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● *Original Contribution*

USING SPEED OF SOUND IMAGING TO CHARACTERIZE BREAST DENSITY

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Abstract—A population of 165 women with negative mammographic screens also received an ultrasound tomography (UST) examination at the Karmanos Cancer Institute in Detroit, MI. Standard statistical techniques were employed to measure the associations between the various mammographic- and UST-related density measures and various participant characteristics such as age, weight and height. The mammographic percent density (MPD) was found to have similar strength associations with UST mean sound speed (Spearman coefficient, r_s = 0.722, $p < 0.001$) and UST median sound speed (r_s = 0.737, $p < 0.001$). Both were stronger than the associations between MPD with two separate measures of UST percent density, a k-means (r_s = 0.568, $p < 0.001$) or a threshold (r_s = 0.715, $p < 0.001$) measure. Segmentation of the UST sound speed images into dense and non-dense volumes showed weak to moderate associations with the mammographically equivalent measures. Relationships were found to be inversely and weakly associated between age and the UST mean sound speed (r_s = −0.239, p = 0.002), UST median sound speed (r_s = −0.226, p = 0.004) and MPD (r_s = −0.204, p = 0.008). Relationships were found to be inversely and moderately associated between body mass index (BMI) and the UST mean sound speed (r_s = −0.429, $p < 0.001$), UST median sound speed (r_s = −0.447, $p < 0.001$) and MPD (r_s = −0.489, $p < 0.001$). The results confirm and strengthen findings presented in previous work indicating that UST sound speed imaging yields viable markers of breast density in a manner consistent with mammography, the current clinical standard. These results lay the groundwork for further studies to assess the role of sound speed imaging in risk prediction. (E-mail: msak@delphinusmt.com) © 2016 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Breast density, Ultrasound tomography, Mammography, Breast Cancer, Sound speed, Dense and non-dense breast volumes, Risk assessment.**

INTRODUCTION

Of the many factors that affect the risk of developing breast cancer, breast density has been shown to be one of the strongest. Numerous epidemiologic studies conducted over the past four decades have consistently demonstrated that increased mammographic density is related to increased breast cancer risk (Huo et al. 2014; McCormack and dos Santos Silva 2006; Pettersson et al. 2014; Sak et al. 2015). It was determined that, compared with women with lower densities, women with the highest mammographic densities showed a 4- to 6-fold increased risk of breast cancer.

Breast density generally refers to the amount of dense tissue visible on a mammographic image. Dense breast tissue attenuates more X-rays than non-dense tissue and therefore appears radiopaque on a mammogram. Measuring breast density is ultimately a measure of the amount of white regions in the image and can be done both qualitatively and quantitatively. Mammographic percent density (MPD) is defined as the ratio of dense breast tissue relative to the total amount of breast tissue seen on a mammogram and is measured using computer-assisted programs such as Cumulus (Byng et al. 1994) or can be measured volumetrically using programs such as Volpara (Eng et al. 2014; Jeffreys et al.

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2010) and Quantra (Ciatto et al. 2012; Regini, et al. 2014). However, despite being the current gold standard for breast imaging, mammography poses some shortcomings for the measurement of breast density (Kopans 2008; Sak et al. 2015).

Ultrasound tomography (UST) is an emerging imaging modality that produces 3-D images of breast tissue (Duric et al. 2005, 2010). In UST, sound waves are used to measure the reflection and transmission properties of breast tissue (Li et al. 2008). Physical breast density can be directly measured using UST by measuring the transmission property known as sound speed. Ignoring shear waves, the sound speed of any material is given by $v = (C/\rho)^{1/2}$ where C is the bulk modulus and ρ is the density of the material in question. Studies have shown that for breast tissues, the bulk modulus scales as the cube of density (Mast 2000; Masugata et al. 1999; Weiwad et al. 2000). Substituting this into the equation for sound speed removes the dependence on bulk modulus and leaves a direct relationship between tissue density and the measured tissue sound speed, ($v \propto \rho$). This direct relationship suggests that sound speed images may be a useful tool for directly measuring physical breast density and its distribution throughout the breast.

Previous work (Duric et al. 2013a; Sak et al. 2011, 2012; Sak 2013) has compared breast density measurements between mammographic percent density with volume averaged sound speed and shown that the two different imaging modalities correlate strongly with each other. These results were accomplished using symptomatic participants that were not screened according to a standardized research protocol. The work presented here examines, for the first time, the 3-D sound speed properties of the breast among healthy women who were screen negative on mammography.

METHODS

Participant recruitment

The study described here is part of a larger, ongoing observational study, the Ultrasound Study of Tamoxifen, aimed at measuring breast density changes among women aged 30–70 y undergoing treatment with tamoxifen (Sak et al. 2013). Exclusion criteria included weight >250 lbs, breast diameter >20 cm (the maximum allowable for the scanner), pregnancy, breastfeeding, current breast implants and active breast skin infections. The study includes two groups: (i) women receiving tamoxifen for clinical indications and (ii) a comparison group of screen negative women frequency matched on age, race and menopausal status. The main aim of the Ultrasound Study of Tamoxifen is to evaluate changes in breast density as measured using both mammography and UST 12 mo after a baseline scan for both groups. The analysis presented herein involves only the baseline UST scans and mammograms that became available for the comparison group of 165 women with negative mammographic screens.

To be eligible for the comparison group, a screening mammogram was first identified with the recommendation to continue routine screening. Any potential participant was then age-, race-, and menopausal status–matched to the case group before then being offered a UST scan. There was, therefore, a short temporal delay between the scans. Digital mammograms were obtained at the Karmanos Cancer Institute or at the nearby referring Henry Ford Hospital in Detroit, MI. Both sites are certified by the American College of Radiology's Mammography Accreditation Program and maintain image quality control according to the Mammography Quality Standards Act. All UST scans were performed with a UST imaging device located at the Karmanos Cancer Institute. The scans were collected over a period of 3 y, ranging from 2011 to 2014. At the time of the UST scan, additional participant characteristics such as measured weight and height were also collected. All imaging procedures were performed under an Institutional Review Board–approved protocol, in compliance with the Health Insurance Portability and Accountability Act, with informed consent obtained from all patients.

Mammographic image acquisition

Digital mammograms were obtained and analyzed for all 165 participants. Mammograms from Karmanos Cancer Institute were obtained on a GE Senographe Essential digital mammography unit (General Electric Company, Fairfield, CT, USA) while participants imaged at Henry Ford Hospital were imaged on a Hologic Lorad Selenia digital mammography unit (Hologic, Bedford, MA, USA). One craniocaudal view of one breast for each participant was analyzed. All mammographic images were of diagnostic quality and were obtained with clinical image quality standards (*e.g.,* exposure, pectoralis visualization, *etc.*). The breast that was chosen to be analyzed (left or right) was randomized. Mammographic percent density was measured by one reader (N.B.) using the CUMULUS 4 software (University of Toronto, Ontario, Canada) (Byng et al. 1994). This interactive computer-assisted method was used to obtain measurements of the areas of dense tissue and total breast area on each mammogram in a similar manner to that reported in earlier work (Duric et al. 2013a; Sak et al. 2011, 2012; Sak 2013). From these measurements, the area of non-dense tissue and percent density (dense area divided by total breast area) was calculated. Reproducibility of the mammographic methods was