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Original Research

Whole Breast Sound Speed Measurement from US Tomography Correlates Strongly with Volumetric Breast Density from Mammography

Mark Sak, PhD,[1] **Peter Littrup, MD,**[1] **Rachel Brem, MD,**[3]
Neb Duric, PhD*[1,2]

[1]Delphinus Medical Technologies, Inc, Novi, MI; [2]Wayne State University, Barbara Ann Karmanos Cancer Institute, Department of Oncology, Detroit, MI; [3]George Washington University, Department of Radiology, Washington, DC

*Address correspondence to N.D. (e-mail: nduric@delphinusmt.com)

Abstract

Objective: To assess the feasibility of using tissue sound speed as a quantitative marker of breast density.
Methods: This study was carried out under an Institutional Review Board–approved protocol (written consent required). Imaging data were selected retrospectively based on the availability of US tomography (UST) exams, screening mammograms with volumetric breast density data, patient age of 18 to 80 years, and weight less than 300 lbs. Sound speed images from the UST exams were used to measure the volume of dense tissue, the volume averaged sound speed (VASS), and the percent of high sound speed tissue (PHSST). The mammographic breast density and volume of dense tissue were estimated with three-dimensional (3D) software. Differences in volumes were assessed with paired t-tests. Spearman correlation coefficients were calculated to determine the strength of the correlations between the mammographic and UST assessments of breast density.
Results: A total of 100 UST and 3D mammographic data sets met the selection criteria. The resulting measurements showed that UST measured a more than 2-fold larger volume of dense tissue compared to mammography. The differences were statistically significant ($P < 0.001$). A strong correlation of $r_s = 0.85$ (95% CI: 0.79–0.90) between 3D mammographic breast density (BD) and the VASS was noted. This correlation is significantly stronger than those reported in previous two-dimensional studies ($r_s = 0.85$ vs $r_s = 0.71$). A similar correlation was found for PHSST and mammographic BD with $r_s = 0.86$ (95% CI: 0.80–0.90).
Conclusions: The strong correlations between UST parameters and 3D mammographic BD suggest that breast sound speed should be further studied as a potential new marker for inclusion in clinical risk models.

Key words: US tomography; breast density; sound speed; breast cancer risk.

Introduction

Increased breast density (BD) significantly reduces the sensitivity of breast cancer detection on mammography. For women with extremely dense breast tissue, up to 50% of breast cancers may not be mammographically visible (1). Increased BD is also a strong independent risk factor for

Key Messages

- Sound speed measurements derived from US tomography correlate strongly with volumetric breast density (BD) measurements from mammography.
- The volume averaged sound speed (VASS) of the breast is a quantitative marker of BD that can be safely measured for women of all ages.
- The VASS has the potential to be used in clinical models to improve breast cancer risk prediction in individuals.

breast cancer. Women with extremely dense breasts have up to a 4- to 6-fold increased risk of developing breast cancer relative to women with entirely fatty breasts (2–4).

Clinical risk assessment facilitates preventive strategies and improves clinical decision making (5). The most widely used current methods of evaluating the risk of breast cancer are the Gail model (6) and the Tyrer–Cuzick model (7). Mammographic BD is a biomarker associated with breast cancer risk (2,8–12), and its addition to these models increases individual risk prediction (7,11). However, BD is not routinely used in clinical settings for risk prediction. While mammographic BD is a strong population-based risk factor, it has only a modest impact on predictions of individual risk (7,11).

Measurement of BD has been attempted with other imaging modalities. MRI BD measurements, for example, have been shown to yield a high degree of correlation with mammographic BD (13–20). However, MRI is not tolerated well by everyone and is not widely available at a reasonable price to make it practical for routine BD measurements.

US tomography (UST) is an emerging technology that can measure the sound speed properties of breast tissue (21–30). In human breast tissue, there is a linear relationship between tissue sound speed and tissue density (31,32). Since increased BD is a known risk factor for breast cancer, sound speed images can potentially offer new insight into this relationship without the use of ionizing radiation.

The largest previous UST study of BD showed a strong correlation between breast sound speed and mammographic BD (21). However, the study was limited for two reasons. First, the UST sound speed images were of low spatial resolution (5 mm) and, second, only two-dimensional (2D) estimates of mammographic density were used. In this study, a newly developed UST reconstruction algorithm yielding much higher resolution (0.7 mm) sound speed images was used (Figure 1). The improved UST imaging, combined with the use of three-dimensional (3D) mammographic BD estimates, represents a major advance relative to past studies.

