Screening US in Patients with Mammographically Dense Breasts: Initial Experience with Connecticut Public Act 09-41[1]

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Purpose: To determine performance and utilization of screening breast ultrasonography (US) in women with dense breast tissue who underwent additional screening breast US in the 1st year since implementation of Connecticut Public Act 09-41 requiring radiologists to inform patients with heterogeneous or extremely dense breasts at mammography that they may benefit from such examination.

Materials and Methods: Informed consent was waived for this institutional review board–approved, HIPAA-compliant retrospective review of 935 women with dense breasts at mammography who subsequently underwent handheld screening and whole-breast US from October 1, 2009, through September 30, 2010.

Results: Of 935 women, 614 (65.7%) were at low risk, 149 (15.9%) were at intermediate risk, and 87 (9.3%) were at high risk for breast cancer. Of the screening breast US examinations, in 701 (75.0%), results were classified as Breast Imaging Reporting and Data System (BI-RADS) category 1 or 2; in 187 (20.0%), results were classified as BI-RADS category 3; and in 47 (5.0%), results were classified as BI-RADS category 4. Of 63 aspirations or biopsies recommended and performed in 53 patients, in nine, lesions were BI-RADS category 3, and in 54, lesions were BI-RADS category 4. Among 63 biopsies and aspirations, three lesions were malignant (all BI-RADS category 4, diagnosed with biopsy). All three cancers were smaller than 1 cm, were found in postmenopausal patients, and were solid masses. One cancer was found in each risk group. In 44 of 935 (4.7%) patients, examination results were false-positive. Overall positive predictive value (PPV) for biopsy or aspirations performed in patients with BI-RADS category 4 masses was 6.5% (three of 46; 95% confidence interval [CI]: 1.7%, 19%). Overall cancer detection rate was 3.2 cancers per 1000 women screened (three of 935; 95% CI: 0.8 cancers per 1000 women screened, 10 cancers per 1000 women screened).

Conclusion: Technologist-performed handheld screening breast US offered to women in the general population with dense breasts can aid detection of small mammographically occult breast cancers (cancer detection rate, 0.8–10 cancers per 1000 women screened), although the overall PPV is low.

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There is an increasing demand for improved breast cancer detection, by both the medical community and the general public, because of the known limitations of mammography and an increase in breast cancer awareness. Mammography is the only screening test that has been shown to reduce deaths caused by breast cancer. The overall sensitivity of mammography is 70%–90%. However, this sensitivity is variable and can range from as high as 80%–98% in women with fatty breast tissue to as low as 30%–48% in women with dense breast tissue (1,2).

At mammography, heterogeneous or extremely dense breast tissue is visually determined by the radiologist. It poses a challenge to radiologists, as cancers in dense breasts may be mammographically very subtle or occult. Dense tissue is a common finding, present in more than one-half of women younger than 50 years and in nearly one-third of women older than 50 years (3). Women with dense breast tissue have up to a sixfold greater risk of interval cancer (2) and an overall worse prognosis for subsequent cancers detected clinically (4). In addition, the risk of developing cancer is four to six times higher in women with dense breast tissue compared with the risk in women without dense breast tissue (5).

Breast ultrasonography (US) is an attractive screening tool, as it is widely available, is well tolerated by patients, and is similar in cost to a mammogram. High-resolution linear transducers allow detailed characterization of solid masses. Multiple studies demonstrate that supplemental screening breast US generates an incremental cancer detection rate of 2.3–4.6 cancers per 1000 women screened (1,6–12). However, screening breast US is limited by low specificity and low positive predictive values (PPVs) compared with those of screening mammography. Because there is no direct proved mortality benefit from screening breast US, it is also controversial (13,14).

In October 2009, Connecticut passed Public Act 09-41, requiring radiologists to communicate breast density information to patients undergoing mammography. Under a separate, preexisting law, insurance companies in Connecticut are also mandated to pay for screening (or whole-breast) US if recommended by a physician. Prior to this date, our facility did not offer screening breast US to any of our patients. The purpose of this study was to determine the utilization and performance of screening breast US in women who presented to our breast imaging practice with dense breast tissue in the 1st year since the implementation of this law.

Advances in Knowledge

- Technician-performed handheld screening breast US in women in the general population with dense breast tissue resulted in a cancer detection rate of 3.2 cancers per 1000 women screened.
- The three cancers detected with screening US were all smaller than 1 cm, node negative, and mammographically occult.
- Breast Imaging Reporting and Data System (BI-RADS) category 4 lesions may be assessed in 5.0% of screening breast US cases, with a positive predictive value of 6.5%.
- Twenty percent of patients who undergo screening breast US may have a result classified as a BI-RADS category 3 and receive a recommendation for short-term follow-up; BI-RADS category 3 utilization could be reduced to 9.5% if solitary, oval, well-circumscribed complicated cysts of 5 mm or smaller and nonsimple cysts in the setting of multiple or bilateral cysts were reclassified as BI-RADS category 2 lesions, and sensitivity would not be altered.

Implication for Patient Care

- Women with dense breast tissue at mammography who choose screening breast US should be aware of frequent false-positive results and the potential for requiring additional follow-up examinations; with technologist-performed handheld screening breast US, a cancer detection rate can be achieved that is similar to that with physician-performed examinations.

Materials and Methods

Our institutional review board approved this Health Insurance Portability and Accountability Act–compliant, retrospective study. Informed consent was waived. We retrospectively reviewed results from all screening breast US examinations performed in women at our facility from October 1, 2009, to September 30, 2010.

