

● *Original Contribution*

USING SPEED OF SOUND IMAGING TO CHARACTERIZE BREAST DENSITY

MARK SAK,* NEB DURIC,* PETER LITTRUP,*[†] LISA BEY-KNIGHT,[‡] HAYTHEM ALI,[§] PATRICIA VALLIERES,[§]
MARK E. SHERMAN,[¶] and GRETCHEN L. GIERACH^{||}

*Delphinus Medical Technologies, Plymouth, MI, USA; [†]Brown University, Rhode Island Hospital, Providence, RI, USA;

[‡]Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA; [§]Henry Ford Health System, Detroit, MI, USA;

[¶]Division of Cancer Prevention, National Cancer Institute, Department of Health and Human Services, Bethesda, MD, USA;

and ^{||}Metabolic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA

(Received 2 February 2016; revised 7 June 2016; in final form 16 August 2016)

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.

Address correspondence to: Mark Sak, Delphinus Medical Technologies, 45525 Grand River Avenue, Novi, MI 48374, USA. E-mail: msak@delphinusmt.com

Conflicts of Interest: Neb Duric and Peter Littrup have financial interests in Delphinus Medical Technologies Inc. whose SoftVue scanner was used in this study. Financial conflicts of interest are being managed by Wayne State University. No other authors declare any financial conflicts of interest.

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

assessed by rereading a randomly selected sample of images, randomly distributed among the images being read, within and between each reading session. In total, 17 participants had their mammographic density reread and an ICC of 0.71 for the percent density values was measured which indicates good reliability.

UST image acquisition

Operation of the UST devices has been described previously (Duric *et al.* 2007, 2009, 2013a; Sak *et al.* 2011, 2012; Sak 2013). The participant lies prone on the device with their breast submerged in a water bath to act as an ultrasound coupler. The UST hardware creates tomographic sound speed images of the breast from the chest wall to the nipple. Sound speed and density information were extracted from the images using a semi-automated method in the software package ImageJ (US National Institutes of Health, Bethesda, MD, USA) (Rasband 1997–2012) by one reader (M.S.). There is a demonstrated reliability in sound speed estimates when processing UST scans in this manner, with a reported ICC of 0.934 for sound speed measurements (Khodr *et al.* 2015). The sound speed of the surrounding water bath is intermediate to the sound speeds of the breast tissue and must therefore be segmented from each image manually. Also, the reader removed image slices that corresponded to the chest wall and the nipple as these regions are not relevant to breast density measurements. Over the course of the study, the UST hardware used to create UST sound speed images was upgraded. Initially, a clinical UST prototype known as the Computed Ultrasound Risk Evaluation (Karmanos Cancer Institute, Detroit, MI, USA) system was used (N = 27) (Duric *et al.* 2007). An upgraded version of the hardware known as SoftVue (Delphinus Medical Technologies, Plymouth, MI, USA) was installed early into the recruitment period (N = 138) (Duric *et al.* 2013b; Sak *et al.* 2014). Comparability of sound speed estimates generated by both devices was found to be excellent.

UST image and statistical analysis

Quantitative volumetric sound speed. Once manual segmentation of breast tissue from the water bath was complete, the sound speed of each voxel within a defined volume of breast tissue (1–3 mm³ depending on slice thickness) was defined. The volume averaged sound speed is the mean value of the sound speed of the manually defined breast tissue and was calculated for each participant. However, the distribution of sound speed within a single participant may be skewed (*i.e.*, not normally distributed). The mean sound speed value may not be sensitive to these distributions and may not

be the best measure of determining the average breast density. Novel techniques of using the volumetric median and modal sound speed values were therefore also calculated for each participant. The median sound speed was calculated by sorting an array containing the sound speed value of each voxel and selecting the value contained in the central position of the array. A histogram of the distribution of the sound speed values was created for each participant with a range of 1300 m/s to 1600 m/s and divided into ImageJ's default setting of 256 bins. The modal sound speed corresponded to the bin with the greatest number of counts.

Subregion sound speed. UST breast density is measured fundamentally differently from mammographic density because of the quantitative nature of UST sound speed images, as noted above. This quantification also allows additional options for segmentation. An attempt to measure UST density in a manner similar to mammographic density was thereby performed by separating the UST sound speed images into volumes of dense and non-dense tissue. The measured volumes could be used to calculate a UST percent density value in a similar fashion to how MPD is calculated. In addition, the mean sound speed of each subregion was also calculated by measuring the mean voxel value for each subregion. These estimates are referred to as subregion density measures in this paper.

This segmentation of the UST sound speed images into dense and non-dense tissue was done in two different ways (Fig. 1):

- i. *K-means segmentation method*—A k-means clustering plugin for ImageJ was used to separate each sound speed image for each participant into dense and non-dense subregions (Jain and Dubes 1988).
- ii. *Threshold segmentation method*—An operator-independent threshold of 1460 m/s was used to separate each image into dense and non-dense regions. Voxels that had a sound speed greater than or equal to 1460 m/s were classified as dense and voxels that had a sound speed less than 1460 m/s were classified as non-dense. After a brief initial review of the data, the threshold of 1460 m/s was determined to produce the widest possible range of percent density values. Setting a higher or lower threshold caused the measured percent density to be pushed toward 0% or 100%, respectively, and therefore limited the range of values.

RESULTS

Characteristics of the study population

The cohort-averaged participant characteristics, UST and mammographic density measurements and

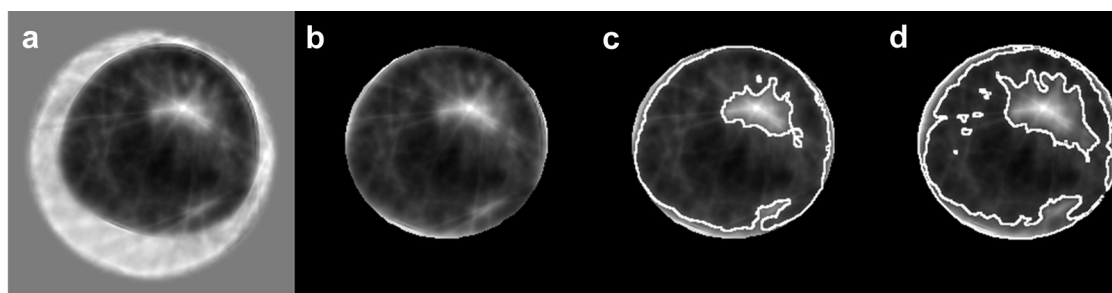


Fig. 1. A standard ultrasound tomography (UST) sound speed image (a); the same image after it has been masked to separate it from the background water (b); the masked image segmented into dense and non-dense tissue using the k-means clustering method (c); and the masked image segmented into dense and non-dense tissue using the threshold method (d).