The purpose of this study is to quantify the correlation between UST and 3D mammographic BD to (1) assess the feasibility of using volume averaged sound speed (VASS) and the percentage of high sound speed tissue (PHSST) as independent measures of BD, (2) determine whether the VASS and the PHSST correlate better with 3D BD versus 2D BD measurements, and (3) discuss the VASS and the PHSST as possible markers for inclusion in clinical risk models.

Methods

Study Population

This study was carried out under an Institutional Review Board–approved protocol, in compliance with the Health

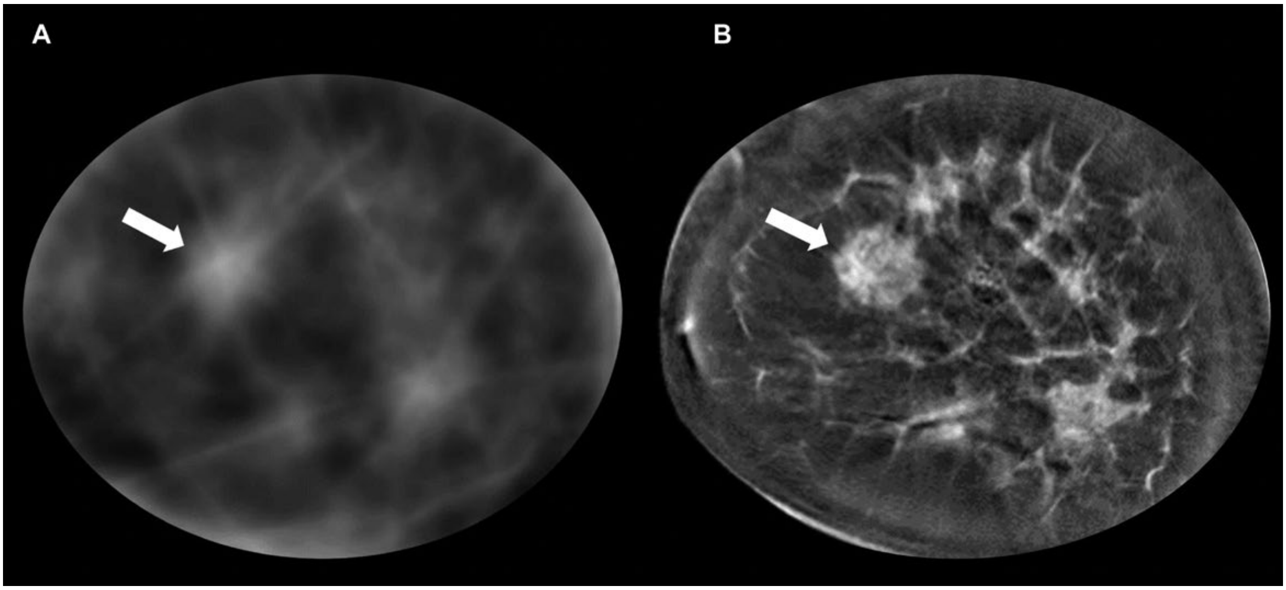

Figure 1. **A**: Example of a ray-based sound speed reconstruction used in previous studies. **B**: A waveform reconstruction of the same data shows superior resolution and visibility of more complex parenchymal structures at 4 o'clock compared with the actual underlying irregular cancer at 10 o'clock (arrow).

Insurance Portability and Accountability Act. Informed consent was obtained from all patients. The UST data used in this study were obtained from a previous study of patients with a suspicious finding in their breast (33). As a result, most subjects had a mass in the breast that was scanned by UST. Patients with locally advanced breast cancer were thus excluded because those tumors may have been large enough to influence the overall breast sound speed and mammographic density.

Imaging data were selected retrospectively by searching patient records. The selection criteria were the availability of an UST exam, a screening mammogram with accompanying volumetric BD data, patient age of 18 to 80 years, and weight less than 300 lbs. Patients with prior breast radiation or with inflammatory breast cancer were excluded, since these processes alter the acoustic properties of the entire breast.

Women who underwent both a UST scan and a volumetric analysis of their mammogram at the Barbara Ann Karmanos Cancer Center (Detroit, MI) over the May 2014 to February 2016 period were included. In order to limit temporal changes in BD, only those patients that received a UST scan within a 365-day period relative to the mammogram were included. In total, 100 UST breast scans were matched with mammograms that included automated BD information.

