AJR FOCUS ON:

Screening Breast Ultrasound: Past, Present, and Future

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OBJECTIVE. This article discusses breast ultrasound for the detection of breast cancer in the screening environment, as well as strategies for integrating screening breast ultrasound, including automated breast ultrasound.

CONCLUSION. Breast density is an increasingly pertinent issue in breast cancer diagnosis. Breast density results in a decrease in the sensitivity of mammography for cancer detection, with a significant increase in the risk of breast cancer. Ultrasound detects additional cancers.

Breast cancer is the most commonly diagnosed malignancy in women worldwide and is the second leading cause of cancer death in women in the United States [1, 2]. Early detection of breast cancer improves outcomes [3]. Screening strategies for detecting early stage breast cancer are now stratified. Mammography is recommended for women beginning at age 40 years by the American College of Radiology, American Cancer Society, and American College of Surgeons. For the women at highest risk women (i.e., those with greater than 20–25% lifetime risk), annual surveillance with MRI is recommended [4–6]. Preliminary data suggest that high-resolution nuclear medicine imaging, such as breast-specific gamma imaging and molecular breast imaging, may be beneficial in detecting mammographically occult breast cancer in high-risk women [7]. This is notable because an approach to detect mammographically occult breast cancers in women who cannot or will not undergo MRI is now available.

Multiple studies have found that screening mammography reduces mortality from breast cancer [8, 9]. Nevertheless, mammography is an imperfect tool and is not equally effective in all women. Overall, the sensitivity of mammography for the detection of breast cancer is 85%. However, in women with dense breast tissue, the sensitivity of mammography is reduced to 47.8–64.4% [10]. Although breast density tends to decrease with age [11], it is a significant issue in women of all ages, with more than 50% of American women having dense breast tissue [12]. The decreased ability of mammography to detect breast cancer is a result of the lack of contrast between the "white" breast tissue and the "white" breast cancer visualized mammographically. Not only is mammography limited in women with dense breast tissue, but women with extremely dense breasts also have a 4.7-fold increased risk of developing breast cancer compared with women with fatty-replaced breasts [13]. Cancers detected in women with dense breast tissue are larger and more frequently node positive [14]. There is an 18-fold increased risk of an interval cancer in women with dense breast tissue, with interval cancers having a worse prognosis than screen-detected cancers [13]. Women with dense breast tissue constitute the largest population of "intermediate risk" women—that is, women with a 15–25% lifetime risk of breast cancer. They have the "perfect storm" of decreased mammographic sensitivity and increased risk of breast cancer.

Although ultrasound has long been a mainstay of breast imaging as a diagnostic tool, studies have shown that ultrasound can and does detect mammographically occult breast cancer in women with dense breast tissue (Fig. 1). In this article, we will review the data showing the impact of screening breast ultrasound, as well as strategies to improve workflow such that ultrasound can be implemented as a screening tool in women with dense breast tissue.

Review of the Literature

Bilateral handheld screening ultrasound using a high-frequency transducer, when

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performed by an experienced technologist or radiologist, has been shown to detect early-stage mammographically occult breast cancers in patients with dense breast parenchyma [15–18]. Therefore, breast imagers have long been asking the question: Is it effective to screen women with dense breast parenchyma with whole-breast ultrasound?

In a single-institution study in 2001, Kaplan [19] evaluated the performance of screening ultrasound in patients with BI-RADS categories 3 and 4 breast parenchymal density. The study included 1862 women with negative mammograms, most of whom had negative clinical breast examinations, although the exact number of asymptomatic women was not reported. Examinations were performed by technologists with extensive experience in breast ultrasound, and studies were reviewed by a breast radiologist in conjunction with the patient's mammogram. A total of 102 procedures (core needle biopsies and fine-needle aspirations) were performed in 97 patients because of suspicious sonographic findings, yielding six breast cancers in five patients, for a positive predictive value (PPV) of 11.8%. This resulted in a diagnostic yield of three additional cancers per 1000 women. The PPV for mammography in that study was approximately 25%. It is notable that the sonographically detected cancers were identified after the mammographically detected cancers were already detected. These were incremental cancers, which would not have been detected without the addition of screening ultrasound. Of note, the sonographically detected cancers were mostly small invasive early-stage cancers with a mean size of 9 mm, and all were stage 0 or 1. In this early study, Kaplan found that ultrasound could be used as a screening tool to detect small invasive early-stage cancers not detected with mammography.