As per CT Public Act 09-41, beginning October 1, 2009, each mammography report provided to our screening and diagnostic patients included information about breast density, on the basis of the Breast Imaging Reporting and Data System (BI-RADS) established by the American College of Radiology. If the patient had either heterogeneous or extremely dense breast tissue at mammography, as noted by the interpreting radiologist, the following notice

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Abbreviations:
BI-RADS = Breast Imaging Reporting and Data System
CI = confidence interval
DCIS = ductal carcinoma in situ
PPV = positive predictive value
PPV_2 = PPV for biopsy recommendation
PPV_3 = PPV for biopsy performed

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Guarantors of integrity of entire study, R.J.H., K.L.G., J.L.G.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, R.J.H., J.L.G.; clinical studies, all authors; statistical analysis, R.J.H., K.L.G., R.M.S., J.L.G.; and manuscript editing, all authors

Potential conflicts of interest are listed at the end of this article.

See also the editorial by D'Orsi and Sickles in this issue.

was also included: "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." Prior to October 1, 2009, a letter was sent to all of our referring clinicians notifying them of the legislation and the upcoming change in our protocol. Screening mammograms are batch read at our facility, and, in general, patients with dense breasts were not instructed by the radiologist to schedule a screening US examination. Rather, as stated in their report, they were encouraged to discuss the risks and benefits with their primary health care provider before scheduling the examination.

Subject Population

A total of 16228 mammograms, including 10408 screening and 5820 diagnostic mammograms, were obtained in 14242 women at our facility during the study period. Mammograms were obtained at one of three locations by using dedicated mammography units (at two, they were obtained by using Selenia units [Hologic, Danbury, Conn], and at one, they were obtained by using Senographic 2000 DS units [GE Healthcare, Milwaukee, Wis]). A total of 1359 bilateral breast US examinations, including 321 bilateral targeted and 1038 bilateral screening and whole-breast US examinations, were performed in 1359 women. One hundred three of these studies were excluded, including three examinations in patients who had undergone prior bilateral mastectomies, 11 examinations in patients whose most recent mammogram was obtained more than 12 months prior, 21 examinations in patients who had no record of a prior mammogram, and 68 examinations performed in women with fatty (three examinations) or scattered (65 examinations) fibroglandular breast tissue.

Of the 935 women included in the study population, 753 women received their breast density notification following a screening mammogram and 182 women received their breast density notification following a diagnostic mammogram, all performed within 1 year preceding the screening US examination. One hundred five of 753 women in whom a yearly screening mammogram was obtained received a BI-RADS category 0 final assessment and returned for diagnostic mammography (Fig 1). The indications for the routine diagnostic mammography were as follows: 120 women with a previous BI-RADS category 3 finding (including 42 women followed up for microcalcifications; 17 women followed up because of a previous benign biopsy; and 61 women followed up for a benign-appearing mass, architectural distortion, or asymmetry); 22 women with a clinical breast finding (including seven women with a palpable mass, 13 women with breast pain, and two women with nipple discharge); 29 women with a remote personal history of breast cancer; and 11 women with unknown reasons. The indications for diagnostic mammography following a recall on the basis of screening were as follows: 54 women with asymmetries, 31 women with microcalcifications, six women with masses, four women with architectural distortions, and 10 women with multiple findings. One hundred seventy-five of 287 (61.0%) women underwent screening whole-breast US at the

Figure 1

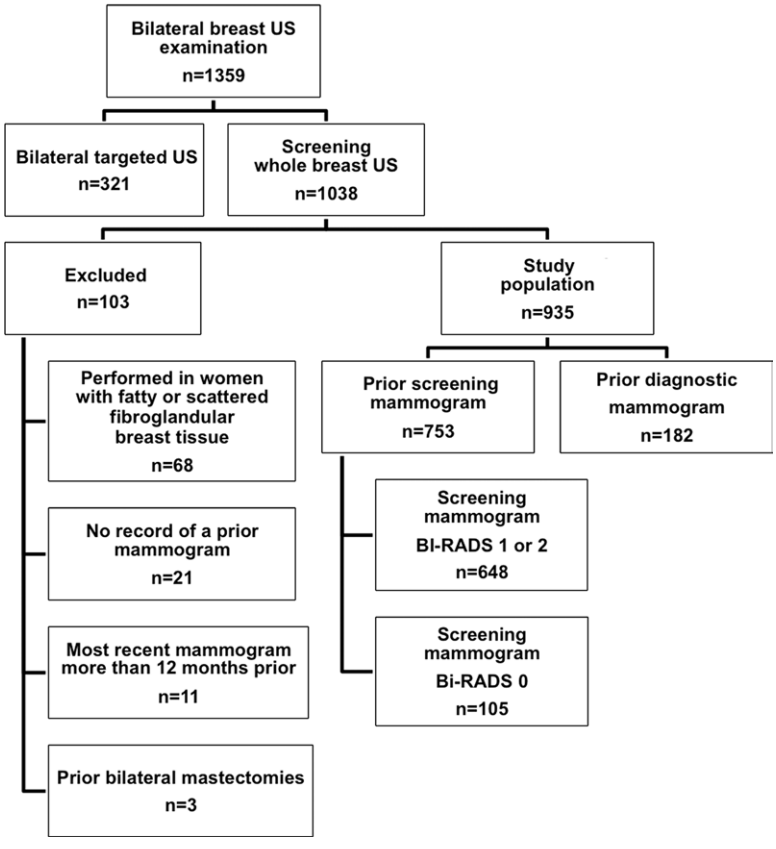


Figure 1: Study population selection. Of 1359 women who underwent bilateral breast US examinations during the study period, 935 women were included in the study; 753 women were notified of their breast density on the basis of prior screening mammography results and 182 women were notified on the basis of prior diagnostic mammography results.

same time as diagnostic mammography. Of these women, 52 of 175 had a mass located in the same quadrant of the diagnostic mammogram or a physical breast finding and were excluded from lesion analysis. No cancers were diagnosed on the basis of the diagnostic mammogram or in any excluded lesions. One hundred twelve of 287 (39.0%) women underwent a screening breast US examination on a separate day following diagnostic mammography, including seven women who also underwent targeted US on the day of diagnostic mammography. Therefore, for the purpose of this study, examinations in patients who underwent diagnostic mammography, as well as targeted US combined with bilateral whole-breast US, were counted as screening US examinations, because screening was performed of the remainder of the breasts and additional lesions could be found. Only the regions of the breast with no US correlates to any mammographic or physical findings were included in this study, and all mammographic findings were negative in the area of the US finding.

