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Quantitative Imaging of Breast Density

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The breast consists mainly of two tissue components: fibroglandular tissue and fat. Fibroglandular tissue is a mixture of fibrous stroma and epithelial cells that line the ducts of the breast. In mammography, fibroglandular tissue appearing bright is referred to as 'mammographic density (MD)'. Evidence from many studies has established the role of MD as an independent risk factor of breast cancer [1-9]. Change (increase or decrease) in MD overtime is also linked to change in cancer risk [10,11]. Additionally, breast morphology is also associated with breast cancer risk [12,13].

MD can be measured qualitatively or quantitatively. Qualitative methods include Wolfe criteria [14] and the Breast Imaging and Reporting Data System (BI-RADS) criteria [15]. More sophisticated methods assign different scores, such as the six categories developed by Boyd et al. [16]. Quantitative MD uses computer-aided calculation of percent dense tissue area on mammograms, and most of studies were done using a Cumulus thresholding segmentation method [17-19]. Overall, two-dimensional (2D) MD suffers from the problem of tissue overlap. The woman's position and degree of compression may also lead to different projection views, and thus different measured densities. Limitations of 2D area-based measures have led research groups to develop volumetric measures of breast density [20-25]. However, researchers have found that volume density did not provide a better cancer risk predictor compared with the 2D MD measured by thresholding method [22]. In recent years, two automated volumetric density quantification tools (Quantra™ (http://www.hologic.com/en/breast-screening/volumetric-assessment/) and Volpara™ (http://www.volparadensity.com/)) have been developed and approved by the FDA. Whether those new analysis methods can provide stronger breast cancer risk estimates is being investigated.

In the breast densitometry community, there is a strong urgency to develop reliable quantitative density measurement methods that can predict individual patients' risks. Magnetic Resonance Imaging (MRI)-based analysis has received great attention [24,26-33], but its clinical role has not been proven yet. MRI provides a detailed three-dimensional (3D) distribution of fibroglandular tissue that is not subject to the tissue overlap problem in mammography. It also allows for slice-by-slice segmentation of fibroglandular and fatty tissues. After adequate segmentation procedures, the entire fibroglandular tissue can be included without contamination with fatty tissue. Efforts in past years have led to the development of a novel computer-aided segmentation method for quantitative analysis of whole breast volume and breast density with 3-D MRI [34,35] and refined methods for evaluating the density morphological distribution pattern [36]. Several studies have compared the density measured by MRI and mammography. A study by Khazen et al. showed high correlation between MD and the density calculated from MRI (r=0.78); mammography, on the other hand, overestimated density by almost a factor of two [27]. Such results were expected given the nature of tissue projection on mammograms. It is therefore believed that the claims of risk and density changes based on 2-D images should be reevaluated [37]. 3-D MRI has been applied to study age- and race-related breast density differences [38] as well as breast density changes in patients receiving chemotherapy [39] and tamoxifen [40]. Although mammograms are less expensive than breast MRI, a recent article by Eng-Wong et al. [26] examining high-risk premenopausal women receiving raloxifene found that MD did not show changes while MR breast density showed significant reduction. Based on their findings, they suggested that MR breast density is more sensitive for detecting small changes, may provide a promising surrogate biomarker, and should be investigated further in breast cancer prevention trials.

In addition to MRI, emerging new technologies including optical imaging [41-46], ultrasound [47-49], digital breast tomosynthesis [50], dual energy imaging [51-53], and dedicated breast Computed Tomography (CT) [54-56] are being developed for assessing fibroglandular tissue volume, percent breast density, and breast tissue compositions. Using optical imaging, researchers noted that dense breasts tend to contain a greater proportion of water, lipid, and total hemoglobin concentration, and therefore have greater scattering than fatty breasts [41-44]. A strong correlation was noted between MD and an optical index based on tissue composition and scattering parameters derived from optical measurements [45]. A study comparing the measurements of breast density using 3D automated whole breast ultrasound and MRI showed high correlation between breast density and breast volume quantification [48]. Digital Breast Tomosynthesis (DBT) is increasingly being used in clinical practice. A high correlation between percent density estimated by digital mammograms and central DBT projections was noted [50]. Another study, however, found that digital mammography overestimated breast density by 15.1% in comparison to DBT [57]. Another technology, dual energy imaging, exploits differences between the effective atomic numbers of different tissues to provide separate quantitative thickness measurements for each tissue [51]. It can therefore be used to quantify glandular and adipose tissue thicknesses for breast density measurement [51]. Dual energy mammography can also potentially be used to perform compositional breast imaging, which can separate water, lipid, and protein thickness in the breast tissue [53]. Lastly, the development of dedicated breast CT systems has made the measurement of fibroglandular tissue and percent breast density using this new modality possible. The measured volume glandular fraction by CT increased as a function of the reported BIRADS categories of MD [54]. Overall, despite that these new methods may overcome some fundamental problems related to 2D MD, their clinical usefulness is to be further investigated. Factors including cost, radiation exposure, patient compliance, and ability to predict cancer risk will determine the likelihood of these new modalities to be used for clinical management in the future.

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