Study Design

This study was designed to compare UST parameters with 3D mammographic BD measurements. An automated mammographic density measurement software tool that measures BD volumetrically and therefore provides a standard for comparison with UST measurements (Volpara Solutions, LLC, Wellington, New Zealand) was used in this study. Measurements included total breast volume, total dense tissue volume, percent density, and the density grade from each mammogram per the Breast Imaging Reporting and Data System (BI-RADS) (34).

The sound speed measurements were performed with a UST scanner (Delphinus Medical Technologies, Inc., Novi, MI). The UST images were obtained with the patient in a prone position on a table, with the breast immersed in a warm water bath. The UST system generates an image at each position of the transducer, yielding a stack of images representing the 3D volume distribution of sound speed for each breast scanned. The sound speed images (Figure 2) were produced from waveform tomography algorithms yielding sub-mm spatial resolution (24). By comparison, in previous work, sound speed images were produced from bent ray algorithms that yielded sub-cm resolution (26).

Total breast volume, volume of high sound speed tissue, the VASS, and the PHSST were calculated from the sound speed image stacks. The VASS is the average sound speed of the breast expressed in units of meters per second. It is calculated by summing the sound speed in all voxels that correspond to the breast tissue and then dividing it by the total number of voxels. On the other hand, PHSST is analogous to mammographic percent density and is expressed as the percentage of the breast volume that is dense, in the range 0%–100%. The PHSST is determined using a k-means segmentation algorithm that separates the sound speed image into dense and nondense regions. Each UST measurement was paired with its corresponding volumetric BD measurement.

Examples of images used in this study are shown in Figure 3. Representative mammograms and UST sound speed slices are shown for each of the four BI-RADS BD categories.

Statistical Analyses

Paired t-tests were used to assess differences in the UST and mammographic measures. Differences were considered significant for levels of < 0.05. Spearman correlation coefficients and the associated 95% confidence intervals (CIs) were calculated to determine the strength of the correlations between the mammographic measurements of BD and the UST measurements of the VASS and the PHSST.

An analysis of measurement errors was performed relating to the presence of masses in the UST images and mammograms. These masses contributed to all density measurements independently of the normal breast tissue, leading to potential measurement errors. The impact of each mass on BD measurements was assessed by estimating its contribution to the total breast volume and associated mammographic and UST parameters. The resulting contributions were compared to the scatter in the UST volumetric density correlations to determine their significance.

Results

Patient Characteristics

On average, the UST scan was performed 35 (1–365) days before the mammogram with the volumetric density analysis. However, the relative scan timing was skewed due to the short time frame when the density software was in use at the study site (February 2015–March 2016). For 63 of the patients in this study, the UST scan was performed shortly after a suspicious finding was observed on the screening mammogram with the density reading. For 26 patients, the mammogram with the density reading was performed up to a year after their UST scan, as the UST scan would have been more directly linked to a finding on the preceding year's screening mammogram.

Patient characteristics of age, height, weight, and body mass index are summarized in Table 1. Seventy-five percent of the participants were African American, 18.5% were white, and 6.5% were of an other ethnicity. The racial percentages are typical of patients seen at this cancer center.

Mammographic and UST Volume Comparisons

The average volumes of breast tissue that were measured by mammography and UST were compared (Table 2). The UST measured an approximately 10% smaller volume of total

