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The Connecticut Experiment: The Role of Ultrasound in the Screening of Women With Dense Breasts

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■ **Abstract:** The aim of this study was to determine the potential of screening breast ultrasound to improve breast cancer detection in women with mammographically normal, but dense breasts. Six Connecticut radiology practices with 12 total sites participated in a retrospective chart review. The total number of screening mammograms, screening ultrasounds broken down by BIRADS (Breast Imaging Reporting and Data System) codes, and the number of positive and negative biopsies were collected from November 2009 through November 2010. Demographic data on the patients with positive biopsies as well as cancer staging were also collected. Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value were calculated. A total of 72,030 screening mammograms and 8,647 screening ultrasounds were performed at the research sites during the study period. Relevant research indicates that 41% of the female population has dense breasts. In this study, 12% (8,647/72,030) underwent follow-up breast ultrasound screening. A total of 86% (7,451/8,647) of the ultrasounds were BIRADS 1 or 2, 9% (767/8,647) were BIRADS 3, 5% (429/8,647) were BIRADS 4 or 5. Of those 429 recommended to undergo biopsy 418 were performed and 28 cancers were found. There was one false negative. Screening breast ultrasound in women with mammographically normal, but dense breasts has a Positive Predictive Value (PPV) of 6.7% (28/418), Negative Predictive Value (NPV) of 99.9% (7,450/7,451), sensitivity of 96.6% (28/29), and a specificity of 94.9% (7,450/7,851). Screening ultrasound had an additional yield of 3.25 per 1,000 cancers in women with dense breasts and normal mammograms and no additional risk factors. As with all screening tests, time, cost, and false positive risk must be considered. ■

Key Words: breast cancer, breast density, breast ultrasound, mammography

Although mammography is currently the best screening tool available for diagnosing breast cancer, it is not perfect, particularly in the case of dense breast parenchyma. While mammography detects 98% of cancers in women with fatty breasts, it detects only 48% of cancers in women with dense breast tissue (1). The similarities in density between fibro glandular tissue and soft tissue masses can be difficult to differentiate using mammography.

The implication of mammography's unreliability for detecting cancers in dense-breasted women have been intensified by recent studies citing breast tissue density as an independent risk factor for cancer. Relevant research indicates that 41% of the female population has dense breasts (2). A study published in New England Journal of Medicine (NEJM) demonstrated that breast cancer risk is increased by a factor of five in women with dense breasts (3). Another study also found similar results showing a fourfold to sixfold increased risk of breast cancer in women with 75% breast density (4). The American College of Radiology Imaging Network published a large trial comparing adjunct ultrasound imaging and screening mammography in Journal of American Medical Association (JAMA) in 2008. This study found an additional 4.2 cancers per 1,000 in high-risk patients (5).

Recent research demonstrates the potential for ultrasound as an additional breast cancer diagnostic tool. A 1995 study by Gordon and Goldenberg illustrated the promising capability of whole breast ultrasound to detect 1,575 tumors in 12,706 women. The tumors were not palpable or visible by mammography (6) similar to a 2002 study in which women with dense breast tissue received both screening mammograms and breast ultrasounds. The ultrasound demonstrated and increased sensitivity compared to mammograms (75% compared to 64%) detecting an additional 2.7 cancers per 1,000 individuals in this population (7).

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Most significantly, a 2004 study found that 90% (36 of 40) cancers detected by ultrasound alone were categorized as stage 0 or 1 (8), suggesting that breast ultrasound screening can detect breast cancer in early stages thereby having the potential to reduce morbidity and mortality.

Connecticut is the first state in the nation to inform patients of their breast density when they receive a mammogram. Connecticut General Statute Section 38a-530 required that as of October 2009, women in Connecticut must be informed of their breast density. Previously, in 2005, statute 38a-502 mandated insurance companies to provide coverage for comprehensive ultrasound screening of an entire breast or breasts if a mammogram demonstrates heterogeneous or dense breast tissue based on the BIRADS (Breast Imaging Reporting and Data System) established by the American College of Radiology (9). Every woman in the state of Connecticut who undergoes mammography and demonstrates breast density >50% must be informed of the following: ''If your mammogram demonstrates that you have dense breast tissue, which could hide small abnormalities, you might benefit from supplementary screening tests, which can include a breast ultrasound screening or a breast MRI examination, or both, depending on your individual risk factors. A report of your mammography results, which contains information about your breast density, has been sent to your physician's office and you should contact your physician if you have any questions or concerns about this report.''