Patient age, date of prior mammogram, and the presence or absence of risk factors for breast cancer were recorded. A woman's breast cancer risk was derived from National Cancer Institute guidelines (15), and a technologist entered the data into our mammography reporting system (Penrad Technologies, Minnetonka, Minn). Risk was defined as unknown, none or weak (aunt, grandmother, cousin with breast cancer), intermediate (postmenopausal mother or sister with breast cancer), or high or very strong (premenopausal mother or sister, or multiple premenopausal first-degree relatives with breast cancer, *BRCA* positive). Patients with a remote personal history of breast cancer (ie, breast cancer diagnosis and treatment >1 year prior to study date) were considered to be of intermediate risk.

US Examination

One of seven mammography technologists with 10–28 years of mammography experience and 7–10 years of breast US experience performed all of the US screening examinations (five of seven of the technologists were certified in breast US by the American Registry of Radiologic Technologists). All scans were obtained by using a unit (IU22; Philips, Bothell, Wash) with a handheld high-resolution linear-array broadband transducer with a frequency of either 12–5 mHz or 17–5 mHz. Both breasts were evaluated, with overlapping scans in the radial and antiradial planes extending from the nipple to the posterior breast tissue. Images were documented in the 12-, 3-, 6-, and 9-o'clock positions, and an image was also obtained of the retroareolar region and sometimes the axilla. Lesions, if present, were documented and measured in three dimensions, although only the longest dimension was recorded in our database. Specific scan times were not recorded; however, examination appointments were scheduled at 45-minute intervals.

All scans were immediately reviewed by one of eight dedicated breast imagers with 2–32 years of experience in breast imaging. The interpreting radiologist was not blinded to prior mammogram results, was able to review prior images, and had the option of scanning the breasts in real time, regardless of whether or not the technologist identified an abnormality. During the first 6 months, the radiologist routinely rescanned each patient. However, during the following 6 months, as technologist and radiologist experience and confidence improved, patients with negative scans were not rescanned by the radiologist, although patients with any technologist examination demonstrating complicated cysts, solid masses, and questionable findings were rescanned and evaluated in real time by the radiologist. Masses were subsequently classified as benign, probably benign, or suspicious on the basis of established criteria described by Stavros et al (16) and the BI-RADS US lexicon (17).

Each US report was retrospectively reviewed, and the BI-RADS final assessment category, as well as the presence or absence of cysts and solid masses, was recorded. If a cyst, complex mass, or solid mass was found, the lesion size and location were noted. If multiple cysts were described, generally only the size of the largest cyst was documented. Follow-up recommendations were also recorded as none, yearly, short-interval follow-up, aspiration, or biopsy. All data were collected by two radiology residents with 2 and 3 years of radiology training (K.L.G. and R.M.S.), respectively, or by a radiologist with breast fellowship training and 2, 13, and15 years of training (J.L.G., R.S.B., and R.J.H.), respectively. One author (R.J.H.) also reviewed any mammographic and US images, if necessary.

For the purpose of analysis, after the results of the study were determined, potential methods to reduce the number of BI-RADS category 3 cases were retrospectively explored. To reduce the number of cases assigned a BI-RADS category 3 final assessment, nonsimple cysts in the setting of multiple cysts, as well as complicated cysts of 5 mm or smaller, were subsequently reclassified and were assigned to BI-RADS category 2, and sensitivity was assessed. A 5-mm cutoff was selected because it is often difficult for cysts smaller than 5 mm to meet all the criteria for a simple cyst (18).

Follow-up

Follow-up information was obtained by using biopsy results during the study period (if applicable) and results of follow-up mammography and/or US performed at least 15 months after the initial examination. All US-guided biopsies were performed with a 14-gauge automated core biopsy needle (Achieve, Cardinal Health, Dublin, Ohio; or Monopty, Bard, Tempe, Ariz), except in one case, where a 12-gauge vacuum-assisted core biopsy needle (Celero; Hologic, Bedford, Mass) was used. Cytologic examination results of US-guided cyst aspiration were obtained at the discretion of the radiologist. Patients were considered disease positive if biopsy results demonstrated ductal carcinoma in situ (DCIS), invasive ductal cancer, or invasive lobular cancer. The PPV_2 (PPV for biopsy recommended) and PPV_3 (PPV for biopsy performed)

of BI-RADS category 4 lesions, as well as BI-RADS category 3 and 4 lesions combined, were calculated. Procedures performed at the patient's request were not included in PPV calculations.

Cost Calculations

Cost calculations were estimated by using current Connecticut Medicare reimbursement rates (19). Included in the overall cost are costs of all initial US examinations, all follow-up examinations performed at 6 months, all initial and 6-month follow-up US-guided aspirations and cytologic examinations, all initial and 6-month follow-up US-guided core needle biopsies (with biopsy marker clip placement), surgical biopsies (including anesthesia), and histopathologic examinations.

Statistical Analysis

Statistical analysis of the results was performed by using R (R Foundation for Statistical Computing, Vienna, Austria). The Fisher exact test was used for comparison of proportions. Significance was assigned for a P value of less than .05. Confidence intervals (CIs) are shown at the 95% confidence level.

