymmetry could benefit from more sophisticated algorithms which could take into account the breast compression factor. Last but not least, the study could be repeated with other imaging modalities such as MRI for further validation of the underlying principle.

Table 2. Two-tailed p-values of the differences in mean fluctuating breast volume asymmetry between groups of cases. * indicates statistical significance.

METHOD	GROUP 1	GROUP 2	2-tailed p-value
CC	cancer	benign	0.921
	cancer	normal	0.004*
	benign	normal	0.014*
MLO	cancer	benign	0.021*
	cancer	normal	<0.0001*
	benign	normal	<0.0001*
CC+MLO	cancer	benign	0.722
	cancer	normal	<0.0001*
	benign	normal	<0.0001*

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