This landmark legislation made Connecticut the ideal place to conduct a retrospective chart review assessing the potential for beast ultrasound screening to detect breast cancer undetectable with mammography in women with dense breasts as their only risk factor.

MATERIALS AND METHODS

Institutional review board approval was obtained before the beginning of the study as well as a patient consent waiver. Letters requesting participation in this retrospective chart review were sent to Radiology sites throughout Connecticut. Cooperating sites were asked to supply from November 1, 2009 to November 30, 2010 the number of screening mammograms and number of bilateral screening ultrasounds performed on women with mammographically normal, but dense breasts, the BIRADS codes for all the screening breast ultrasounds, and the biopsy results on all patients with a BIRAD code of 4 or 5.

Dense breasts were defined if 50% or more of the breast tissue was dense. Normal mammograms included patients with a BIRAD 1 or 2 and BIRAD 2 were those with stable or known benign findings. Ultrasounds with a BIRAD 1 or 2 were considered benign. Those with a BIRAD 3 were recommended short interval follow-up at 6 months for any change in their BIRAD status, and BIRAD 4 or 5 required surgical evaluation or biopsy. For those patients with positive biopsies additional information including age, risk factors, grade, and stage or lymph node status of cancer was also requested.

Ultrasounds were performed by trained and certified Ultrasound technologists using hand-held high-resolution transducers (12–5 MHz). None of the sites utilized Automated Breast Ultrasound Devices. Images were taken to represent at least the 12, 3, 6, and 9 o'clock sites in the radial and anti-radial position. Additional images were obtained for any questionable findings. These scans were for the most part performed when a radiologist was available for review. In some centers these were scheduled when a radiologist was not present and the patient returned for a diagnostic workup for any questionable findings with the radiologist. The reviewing radiologist determined the BIRAD code and subsequent clinical recommendation. BIRAD 1 or 2 required routine mammographic follow-up, BIRAD 3 required a short interval follow-up and BIRAD 4 and 5 required the recommendation for biopsy.

Some sites utilized an electronic data base, which allowed a search of bilateral screening breast ultrasounds and easy retrieval of BIRADS codes and biopsy results. Other sites did not have advanced tracking systems as part of their electronic medical record and each screening mammogram had to be reviewed to see if the patient qualified for the study. The ultrasound and biopsy information was then collected when available. The constraints and the labor intensity of these methods required that at two of the sites only the first 6 months' worth of ultrasounds were analyzed and at an additional site only the first 3 months' worth of data was analyzed. Once data were collected they were collated to determine the PPV, NPV, sensitivity, and specificity.

To analyze the cost implications, data regarding average reimbursement by CPT-code and insurance company were collected from both hospital-based and private practice billing departments Figure 1.

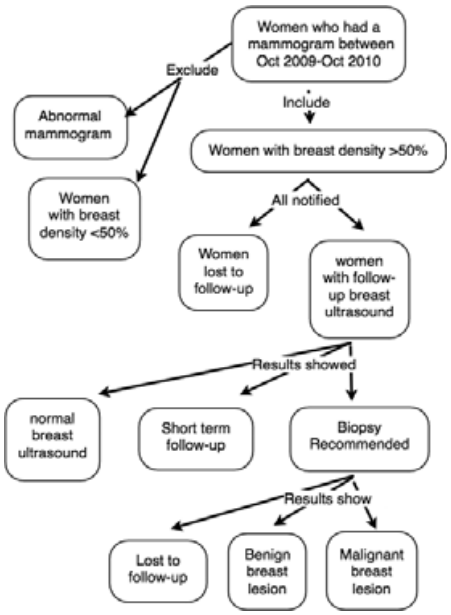

Figure 1. Schematic of the data collection process.

RESULTS AND ANALYSIS

Six radiology practices with 12 sites throughout Connecticut participated in this retrospective study. A total of 72,030 screening mammograms and a total of 8,647 screening ultrasounds were performed on women with mammographically normal, but dense breasts over the course of 1 year. Only 30% (8,647/28,812) of women recommended to undergo follow-up ultrasound actually received a screening ultrasound. In this first year of test availability, the majority of patients did not adhere to the recommendation of an additional ultrasound screening.

Of the screening ultrasounds performed, 86% (7,451/8,647) were BIRADS 1 or 2, 9% (767/8,647) were BIRADS 3, and 5% (429/8,647) were BIRADS 4 or 5. Of the 429 ultrasounds that were recommended to have biopsy, 11 were lost to follow-up and there were 28 positive cancers. There was one false negative. The patient returned within a 6-month period of a negative screening ultrasound with a palpable mass that was malignant on biopsy.