UST subregion density measures are shown in Table 1. On average, participants were 51 y of age and their body mass index (BMI) was classified as obese ($\text{BMI} = 31 \text{ kg/m}^2$). The average values for the mean (1450 m/s), median (1446 m/s) and modal (1440 m/s) sound speed and average MPD (22.4%) indicate that this population had low breast density, which would be consistent with the measured age and BMI. Finally, because the participants were not enrolled into the study until after a negative screening mammogram was identified, the UST scan occurred an average of 42 days

Table 1. Average values for various imaging and participant characteristics (N = 165)

Imaging or patient characteristic	Average value (SD)
UST sound speed image characteristics	
UST mean sound speed, m/s	1450.2 (14.5)
UST median sound speed, m/s	1446.0 (15.4)
UST modal sound speed, m/s	1440.0 (16.7)
UST total volume, cm^3	777.5 (478.6)
Mammographic image characteristics	
Mammographic percent density, %	22.4 (18.0)
Mammographic dense projected area, cm^2	41.9 (31.4)
Mammographic non-dense projected area, cm^2	185.1 (105.0)
Mammographic total projected area, cm^2	227.0 (102.7)
UST K-means clustering subregion characteristics	
K-means mean dense sound speed, m/s	1480.1 (16.5)
K-means mean non-dense sound speed, m/s	1439.9 (10.8)
K-means dense volume, cm^3	180.1 (110.4)
K-means non-dense volume, cm^3	592.9 (405.8)
K-means percent density, %	25.3 (10.5)
UST threshold subregion characteristics	
Threshold mean dense sound speed, m/s	1481.1 (7.5)
Threshold mean non-dense sound speed, m/s	1438.6 (5.1)
Threshold dense volume, cm^3	163.6 (125.3)
Threshold non-dense volume, cm^3	609.5 (427.7)
Threshold percent density, %	25.5 (19.7)
Participant characteristics	
Participant age, years	51.4 (8.0)
Participant height, in.	64.4 (3.3)
Participant weight, lbs.	184.0 (45.6)
Participant BMI, kg/m^2	31.2 (7.7)
Time between mammogram and UST scan, days	42 (23)

BMI = body mass index; SD = standard deviation; UST = ultrasound tomography.

after the mammogram. These were otherwise healthy women that were not undergoing hormonal therapy, and therefore, changes in the composition of glandular tissue between the mammographic and UST scans should be minimal. Changes in breast density modulated by hormonal changes during the menstrual cycle have also been shown to be minimal for UST sound speed measurements (Duric et al. 2013a). Fluctuations in weight between the scans could have affected breast density, as could the known association between increasing age and decreasing breast density. However, given the average time frame of 42 days, both of these factors likely produced minimal, if any measured difference in the glandular tissue composition between modalities.

Frequency distributions of average UST and mammographic density measures

Figure 2 shows the distribution of the mean, median and modal sound speed values over all participants. All three of these UST sound speed distributions are strongly peaked. Figure 3 shows the frequency distributions for the percent density measurements calculated using mammography and for both the UST k-means and thresholding clustering methods. The distribution of MPD is different from that of the UST sound speed values by being less peaked at lower values. Although most participants have low breast density irrespective of the imaging modality employed, the MPD distribution is more spread out over these smaller values. The k-means and threshold clustering methods produce similar UST percent density measurements (25.3% and 25.5%, respectively), but the distribution of the measurements differs. The UST threshold percent density measure is peaked sharply toward lower values, resembling the distribution of UST sound speed in this study population. The distribution of the UST k-means clustering percent density values covers a smaller range (10%–60% instead of 10%–100%). This aligns more closely with other volumetric analyses of percent density, such as Quantra and Volpara, which tend to measure much lower percent

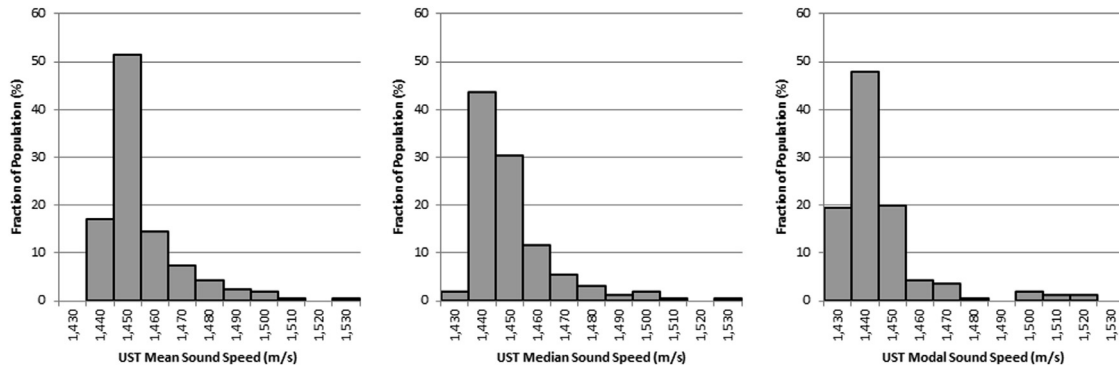


Fig. 2. Participant frequency distributions of the ultrasound tomography (UST) mean (left), median (middle) and modal (right) sound speed.

density and a narrower range than Cumulus does (Ciatto *et al.* 2012; Eng *et al.* 2014; Jeffrey *et al.* 2010; Regini *et al.* 2014).

Subregion frequency distributions

Figures 4, 5 and 6 show the frequency distributions for the dense, non-dense and total breast areas and volumes respectively, as calculated using mammography and UST. The dense (Fig. 4) and non-dense (Fig. 5) tissue measures have similar distributions for both mammography and the UST threshold method, but the k-means clustering method gives a slightly more peaked non-dense volume distribution. The whole breast area and volume measures (Fig. 6) are similarly distributed between the 2-D mammography and 3-D UST modalities.

Associations between UST and mammographic density measures

UST breast density measures were found to be strongly correlated with mammographic breast density measures. Plots demonstrating the positive correlations of mean, median and modal sound speed values with mammographic percent density are shown in Figure 7. Table 2 shows the measured Spearman correlation

coefficients between MPD and mean, median and modal UST sound speed values with the various UST and mammographic subregion density measures. For most measures, the mean, median and modal sound speed show similar associations, in both strength and magnitude. The median and mean sound speed show almost identical correlations while the modal sound speed shows slightly weaker correlations. In particular, MPD shows positive correlations with median sound speed ($r_s = 0.737, p < 0.001$) and mean sound speed ($r_s = 0.722, p < 0.001$) that were slightly stronger than that observed with modal sound speed ($r_s = 0.651, p < 0.001$). This indicates a strong relationship between 2-D mammographic density measures and 3-D UST density measures.