Results

Study Population

Of the 935 women included in our study, the mean patient age was 52 years (standard deviation, ± 9.6 years; range, 29–89 years). The mean time between mammography and US was 60.8 days (standard deviation, ± 66 days; range, 0–361 days). In these 935 patients, patient risk factors for breast cancer were as follows: low or average risk in 614 (65.7%; 95% CI: 63%, 69%), intermediate risk in 149 (15.9%; 95% CI: 14%, 18%), and high or very strong risk in 87 (9.3%; 95% CI: 8%, 11%). Risk factors were unknown in 85 (9.0%; 95% CI: 7%, 11%). In these 935 patients, the distribution of the final BI-RADS assessment category was as follows: BI-RADS category 1 in 308 (32.9%; 95% CI: 30%, 36%), BI-RADS category 2 in 393 (42.0%; 95% CI: 39%, 45%), BI-RADS category 3 in 187 (20.0%, 95% CI: 18%, 23%), and BI-RADS category 4 in 47 (5.0%; 95% CI: 4%, 7%). No BI-RADS category 5 lesions were found. There was no significant relationship between BI-RADS category and risk, with $P = .67$ (Fig 2).

Figure 2

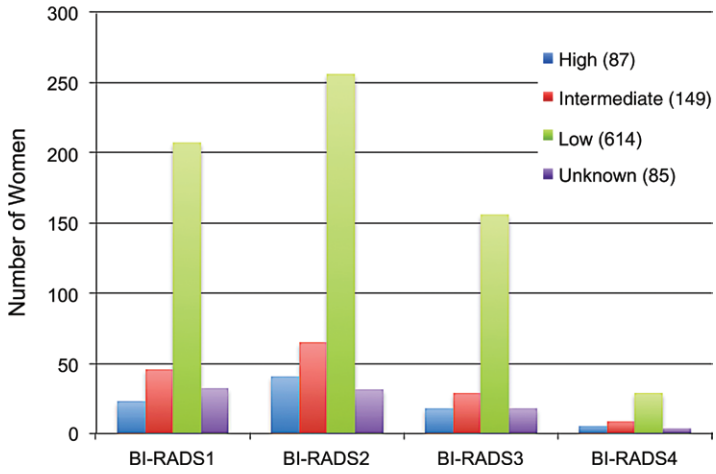


Figure 2: Histogram demonstrates risk factor stratification according to BI-RADS category. Most patients with lesions in all BI-RADS categories were at low risk. There was no significant relationship between BI-RADS category and risk ($P = .67$).

Also, although there was a significant difference between patients who underwent screening mammography and patients who underwent diagnostic mammography in regard to final US BI-RADS assessment of categories 1–3, there was no significant difference in regard to risk factors, patients receiving a biopsy recommendation on the basis of the results of screening whole-breast US (ie, US BI-RADS category 4) examination, and biopsies performed (Table 1).

Cancer Detection

Biopsy was recommended for 55 lesions, in 47 women, that were classified as BI-RADS category 4 at the initial screening US. One lesion initially classified as BI-RADS category 4 was thought to be benign at the time of biopsy, and, therefore, biopsy was cancelled. This mass was stable at 12-month follow-up US. Of the 54 lesions sampled, 46 were sampled with US-guided core needle biopsy, three were sampled with surgical excisional biopsy, and five were sampled with US-guided cyst aspiration performed in complicated cysts. Three cancers were found, including one 5-mm DCIS and two invasive ductal carcinomas, measuring 9 and 5 mm, respectively (Table 2). All three cancers were found in women with negative results (BI-RADS category 1) on a screening mammogram obtained within 1–2 months of the screening US, and none of the cancers were retrospectively visualized on the mammogram (Figs 3–5). The overall cancer yield was 3.2 cancers per 1000 women screened (95% CI: 0.8 cancers per 1000 women screened, 10 cancers per 1000 women screened). The cancer yield per risk group was as follows: low risk, 1.6 cancers per 1000 women screened (95% CI: 0.09 cancers per 1000 women screened, 11 cancers per 1000 women screened); intermediate risk, 6.7 cancers per 1000 women screened (95% CI: 0.3 cancers per 1000 women screened, 42 cancers per 1000 women screened); and high risk, 11.5 cancers per 1000 women screened (95% CI: 0.6 cancers per 1000 women screened, 71 cancers per 1000 women screened), although the difference was not significant ($P = .19$). The overall PPV for all biopsies performed on BI-RADS category 4 lesions (including aspirations of complicated cysts) was 5.6% (three of 54; 95% CI: 1.4%, 16%), and the overall PPV for all

Table 1

Comparison of Women Who Underwent Diagnostic or Screening Mammography prior to Screening Whole Breast US

Factor	Yearly Diagnostic Mammography ($n = 182$)*	Screening BI-RADS Category 0 ($n = 105$)*	Screening BI-RADS Category 1 or 2 ($n = 648$)*	*P* Value
Risk				
Low or average	110 (60.4)	69 (65.7)	435 (67.1)	.25
Intermediate	38 (20.9)	12 (11.4)	99 (15.3)	.09
High	23 (12.6)	13 (12.4)	51 (7.9)	.07
Unknown	11 (6.0)	11 (10.5)	63 (9.7)	.28
US BI-RADS category				
1	39 (21.4)	31 (29.5)	238 (36.7)	.0003
2	91 (50.0)	45 (42.9)	257 (39.7)	.003
3	44 (24.2)	28 (26.7)	115 (17.7)	.03
4	8 (4.4)	1 (1.0)	38 (5.9)	.07
Aspiration or biopsy performed†	15 (8.2)	5 (4.8)	46 (7.1)	.58

* Numbers in parentheses are percentages.

† Includes 13 women who requested biopsy or aspiration of a BI-RADS category 2 or 3 lesion.

Table 2

Summary of Demographics in Patients with Positive Results at Screening US

Patient No.	Age (y)	Risk Factor	BI-RADS Category*	Density	Size (mm)	Pathologic Finding	Lymph Nodes
1	77	High	1	Heterogeneous	9	Invasive ductal carcinoma	Negative
2	60	Intermediate	1	Heterogeneous	4	Invasive ductal carcinoma	Negative
3	63	Low	1	Heterogeneous	5	DCIS	Negative

* The BI-RADS category was assessed on mammograms. All prior mammograms were screening mammograms obtained between 1 and 2 months prior to the screening US examination.