This data resulted in a PPV of 6.7% (28/418) and NPV 99.9% (7,450/7,451). The sensitivity was 96.6% (28/29) and the specificity 94.9% (7,450/7,851). Additional demographic data were available for only half of the cases. Age reported for 18 of the cases of malignancy ranged from to 42–78 years of age with an average of 54.5 years. Tumor size was reported in 17 cases and ranged from 0.4×0.7 to 8 cm with an average of 1.9 cm. There was only one reported case of lymph node involvement and it was limited to the sentinel node. Physicians recommended patients whose ultrasounds resulted in BIRADs 3′s to be tracked via follow-up ultrasounds in 6 months from the original study. Most complied and there were no malignancies diagnosed in this group to date Table 1.

On the basis of the average reimbursement by CPT-code and insurance company data which were collected from both hospital-based and private practice billing departments the following analysis was performed. The average cost of a breast ultrasound is $250. However, average insurance reimbursement is only $72. The average professional fee for radiologist's interpretation is $85, but Medicare reimbursement averages $30. The average cost of Ultrasound guided biopsy is $2,400. (in a hospital setting) Using $250 per screening ultrasound and $2,400 per ultrasound guided biopsy to estimate the cost; the cost per breast cancer found is estimated to be $110,241 (3,086,750/28). The actual cost for insurance will be less, if one uses the true reimbursement, probably closer to $50,000. This cost analysis also assumes that 10% of women with BIRADs 4 or 5 on screening ultrasound will not elect to have a biopsy performed. The time requirements to perform hand-held bilateral breast ultrasound depend on the size of the breast and the skill of the sonographer. On average, each bilateral screening breast ultrasound takes 10–20 minutes to perform and additional time for the radiologist's interpretation Table 2.

DISCUSSION

Mammography is currently the only breast cancer screening tool proven to reduce cancer mortality. However, mammography is less effective in detecting cancer in women with dense breast tissue compared to women with fatty replaced tissue. Studies have shown that dense breast tissue is an independent risk factor for developing breast cancer.

In 2009, legislation in the state of Connecticut was passed requiring that women be notified of their breast tissue density and recommended that those with breast tissue density greater than 50% be recommended to undergo supplemental screening breast ultrasound. Prior legislation passed in 2005 mandated that such breast ultrasounds be paid for by insurance. Connecticut is the first and currently only state to have such a policy.

Table 1. List of Positive Malignancies by Site Including, When Available, Type of Cancer, Cancer Grade, Size of Tumor, Age of Patient, and Family History of Breast Cancer

Site	Type	Grade	Size (cm)	Age	Family history	Node status
1	Mucinous/colloid	II/III	8	45	neg	neg
1	Invasive lobular carcinoma	II/III	2.5 × 2.0	78	neg	neg
1	DCIS	II/III	3.7 × 3.0	50		neg
1	Invasive ductal/lobular carcinoma	III/III	1.2	61	neg	Positive sentinal node
1	Invasive ductal carcinoma	I/II	1.5	57	Maternal cousin	neg
1	DCIS papillary intracystic	II/III	1.2	50	neg	neg
1	Carcinoma with mixed ductal and lobular	III	1.5	57	neg	neg
1	Infiltrating ductal carcinoma	II/III	2.2	50	neg	neg
1	Invasive mixed ductal and lobular/DCIS	II/III	1.2 × 0.8	58	neg	neg
1	Invasive lobular	II/III	3.0 × 3.0	50	neg	neg
1	Invasive ductal	II/III	1.5	48	Maternal grandmother	neg
2	Invassive papillary	2	0.8		Personal history	
2			1.5	42		
3	Ductal carcinoma	2/3	0.7 × 0.4	62		
3	Ductal carcinoma		1.1 × 0.8	42		
3	Ductal carcinoma	2/3	0.8 × 0.5	49		
3	Ductal carcinoma	3/3	0.6 × 0.6	67		
4	Invasive lobular carcinoma					
4	Invasive lobular carcinoma					
4	Lobular carcinoma *in situ*					
4	DCIS					
4	Invasive					
4	Invasive ductal carcinoma					
4	DCIS					
4	Atypical ductal hyperplasia					
4	Atypical ductal hyperplasia					
5		3a		71		
5		2a		44		

