Comparison of breast density measurements made using ultrasound tomography and mammography

Mark Sak[1], Neb Duric[1,2], Peter Littrup[1,2], Lisa Bey-Knight[1], Mark Krycia[2], Mark E. Sherman[3], Norman Boyd[4], Gretchen L. Gierach[5]

[1]Karmanos Cancer Institute, Wayne State University, 4100 John R Street, Detroit MI 48201

[2]Delphinus Medical Technologies, 46701 Commerce Center Dr, Plymouth, MI, 48170

[3]National Cancer Institute, Division of Cancer Prevention, Breast and Gynecologic Cancer Research Group, 9609 Medical Center Drive, Room 5E334, Bethesda, MD 20892

[4] Princess Margaret Hospital, 610 University Ave., Toronto, Ontario, Canada M5G 2M9

[5]National Cancer Institute, Division of Cancer Epidemiology and Genetics, Hormonal and Reproductive Epidemiology Branch, 9609 Medical Center Drive, Rm. 7-E108, Bethesda, MD 20892

ABSTRACT

Women with elevated mammographic percent density, defined as the ratio of fibroglandular tissue area to total breast area on a mammogram are at an increased risk of developing breast cancer. Ultrasound tomography (UST) is an imaging modality that can create tomographic sound speed images of a patient's breast, which can then be used to measure breast density. These sound speed images are useful because physical tissue density is directly proportional to sound speed. The work presented here updates previous results that compared mammographic breast density measurements with UST breast density measurements within an ongoing study. The current analysis has been expanded to include 158 women with negative digital mammographic screens who then underwent a breast UST scan. Breast density was measured for both imaging modalities and preliminary analysis demonstrated strong and positive correlations (Spearman correlation coefficient $r_s = 0.703$). Additional mammographic and UST related imaging characteristics were also analyzed and used to compare the behavior of both imaging modalities. Results suggest that UST can be used among women with negative mammographic screens as a quantitative marker of breast density that may avert shortcomings of mammography.

Keywords: Ultrasound tomography. Breast density. Breast cancer risk. Mammography. Sound speed.

1. INTRODUCTION

Ultrasound tomography (UST) is an emerging imaging modality that is currently used to produce three-dimensional images of breast tissue[1, 2]. UST uses sound waves to measure the transmission and reflection properties of the breast anatomy[3]. One of these transmission properties is tissue sound speed. High breast density is a strong breast cancer risk factor[4-6] and sound speed is directly proportional to physical breast density. The longitudinal sound speed of any material is given by:

$$v = \sqrt{\frac{C}{\rho}}$$

where C is the bulk modulus and ρ is the density of the material in question. Studies have shown that the bulk modulus of breast tissue scales with the cube of its density[7-9]. This suggests that for breast tissue, the velocity has a direct relationship with density.

Mammography is currently the primary method of breast cancer screening. As such, it is also commonly used to measure breast density. Breast density can quantitatively be measured from a mammogram by the calculation of a computer-generated value known as mammographic percent density (MPD). MPD is the ratio of fibroglandular to total breast area as measured on a mammogram. MPD is likely to bear some relationship to the actual tissue density of the breast, but the relationship is not direct. Notably, density measurement with mammography is inherently limited because it is based on a two dimensional representation of three dimensional anatomy[10].

Previous work[11-13] has compared the density measurements made by both UST and mammography and shown that the two different imaging modalities correlate strongly with each other. However, these results were accomplished using patients that were enrolled for various other research topics. A uniform data set was not used as patients that were imaged before were not screened according to a standardized research protocol. The work presented here is the analysis and comparison of the two different imaging modalities among women who had negative mammographic screening results and are participating in a larger epidemiologic study.

2. METHODS AND MATERIALS

As part of a larger ongoing study[14], 158 women with negative mammographic screens have undergone UST scans. The UST hardware creates tomographic sound speed images of the breast from the chest wall to the nipple. These sound speed images were analyzed by one reader using a semi-automated method in ImageJ as previously described[11, 15]. Each slice containing breast tissue was manually segmented from the surrounding water bath using an elliptical approximation. This was required as the sound speed of water is intermediate to the range of sound speeds of breast tissue and therefore simple thresholding could not be used to separate breast tissue from water. Once segmentation was complete, the remaining voxels represent breast tissue and were averaged to calculate the average breast sound speed for each patient.