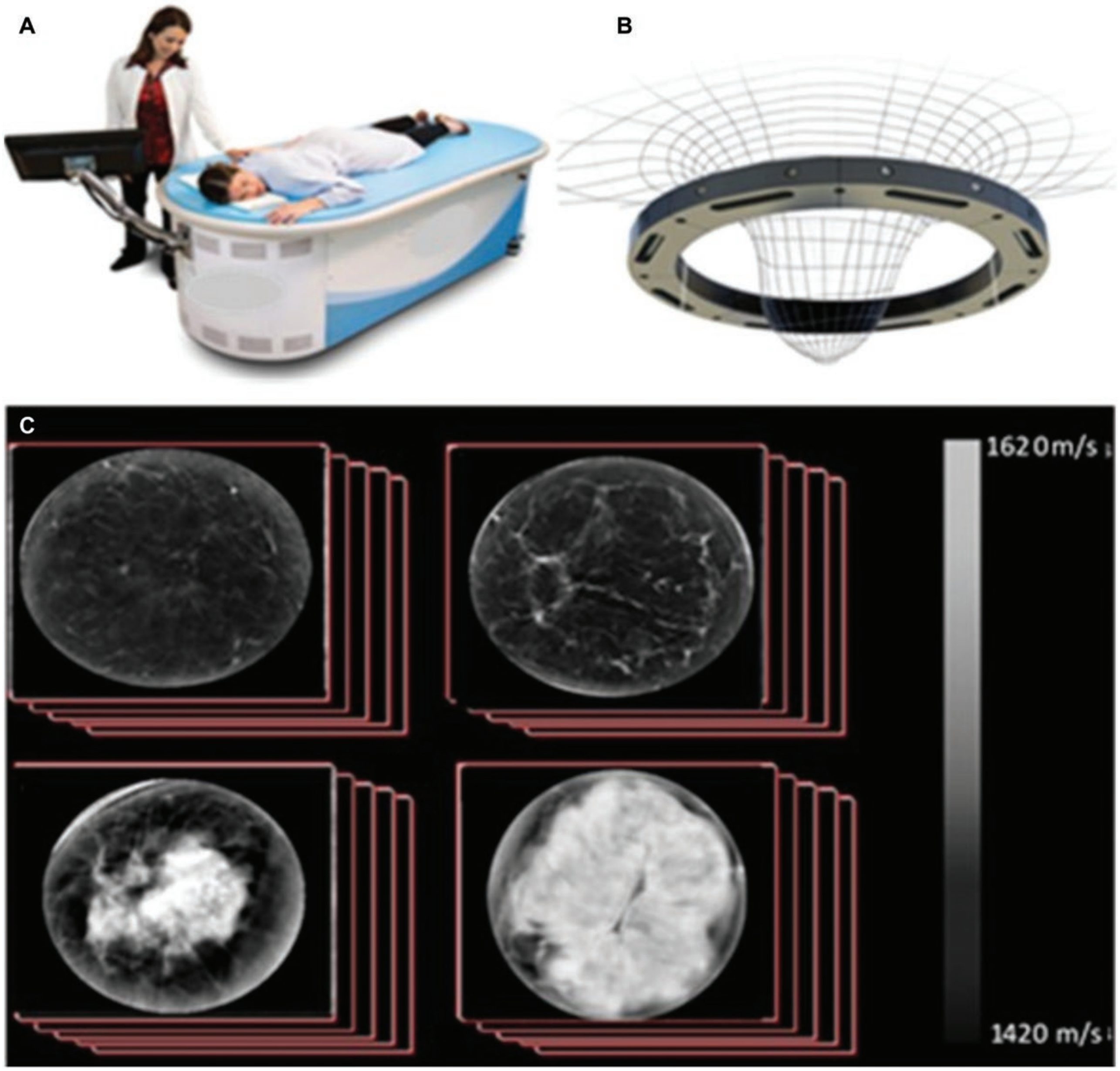

Figure 2. **A:** The clinical UST scanner. A patient lies prone on the table such that the breast is suspended inside a water tank that contains the US ring array transducer. **B:** The transducer moves vertically to scan the whole breast. **C**: Example image stacks of sound speed, as shown for cases ranging across the four BI-RADS breast density categories. The quantitative scale shown indicates the absolute measurements acquired. Abbreviations: BI-RADS, Breast Imaging Reporting and Data System; UST, US tomography.

breast tissue but a more than 2-fold larger volume of dense tissue. All UST versus mammography comparisons showed statistically significant differences in the average values using a paired t-test ($P < 0.001$).

Very strong correlations (Spearman) were found between mammographic and UST total volume and fatty volume (Table 2). However, there is only a moderate correlation between the mammographic and UST volumes of dense tissue.

Mammographic BD and UST Sound Speed Comparisons

The VASS and the PHSST parameters were found to be strongly correlated with mammographic BD. Figure 4 shows the correlations of the VASS versus mammographic BD and correlations of PHSST versus mammographic BD. The correlations are characterized by Spearman correlation coefficients of 0.85 (95% CI: 0.79–0.90) and 0.86 (95% CI: 0.80–0.90), respectively.