Figure 3

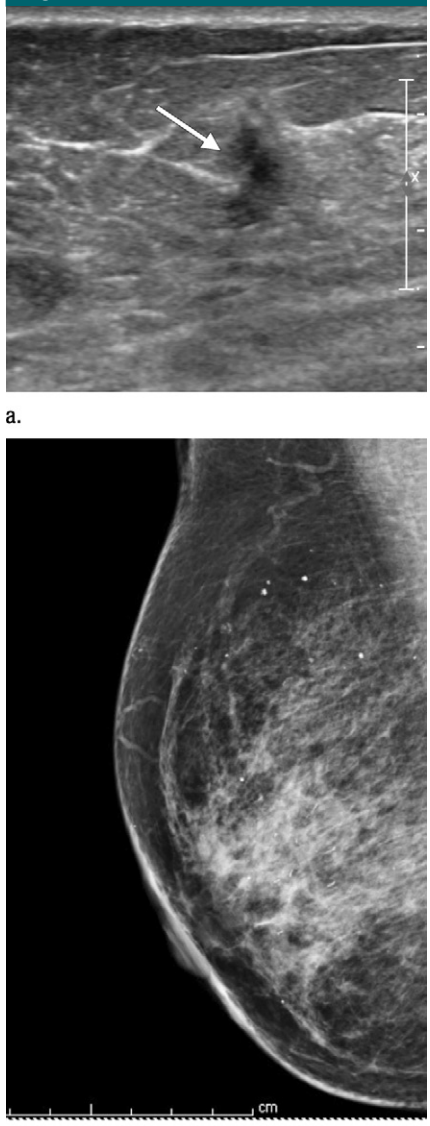


Figure 3: Mammographically occult cancer detected at screening breast US. **(a)** Gray-scale screening US image in a 77-year-old woman with a history of Huntington disease shows a 9-mm infiltrating ductal carcinoma (arrow) in the right breast. **(b)** Corresponding digital screening mammogram obtained 1 month prior was negative for cancer (BI-RADS category 1).

biopsies and aspirations performed in patients with suspicious BI-RADS category 4 findings was 6.5% (three of 46; 95% CI: 1.7%, 19%) (Table 3).

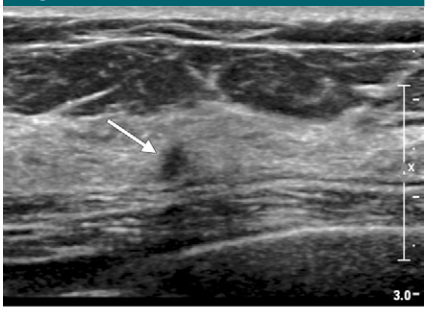
The most common benign BI-RADS category 4 biopsy result was fibroadenoma, which was found in 27 of 51 benign lesions. Of the remaining 24 benign lesions, there were six each of fibrocystic changes, benign cysts, and benign breast tissue, as well as two cases of sclerosing adenosis and one case each of benign lymph node, usual ductal hyperplasia, fibrous breast tissue, and stromal fibrosis.

Benign and Probably Benign Masses

Three hundred ninety of 935 (41.7%; 95% CI: 39%, 45%) women had cysts: In 188, they were unilateral; in 202, they were bilateral; in 246, they were multiple; and in 144, they were solitary. There were 204 women with nonsimple cysts (Table 4).

Two hundred thirty-three of 393 (59.3%; 95% CI: 54%, 64%) women with a BI-RADS category 2 final assessment had cysts, including 171 with simple cysts alone and 62 with a mixed variety of cysts (simple, complicated, and/or cluster microcysts). Other specific benign findings given a BI-RADS category 2 final assessment in women without cysts included the following: 22 benign solid masses (six intramammary lymph nodes and 16 fibroadenomas thought to be stable on the basis of findings at prior mammography or targeted US), four postoperative findings or scar, one prominent fat lobule, and two dilated ducts. Of note, three patients with benign-appearing lesions requested definitive diagnosis (two women underwent

Figure 4



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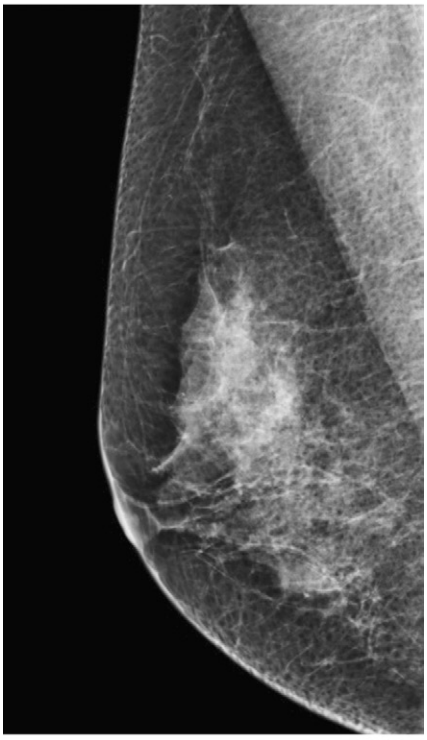
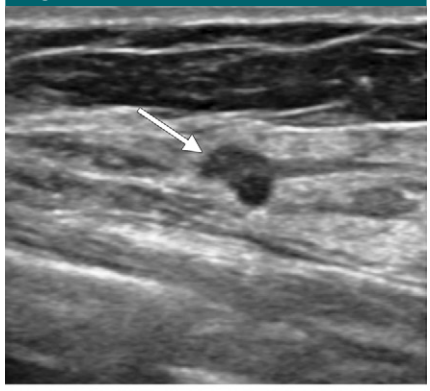


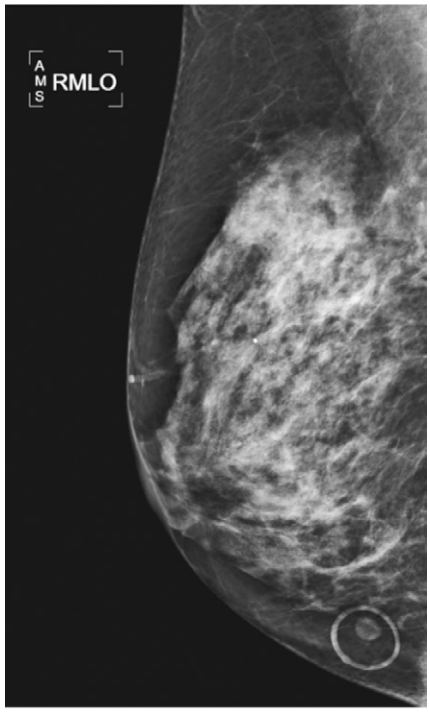
b.