The quantitative nature of the sound speed images allowed for additional information to be obtained. A sound speed threshold value was applied to segment the sound speed images into dense and fatty regions. This approach was similar to how mammographic percent density is calculated. However, unlike mammography, this threshold value was uniformly applied to all sound speed images. In addition, these dense and fatty regions then had their average sound speed calculated.

In addition, 138 of the participants had also received a digital mammogram with a recommendation for continued routine screening. Mammographic density was assessed by one reader using CUMULUS[16]. This interactive computer assisted method was used to obtain measurements of the areas of dense tissue and total area on each mammogram. From these measurements, the area of non-dense tissue and percent density were calculated. Additional patient characteristics, including age, race, menopausal status and measured weight and height were collected at the time of the UST scan.

3. RESULTS AND DISCUSSION

3.1 Correlations with Breast Density Measurements

Table 1 shows the Spearman correlation coefficients between the two breast density measures, UST sound speed and mammographic percent density, with the various imaging and patient characteristics. Figure 1 shows the correlation between the two breast density measures, the UST volume averaged sound speed and the mammographic percent density.

The plot in Figure 1 shows a strong and positive correlation of $r_s = 0.703$ between UST volume average sound speed and mammographic percent density. This suggests that UST whole volume sound speed is an accurate measure of breast density, on par with the current standard of mammography. This result is similar to the results produced previously comparing the two different imaging modalities. However, previous results used mixed patient data collected from assorted studies whereas, the results here are from a set of study participants with negative mammographic screening results. The range of breast densities measured here is low, with a majority of patients displaying low or moderate breast densities and only a few patients with high densities.

Table 1 – Correlations Between Different Density Measurements and Various Patient and Imaging Characteristics

	UST Volume Average Sound Speed Correlations			Mammographic Percent Density Correlations		
	Count	Spearman Coefficient	p-value	Count	Spearman Coefficient	p-value
Patient Related Characteristics						
Age (years)	158	-0.260	< 0.001	138	-0.167	0.050
BMI (kg/m^2)	158	-0.437	< 0.001	138	-0.547	< 0.001
Weight (pounds)	158	-0.439	< 0.001	138	-0.542	< 0.001
Height (inches)	158	0.145	0.117	138	0.087	0.309
Mammography Related Imaging Characteristics						
Mammographic Percent Density	138	0.703	< 0.001		N/A	
Dense Area (cm^2)	138	0.609	< 0.001	138	0.797	< 0.001
Non Dense Area (cm^2)	138	-0.481	< 0.001	138	-0.758	< 0.001
Total Breast Area (cm^2)	138	-0.330	< 0.001	138	-0.586	< 0.001
UST Related Imaging Characteristics						
Mean Sound Speed (km/s)		N/A		138	0.703	< 0.001
Dense Volume (cm^3)	158	0.411	< 0.001	138	0.156	0.068
Dense Fraction	158	0.932	< 0.001	138	0.684	< 0.001
Dense Sound Speed (km/s)	158	0.426	< 0.001	138	0.294	< 0.001
Non-Dense Volume (cm^3)	158	-0.496	< 0.001	138	-0.520	< 0.001
Non-Dense Fraction	158	-0.932	< 0.001	138	-0.684	< 0.001
Non-Dense Sound Speed (km/s)	158	0.810	< 0.001	138	0.522	< 0.001
Total Volume (cm^3)	158	-0.299	< 0.001	138	-0.405	< 0.001

The results in Table 1 show that UST sound speed correlations with other UST related imaging characteristics are stronger than mammographic percent density. Also, mammographic percent density correlates better with mammographic imaging characteristics than UST sound speed.

Age and weight are known factors that affect breast density and breast cancer risk. In these results, age shows a weak but negative correlation with both density measurements. Weight and BMI do show the expected result of moderate and negative correlations with breast density. In this study population, BMI and weight have a stronger correlation with density measures than age.