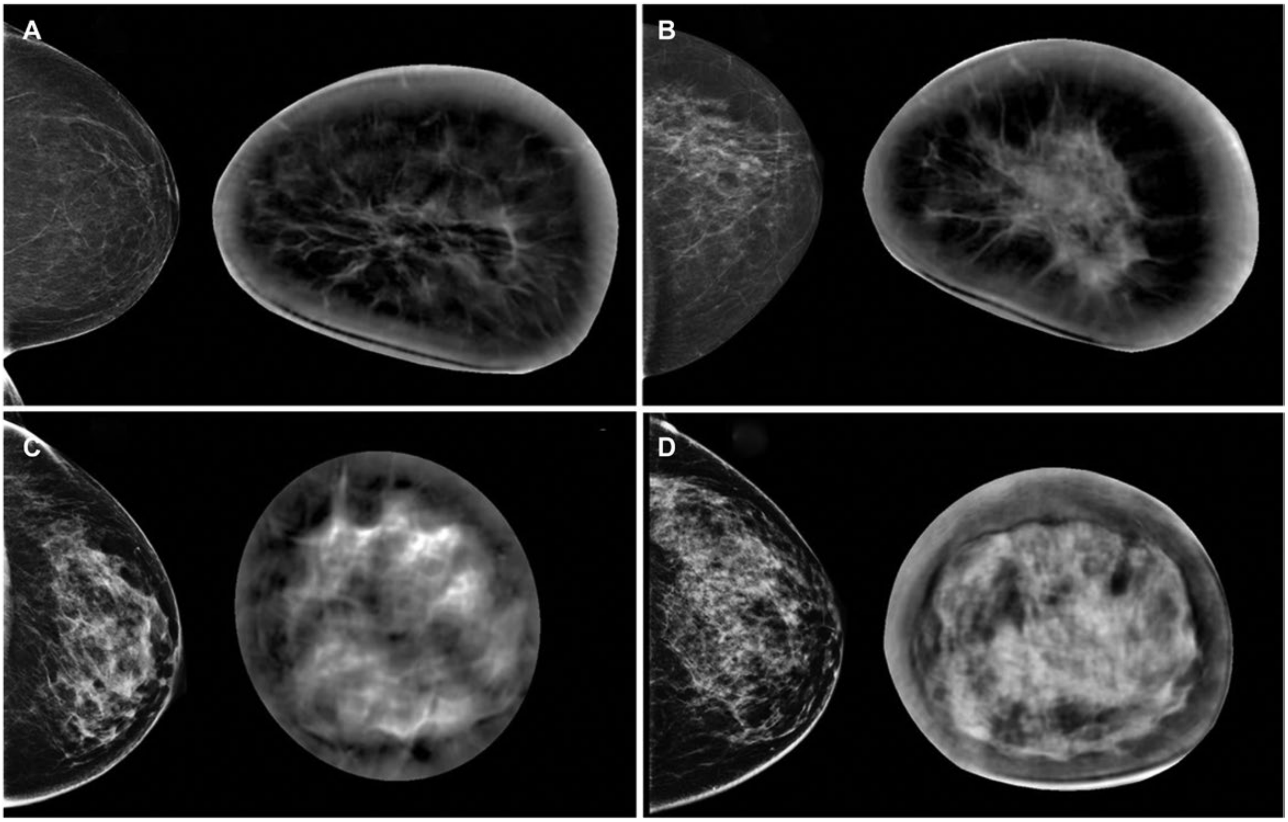

Figure 3. Examples of mammograms and representative sound speed slices corresponding to the four BI-RADS breast density categories: fatty (**A**), scattered (**B**), heterogeneous (**C**), and extremely dense (**D**). Within each frame, the mammogram is to the left of the sound speed image. The sound speed slices are approximately midbreast and are shown in the coronal view. Abbreviation: BI-RADS, Breast Imaging Reporting and Data System.

Table 1. Patient Characteristics of the Study Group

Characteristic	Average	Standard Deviation	Range
Age (years)	51.5	10.6	27–77
Height (inches)	64.7	2.8	57–73
Weight (lbs)	178.9	37.8	115–294
BMI (kg/m^2)	30.0	6.2	20–48

Abbreviation: BMI, body mass index.

The mammography density software also produces a BI-RADS density score for each mammogram based on the highest percent density measure. For this group, the software counted 23 as fatty (BI-RADS), 28 as scattered, 36 as heterogeneous, and 13 as extremely dense breasts. The mean VASS and mean PHSST were calculated for each of these groups from the sound speed data. Boxplots show a similar separation of BI-RADS density scores for the PHSST versus the VASS (Figure 5).