In 2002, Kolb et al. [10] investigated the performance of screening mammography, screening ultrasound, and physical examination in the detection of breast cancer in 13,547 women. Kaplan [19] had excluded women with nondense breast tissue, but Kolb et al. initially included all women, regardless of breast density. After finding no additional cancers in the first 700 women with BI-RADS category 1 density, only women with BI-RADS categories 2–4 density were designated as having "dense breasts" and were included. Another notable difference in this study was that a radiologist, not a technologist, performed all of the screening ultrasound examinations. Kolb et al. analyzed the effect of age, breast density, and hormonal status on mammographic sensitivity. Of these factors, breast density was the most significant predictor of decreased mammographic sensitivity.

When compared with "conventional screening," consisting of mammography and physical examination, screening mammography with the addition of screening ultrasound was more sensitive for breast cancer detection (97.3% vs 74.7%). Specifically, the mammographic sensitivity for breast cancer in women with BI-RADS category 4 breast density was 47.6%, which increased to 76.1% with ultrasound screening. The false-positive rate for masses requiring biopsy, identified by ultrasound screening, was 2.4%. More ultrasound-detected lesions underwent biopsy, decreasing the PPV to 20.5% with screening ultrasound alone, versus 35.8% with mammography. Suspicious physical examination alone resulted in 16 biopsies, of which six were cancer. Although this represents a high yield for physical examination, these cancers make up only 2% and 3% of total breast cancers found in fatty and dense breasts, respectively. Additionally, cancers found on physical examination were the largest, with a mean size of 21.8 mm. Of note, none of the cancers detected with physical examination were smaller than 1 cm. In comparison, the mean size of cancers found with mammography was 9.8 mm, with 73% measuring less than 1 cm, and those found with ultrasound in women with normal mammograms measured a mean of 9.9 mm, with 70% being smaller than 1 cm. These findings support the use of ultrasound to detect mammographically occult clinically significant small invasive breast cancers.

In 2003, Leconte et al. [20] compared the use of bilateral whole-breast screening ultrasound in women with dense versus nondense breast tissue. That study reported the sensitivities of breast cancer detection with mammography versus mammography plus screening ultrasound in patients who had nondense (BI-RADS categories 1 and 2) and dense (BI-RADS categories 3 and 4) breast tissue. For BI-RADS density categories 1 and 2, the sensitivities of mammography and sonography were 80% and 88%, respectively, and not statistically significant. However, the sensitivities for these examinations in women with BI-RADS categories 3 and 4 breast density were 56% for mammography and 88% for mammography plus ultrasound, a finding that achieved statistical significance. A large European study published in 2010 by Schaefer et al. [21] showed similar results, where bilateral screening ultrasound performed in the setting of a negative mammogram yielded a 15.9% increase in breast cancer detection in women with BI-RADS categories 3 and 4 breast density, with the highest rate of detection of mammographically occult cancer in the category 4 subgroup. In density categories 1 and 2, the increase in breast cancer detection was 8.5%.

In 2008, Berg et al. [22] published the results of the first year of the American College of Radiology Imaging Network (ACRIN) 6666 trial. This was a prospective randomized multiinstitutional trial of 2809 women to access the use of screening ultrasound in addition to mammography using a standardized protocol. In that study, the inclusion criteria required women to be at high risk for the development of breast cancer, with dense breast tissue in at least one quadrant of the breast. High-risk women included those with a personal history of breast cancer, a lifetime risk greater than 25% as quantified by either the Gail or Claus model, previous biopsy yielding a high-risk lesion, *BRCA1* or *BRCA2* genetic mutation, or chest mediastinal or axillary radiation. Although there is strong evidence to support the use of surveillance MRI in the highest-risk patients, 56% of the women in the study would not qualify for MRI surveillance by American Cancer Society criteria [23].

That study found an increase in the diagnostic yield of breast cancer of 4.2 per 1000 women screened. Similar to previous studies, most cancers detected were invasive (91.7%), with a mean size of 10 mm, and 11 of the 12 cancers detected with supplemental screening ultrasound were node negative. The biopsy rates were 4.4% for mammography, 8.1% for ultrasound alone, and 10.4% for both. The PPV of breast biopsy decreased from 22.6% for mammography alone to 11.2% for mammography plus handheld screening ultrasound.

