Translational Oncology
www.transonc.com

Volume 8 Number 6 December 2015 pp. 435–445 435

Imaging Breast Density: Established and Emerging Modalities[1]

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Abstract

Mammographic density has been proven as an independent risk factor for breast cancer. Women with dense breast tissue visible on a mammogram have a much higher cancer risk than women with little density. A great research effort has been devoted to incorporate breast density into risk prediction models to better estimate each individual's cancer risk. In recent years, the passage of breast density notification legislation in many states in USA requires that every mammography report should provide information regarding the patient's breast density. Accurate definition and measurement of breast density are thus important, which may allow all the potential clinical applications of breast density to be implemented. Because the two-dimensional mammography-based measurement is subject to tissue overlapping and thus not able to provide volumetric information, there is an urgent need to develop reliable quantitative measurements of breast density. Various new imaging technologies are being developed. Among these new modalities, volumetric mammographic density methods and three-dimensional magnetic resonance imaging are the most well studied. Besides, emerging modalities, including different x-ray–based, optical imaging, and ultrasound-based methods, have also been investigated. All these modalities may either overcome some fundamental problems related to mammographic density or provide additional density and/or compositional information. The present review article aimed to summarize the current established and emerging imaging techniques for the measurement of breast density and the evidence of the clinical use of these density methods from the literature.

Translational Oncology (2015) 8, 435–445

Introduction

The breast tissue mainly consists of two components: fibroglandular tissue and fat. Fibroglandular tissue is a mixture of fibrous stroma and the epithelial cells that line the ducts of the breast, and it is denser compared with fat. X-ray is less likely to penetrate fibroglandular tissue and appears bright on mammography. In general, fibroglandular tissue is commonly referred to as breast density or "mammographic density" (MD). MD has been proven as an independent risk factor for breast cancer [1–6]. Women with dense tissue visible on a mammogram have a cancer risk 1.8 to 6.0 times that of women with little density [7]. Increasing evidence has also found that the morphological distribution pattern of the projected dense tissue (texture) on mammograms may affect breast cancer risk [8–10].

Starting from 2009, 20 states have passed breast density notification legislation. At a national level, the Breast Density and Mammography Reporting Act (H.R. 1302) was introduced in the U.S. Congress in October 2011, which requires that every mammography report provide information regarding the patient's breast density [11]. Currently, the Breast Imaging and Reporting Data (BI-RADS) score of I to IV based on radiologists' subjective assessment is being reported, which is a coarse qualitative measure. As the H.R. 1302 Breast Density Act is being proactively debated, quantitative imaging methods are also being developed to provide a robust, reproducible, and accurate clinical

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[1] This study was supported in part by National Institutes of Health/National Cancer Institute R01 CA127927, National Institutes of Health/National Cancer Institute R21 CA170955, and California Breast Cancer Research Program #16GB-0056.
Received 31 August 2015; Revised 30 September 2015; Accepted 6 October 2015

1936-5233/15
http://dx.doi.org/10.1016/j.tranon.2015.10.002

measurement of breast density [12]. Many research studies are investigating how the breast density can be used in disease management, e.g., incorporating density into risk prediction model for risk-based screening and using the change of density after hormonal therapy to predict which patients will benefit from the treatment. A reliable quantitative measurement of breast density is required before these potential clinical applications can be implemented.

In this article, we review the currently established and emerging imaging methods used for the measurement of breast density. Some of these imaging techniques, although not well known to clinicians and breast cancer researchers, may have a great potential for the quantification of breast density and/or breast composition.

Established Imaging Modalities for Evaluating Breast Density

Mammographic density (MD). Dense tissues attenuate x-ray more than fat and thus show higher signal intensity than fat on mammography. Because mammography is a widely used screening modality, the clinical role of breast density was mainly established based on the measurement of MD. MD can be assessed qualitatively or measured quantitatively. Qualitative methods include the Wolfe criteria [13] and the BI-RADS criteria [14]. The Wolfe criteria comprise N1 (lowest risk), P1 (low risk), P2 (high risk), and DY (highest risk) [13]. The new breast composition categories according to the fifth edition of the American College of Radiology BI-RADS [15] are as follows: (I) the breasts are almost entirely fatty; (II) there are scattered areas of fibroglandular density; (III) the breasts are heterogeneously dense, which may obscure small masses; and (IV) the breasts are extremely dense, which lowers the sensitivity of mammography. Other more sophisticated method assigns different scores, such as the six categories developed by Boyd et al.: 0%, 0% to 10%, 10% to 25%; 25% to 50%, 50% to 75%, and ≥75% [16]. The assessment is observer dependent, and the high inter- or intrareader variation was a major concern in these approaches [17].