Figure 4: Mammographically occult cancer detected at screening breast US. **(a)** Gray-scale screening US image in a 60-year-old woman shows a 4-mm infiltrating ductal carcinoma (arrow) in the right breast. (Reprinted, with permission, from reference 20.) **(b)** Corresponding digital screening mammogram obtained 1 month prior was negative for cancer (BI-RADS category 1).

Figure 5



a.



b.

Figure 5: **(a)** Mammographically occult cancer detected at screening breast US. Gray-scale screening US image in a 63-year-old woman shows a 5-mm DCIS (arrow) in the right breast. **(b)** Corresponding digital screening mammogram obtained 2 months prior was negative for cancer (BI-RADS category 1).

aspiration and another underwent a benign core biopsy). In 131 women, a final assessment was BI-RADS category 2, although no specific finding was mentioned in the report.

One hundred thirty-one of 187 (70.0%; 95% CI: 63%, 76%) women with a BI-RADS category 3 final assessment were followed up for nonsimple cysts (Table 5). There were 79 nonsimple cysts in the setting of multiple cysts classified as BI-RADS category 3. If we reclassified these masses as BI-RADS category 2, then the BI-RADS category 3 lesions in patients who were recalled would have decreased from 20.0% (187 of 935) to 11.6% (108 of 935). Moreover, if we also excluded 19 solitary, oval, well-circumscribed, complicated cysts of 5 mm or smaller, this rate would be further reduced to 9.5% (89 of 935). Among the 56 of 187 (29.9%; 95% CI: 24%, 37%) women without cysts, other specific benign findings classified as a BI-RADS category 3 final assessment included the following: 48 with solid masses, four with areas of fibrocystic change, two with postoperative scars, and two with unknown lesions.

Despite a BI-RADS category 3 classification recommendation, 17 of 187 women underwent a procedure. Thirteen lesions in 10 women (10 core needle biopsies and three aspirations) were sampled at the patient's request. Sampling in nine lesions in seven women was performed at the radiologist's request, including eight aspirations and one core needle biopsy performed following an aspiration attempt. Histopathologic and cytologic examinations (if performed) of all BI-RADS category 3 lesions with biopsies were benign and included five fibroadenomas, two fibrocystic changes, two cysts, and one each of fat necrosis, fibroepithelial hyperplasia, and sclerosing papilloma.

Follow-up Studies

Of the 187 BI-RADS category 3 cases, short-interval follow-up was recommended for 178 women. Of the 178 women recommended for 6-month follow-up US, 145 of 178 (81.5%; 95% CI: 75%, 87%) returned as advised. At this time, four additional new pertinent findings were identified, including two BI-RADS category 3 lesions and two BI-RADS category 4 lesions. Seven additional procedures were performed, including three aspirations and four biopsies. All findings were BI-RADS category 4 lesions; two were new findings and five were probably benign masses that were increased in size or appeared more prominent. To date, no malignancies were found in any of the lesions initially discovered and classified as BI-RADS category 3, although there was one false-negative result at follow-up

Table 3

PPV Data

Value	BI-RADS Category 4		BI-RADS Category 3+ BI-RADS Category 4*	
	No. of Lesions	No. of Patients	No. of Lesions	No. of Patients
PPV_2	3/55 (5.4; 1.4, 16)	3/47 (6.4; 1.7, 19)	3/64 (4.7; 1.2, 14)	3/54 (5.6; 1.4, 16)
PPV_3	3/54 (5.6; 1.4, 16)	3/46 (6.5; 1.7, 19)	3/63 (4.8; 1.2, 14)	3/53 (5.7; 1.5, 17)

Note.—Numbers in parentheses are percentages and the 95% CIs, as percentages.

* BI-RADS category 3 includes only procedures performed in BI-RADS category 3 lesions recommended by the radiologist. Procedures performed at the patient's request were not included in PPV calculations.

Table 4

BI-RADS Category and Distribution of Nonsimple Cysts

Type of Cysts	BI-RADS			Overall
	Category 2	Category 3	Category 4	
Multiple cysts*	46	79	9	134
Solitary complicated cysts	8	36	2	46
Solitary clustered microcysts	8	16	0	24
Total	62	131	11	204

* Multiple cysts include multiple unilateral or bilateral mixed cysts, including complicated cysts, clustered microcysts, and/or simple cysts.

Table 5

Size and Distribution of Nonsimple BI-RADS Category 3 Cysts

Size (mm)	Multiple	Solitary	Overall
3	2	1	3
4	5	4	9
5	8	14	22
6	18	11	29
7	16	11	27
8	5	2	7
9	6	3	9
10	8	2	10
11	4	0	4
12	2	3	5
13	1	1	2
14	1	0	1
≥15 mm	3	0	3
Total	79	52	131

Table 6

Approximate Cost of Screening

Modality	Cost ($)
Breast US*	98971
Aspiration†	9684
Biopsy‡	72147
Total	180802
Cost per each breast cancer	60267

Note.—Costs are based on Global Connecticut Medicare Reimbursement Rates (19).

* Includes initial US examination and all follow-up examinations performed at 6 months.

† Includes all initial and 6-month follow-up US-guided aspirations, US-guided cyst aspirations, and cytologic examinations (if performed).