In a follow-up study, in 2012, Berg and colleagues [24] reported years 2 and 3 follow-up mammography and ultrasound screening findings of the ACRIN 6666 trial. In addition to ultrasound screening, women who completed year 3 were also invited to screen with MRI. Again, screening ultrasound increased the cancer detection yield over mammography alone. A total of 111 breast cancers were detected during the study, of which 59 (53%) were detected with mammography alone, 32

(29%) were detected with ultrasound alone, and nine (8%) were detected by MRI alone. Of note, 11 (10%) cancers were not seen by any imaging modality but were detected clinically. In years 2 and 3, an additional 3.7 cancers were detected with screening breast ultrasound per 1000 women screened. The sensitivity of mammography combined with ultrasound was higher than that for mammography alone (76% vs 52%), with a decrease in specificity from 91% with mammography alone to 84% with mammography plus ultrasound. Interestingly, of the 1215 women offered MRI screening, 512 (42.1%) declined to participate. Of those who declined, more than 25% noted claustrophobia as their reason for not participating. It is for this population of women that physiologic imaging, such as breast-specific gamma imaging or molecular breast imaging, may be helpful [25].

Although false-positive findings did decrease with incident screens, there was still a substantial rate of biopsy as a result of ultrasound screening, averaging 5% of all participants. The PPV of biopsy for mammography in the first year was 20%, increasing to 38% in years 2 and 3. For mammography plus handheld ultrasound, the PPV increased from 11% in year 1 to 16% in years 2 and 3. Of the 20 women whose cancer went undetected by mammography, nine additional cancers were detected by MRI; however, fewer women were willing to undergo MRI, with only 612 women accepting MRI screening. Furthermore, given that in the ACRIN 6666 year 1 study, there was a low interval cancer rate of 8% and that all interval cancers were node negative, it is unlikely that the cost and added discomfort of undergoing routine screening with MRI are beneficial in this intermediate-risk group [24]. Moreover, the ACRIN 6666 study found that an average of 19 minutes of physician time was required for handheld ultrasound breast screening, not including interpretation or reporting time. This is a significant workflow issue when considering screening breast ultrasound.

Many studies have evaluated ultrasound screening in women with dense breast tissue who are at increased risk of breast cancer [5, 11, 16–22, 24]. These studies have shown that screening breast ultrasound results in the detection of small invasive node-negative breast cancer. What about screening women whose only risk factor is having dense breast tissue, without other risk factors?

In 2009, Connecticut was the first state to pass an "inform" law requiring physicians to advise women of their breast density. They must also be informed that they may benefit from additional screening, such as ultrasound or MRI. Currently, a number of states have passed similar laws, with more in progress, including a national law pending in Congress. Two states, Connecticut and Illinois, require insurance coverage for additional screening of women with dense breast tissue. When Connecticut's law was enacted, that state became an opportune environment to evaluate screening breast ultrasound in women with dense breast tissue.

In 2012, Weigert and Steenbergen [26] reported initial results of ultrasound screening in 12 practices in Connecticut, where 72,030 screening mammography and 8647 screening ultrasound examinations over 1 year were included. Twenty-eight additional cancers were detected, for an additional cancer yield of 3.25 cancers per 1000 women screened. The PPV was 6.7%, and 14% of patients were recalled. However, patient compliance with screening ultrasound was low: only 28% of women offered ultrasound screening accepted. Perhaps this low compliance may be the result of the first year experience. It is likely that with greater awareness and time, a higher percentage of women may opt for screening ultrasound.

In a single-institution study by Hooley et al. [27] reporting their first-year experience in Connecticut with 935 women, similar findings were reported. Of the 55 lesions for which biopsies were recommended, 54 underwent biopsy, yielding three cancers. Although this study included diagnostic patients, no lesions with mammographic or physical correlates were included; only findings from screening ultrasound were included. In contrast to the ACRIN 6666 studies, the vast majority of these patients were of intermediate risk for breast cancer, with increased risk due to breast density alone. Both the study by Hooley et al. and that by Weigert and Steenbergen [26] found an increase in cancer detection yield of 3.2 per 1000 patients with screening ultrasound, similar to previous studies. The PPV found by Hooley et al. was 6.5%. The rate of ultrasound findings classified as BI-RADS category 3 and recommended for short-interval follow-up was 20%. However, by reclassifying nonsimple cysts in the setting of multiple cysts and solitary oval well-circumscribed complicated cysts smaller than 5 mm, this rate is substantially decreased to 9.5%. In contrast to the ACRIN 6666, in both the study by Weigert and Steenbergen and that by Hooley et al., the ultrasound examinations were performed by technologists, not radiologists.