Quantitative method uses computer-aided segmentation of fibroglandular area from digitized mammograms [18–22] (Figure 1). Interactive thresholding is a commonly used tool. The threshold is first set to segment the breast from the surrounding background and subsequently to select the region of dense tissue. The ratio of the dense tissue area divided by the breast area is calculated as a percentage for MD. This is a relatively rapid procedure. Many studies have used this method to measure MD from digitized mammograms [23,24]. However, this technique is subjective and requires the operator to interactively select threshold values for the whole breast and the fibroglandular tissue area [25], which may lead to large intraoperator and interoperator measurement variation. To overcome this problem, an alternative approach is to use cluster-based segmentation such as fuzzy c-means (FCM) or k-means algorithms [26]. Several cluster centroids are established using heuristics, and pixels are segregated according to their proximity to the cluster's centroid values. Because this method is based on computer algorithms, when the number of clusters is fixed, the reproducibility is very high. Therefore, the FCM approach for quantitative breast density segmentation may be useful for detecting small density changes after interventions, such as chemo/hormonal therapy, diet/supplement, or other lifestyle changes [26].

Because mammography takes two-dimensional (2D) projection image, it suffers from tissue-overlapping problem and cannot accurately and sensitively differentiate between fatty and fibroglandular tissues. The position of the woman and the degree of compression may lead to different projection views and thus measured densities [27]. This is a serious concern when trying to measure changes over time. A recent study has shown considerable variability in breast density assessments in repeated imaging with digital mammography. The variation was particularly obvious in women with younger age and greater breast density and when examined using different types of mammography [28]. Calibration of mammography unit is extremely important for control of the x-ray exposure for quantitative analysis. A small calibration variation may render evaluation of small changes unreliable [29]. Recently, a lateral phantom for calibration of mammographic density was developed, but its use is still under research investigation [30].

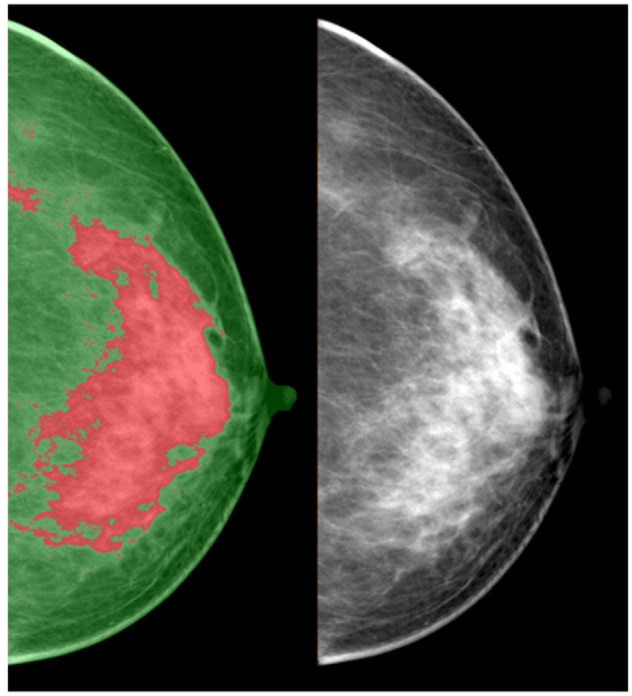

Figure 1. Quantitative measurement of 2D mammographic density. Note that the green color defines the breast boundary and the red color outlines the fibroglandular tissue area.

Limitations of 2D area-based measures of breast density have led to the development of volumetric measures of breast density. The Standard Mammogram Form (SMF) analysis program was introduced [31,32]. SMF provides a representation of the amount of nonfat tissue at each location in a mammogram, estimated by an evolving series of computer programs. If the separation between the mammography compression plates is known, then the SMF representation can potentially provide a volume-based estimate of the amount of dense tissue in a breast [33]. However, this method showed a poor left-right symmetry between two breasts of the same woman, thus raising some concern about its validity [34]. Apart from SMF, several volumetric assessment methods using full-field digital mammography with calibration data have been developed and validated [35,36]. Whether this analysis method can provide true volumetric breast density for cancer risk estimation needs to be investigated.

Recently, two automated breast assessment tools have been approved by the FDA and are increasingly being used. One is Quantra (http://www.hologic.com/wh/news-101107.htm), and the