‡ Includes all initial and 6-month follow-up US-guided core needle biopsies (with biopsy marker clip placement), surgical biopsies (including anesthesia), and histopathologic examinations. In total, 73 women underwent 86 procedures.

US performed at 6 months in which a new mass was classified as a probably benign complicated cyst. This mass was subsequently found to be a malignant melanoma 2 months later (Fig 6).

Seven hundred fifty-four of 935 (80.6%; 95% CI: 78%, 83%) women returned for yearly diagnostic or screening mammography; 420 of 935 (44.9%; 95% CI: 42%, 48%) also underwent screening whole-breast US. Thirty-five women underwent targeted US at 1 year, although whole-breast screening US was not performed at that time.

Cost

On the basis of the current Connecticut global Medicare reimbursement rates for initial screening whole-breast US, follow-up examinations, biopsy, and aspiration, the estimated total cost of initiating screening breast US was approximately $180802 or approximately $60267 per cancer diagnosed (Table 6).

Discussion

In this study, technician-performed handheld supplemental screening US in patients with dense breast tissue at mammography demonstrated a cancer detection rate of 3.2 cancers per 1000 women screened. This is comparable to screening mammography alone, which has a known cancer detection rate of 2–8 cancers per 1000 women screened (21) and is similar to other screening US studies.

As expected, the PPV of suspicious lesions detected at screening US in women who underwent biopsy or aspiration was low, 5.6% (95% CI: 1.4%, 16%). Investigators in prior US studies (7,10,22) have reported an overall PPV ranging from 6.6% to 19%. However, unlike in most of the prior studies, our screening US examinations were performed by a technologist, and not a radiologist, and included patients at average risk for breast cancer. Although the cancer detection rate was higher in the intermediate- and high-risk groups, the difference was not significant, likely secondary to the small number of patients in each group.

Seventy-five percent (701 of 935; 95% CI: 72%, 78%) of our patients had a negative result at screening breast US examination and 20.0% (187 of 935; 95% CI: 18%, 23%) had an examination with probably benign findings. Nonsimple cysts were the main reason that short-interval follow-up was recommended in our study, accounting for 70.0% (131 of 187; 95% CI: 63%, 76%) of lesions. Traditional US teaching states that complicated cysts and clustered microcysts should be followed up because in rare cases, a cystic cancer can mimic the appearance of these nonsimple

Figure 6

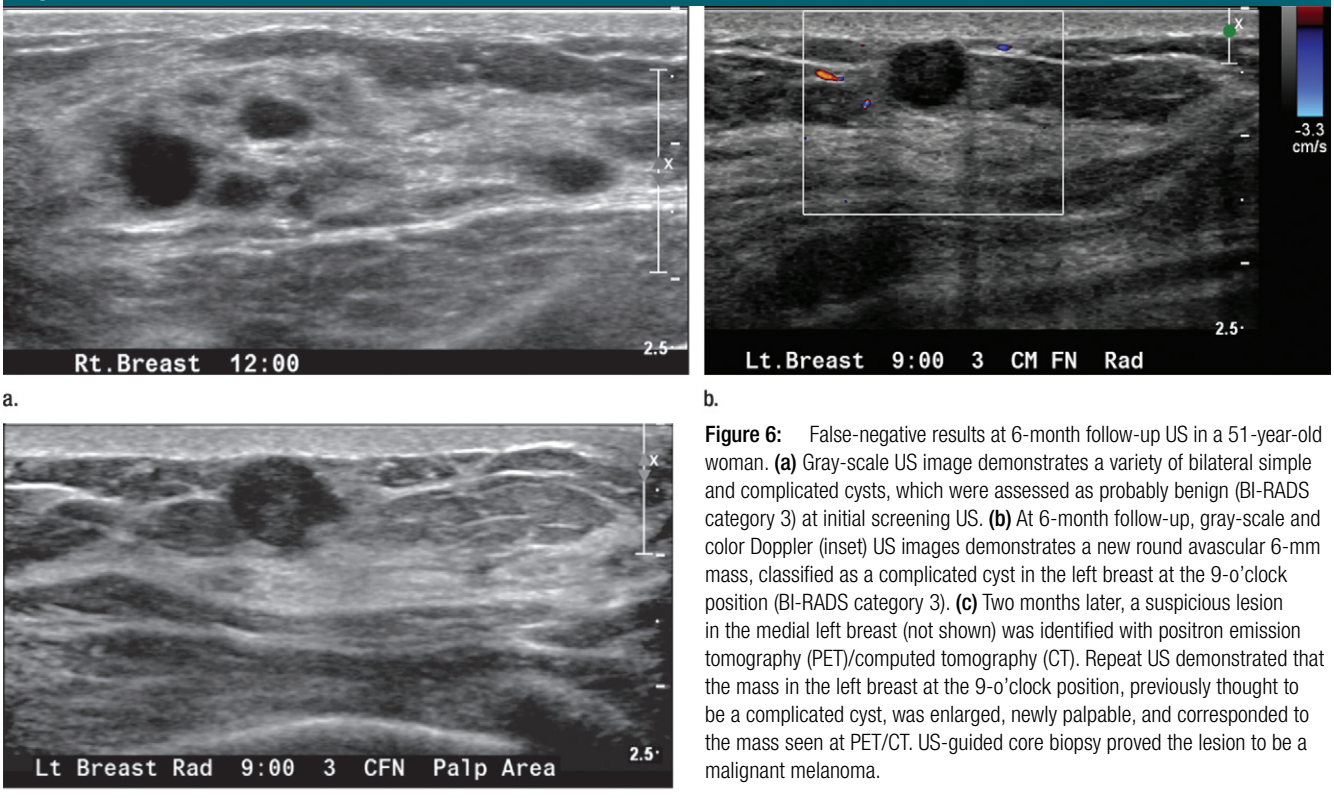


Figure 6: False-negative results at 6-month follow-up US in a 51-year-old woman. **(a)** Gray-scale US image demonstrates a variety of bilateral simple and complicated cysts, which were assessed as probably benign (BI-RADS category 3) at initial screening US. **(b)** At 6-month follow-up, gray-scale and color Doppler (inset) US images demonstrates a new round avascular 6-mm mass, classified as a complicated cyst in the left breast at the 9-o'clock position (BI-RADS category 3). **(c)** Two months later, a suspicious lesion in the medial left breast (not shown) was identified with positron emission tomography (PET)/computed tomography (CT). Repeat US demonstrated that the mass in the left breast at the 9-o'clock position, previously thought to be a complicated cyst, was enlarged, newly palpable, and corresponded to the mass seen at PET/CT. US-guided core biopsy proved the lesion to be a malignant melanoma.