Studies have shown that screening breast ultrasound in women with dense breast tissue is effective in detecting mammographically occult predominantly small node-negative breast cancer. However, the practical workflow of nearly 20 minutes for the performance of bilateral handheld ultrasound makes it a challenge for screening, regardless of whether it is performed by a radiologist or a technologist. There is a shortage of both physicians and well-trained technologists to perform screening breast ultrasound [24]. With nearly 40 million mammography examinations and with half of those in women with dense tissue, handheld ultrasound screening would require more than 6 million work hours per year. If the examination acquisition could be uncoupled from the interpretation, then the study could be obtained independently of physician input and then interpreted at a separate time and place with the entire dataset of the images available to the radiologist. To harness the potential of ultrasound screening in a workflow-efficient approach, automated breast ultrasound was developed.

Automated breast ultrasound is a novel approach for screening breast ultrasound in which image acquisition is uncoupled from the interpretation (Fig. 2). The study is reviewed by the radiologist on a dedicated workstation using the entire dataset for interpretation. Compared with technologist-performed bilateral handheld ultrasound, in which representative images are presented for interpretation, automated breast ultrasound allows the physician to interpret the entire study and identify the suspicious lesions. Furthermore, automated breast ultrasound allows improved consistency and reproducibility of images, minimizes operator dependence, and aids with inclusion of the entirety of the breast. It does not require physician time for image acquisition and allows review of the study at either the time of acquisition or a later time. There are several types of automated breast ultrasound available commercially with various designs, including differences in image acquisition approaches and workstation features. However, all of them separate the image acquisition from the interpretation of the study, allowing more efficient integration of screening breast ultrasound. With this configuration, the use of automated breast ultrasound is more similar to screening mammography, thereby al-

TABLE 1: Summary of Findings in Reviewed Literature

Study	Study Aim	No. of Screening Ultrasound Examinations	No. of Ultrasound-Only Cancers	Mammography Plus Ultrasound			Additional Cancer Yield From Ultrasound per 1000 Women screened
				Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	
Kaplan [19]	BI-RADS 3–4 density; technician performed screening ultrasound on patients with normal mammograms, some with clinical symptoms	1862	6	—	—	11.8	3
Kolb et al. [10]	BI-RADS 2–4 density; radiologist performed screening ultrasound on patients with no clinical symptoms	13,547	37	97.3	—	—	2.73
Ultrasound only				75.3	96.8	20.5	
Leconte et al. [20]	All densities included; radiologist performed ultrasound	4236	16	88	—		3.8
Schaefer et al. [21]	BI-RADS 3–4 density; ultrasound performed on patients with no clinical symptoms	41,564	84	—	—	25.4	2.02
Berg et al. [22]	BI-RADS 3–4 density in at least one quadrant and at high risk; radiologist performed ultrasound screening; blinded to mammography and physical examination findings	2809	12	77.5	—	11.2	4.2
Berg et al. [24]	BI-RADS 3–4 density in at least one quadrant and at high risk; radiologist performed ultrasound screening; blinded to mammography and physical examination findings	2809 (× 3 years of ultrasound screening for each subject)	32	76	84	16	3.7
Weigert and Steenbergen [26]	BI-RADS 3–4 density; ultrasound performed on patients with normal mammograms; no clinical symptoms	8647	28	96.6	94.9	6.7	3.25
Hooley et al. [27]	BI-RADS 3–4 density; technician performed screening ultrasound on patients with no clinical symptoms; mammographic findings excluded	935	3	—	—	6.5%	3.2
Kelly et al. [29]	Automated whole-breast ultrasound screening in BI-RADS 3–4 density or high-risk patients with no clinical symptoms	6425	23	81	98.7	38.4	3.6
Automated whole-breast ultrasound only				67	89.9		

Note—Dashes indicate parameter was not reported in cited article.

lowing more seamless integration into the screening workflow environment.