Table 2. Data Collected from 6 Radiology Groups Covering 12 Women's Imaging Sites from November 1 2009 to November 30 2010. Numbers represent the participating groups and the letters correspond to the sites within a group. Only 5 months of data from November 1, 2009 to March 31, 2010 was collected at sites a + b and only 3 months worth of data from November 1, 2009 to January 31, 2010 was collected at site six. ''FN'' is the false negative column, ''Lost to f/u'' is the lost to follow-up column, and ''U'' signifies that the number is not known

Sites	Screening mammograms	Screening ultrasounds	BIRADS 1 or 2	BIRADS 3	BIRADS 4 or 5	Cancers found	FN	Lost to f/u
1a	6,807	334	271	40	23	7		u
1b	10,003	766	630	77	59	0		u
1c	4,561	267	207	35	25	1		u
1d	9,299	1,335	1,269	22	44	3	1	u
2a + b	8,540	1,125	946	156	23	1		2
2c	3,057	747	562	135	50	1		u
3a + b	9,943	512	386	42	84	4		9
4	8,725	1,703	1,493	110	100	9		u
5	8,845	1,753	1,591	142	20	2		u
6	2,250	105	96	8	1	0		u
Total	72,030	8,647	7,451	767	429	28		11

Because of this unique legislation, Connecticut becomes the ideal state to study the effectiveness of breast ultrasound as a breast cancer screening tool. A retrospective chart review from Radiology practices throughout Connecticut on the use of bilateral breast ultrasounds for women with normal, but dense breasts on screening mammography was initiated to determine if the addition of screening breast ultrasound in such women improves breast cancer detection The addition of screening breast ultrasound in 8,647 women with mammographically normal, but dense breasts led to the detection of 28 additional cancers. Screening mammography detects 4 to 5 cancers per 1,000 women screened per year (10). In this study

the addition of ultrasound screenings found 3.25 cancers per 1,000 dense-breasted women with normal mammograms. These results are significant and suggest a powerful role for ultrasound in breast cancer screening for women with dense breasts as their only risk factor. This is especially important since multiple studies have shown that women with dense breasts are more likely to have breast cancer and mammography alone is only capable of detecting about half of cancers in those women. The high NPV in this study further indicates that patients whose supplemental screening ultrasound is negative are 99.9% likely to be free of a breast malignancy. These results provide reassurance for women whose dense breasts limit the reliability of mammograms for ruling out breast cancer.

Our study demonstrates that only 30% of eligible patients received screening breast ultrasound in the first year following implementation of the new legislation. The low participation rate may have been due to a lack of information regarding the benefit of the test and the fear that the procedure would lead to many false positives and unnecessary biopsies. Also there was confusion regarding insurance reimbursement. Although some insurance companies pay for the test outright, many added the test's cost to the patient's deductible. In this era of high deductible insurance plans, this may have been a deterrent for many women.

As with all retrospective studies, the study's scope was limited by participation and available data. We did approach the majority of large practices around the state with active Breast Imaging sections. Unfortunately, two of the larger practices did not participate because they were planning on performing their own data analysis. The labor intensity associated with tracking patients from mammogram through biopsy and subsequent follow-up led to reduced state-wide participation from the radiology practices. In addition, three sites could only provide 3–6 months data at the time of collection. Three of the sites perform ultrasounds on the patients referred to them by sites that only read mammograms and therefore the number of mammograms reported in this study is likely to be understated. Although this should not greatly impact the outcome, the availability of this data would strengthen the results. Approximately 10% (11/107) of patients with breast ultrasound BIRADS of 4 or 5 were lost to follow-up based on data from four sites (sites2a + b and 3a + b). We have to assume that these women either refused a biopsy or they had a biopsy performed at another site. We would anticipate that had more data been available, there would have been more cancers detected. We cannot know if this would have increased or decreased the Positive Predictive Value as there may have been many more negative biopsies performed as well Furthermore, there is likely to be a learning curve in the acquiring and interpreting of breast ultrasounds with expected improvement in future years. There should be fewer false positives and more cancers found that are smaller in size and therefore at a lower stage.

We are planning on continuing our research to include the second and third year of data acquisition. Because the sites already involved know our plans, some have already created more user-friendly data bases and have been keeping better records regarding these studies. We anticipate a much better clinical follow-up rate with more complete data inclusion.

This retrospective study demonstrates that addition of screening ultrasound in women with dense breasts as their only risk factor, improves breast cancer detection. Additional research must be done to assess if the detection of these additional breast cancers improves survival in this population.

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