The UST and mammographic subregion measures were compared with each other using Spearman correlations. Table 3 shows the comparison of the two different UST segmentation methods and finds that dense volume, non-dense volume and UST percent density correlate strongly and positively for the two segmentation methods. Table 4 compares the two UST subregion measures with the mammographic measures. Here, the correlations of both measures of dense volume with the

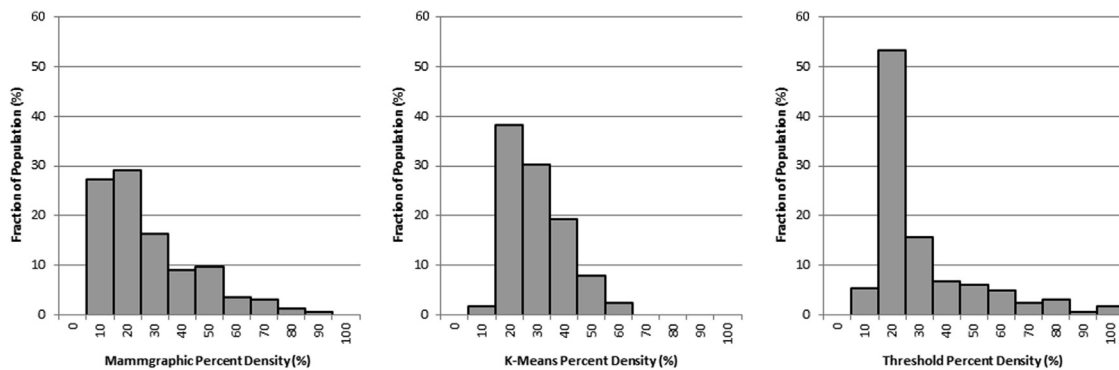


Fig. 3. Participant frequency distributions of the mammographic percent density (left) along with the ultrasound tomography (UST) k-means percent density (middle) and UST threshold percent density (right).

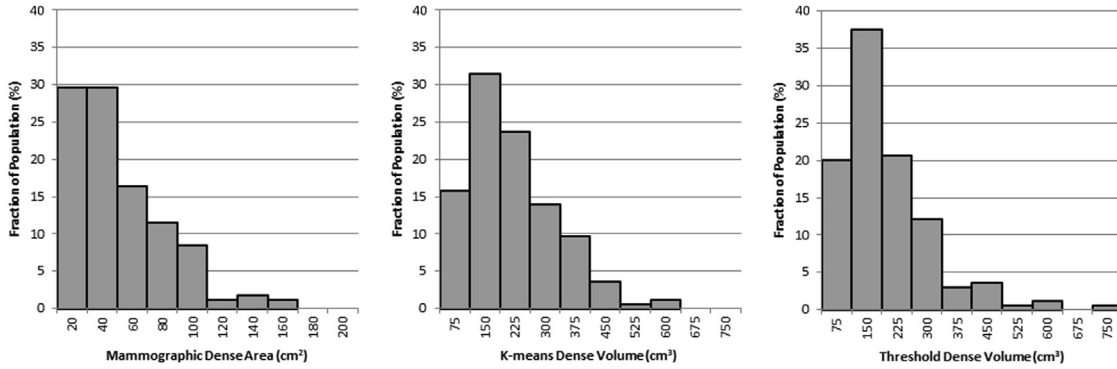


Fig. 4. Participant frequency distributions of the projected mammographic dense area (left), ultrasound tomography (UST) k-means dense volume (middle) and UST threshold dense volume (right).

mammographic dense area were weak to moderate ($r_s = 0.198, p = 0.011$ for k-means segmentation and $r_s = 0.466, p < 0.001$ for threshold segmentation). Although UST dense volume is assumed to be the 3-D equivalent of the mammographic dense area, differences in how each technique measures the same structures are evident in these results as the correlations do not always align strongly with each other.

Associations with continuous participant characteristics

The continuous participant characteristics of age, height, weight and BMI were associated with average mammographic and UST density and subregion density measures. The results are shown in Table 5. In general, the correlations involving height were not statistically significant. The average UST and mammographic density measures were inversely related to the participant factors of age, weight and BMI with the associations involving weight and BMI being of moderate strength while those involving age were weaker. Both age and weight are known factors that affect MPD (Byrne et al. 1995; Schetter et al. 2014).

DISCUSSION

Elevated breast density is a strong risk factor for developing breast cancer, but developing the most clinically useful methods for measuring density is a topic of ongoing research. Herein, we demonstrate that volumetric breast density measurements using sound speed correlate with mammographic density (the current clinical standard) in a relevant participant group—healthy women with negative mammographic screens for whom estimating risk might have relevance for guiding future screening and prevention procedures.

Previous work (Duric et al. 2013a; Sak et al. 2011, 2012; Sak 2013) that examined the relationship between MPD and UST sound speed was based on participants with abnormalities, who were not representative of the general (healthy) population. Density measurements from that group may have been influenced by (i) the presence of high sound speed masses which contaminated the breast density measurements and (ii) characteristics of a participant population that is not disease free and whose breast density may therefore differ from the general population. To address these potential concerns, we have performed the current

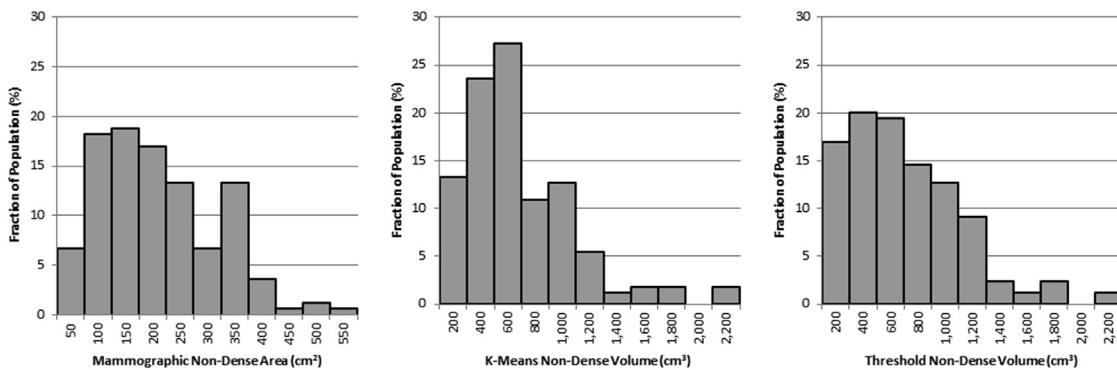


Fig. 5. Participant frequency distributions of the projected mammographic non-dense area (left), Ultrasound tomography (UST) k-means non-dense volume (middle) and UST threshold non-dense volume (right).