Kelly et al. [28] studied the ability of automated whole-breast ultrasound (AWBUS) with the SonoCiné device to improve breast cancer detection, in more than 4000 women with dense breasts at increased risk for breast cancer. Results showed an increase in the diagnostic yield by 3.6 cancers per 1000 screening examinations. This was achieved with an increase in sensitivity from 40% with mammography alone to 81% for mammography plus automated whole-breast ultrasound. Similar to prior studies, there was an increase in recalls, from 4.2% to 9.6%. Many of the ultrasound-detected cancers were 10 mm or less in size. Of note, this study used automated breast ultrasound in women with dense breasts with an increased risk of breast cancer. Two of three mammography examinations in this study were analog, and 21% of the study population were described as having "annual asymptomatic diagnostic" examinations, including some with pain or nodularity. This implies that there were symptomatic patients included in this study.

Another study by Kelly et al. [29] investigated the ability of automated breast ultrasound used by community radiologists to improve breast cancer detection in women with dense breast tissue. They found that automated breast ultrasound resulted in an increase in the sensitivity of breast cancer detection from 50% to 81%. All readers found more cancers with the addition of automated whole breast screening ultrasound, and all found 16–29% more cancers than even the best performing mammographer.

Recently, a large multiinstitutional trial evaluating more than 15,000 asymptomatic women with dense breasts using mammography and supplemental ABUS found that mammography detected 5.4 cancers per 1000 women, whereas mammography with supplemental ABUS detected 7.3 cancers per 1000 women, an increase of 1.9 cancers per 1000 women. The increase in sensitivity at screening for the combined imaging approach versus mammography alone was 26.7%. There was a corresponding increase in the recall rate, from 150 per 1000 women with mammography to an additional 135 per 1000 women with ABUS, a specificity decrease of 13.4%. Of note, the additional cancers detected with ABUS (93.3%) were invasive node-negative breast cancers [30]. This approach uncoupled the image acquisition from the interpretation, allowing the physician to interpret the

entire dataset and not rely on other personnel to detect abnormalities, while decreasing the amount of physician time for interpretation.

In a review of the cost-effectiveness of breast cancer screening modalities, Feig [31] found that ultrasound screening can be cost-effective, particularly when automated whole-breast ultrasound is used. The ACRIN 6666 trial and eight other nonblinded screening ultrasound trials from 1995 through 2003 show promise with ultrasound screening because of increased cancer detection and the small size of cancers detected. The low PPV in all of these studies does not meet the 25–40% PPV_2 (i.e., the percentage of examinations with an abnormal final interpretation that result in a tissue diagnosis of cancer within 1 year) recommended by the ultrasound Agency for Health Care Policy and Research: the PPV_2 in the ACRIN 6666 trial was 8.9% for ultrasound, compared with 22.6% for mammography. The author found the results from the study by Kelly et al. [29] to be even more promising, with a higher biopsy PPV of 38.4%, similar to the 39.0% PPV of mammography in the same study. Ultimately, the examination is trending toward being more cost effective. At $300 per screening, it is in an acceptable range and is "more cost-effective than MRI for most populations" [31].

A more recent reader study used automated breast ultrasound (ABUS, U-Systems and GE Healthcare) to evaluate reader performance of screening mammography alone and screening mammography with ABUS in women with dense breast tissue. There was a statistically significant 24% increase in cancer detection with the addition of automated screening ultrasound, with a statistically insignificant decrease in specificity [32]. As a result of this study, the U.S. Food and Drug Administration approved ABUS as the only approved such system for screening women with dense breast tissue. Although this creates a large dataset, it is presented efficiently; reported physician time for interpretation of this examination is 3 minutes [33], which is more feasible for integration in the screening environment than the 19 minutes reported for physician time for the scanning as noted in the ACRIN 6666 trial. Additional large-scale studies are ongoing to evaluate ABUS in clinical practice. The cost-effectiveness has also not been established.

In summary, screening breast ultrasound may be a solution to the as-of-yet unmet challenge of detecting mammographically occult cancers in women with dense breast tissue for whom mammography is less effective and who have an increased risk of breast cancer. Women with dense breast tissue constitute the largest group of intermediate-risk women for whom mammography may not be sufficient but for whom MRI or breast-specific gamma imaging may not be warranted. Ultrasound detects small, clinically significant, invasive, and predominantly node-negative cancers.