Impact of Measurement Errors

As noted in the "Methods" section, an analysis of measurement errors was performed relating to the presence of masses in the UST images and mammograms. Most masses ranged in size from 1 to 2 cm (~1–5 cm^3 in volume), and for a typical breast volume of 1000 cm^3 this represented < 0.5% of the net volume of the breast. Furthermore, the masses were present in both the UST and mammography measurements, so a significant bias in the comparison of the two modalities was further mitigated. These uncertainties were found to be well below the scatter in the observed correlations between the UST and mammographic BD measurements (Figure 4).

Discussion

Overall, very strong correlations between the UST measures of the VASS and the PHSST with 3D mammographic BD were found. The higher resolution UST sound speed images may better separate dense and nondense tissue compared to estimates that are made from a mammogram. The ability to better visualize and characterize dense tissue may ultimately improve risk stratification compared to density measurements made with mammography.

The average UST breast volume was slightly lower than that of mammography measured by the automated BD software. Additional evidence to that effect can be found in some studies that compare MRI BD versus mammographic BD

Table 2. Direct Breast Volume Comparisons of the Major Breast Tissue Components Between Mammographic and UST Measurements

Volume Measure	BD Average	UST Average	Spearman Coefficient (BD vs UST) (95% CI)
Total breast volume (cm^3)	1103	1003	0.80 (CI: 0.72–0.86)
Dense tissue volume (cm^3)	80	191	0.59 (CI: 0.44–0.70)
Fatty tissue volume (cm^3)	1023	812	0.82 (CI: 0.75–0.88)
Percent dense tissue—PHSST (%)	8.8	22.6	0.86 (CI: 0.80–0.90)

Abbreviations: BD, breast density; CI, confidence interval; PHSST, percent high sound speed tissue; UST, US tomography.

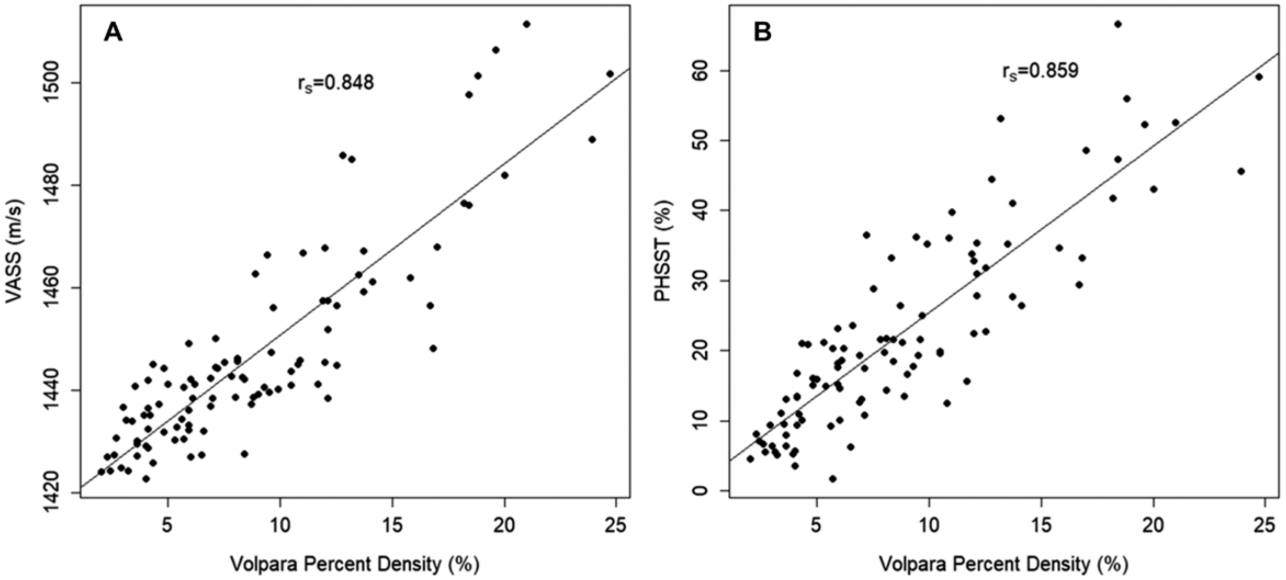

Figure 4. Comparison between UST and mammography density measurements. **A**: VASS compared to volumetric mammography measurement (Volpara, Volpara Solutions LLC, Wellington, NZ). **B**: PHSST compared to volumetric mammography measurement. Abbreviations: BD, breast density; PHSST, percent high sound speed tissue; UST, US tomography; VASS, volume averaged sound speed.

(13), which find that the software tends to overestimate the breast volume relative to MRI. However, not all studies show a significant discrepancy (14). Any differences are likely due to the different whole breast segmentation methods that were used.