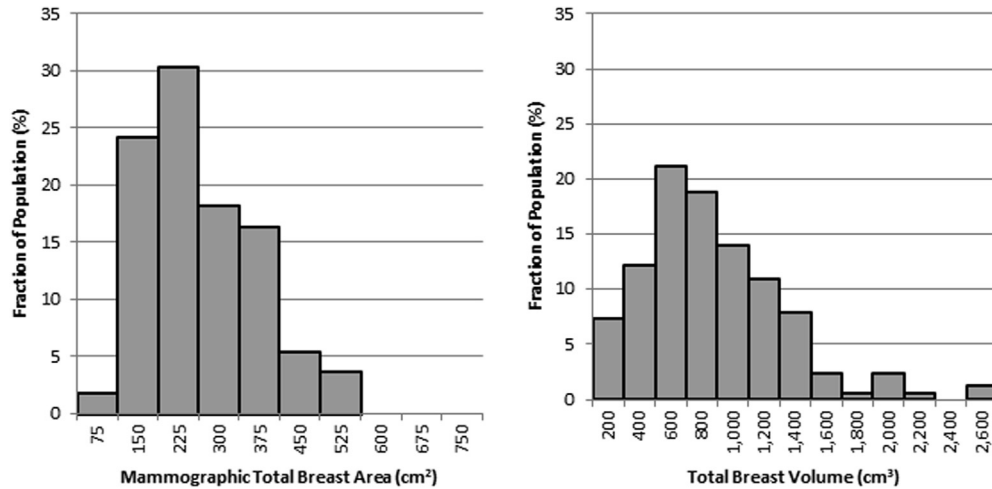


Fig. 6. Participant frequency distributions of the total projected mammographic breast area (left) and the ultrasound tomography (UST) total breast volume (right).

analysis on a population of screen negative women, which confirms and extends the previous work (Duric *et al.* 2013a; Sak *et al.* 2011, 2012; Sak 2013) demonstrating strong, positive correlations between breast density measures obtained from UST sound speed imaging and digital mammography.

A similar strength of correlation between mean UST sound speed and MPD was observed as before ($r_s = 0.710$, $p < 0.001$) (Duric *et al.* 2013a) and in this work ($r_s = 0.722$, $p < 0.001$). The distributions of the UST mean sound speed and MPD were similar in shape and the associations with age and weight were similar. These results minimize the uncertainty in breast density measurements made on a symptomatic population that was present in the previous work. They also confirm the previously offered conclusions that UST is capable of safely producing consistent measurements of breast density that correlate with MPD, the metric that is best established as a measure of breast cancer risk.

From the results listed in Table 1, the UST mean sound speed (1450.2 m/s) is seen to be higher than both the median (1446.0 m/s) and modal (1440.0 m/s) sound speed. This suggests that for an average participant in our study population, there is a positively skewed distribution of sound speed with the majority of the sound speed values concentrated on low sound speeds with a tail stretching to higher sound speed values. Inspection of the distribution of the mean, median and modal sound speeds throughout the participant population (Fig. 2) shows that the mean sound speed is peaked at a higher value than the median and modal sound speed. This observation once again points to the skewness of the individual participants sound speed distributions.

Previous works (Duric *et al.* 2007, 2013a; Sak 2013) involving UST density measurements have used the mean sound speed as a measure of breast density. The results from Table 2 suggest that the median sound speed value is comparable to the mean sound speed as a measure of

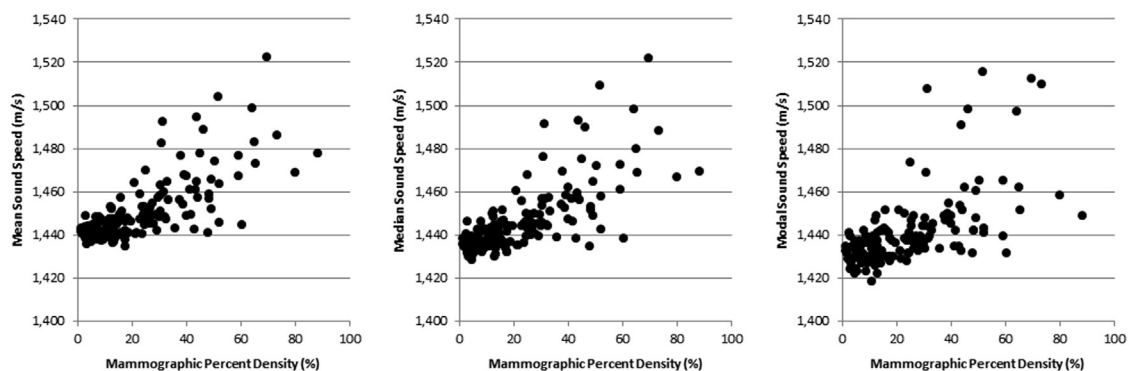


Fig. 7. Plots of the ultrasound tomography (UST) mean (left), median (middle) and modal (right) sound speed versus the mammographic percent density.

Table 2. Correlations of average density measures and subregion density measures for UST and mammography

UST, mammographic or subregion measure	UST mean sound speed, km/s	UST median sound speed, km/s	UST modal sound speed, km/s	Mammographic percent density
UST median sound speed, km/s	0.984			
UST modal sound speed, km/s	0.883	0.913		
Mammographic percent density	0.722	0.737	0.651	
K-means mean dense sound speed, m/s	0.688	0.633	0.577	0.451
K-means mean non-dense sound speed, m/s	0.915	0.908	0.866	0.612
K-means dense volume, cm ³	-0.014 (0.863)	-0.029 (0.715)	-0.116 (0.137)	-0.099 (0.207)
K-means non-dense volume, cm ³	-0.464	-0.492	-0.473	-0.526
K-means percent density, %	0.572	0.592	0.454	0.568
Threshold mean dense sound speed, m/s	0.411	0.340	0.264	0.295
Threshold mean non-dense sound speed, m/s	0.813	0.831	0.817	0.545
Threshold dense volume, cm ³	0.439	0.390	0.278	0.233 (0.003)
Threshold non-dense volume, cm ³	-0.549	-0.566	-0.539	-0.580
Threshold percent density, %	0.929	0.885	0.754	0.715
UST total volume, cm ³	-0.371	-0.395	-0.401	-0.447
Mammographic total breast area, cm ²	-0.378	-0.402	-0.359	-0.557
Mammographic dense area, cm ²	0.614	0.624	0.544	0.850
Mammographic non-dense area, cm ²	-0.539	-0.561	-0.499	-0.757

UST = ultrasound tomography.