cysts. However, in multiple prior studies (23–29) in which researchers evaluated more than 1200 complicated cysts and 216 clustered microcysts, the malignancy rates were 0%–0.44% and 0%–0.8%, respectively (with only one clustered microcyst which was ultimately proved to be a 4-mm infiltrating lobular cancer). With current high-resolution US equipment, internal echoes and thin septations are visualized frequently, and few guidelines exist in regard to the treatment of masses detected only at US that do not meet the strict criteria for simple cysts. In the American College of Radiology Imaging Network 6666 trial, multiple bilateral complicated and simple cysts (ie, at least three cysts, with at least one in each breast) were classified as benign (23). Similar initial guidelines were not utilized in our practice prior to initiating our screening breast US program, and, therefore, this is likely the reason for the high number of our cases being classified as BI-RADS category 3. Indeed, reclassification of the 79 nonsimple cysts in the setting of multiple cysts, as well as 19 solitary, oval well-circumscribed, complicated cysts of 5 mm or smaller classified as BI-RADS category 2 would have decreased our initial overall BI-RADS category 3 lesions from 20% to 10% without a loss in sensitivity. Although one 6-month follow-up US was recommended in a patient with multiple bilateral complicated cysts, and a new, round mass diagnosed as a complicated cyst was subsequently determined to be a metastatic melanoma detected at PET/CT, to date no primary breast cancers have been found in the BI-RADS category 3 lesions in this study.

Benign-appearing, solid masses were also a very common finding in our study, accounting for 25.7% (48 of 187; 95% CI: 20%, 33%) of BI-RADS category 3 masses. Benign fibroadenomas were found in 50.0% (27 of 54; 95% CI: 37%, 63%) of BI-RADS category 4 masses that were sampled. Follow-up US is an acceptable alternative to biopsy of solid masses with benign morphologic features specified in the BI-RADS US lexicon as category 3, as several studies show a high negative predictive value ranging from 99.3% to 100% (16,30–32). However, finding a benign-appearing solid mass at screening US with no mammographic correlate creates anxiety in an asymptomatic woman, and the radiologist may be more inclined to recommend US-guided core biopsy and classify these lesions as BI-RADS category 4. New criteria and methods to better classify both benign-appearing solid and cystic masses seen at screening US would be beneficial to decrease the need for short-interval follow-up and biopsy.

During the study period, 14242 women underwent screening or diagnostic mammography at our facility, and although we were unable to directly calculate the number of women in this group who had either heterogeneously or extremely dense breast tissue, studies

have shown that approximately 40% of all women have dense breast tissue (3). Therefore, approximately 5697 women were eligible, but only 16.4% (935 of 5697; 95% CI: 15%, 17%) chose the optional examination. Our referring clinician's practices are variable, and while some routinely send all patients with dense breast tissue for screening breast US, others do not. Only 44.9% (420 of 935) of patients who underwent screening breast US at our facility during the study period returned for 1-year follow-up screening US, but 80.6% (754 of 935) underwent 1-year follow-up mammography.

In this study, the mean time between mammography and screening breast US was 61 days. In this initial year, this is likely due to the time for the patients to receive the mammography report, have a discussion with their physician, and subsequently schedule the examination. For subsequent years, scheduling of both mammography and US simultaneously is being performed, if the patient so desires.

Our study had limitations. We do not know how the mammography interpretations were influenced by the radiologists' knowledge that women were going to be given information in regard to their breast density, although when the legislation came into effect, our mammographers paid more careful attention to accurately estimate breast density. This study is retrospective, and both the radiologists and technologists knew the mammography results prior to performing the US. The patients were, to some extent, a self-selected population and were likely more aware of their mammography results as reflected by the higher percentage of women undergoing recent diagnostic mammography. These patients, also being more proactive in their health care, may have heightened anxiety over any US findings and, thereby, possibly may have influenced the rate at which the radiologist recommended follow-up or biopsy. Our US examinations were performed by a technologist, and we did not collect specific data on how often a radiologist also scanned the patient or, if during this time, additional findings were made. Our study was a single-institution study performed in a dedicated breast center at a major cancer hospital, with all examination results interpreted by radiologists specializing in breast imaging. Therefore, our results may not be attributable to other centers, perhaps with different patient populations or less experience with breast US. Furthermore, although we determined the cost per cancer diagnosed, we are unaware of current similar data in regard to screening mammography. Finally, our actual false-negative rate is also yet to be determined. Only 420 patients underwent 1-year follow-up US, and no interval breast cancers have been detected.

In conclusion, in our 1st year of offering technologist-performed handheld screening breast US to Connecticut women with dense breast tissue, small mammographically occult breast cancers were discovered with a detection rate of 3.2 cancers per 1000 women screened, and while this study revealed a relatively high rate of BI-RADS category 3 and 4 lesions, our BI-RADS category 3 rate could have been decreased nearly 50% by classifying nonsimple cysts in the presence of multiple cysts, as well as solitary, oval, well-circumscribed complicated cysts of 5 mm or smaller, as benign lesions without a loss in sensitivity. Validation of this practice by others is required. Further studies are needed to determine the optimal interval for screening breast US and to investigate potential strategies and methods to reduce the number of benign lesions recommended for short-term follow-up or biopsy.

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