The PHSST method classifies significantly more tissue as dense, leading to a much higher percent densities compared to mammography. This difference could be attributed to several factors. First, UST sound speed is a measure of physical density, while x-ray absorption arises from both density and composition. Second, the k-means clustering used in the PHSST estimation is likely very different from the proprietary technique used by the mammography software. And finally, the automated BD software attempts to recover 3D information from a compressed volume, which likely results in both random and systematic errors compared to a true 3D estimation. Further evidence of this effect can be found in studies that compare MRI BD versus mammographic BD (13,14). These studies find that mammographic BD is lower by a factor of 2 compared to MRI-based BD, whereas studies comparing UST versus MRI show that the density measures are more similar (23).

By comparing the UST method against modalities that produce progressively more accurate volumetric measurements, it was found that the correlation coefficient for UST increases steadily (Table 3). This result is consistent with UST being a more volumetric measure of BD compared to any mammographic methods. Comparison of MRI with 2D and 3D mammographic BD shows a remarkably similar trend with similar Spearman coefficient values when comparing MRI versus mammography and comparing UST versus mammography. These similarities suggest that UST methods of measuring BD may be effective, low-cost surrogates for MRI measurements. In fact, a previous study has reported that UST VASS correlates with noncontrast MRI PD with a correlation coefficient as high as 0.96 (23). Should UST be accepted as a screening modality in the future, it will have the potential to be a more accurate alternative to mammographic measures of BD by removing the barriers that prevented MRI from becoming an effective alternative. Furthermore,

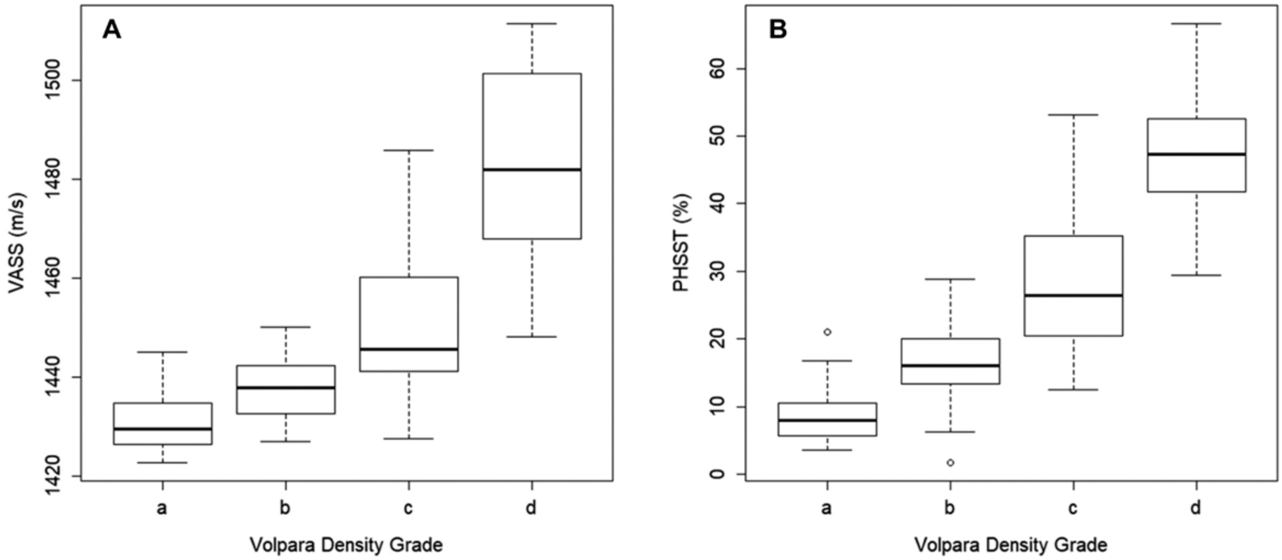

Figure 5. US tomography results averaged by BI-RADS density category (fatty [a], scattered [b], heterogeneous [c], and extremely dense [d]), as generated by automated breast density software (Volpara, Volpara Solutions LLC, Wellington, NZ). **A**: Boxplot of VASS. **B**: Boxplot of PHSST. Abbreviations: BI-RADS, Breast Imaging Reporting and Data System; PHSST, percent high sound speed tissue; UST, US tomography; VASS, volume averaged sound speed;

Table 3. Comparison of Published Studies of UST and MRI Techniques with Mammographic BD Methods

UST vs	Correlation Coefficient Range	MRI vs	Correlation Coefficient Range
2D mammography	0.7–0.75 (21,25,26)	2D mammography	0.70–0.80 (13–15,17–20)
3D mammography	0.85–0.86 [this work]	3D mammography	0.80–0.88 (16,18)
MRI	0.94–0.96 (23)		

Abbreviations: BD, breast density; UST, US tomography.

it may be possible to address discrepancies in the literature about the correlation of BD and background parenchymal enhancement (BPE), where some literature (14,15) suggests that BPE is a biomarker of risk independent of BD.