Each cell contains the Spearman correlation coefficient with the *p* value shown in brackets. For entries without brackets, the *p* value was *p* < 0.001. Blank entries correspond to redundant correlations or correlations of the same density value.

average breast density. Correlations with MPD and most of the subregion measurements are of a similar strength when using the median sound speed instead of the mean sound speed. Manual segmentation of the breast from the water bath is imperfect and on some slices, a small number of voxels that correspond to the water bath are not removed. The sound speed of the water bath is higher than most breast tissue, so these voxels may skew the mean sound speed to a slightly higher value. The median value is less sensitive to these higher sound speed voxels than the mean value and may theoretically be a slightly better measure. However, the advantages of using the median value are small, as the mean value does provide correlations with a similar strength. Further study of this relationship is needed.

In Table 1, the average modal sound speed of the group is very similar to the mean sound speed of the

non-dense tissue using either segmentation method. Also, the correlations in Table 2 and Table 4 involving the modal sound speed are relatively similar to those involving the sound speed of the non-dense tissue. The modal sound speed value is the most common sound speed value. For the population studied here, the segmented non-dense tissue is more common than segmented dense tissue, as the average breast density is low relative to the general population (Sprague et al. 2014). Therefore, the mean sound speed of the non-dense tissue is likely very similar to the modal value of the entire breast. For fatty breasts, the modal sound speed can be used as an approximation of the sound speed of the non-dense tissue without requiring the use of segmentation of the UST sound speed images.

This study enabled a direct comparison of breast anatomy and the corresponding breast subregions (dense

Table 3. Correlations of subregion density measures made by both segmentation methods

UST subregion measure	K-means dense sound speed, m/s	K-means non-dense sound speed, km/s	K-means dense volume, cm ³	K-means non-dense volume, cm ³	K-means percent density	Total breast volume, cm ³
Threshold dense sound speed, m/s	0.788	0.323	-0.024 (0.762)	-0.161 (0.039)	0.159 (0.041)	-0.126 (0.106)
Threshold non-dense sound speed, m/s	0.394	0.869	0.021 (0.786)	-0.308	0.419	-0.238 (0.002)
Threshold dense volume, cm ³	0.440	0.400	0.743	0.432	0.219 (0.005)	0.547
Threshold non-dense volume, cm ³	-0.363	-0.441	0.634	0.972	-0.508	0.956
Threshold percent density, %	0.690	0.762	-0.001 (0.991)	-0.494	0.637	-0.398
Total breast volume, cm ³	-0.205 (0.008)	-0.290	0.781	0.970	-0.366	N/A

N/A = not applicable.

Each cell contains the Spearman correlation coefficient with the *p* value shown in brackets. For entries without brackets, the *p* value was *p* < 0.001.

Table 4. Correlations of mammographic subregion density measures with UST density measures

UST subregion measure	Mammographic dense area, cm ²	Mammographic non-dense area, cm ²	Total mammographic breast area, cm ²
K-means mean dense sound speed, m/s	0.367	-0.323	-0.194 (0.012)
K-means mean non-dense sound speed, m/s	0.584	-0.381	-0.212 (0.006)
K-means dense volume, cm ³	0.198 (0.011)	0.408	0.501
K-means non-dense volume, cm ³	-0.168 (0.031)	0.764	0.764
K-means percent density, %	0.412	-0.542	-0.451
Threshold mean dense sound speed, m/s	0.178 (0.022)	-0.277	-0.196 (0.012)
Threshold mean non-dense sound speed, m/s	0.579	-0.292	-0.135 (0.084)
Threshold dense volume, cm ³	0.466	0.153 (0.050)	0.326
Threshold non-dense volume, cm ³	-0.233	0.780	0.748
Threshold percent density, %	0.569	-0.577	-0.428
Total breast volume, cm ³	-0.082 (0.296)	0.720	0.745

UST = ultrasound tomography.

Each cell contains the Spearman correlation coefficient with the *p* value shown in brackets. For entries without brackets, the *p* value was *p* < 0.001.

and non-dense tissue) in a 2-D mammographic form versus a 3-D UST form. The segmentation of the UST sound speed images using the methods described here created volumes of dense and non-dense tissue, which should strongly correlate with the corresponding mammographic areas. For the MPD, which is an area measure, the correlations with the mean and median sound speed values ($r_s = 0.722, p < 0.001$ and $r_s = 0.737, p < 0.001$) were stronger than with the corresponding k-means UST percent density measures ($r_s = 0.568, p < 0.001$), but similar to the correlation with threshold UST percent density ($r_s = 0.715, p < 0.001$). Although the mean and median sound speed values are volumetric measurements that do not have a corresponding mammographic density measure, they still appeared to be a strong measure of average breast density.

Results from the direct comparisons of the UST created dense and non-dense volumes with the mammographic dense and non-dense areas are mixed. It is known that mammographic dense and non-dense areas relate to MPD and breast cancer risk (Bertrand *et al.* 2015; Pettersson *et al.* 2011). The results in Table 2 show moderate to strong associations between the dense and non-dense mammographic areas with the average breast density measures of UST mean, median and modal sound speed and with MPD (ranging from $r_s = 0.544, p < 0.001$ to $r_s = 0.840, p < 0.001$ for dense areas and $r_s = -0.499, p < 0.001$ to $r_s = -0.757, p < 0.001$ for non-dense areas). However, there are no statistically significant associations between the k-means dense volume and the average density measures ($r_s = -0.014, p = 0.863$ to $r_s = -0.116, p = 0.137$)

Table 5. UST and mammographic density correlations with participant characteristics

UST, mammographic or subregion measure	Age, y	Height, in.	Weight, lbs.	BMI, kg/m ²
UST sound speed image characteristics				
UST mean sound speed, m/s	-0.239 (0.002)	0.118 (0.131)	-0.429	-0.429
UST median sound speed, m/s	-0.226 (0.004)	0.114 (0.144)	-0.447	-0.447
UST modal sound speed, m/s	-0.114 (0.144)	0.061 (0.433)	-0.417	-0.409
UST total volume, cm ³	-0.089 (0.256)	-0.004 (0.955)	0.499	0.513
Mammographic image characteristics				
Mammographic percent density, %	-0.204 (0.008)	0.105 (0.180)	-0.477	-0.489
Mammographic total projected area, cm ²	-0.040 (0.611)	0.021 (0.793)	0.573	0.570
Mammographic non-dense projected area, cm ²	0.036 (0.649)	-0.012 (0.882)	0.600	0.599
Mammographic dense projected area, cm ²	-0.262	0.122 (0.119)	-0.209 (0.007)	-0.213 (0.006)
UST K-means clustering subregion characteristics				
K-means mean dense sound speed, m/s	-0.097 (0.213)	0.080 (0.308)	-0.226 (0.004)	-0.231 (0.003)
K-means mean non-dense sound speed, m/s	-0.160 (0.040)	0.104 (0.183)	-0.324	-0.334
K-means dense volume, cm ³	-0.256	0.074 (0.344)	0.233 (0.003)	0.252
K-means non-dense volume, cm ³	-0.012 (0.880)	-0.026 (0.742)	0.548	0.557
K-means percent density, %	-0.247 (0.001)	0.134 (0.087)	-0.443	-0.446
UST threshold subregion characteristics				
Threshold mean dense sound speed, m/s	-0.038 (0.387)	0.097 (0.213)	-0.151 (0.053)	-0.161 (0.039)
Threshold mean non-dense sound speed, m/s	-0.155 (0.047)	0.084 (0.282)	-0.263	-0.280
Threshold dense volume, cm ³	-0.306	0.064 (0.412)	0.0140 (0.854)	0.045 (0.567)
Threshold non-dense volume, cm ³	-0.003 (0.973)	-0.020 (0.777)	0.552	0.557
Threshold percent density, %	-0.224 (0.004)	0.112 (0.153)	-0.450	-0.448

BMI = body mass index; UST = ultrasound tomography.