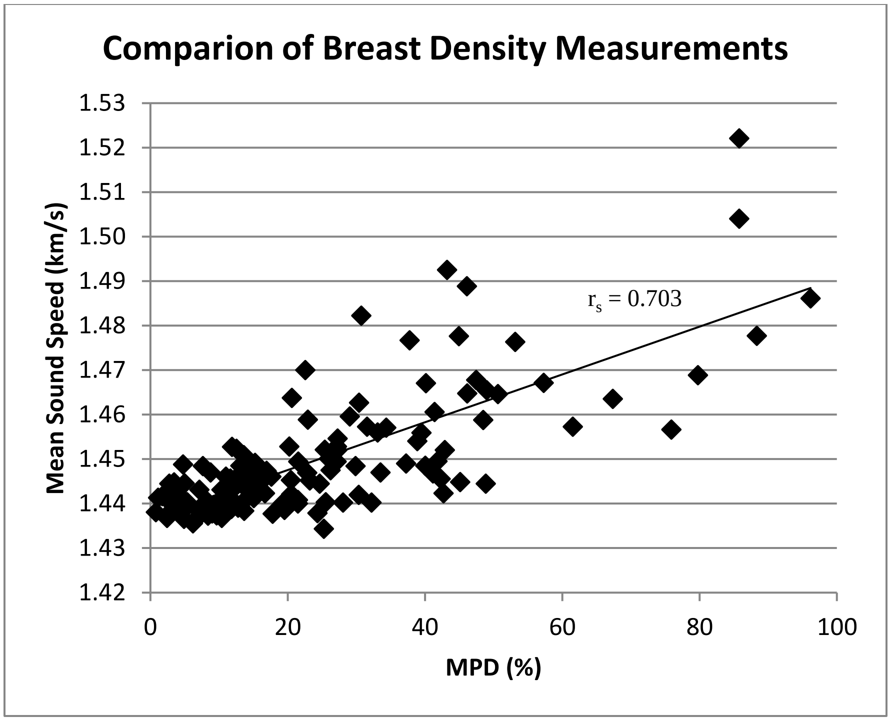

Figure 1 – Plot of UST whole volume average sound speed versus mammographic percent density.

Table 2 – Correlation Matrix Between Other Mammographic and UST Characteristics

		Patient Characteristics				Mammography Characteristics		
		Age	**BMI**	**Weight**	**Height**	**Dense Area**	**Non Dense Area**	**Total Area**
Patient Characteristics	**Age**	N/A	N/A	N/A	N/A	-0.217 (0.010)	0.053 (0.536)	0.003 (0.970)
	BMI	0.020 (0.800)	N/A	N/A	N/A	-0.268 (0.001)	0.578 (< 0.001)	0.538 (< 0.001)
	Weight	0.036 (0.651)	0.898 (< 0.001)	N/A	N/A	-0.265 (0.002)	0.583 (< 0.001)	0.540 (< 0.001)
	Height	-0.043 (0.583)	-0.177 (0.024)	0.201 (0.010)	N/A	0.140 (0.103)	0.011 (0.894)	0.033 (0.704)
UST Characteristics	**Dense Volume**	-0.240 (0.002)	0.057 (0.475)	0.023 (0.776)	0.031 (0.701)	0.412 (< 0.001)	0.175 (0.040)	0.322 (< 0.001)
	Dense Fraction	-0.250 (0.002)	-0.453 (< 0.001)	-0.454 (< 0.001)	0.116 (0.147)	0.538 (< 0.001)	-0.521 (< 0.001)	-0.385 (< 0.001)
	Dense Sound Speed	-0.071 (0.375)	-0.196 (0.014)	-0.187 (0.019)	0.088 (0.271)	0.161 (0.059)	-0.268 (0.002)	-0.200 (0.019)
	Non-Dense Volume	0.039 (0.630)	0.566 (< 0.001)	0.531 (< 0.001)	-0.061 (0.446)	-0.157 (0.065)	0.691 (< 0.001)	0.679 (< 0.001)
	Non-Dense Fraction	0.251 (0.001)	0.453 (< 0.001)	0.454 (< 0.001)	-0.112 (0.161)	-0.538 (< 0.001)	0.521 (< 0.001)	0.385 (< 0.001)
	Non-Dense Sound Speed	-0.172 (0.031)	-0.282 (< 0.001)	-0.266 (< 0.001)	0.081 (0.313)	0.579 (< 0.001)	-0.246 (0.004)	-0.096 (0.264)
	Total Volume	-0.052 (0.518)	0.500 (< 0.001)	0.458 (< 0.001)	-0.047 (0.559)	-0.026 (0.760)	0.634 (< 0.001)	0.668 (< 0.001)

Spearman correlation coefficient with p-value listed in brackets. For all correlations involving mammography measures, n=138, for all other correlations, n=158.