As noted in all studies reported, the detection of additional cancers is associated with a substantial callback rate as well as an increased false-positive biopsy rate (Table 1). Whole-breast ultrasound is being more widely integrated into clinical practice, and more extensive experience and additional studies may prove beneficial in the screening environment. With additional experience, both for technologists acquiring the images and radiologists interpreting them, the hope is that the false-positive rate as well as biopsy rate should decrease. Furthermore, there are ongoing efforts to develop computer-aided detection for increased detection of lesions, to improve sensitivity, and enhanced characterization of lesions, to improve specificity. With the increasing availability of automated breast ultrasound, screening breast ultrasound will become faster and more efficient, likely with the concomitant increase in the detection of small invasive node-negative breast cancers. Further work is needed to improve the specificity and increase the PPV of biopsy. Until then, with the increased integration of ultrasound screening, particularly with ABUS, there will probably be increased numbers of smaller node-negative breast cancers detected.

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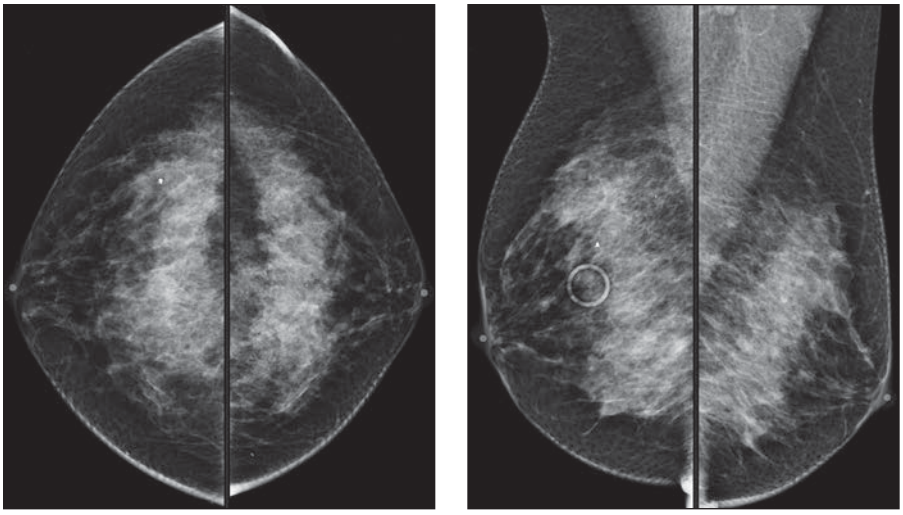
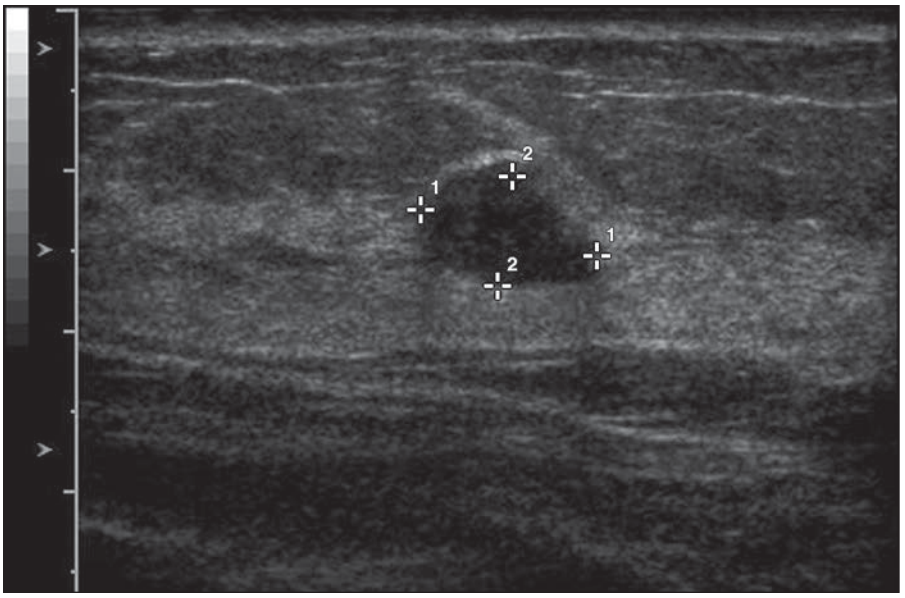