Each cell contains the Spearman correlation coefficient with the *p* value shown in brackets. For entries without brackets, the *p* value was *p* < 0.001.

and only weak to moderate associations involving the threshold dense volume ($r_s = 0.233$, $p = 0.003$ to $r_s = 0.439$, $p < 0.001$).

As shown in [Table 5](#), the UST dense volumes show a weak yet statistically significant correlation with mammographic dense area ($r_s = 0.198$, $p = 0.011$ for k-means and $r_s = 0.466$, $p < 0.001$ for threshold). The associations of the non-dense and total breast volumes with the non-dense and total breast area are much stronger (ranging from $r_s = 0.745$, $p < 0.001$ to $r_s = 0.780$, $p < 0.001$). Because the study population had relatively low breast density, small variations in the output of the segmentation algorithms had larger effects on the associations involving the dense regions relative to the non-dense regions.

Breast density has typically been defined in a binary fashion as the relative amount of dense and non-dense tissue in the breast. Therefore, the methods used to segment the breast into the dense and non-dense subregions are critical in order to accurately define the internal breast anatomy and discover their relationship with breast cancer risk. Results presented here suggest that relative to mammography, the segmentation methods made using UST do not appear to be as effective at separating dense from non-dense tissue. Therefore, further study of how to properly define subregions in UST sound speed images is still required.

No matter what methods are used to segment the breast, the dense and non-dense regions are treated as homogenous parts of the breast anatomy from scan to scan. Although recent changes to the Breast Imaging Reporting and Data System breast composition categories have begun to address the relative density of the dense breast tissue ([Sickles et al. 2013](#); [Slanetz et al. 2015](#)), the characterization of density when using mammography still uses this binary model and is therefore highly subjective. The additional quantitative information stored in the UST images can provide useful information regarding the relative density of these subregions that mammography cannot.

Using the quantitative nature of the UST sound speed measurements, the dense and non-dense regions were analyzed by measuring the mean sound speed values of the subregions. As expected, the dense subregions show higher sound speed than the non-dense regions. By comparing the standard deviations of the subregion sound speed values, the dense subregions also have a wider range of possible sound speed values relative to the non-dense regions. Furthermore, the k-means method shows a wider range of possible values than the threshold method. By definition, the threshold method will produce a cap on the possible values the subregion sound speed can have, with the non-dense region having a mean value of 1460 m/s or lower and the dense region having a mean

value of 1460 m/s or greater. The k-means method does not have this limitation and therefore the range of possible values is much larger. For the k-means method, the minimum dense subregion sound speed measured was 1451 m/s and the maximum non-dense subregion sound speed measured was 1505 m/s. This indicates that when using the k-means method, some participants with very dense breasts have non-dense regions that are of greater density than the dense regions in women with very fatty breasts. However, the clinical importance of these differences is still unknown.

Irrespective of the method used to define the subregions, the sound speed of the subregions showed correlations with the UST and mammographic average breast density measures. Both the non-dense and dense sound speed show moderate to strong positive correlations with the average UST breast density measures and MPD measurements. Correlations with UST measurements are stronger than those with MPD and the correlations with the non-dense subregion sound speed are stronger than those with the dense sound speed. These results further indicate that dense and non-dense tissues are not uniform across participants.

The participant factors examined here are known to have an effect on both breast cancer risk and breast density. The results from [Table 5](#) show that participant height has no statistically significant relationship with any UST or mammographic density measure. Participant age shows inverse and weak relationships with the density measures. Participant weight and BMI show stronger and positive correlations relative to those with age.

The average BMI of the studied group is 31.2 kg/m^2 , which is greater than that of the average adult woman in the United States (28.7 kg/m^2) ([Flegal et al. 2012](#)). This increased BMI also likely explains why the breast density for this group skews low with only a few participants with high breast density. Increased weight and BMI are also strongly associated with increased non-dense tissue ([Schetter et al. 2014](#)). This increased non-dense tissue tends to lead to increased total volume and total projected breast area. Given that women with high BMI have more fat tissue in the breast on average and that MPD reflects the relative amounts of dense and non-dense tissue in the breast, it is perhaps expected that correlations between MPD and BMI are stronger than those between BMI and the UST sound speed measurements. The UST sound speed measurements are direct measurements of the breast tissue properties and therefore are less strongly related to the relative amounts of fatty and non-fatty breast tissue than MPD.

Mammography is a tool whose primary use is in the detection of cancer. Measurement of breast density is a secondary use of mammography. Therefore, many of the techniques used to aid in detection can introduce

uncertainty into mammographic breast density measurements (Yaffe 2008). Compression of the breast is applied to reduce the amount of radiation used and to improve image quality but can be variable between scans, even for the same patient, due to perceived discomfort. Compressed breast tissue in either craniocaudal or mediolateral oblique projection also has inherent differences when transitioning from 2-D area assessments to 3-D volumetric assessments. There is also some discussion that without additional mammographic imaging characteristics that are not commonly considered when density measurements are made, an accurate volume of dense tissue cannot properly be determined in mammography (Kopans 2008).

It may therefore seem that the physiologic differences in breast density may be difficult to distinguish from the technical variabilities of mammography. However, no matter how mammographic density was measured, it has been consistently shown that women with higher breast densities have an increased risk of developing breast cancer. This was true when mammographic density was measured qualitatively using visual estimations of breast density (Saftlas *et al.* 1991), quantitatively using area-based measurements (Boyd *et al.* 1995) or even using volumetric measures (Ciatto *et al.* 2012; Jeffreys *et al.* 2010), which more directly incorporate the uncertainties of breast compression. Therefore, despite the concerns regarding the distribution of dense tissue throughout the breast, mammographic density is a robust measurement that is currently well accepted in a wide variety of forms.

UST imaging shares a similar geometry to breast magnetic resonance imaging (MRI), because for both of these modalities the patient lays face down with their uncompressed breast free-hanging. Previous studies have shown strong correlations of a similar strength to those reported here between volumetric MRI density measures and mammographic breast density measures (Khazen *et al.* 2008; Thompson *et al.* 2009). While not directly compared here in this work, these other results suggest that breast MRI and UST imaging likely handle the technical variabilities introduced by mammography in a similar fashion.