Correlations between the additional density characteristics, such as dense area and dense volume were calculated and shown in Table 2. Among the correlations listed, correlations between comparable UST and mammography measures (i.e. dense area vs dense volume, non-dense area vs non-dense volume) are shown. These compare similar measurements made by a three dimensional imaging modality (UST) versus a two dimensional imaging modality (mammography). The correlation between total volume and total area is $r_s = 0.668$, between non-dense volume and non-dense area, the correlation is $r_s = 0.691$ and between dense volume and dense area, the correlation is $r_s = 0.412$. These are strong and positive correlations, but they are not as strong as the correlation between UST sound speed and MPD.

The correlations between MPD and the mammographic area measurements from Table 1 are stronger than the UST volume and mammographic area correlations from Table 2. However, UST sound speed correlations with UST volume measurements are not as strong as the comparison between UST volume and mammographic area.

Despite age being weakly correlated with sound speed and MPD, age has no statistically significant correlation with non-dense volume or area. However, there is a weak, but negative, correlation of age with both UST dense volume ($r_s = -0.240$) and mammographic dense area ($r_s = -0.217$). As a woman's age increases, the amount of dense tissue as measured by both UST and mammography appears to decline slowly.

Non-dense UST volume shows positive and strong correlations with weight and BMI ($r_s = 0.531$ and $r_s = 0.566$ respectively) as does non-dense mammographic area ($r_s = 0.583$ and $r_s = 0.578$ respectively). Total breast area and volume show similar correlations with weight and BMI. As weight increases, the amount of fatty tissue in the breast increases as measured by both imaging modalities. Since percent density is low for most of our study participants, a majority of the breast tissue is non-dense. Therefore, the factors that affect non-dense tissue also have a greater effect on total breast area and volume.

The correlations between weight and BMI with dense UST volume differ from the correlations between weight and BMI with dense mammographic area. Dense mammographic area shows weak but negative correlations with weight and BMI ($r_s = -0.265$ and $r_s = -0.268$) which indicates that the amount of dense tissue decreases as weight increases. However, dense UST volume shows no statistically significant correlations with weight and BMI. These findings highlight a potential difference in how UST and mammography measure dense tissue.

Dense UST volume is defined as tissue that has a sound speed above a specific threshold value. This threshold sound speed value corresponds to a tissue density that above which, breast tissue can be considered dense and below which can be considered fatty. Because fatty tissue has lower sound speeds that are likely to fall below the threshold value, as weight and BMI increase, there should be little difference in the amount of dense tissue that has a sound speed above this threshold. The threshold can be uniformly applied to all study participants because of the quantitative nature of the UST scans. The volumetric capabilities of UST also ensure that the dense tissue will be imaged wherever it is located in the breast.

For mammography, dense area is defined as those pixels with a gray scale value above a certain threshold that, in CUMULUS, is subjectively set for each image. As weight increases, the amount of non-dense adipose tissue in the breast may also increase. The additional adipose tissue may affect how the breast compresses when it is imaged. Compression in mammography is necessary to ensure good image quality, but breast compression may not be the same for every scan. Larger breasts cannot be compressed as much as smaller breasts and different patients will tolerate different levels of compression. However, compression distorts the breast anatomy. A breast with greater amounts of fatty tissue could change how the dense regions distort under compression and this could cause a smaller dense area to be projected onto the mammogram.

Dense tissue appears white on a mammogram because it attenuates more x-rays than fatty tissue. However, the increase in non-dense breast adipose tissue that may be observed at higher weights will also cause the entire breast to attenuate more x-rays as there will be more tissue in the path of the x-ray beam. The final image would then have reduced contrast between dense and non-dense regions. As the amount of non-dense tissue increases, dense tissue would be harder to differentiate from non-dense tissue. To ensure that non-dense tissue is labeled as non-dense, higher density thresholds would likely be chosen when performing density measurements using CUMULUS. Correlations between the density threshold value selected in CUMULUS and weight and BMI in this study population (r_s = 0.317, $p < 0.001$ and r_s = 0.320, $p < 0001$) indicate that there is in fact a moderate and positive increase in the mammographic density threshold value as weight increases.

3.2 Comparison of Average Breast Density Measurements between Patient Subgroups

Menopause is associated with lower breast density. For the patients in this study, the effect of menopause status on density measurements was calculated and compared using an independent t-test based on average values. The results are shown below in Table 3.