A **B**

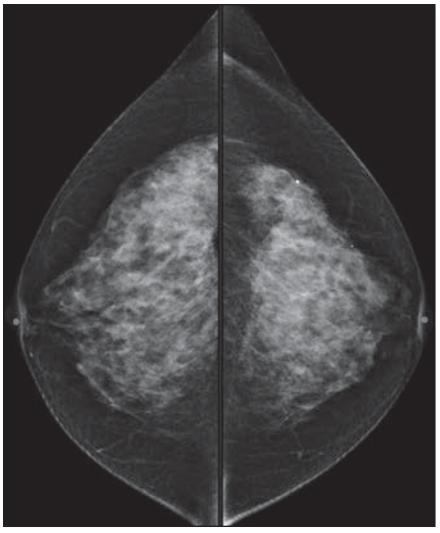
Fig. 1—48-year-old woman with mammographically occult cancer seen on ultrasound.
A, Craniocaudal views show normal BI-RADS category 2 mammogram.
B, Mediolateral oblique views. Circle denotes mole.

(Fig. 1 continues on next page)



C

Fig. 1 (continued)—48-year-old woman with mammographically occult cancer seen on ultrasound. **C,** Cancer is seen on ultrasound. Pathologic analysis revealed ductal carcinoma in situ.



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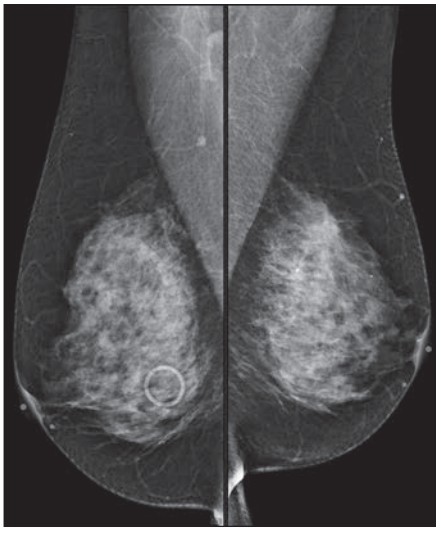
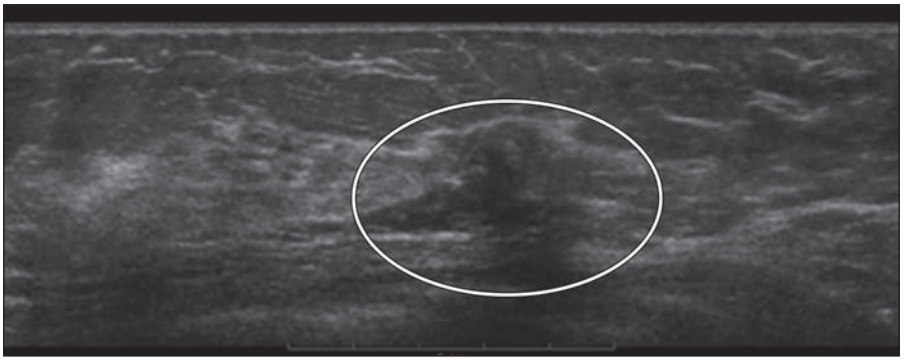


B



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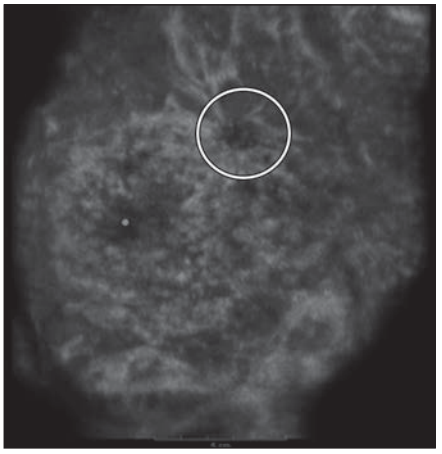

D

Fig. 2—54-year-old woman with mammographically occult cancer seen on automated breast ultrasound. **A,** Craniocaudal mammographic views show normal BI-RADS density category 3 mammogram. **B,** Mediolateral oblique views. Circle denotes mole. **C,** Three-dimensional automated ultrasound image acquired transversely shows 1.5-cm invasive mammary carcinoma. Oval shows area of dark cancer. **D,** Transverse image reconstructed in coronal plane shows same 1.5-cm invasive mammary carcinoma Circle shows area of dark cancer.

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