Finally, this work was meant to compare how the two unique imaging modalities of UST and mammography represent dense tissue. UST sound speed imaging is a novel imaging modality and gives a more direct representation of the tissue density than mammography does. These unique properties of UST sound speed imaging may ultimately overcome the limitations present in mammography in regards to the measurement of breast density. This work therefore lays the groundwork for further studies that will assess the role of sound speed imaging in risk prediction.

CONCLUSIONS

In this group of women with negative mammographic screens (N = 165), various volumetric breast density measurements made using UST were found to correlate strongly with 2-D breast density measurements made with mammography. The results presented here validate previous work done involving UST sound speed measures in symptomatic populations. These results reduce the uncertainties that were present in the previous work regarding breast density measurements and increase the confidence in the ability of UST to accurately measure breast density in a wider range of participants.

The mean and median sound speed values showed stronger correlations with MPD than UST percent density measures. The amount of dense tissue, whether measured using projected areas on a mammogram or volumetrically using one of two different methods on the UST sound speed images, was positively associated with the average UST and mammographic density measures. Although the segmentation methods used to create dense and non-dense volumes could still be improved, initial analysis of the dense and non-dense subregions using UST sound speed provides evidence that breast density is more than just the relative amounts of these tissues as visualized on an image. The relative density of these regions can vary, as the average density of the entire breast varies, but it is currently unknown whether this provides additional breast cancer risk information. Mammography and UST also show similar behavior when associated with participant age, weight and BMI.

UST is a useful tool that can be used to analyze breast density in ways that mammography cannot. These results suggest that UST and mammography provide different information about breast tissue composition. UST sound speed measurements have not been evaluated prospectively to estimate risk of developing breast cancer. However, given that UST breast density measures and MPD correlate strongly, it is expected that UST density measures will also be strong breast cancer risk factors. Future studies are needed to compare UST and MPD in risk prediction.

Acknowledgments—The authors wish to thank Dr. Norman Boyd for his work analyzing all mammograms and Ms. Vivian Linke for research assistance. The authors are indebted to the participants in the Ultrasound Study of Tamoxifen for their outstanding cooperation and to the physicians, pathologists, nurses and technologists for their efforts in the field. This research was supported in part by the Intramural Research Program of the National Institutes of Health, National Cancer Institute. The authors acknowledge the support of the National Institutes of Health through contract No HHSN261201400038P and grant No R44 CA165320 from the National Cancer Institute.

REFERENCES

- Bertrand KA, Scott CG, Tamimi RM, Jensen MR, Pankratz VS, Norman AD, Visscher DW, Couch FJ, Shepherd J, Chen YY,