Table 3 – Comparison of Average Imaging and Patient Characteristic Values for Menopausal Status

	Post-Menopausal	**Pre-Menopausal**	**p-value[a]**
Patient Related Characteristics	**n = 71**	**n = 87**	
Age (years)	58.5	45.8	< 0.001
BMI	31.3	30.7	0.632
Weight (pounds)	183.2	181.0	0.766
Height (inches)	64.3	64.5	0.743
Mammography Related Characteristics	**n = 67**	**n = 71**	
Mammographic Percent Density	19.9	27.7	0.021
Dense Area (cm^2)	38.8	53.5	0.011
Non-Dense Area (cm^2)	200.6	192.9	0.723
Total Breast Area (cm^2)	239.4	246.4	0.748
UST Related Characteristics	**n = 71**	**n = 87**	
Mean Sound Speed (km/s)	1.4464	1.4537	0.002
Dense Volume (cm^3)	157.9	243.2	0.006
Dense Fraction	0.204	0.308	0.002
Dense Sound Speed (km/s)	1.4802	1.4821	0.135
Non-Dense Volume (cm^3)	862.3	657.8	0.077
Non-Dense Fraction	0.796	0.692	0.002
Non-Dense Sound Speed (km/s)	1.4373	1.4396	0.004
Total Volume (cm^3)	1,025.0	906.3	0.366

[a]p-value is calculated from an independent t-test

In our study population, menopausal status (Table 3) has a very pronounced effect on breast density. For both mammography and UST sound speed, post-menopausal women have reduced density measures compared with pre-menopausal women. The age of post-menopausal women is greater than the pre-menopausal group and increased age is known to lead to a decrease in breast density[17]. Weight and BMI do not show a statistically significant difference between pre- and post-menopausal women.

The amount of non-dense tissue does not show a statistically significant difference by menopausal status. The decline in density during menopause therefore appears to be driven largely by the amount of dense tissue in the breast decreasing. The design of this study cannot be used to determine this as ideally women would be followed during the menopause transition. But, in this cross-sectional comparison, the amount of dense tissue, as measured using both UST and mammography, was statistically significantly lower after menopause.

The additional quantitative measurements provided by UST imaging allowed for the average sound speed of the dense and non-dense fractions to be analyzed. From the UST measurements, not only does the volume of dense tissue and dense fraction differ significantly by menopausal status, but there is a statistically significant difference in the properties of the non-dense tissue as well. When comparing between pre- and post-menopause, the average sound speed of the non-dense tissue was lower after menopause. This is information that could not be determined from examining a mammogram as density is calculated based on the relative amount of white pixels. These results show that the information stored in the tissue can be extracted using UST imaging.

4. CONCLUSIONS

Ultrasound tomography was used to create sound speed images of the breast in women who had negative digital mammographic screens. Breast density and other imaging characteristics were measured using both UST and mammography. Mammographic percent density and whole volume average sound speed correlated strongly and positively for these patients. Additional imaging characteristics, including measurements of the amount of dense and non-dense tissue in the breast also correlated with overall density measurements, but not as strongly as the two different density measurements. When comparing density measurements by menopausal status, breast density and the amount of dense tissue in the breast was lower after menopause. Results suggest that UST can be used among women with negative mammographic screens as a quantitative marker of breast density that may avert shortcomings of mammography.