The methods studied here represent an absolute quantitative measure (VASS) and a relative quantitative percentage (PHSST). The VASS, unlike methods based on other modalities, is expressed in physical units (meters per second) and, unlike the percentage methods, VASS does not contain any subjective elements, assumptions, segmentation, or thresholding. In this study it has been shown to correlate with mammographic BD as strongly as the percentage methods while maintaining its quantitative aspect. The PHSST, on the other hand, calculates percentages based on a k-means segmentation algorithm that selects dense and fatty regions. A third method called quantitative BD (QBD) has recently been proposed for comparing UST with mammographic BD (30). In this method, a threshold on the sound speed image is used to separate dense tissue from fat. In a study of 25 cases, a strong correlation was found between QBD and mammographic BD (30); however, this method is also limited to only calculating percentages. The three methods are all highly differentiated from each other, yet they all confirm the strong correlation between UST sound speed and mammographic BD.

This study was performed in a hospital under routine clinical conditions, which provided insight into the practical use of the VASS and PHSST methods. With a typical scan time of 1 to 2 minutes per breast, the UST exams were well tolerated by patients and the impact on workflow was minimal.

The VASS can be used as a relatively objective representation of BD that is not impacted by image processing, as it relies on a fixed physical unit derived from the sound speed image. Reducing the technical variations in BD measurements (as in mammography) would likely improve risk prediction and assist with clinical decision making. Recent studies suggest that breast cancer risk assessment using VASS may in fact be stronger than that performed with mammography (35). These results show that VASS may present a finer grade of density and, therefore, risk assessment compared to mammography. Breast density-related measurements such as the VASS may ultimately be better indicators of individual risk compared to mammographic measures.

Breast density in younger women is an understudied area. In the United States, approximately 70 million women are between 18 and 40 years of age and largely ineligible for mammographic screening. Having a technique that could track changes in BD without ionizing radiation could be highly beneficial for predicting disease development later in life. Furthermore, since BD is inversely related to age, these younger women are more likely to have higher BD. Measuring differences at these systematically higher densities would be challenging for mammography. However, the quantitative aspect of the VASS, for example, could facilitate the measurement of such differences.

A limitation of our study is that patients had both benign and malignant masses that were not segmented out from the mammograms or the UST images. While it has been shown previously that the presence of these findings is unlikely to greatly affect the ability to accurately classify BD using UST (21,25), a study focused on the contralateral breast would be preferred. In addition, this particular sample may be biased toward higher BD compared to the general population. The skewed racial distribution of the population studied may have introduced a bias, as no attempt was made to identify a matched cohort between African American and Caucasian women. Nevertheless, since these effects are likely minor and since both UST and mammography are biased the same way, the relative comparison remains valid while providing insight into this understudied population. Finally, the study size is small, limited by the availability of automated BD software at this institution. Future studies are needed to validate these results in a larger population.

Conclusions

The purpose of this work was to provide a direct comparison of volumetric sound speed measurements versus volumetric mammographic measurements and to assess the viability of sound speed as a quantitative marker of BD. In this study of 100 breasts, very strong correlations were found between mammographic BD and the UST parameters of the VASS and the PHSST. The VASS correlation is significantly stronger than those reported in previous 2D studies ($r_S = 0.85$ vs $r_S = 0.71$, respectively). Based on this strong correlation and its practicality, compared to percentage measurements, it is proposed that the VASS would be a viable candidate for inclusion in clinical risk models. Future studies will test the potential of the VASS to provide better stratification of breast cancer risk compared to mammographic BD. Furthermore, since UST is nonionizing, the VASS could be studied in a broader population of women, including those below the screening age.

Funding

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Conflict of Interest Statement

N. Duric and P. Littrup are coinventors of and have intellectual property interests in the ultrasound technology used for the measurements described in this paper. R. Brem sits on the board of directors and M. Sak is an employee of Delphinus.

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