- Fan B, Wu FF, Ma L, Beck AH, Cummings SR, Kerlikowske K, Vachon CM. Dense and nondense mammographic area and risk of breast cancer by age and tumor characteristics. *Cancer Epidemiol Biomarkers Prev* 2015;24:798–809.
- Boyd NF, Byng JW, Jong RA, Fishell EK, Little LE, Miller AB, Lockwood GA, Tritchler DL, Yaffe MJ. Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. *J Natl Cancer Inst* 1995;87:670–675.
- Byng JW, Boyd NF, Fishell E, Jong RA, Yaffe MJ. The quantitative analysis of mammographic densities. *Phys Med Biol* 1994;39:1629.
- Byrne C, Schairer C, Wolfe J, Parekh N, Salane M, Brinton LA, Hoover R, Haile R. Mammographic features and breast cancer risk: Effects with time, age, and menopause status. *J Natl Cancer Inst* 1995;87:1622–1629.
- Ciatto S, Bernardi D, Calabrese M, Durando M, Gentilini MA, Mariscotti G, Monetti F, Moriconi E, Pesce B, Roselli A, Stevanin C, Tapparelli M, Houssami N. A first evaluation of breast radiological density assessment by QUANTRA software as compared to visual classification. *Breast* 2012;21:503–506.
- Duric N, Boyd N, Littrup P, Sak M, Myc L, Li C, West E, Minkin S, Martin L, Yaffe M, Schmidt S, Faiz M, Shen J, Melnichouk O, Li Q, Albrecht T. Breast density measurements with ultrasound tomography: A comparison with film and digital mammography. *Med Phys* 2013a;40:013501.
- Duric N, Littrup P, Babkin A, Chambers D, Azevedo S, Kalinin A, Pevzner R, Tokarev M, Holsapple E, Rama O, Duncan R. Development of ultrasound tomography for breast imaging: Technical assessment. *Med Phys* 2005;32:1375–1386.
- Duric N, Littrup P, Chandiwala-Mody P, Li C, Schmidt S, Myc L, Rama O, Bey-Knight L, Lupinacci J, Ranger B, Szczepanski A, West E. *In vivo* imaging results with ultrasound tomography: Report on an ongoing study at the Karmanos Cancer Institute. *Proc. SPIE7629. Medical Imaging 2010: Ultrasonic Imaging, Tomography, and Therapy*.
- Duric N, Littrup P, Li C, Rama O, Bey-Knight L, Schmidt S, Lupinacci J. Detection and characterization of breast masses with ultrasound tomography: Clinical results. *Proc. SPIE7265. Medical Imaging 2009: Ultrasonic Imaging and Signal Processing*.
- Duric N, Littrup P, Poulo L, Babkin A, Pevzner R, Holsapple E, Rama O, Glide C. Detection of breast cancer with ultrasound tomography: First results with the Computed Ultrasound Risk Evaluation (CURE) prototype. *Med Phys* 2007;34:773–785.
- Duric N, Littrup P, Schmidt S, Li C, Roy O, Bey-Knight L, Janer R, Kunz D, Chen X, Goll J, Wallen A, Zafar F, Allada V, West E, Jovanovic I, Li K, Greenway W. Breast imaging with the SoftVue imaging system: First results. *Proc. SPIE8675. Medical Imaging 2013b: Ultrasonic Imaging, Tomography, and Therapy*.
- Eng A, Gallant Z, Shepherd J, McCormack V, Li J, Dowsett M, Vinnicombe S, Allen S, dos-Santos-Silva I. Digital mammographic density and breast cancer risk: A case-control study of six alternative density assessment methods. *Breast Cancer Res* 2014;16:439.
- Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among us adults, 1999–2010. *JAMA* 2012;307:491–497.
- Huo CW, Chew GL, Britt KL, Ingman WV, Henderson MA, Hopper JL, Thompson EW. Mammographic density—a review on the current understanding of its association with breast cancer. *Breast Cancer Res Treat* 2014;144:479–502.
- Jain AK, Dubes RC. Algorithms for clustering data. Upper Saddle River, NJ: Prentice-Hall; 1988.
- Jeffreys M, Harvey J, Highnam R. Comparing a new volumetric breast density method (Volpara) to cumulus. In: Martí J, Oliver A, Freixenet J, Martí R, (eds). *Digital mammography*. Heidelberg, Germany: Springer; 2010. p. 408–413.
- Khazen M, Warren RML, Boggis CRM, Bryant EC, Reed S, Warsi I, Pointon LJ, Kwan-Lim GE, Thompson D, Eeles R, Easton D, Evans DG, Leach MO. A pilot study of compositional analysis of the breast and estimation of breast mammographic density using three-dimensional T1-weighted magnetic resonance imaging. *Cancer Epidemiol Biomarkers Prev* 2008;17:2268–2274.
- Khodr ZG, Sak MA, Pfeiffer RM, Duric N, Littrup P, Bey-Knight L, Ali H, Vallieres P, Sherman ME, Gierach GL. Determinants of the reliability of ultrasound tomography sound speed estimates as a surrogate for volumetric breast density. *Med Phys* 2015;42:5671–5678.
- Kopans DB. Basic physics and doubts about relationship between mammographically determined tissue density and breast cancer risk. *Radiology* 2008;246:348–353.
- Li C, Duric N, Huang L. 2008 Clinical breast imaging using sound-speed reconstructions of ultrasound tomography data. *Proc. SPIE6920, Medical Imaging 2008: Ultrasonic Imaging and Signal Processing*.
- Mast TD. Empirical relationships between acoustic parameters in human soft tissues. *Acoust Res Lett Online* 2000;1:37–42.
- Masugata H, Mizushige K, Senda S, Kinoshita A, Sakamoto H, Sakamoto S, Matsuo H. Relationship between myocardial tissue density measured by microgravimetry and sound speed measured by acoustic microscopy. *Ultrasound Med Biol* 1999;25:1459–1463.
- McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: A meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2006;15:1159–1169.
- Pettersson A, Graff RE, Ursin G, Santos Silva Id, McCormack V, Baglietto L, Vachon C, Bakker MF, Giles GG, Chia KS, Czene K, Eriksson L, Hall P, Hartman M, Warren RML, Hislop G, Chiarelli AM, Hopper JL, Krishnan K, Li J, Li Q, Pagano I, Rosner BA, Wong CS, Scott C, Stone J, Maskarinec G, Boyd NF, van Gils CH, Tamimi RM. Mammographic density phenotypes and risk of breast cancer: A meta-analysis. *J Natl Cancer Inst* 2014;106. <http://dx.doi.org/10.1093/jnci/dju078>.
- Pettersson A, Hankinson SE, Willett WC, Lagiou P, Trichopoulos D, Tamimi RM. Nondense mammographic area and risk of breast cancer. *Breast Cancer Res* 2011;13:R100.
- Rasband WS. *ImageJ*. Bethesda, MD: US National Institutes of Health; 1997–2012.
- Regini E, Mariscotti G, Durando M, Ghione G, Luparia A, Campanino P, Bianchi C, Bergamasco L, Fonio P, Gandini G. Radiological assessment of breast density by visual classification (BI–RADS) compared to automated volumetric digital software (Quantra): Implications for clinical practice. *Radiol Med* 2014;119:741–749.
- Saftlas AF, Hoover RN, Brinton LA, Szklo M, Olson DR, Salane M, Wolfe JN. Mammographic densities and risk of breast cancer. *Cancer* 1991;67:2833–2838.
- Sak M, Duric N, Boyd NF, Littrup P, Myc L, Faiz M, Li C, Bey-Knight L. Relationship between breast sound speed and mammographic percent density. *Proc. SPIE7968, Medical Imaging 2011: Ultrasonic Imaging, Tomography, and Therapy*.
- Sak M, Duric N, Boyd N, Littrup P, West E, Li C. Breast tissue composition and breast density measurements from ultrasound tomography. *Proc. SPIE8320, Medical Imaging 2012: Ultrasonic Imaging, Tomography, and Therapy*.
- Sak M, Duric N, Littrup P, Bey-Knight L, Sherman M, Gierach G, Malyarenko A. Comparison of sound speed measurements on two different ultrasound tomography devices. *Proc. SPIE9040, Medical Imaging 2014: Ultrasonic Imaging, Tomography, and Therapy*.
- Sak M, Duric N, Littrup P, Li C, Bey-Knight L, Sherman M, Boyd NF, Gierach G. Breast density measurements using ultrasound tomography for patients undergoing tamoxifen treatment. *Proc. SPIE8675, Medical Imaging 2013: Ultrasonic Imaging, Tomography, and Therapy*.
- Sak MA. The role of tissue sound speed as a surrogate marker of breast density. *Ann Arbor, MI: Wayne State University*; 2013.
- Sak MA, Littrup PJ, Duric N, Mulooly M, Sherman ME, Gierach GL. Current and future methods for measuring breast density: A brief comparative review. *Breast Cancer Management* 2015;4:209–221.
- Schetter S, Hartman T, Liao J, Richie J, Prokopczyk B, DuBrock C, Signori C, Hamilton C, Demers L, El-Bayoumy K, Manni A. Differential impact of body mass index on absolute and percent breast density: Implications regarding their use as breast cancer risk biomarkers. *Breast Cancer Res Treat* 2014;146:355–363.

- Sickles EA, D'Orsi CJ, Bassett LW. ACR BI-RADS mammography. Reston, VA: American College of Radiology; 2013.
- Slanetz PJ, Freer PE, Birdwell RL. Breast-density legislation—practical considerations. *New Engl J Med* 2015;372:593–595.
- Sprague BL, Gangnon RE, Burt V, Trentham-Dietz A, Hampton JM, Wellman RD, Kerlikowske K, Miglioretti DL. Prevalence of mammographically dense breasts in the United States. *J Natl Cancer Inst* 2014; 106. <http://dx.doi.org/10.1093/jnci/dju255>.
- Thompson DJ, Leach MO, Kwan-Lim G, Gayther SA, Ramus SJ, Warsi I, Lennard F, Khazen M, Bryant E, Reed S. Assessing the usefulness of a novel MRI-based breast density estimation algorithm in a cohort of women at high genetic risk of breast cancer: The UK MARIBS study. *Breast Cancer Res* 2009;11: R80.
- Weiward W, Heinig A, Goetz L, Hartmann H, Lampe D, Buchmann J, Millner R, Spielmann RP, Heywang-Koebrunner SH. Direct measurement of sound velocity in various specimens of breast tissue. *Invest Radiol* 2000;35:721–726.
- Yaffe MJ. Mammographic density. Measurement of mammographic density. *Breast Cancer Res* 2008;10:1–10.