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6. REFERENCES

1. Duric, N., P. Littrup, A. Babkin, D. Chambers, S. Azevedo, A. Kalinin, R. Pevzner, M. Tokarev, E. Holsapple, O. Rama, and R. Duncan, *Development of ultrasound tomography for breast imaging: Technical assessment.* Medical Physics, 2005. **32**(5): p. 1375-1386.
2. Duric, N., P. Littrup, P. Chandiwala-Mody, C. Li, S. Schmidt, L. Myc, O. Rama, L. Bey-Knight, J. Lupinacci, B. Ranger, A. Szczepanski, and E. West. *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, 76290M (March 12, 2010).
3. Li, C., N. Duric, and L. Huang. *Clinical breast imaging using sound-speed reconstructions of ultrasound tomography data*. Proc. SPIE6920, Medical Imaging 2008: Ultrasonic Imaging and Signal Processing, 692009 (March 10, 2008).
4. McCormack, V.A. and I. dos Santos Silva, *Breast Density and Parenchymal Patterns as Markers of Breast Cancer Risk: A Meta-analysis.* Cancer Epidemiology Biomarkers & Prevention, 2006. **15**(6): p. 1159-1169.
5. Huo, C.W., G.L. Chew, K.L. Britt, W.V. Ingman, M.A. Henderson, J.L. Hopper, and E.W. Thompson, *Mammographic density—a review on the current understanding of its association with breast cancer.* Breast Cancer Research and Treatment, 2014. **144**(3): p. 479-502.
6. Pettersson, A., R.E. Graff, G. Ursin, I.d. Santos Silva, V. McCormack, L. Baglietto, C. Vachon, M.F. Bakker, G.G. Giles, K.S. Chia, K. Czene, L. Eriksson, P. Hall, M. Hartman, R.M.L. Warren, G. Hislop, A.M. Chiarelli, J.L. Hopper, K. Krishnan, J. Li, Q. Li, I. Pagano, B.A. Rosner, C.S. Wong, C. Scott, J. Stone, G. Maskarinec, N.F. Boyd, C.H. van Gils, and R.M. Tamimi, *Mammographic Density Phenotypes and Risk of Breast Cancer: A Meta-analysis.* Journal of the National Cancer Institute, 2014.
7. Masugata, H., K. Mizushige, S. Senda, A. Kinoshita, H. Sakamoto, S. Sakamoto, and H. Matsuo, *Relationship between myocardial tissue density measured by microgravimetry and sound speed measured by acoustic microscopy.* Ultrasound in Medicine & Biology, 1999. **25**(9): p. 1459-1463.
8. Mast, T.D., *Empirical relationships between acoustic parameters in human soft tissues.* Acoustics Research Letters Online, 2000. **1**(2): p. 37-42.

9. Weiwad, W., A. Heinig, L. Goetz, H. Hartmann, D. Lampe, J. Buchmann, R. Millner, R.P. Spielmann, and S.H. Heywang-Koebrunner, *Direct Measurement of Sound Velocity in Various Specimens of Breast Tissue.* Investigative Radiology, 2000. **35**(12): p. 721-726.
10. Kopans, D.B., *Basic Physics and Doubts about Relationship between Mammographically Determined Tissue Density and Breast Cancer Risk1.* Radiology, 2008. **246**(2): p. 348-353.
11. Sak, M., N. Duric, N.F. Boyd, P. Littrup, L. Myc, M. Faiz, C. Li, and L. Bey-Knight. *Relationship between breast sound speed and mammographic percent density*. Proc. SPIE7968, Medical Imaging 2011: Ultrasonic Imaging, Tomography, and Therapy, 7968 (March 25, 2011).
12. Duric, N., N. Boyd, P. Littrup, M. Sak, L. Myc, C. Li, E. West, S. Minkin, L. Martin, M. Yaffe, S. Schmidt, M. Faiz, J. Shen, O. Melnichouk, Q. Li, and T. Albrecht, *Breast density measurements with ultrasound tomography: A comparison with film and digital mammography.* Medical Physics, 2013. **40**(1): p. 013501-12.
13. Boyd, N.F., L.J. Martin, M. Bronskill, M.J. Yaffe, N. Duric, and S. Minkin, *Breast Tissue Composition and Susceptibility to Breast Cancer.* Journal of the National Cancer Institute 2010 **102** (16): p. 1224-1237
14. Sak, M., N. Duric, P. Littrup, C. Li, L. Bey-Knight, M. Sherman, N.F. Boyd, and G. Gierach. *Breast density measurements using ultrasound tomography for patients undergoing tamoxifen treatment*. Proc. SPIE8675, Medical Imaging 2013: Ultrasonic Imaging, Tomography, and Therapy, 8675
15. Sak, M., N. Duric, N. Boyd, P. Littrup, E. West, and C. Li. *Breast tissue composition and breast density measurements from ultrasound tomography*. Proc. SPIE8320, Medical Imaging 2012: Ultrasonic Imaging, Tomography, and Therapy, 83200Q (February 23, 2012).
16. Byng, J.W., N.F. Boyd, E. Fishell, R.A. Jong, and M.J. Yaffe, *The quantitative analysis of mammographic densities.* Physics in Medicine and Biology, 1994. **39**(10): p. 1629.
17. Boyd, N., L. Martin, J. Stone, L. Little, S. Minkin, and M. Yaffe, *A Longitudinal Study of the Effects of Menopause on Mammographic Features.* Cancer Epidemiology Biomarkers & Prevention, 2002. **11**(10): p. 1048-1053.