Breast Cancer Detected with Screening US: Reasons for Nondetection at Mammography[1]

Min Sun Bae, MD
Woo Kyung Moon, MD
Jung Min Chang, MD
Hye Ryoung Koo, MD
Won Hwa Kim, MD
Nariya Cho, MD
Ann Yi, MD
Bo La Yun, MD
Su Hyun Lee, MD
Mi Young Kim, MD
Eun Bi Ryu, MD
Mirinae Seo, MD

Purpose: To retrospectively review the mammograms of women with breast cancers detected at screening ultrasonography (US) to determine the reasons for nondetection at mammography.

Materials and Methods: This study received institutional review board approval, and informed consent was waived. Between 2003 and 2011, a retrospective database review revealed 335 US-depicted cancers in 329 women (median age, 47 years; age range, 29–69 years) with Breast Imaging Reporting and Data System breast density type 2–4. Five blinded radiologists independently reviewed the mammograms to determine whether the findings on negative mammograms should be recalled. Three unblinded radiologists re-reviewed the mammograms to determine the reasons for nondetection by using the reference location of the cancer on mammograms obtained after US-guided wire localization or breast magnetic resonance imaging. The number of cancers recalled by the blinded radiologists were compared with the reasons for nondetection determined by the unblinded radiologists.

Results: Of the 335 US-depicted cancers, 63 (19%) were recalled by three or more of the five blinded radiologists, and 272 (81%) showed no mammographic findings that required immediate action. In the unblinded repeat review, 263 (78%) cancers were obscured by overlapping dense breast tissue, and nine (3%) were not included at mammography owing to difficult anatomic location or poor positioning. Sixty-three (19%) cancers were considered interpretive errors. Of these, 52 (82%) were seen as subtle findings (46 asymmetries, six calcifications) and 11 (18%) were evident (six focal asymmetries, one distortion, four calcifications).

Conclusion: Most breast cancers (81%) detected at screening US were not seen at mammography, even in retrospect. In addition, 19% had subtle or evident findings missed at mammography.

[1] From the Department of Radiology, Seoul National University College of Medicine, 28 Yongon-dong, Chongno-gu, Seoul 110-744, Korea (M.S.B., W.K.M., J.M.C., H.R.K., W.H.K., N.C., B.L.Y., S.H.L., E.B.R., M.S.); Department of Radiology, Seoul Metropolitan Government Seoul National University, Boramae Medical Center, Seoul, Korea (A.Y.); and Department of Radiology, Konkuk University Medical Center, Seoul, Korea (M.Y.K.). From the 2012 RSNA Annual Meeting. Received March 26, 2013; revision requested May 22; revision received June 20; accepted July 15; final version accepted August 12. Supported by the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education, Science, and Technology (grant no. 2012R1A1A2009414). **Address correspondence to** W.K.M. (e-mail: *moonwk@snu.ac.kr*).

Mammography is the only screening test that has been proved to reduce breast cancer mortality. However, mammography is an imperfect tool, with an overall sensitivity of 75%–85%, which can decrease to 30%–50% in women with dense breast tissue (1–6). Women with dense breast tissue have a three- to sixfold higher risk of interval cancer than do women with fatty breast tissue (1). High breast density is the main cause of false-negative mammograms and is an independent risk factor of breast cancer (7).

Recently, several states, including Connecticut, have passed a breast density notification law, which requires radiologists to inform women if dense breast tissue is found at mammography and that they may benefit from additional screening with ultrasonography (US) or magnetic resonance (MR) imaging (6). US is an attractive screening tool because it is widely available, it is performed without a contrast agent, and it is well tolerated in women. In the American College of Radiology Imaging Network (ACRIN) 6666 study, screening US had a sensitivity of 76% and a specificity of 84% (8). Screening US in women with dense breasts and negative mammograms yielded an incremental cancer detection rate of 2.3–4.6 cancers per 1000 women screened (5,6,8–13). Most breast cancers detected with screening US tend to be node-negative small invasive cancers. The breast screening guidelines from the American College of Radiology and the Society of Breast Imaging state that screening US is optional in women with dense breasts or those who are at intermediate risk for cancer and is recommended in women at high risk for cancer who cannot tolerate MR imaging (14).

The majority of breast cancers detected at screening US are obscured by overlapping dense breast tissue at mammography (12,13). However, some cancers may have subtle or evident mammographic findings that were overlooked or misinterpreted, and other cancers may reside in an anatomic area that is difficult to detect with mammography (15). Results from several studies demonstrated subtle findings on initial normal mammograms in women with breast cancer detected at follow-up screening mammography (16–20). To our knowledge, however, in no published studies have investigators determined the reasons for nondetection at mammography in women with breast cancer diagnosed at supplemental screening US. Most clinical studies of screening US have focused on the performance of US, such as cancer detection rate and positive predictive value for biopsy (3,5,9–13,21,22). Thus, the purpose of this study was to retrospectively review the mammograms of women with breast cancers detected at screening US to determine the reasons for nondetection at mammography.

Advances in Knowledge

- In a blinded review of mammograms with breast density type 2–4, 63 (19%) of 335 US-depicted breast cancers were considered to have manifested with abnormal findings that required immediate action, whereas 272 (81%) manifested with no abnormal findings.
- In an unblinded repeat review, 263 (78%) of 335 lesions were obscured by overlapping dense breast tissue, 63 (19%) were confirmed to be interpretive errors, and nine (3%) were not included owing to difficult anatomic location or poor mammographic positioning.

Materials and Methods

Our institutional review board approved this retrospective study, and the requirement for informed patient consent was waived. Since 2001, our institution (Seoul National University Hospital, Korea) has offered handheld screening US in addition to digital mammography in women with a Breast Imaging Reporting and Data System (BI-RADS) breast density type of 2–4 or women who have a familial or personal history of breast cancer.

Study Population

Between December 2003 and December 2011, 116683 screening US examinations were performed in 106856 women after initial mammographic screening. Both mammography and US were scheduled to be performed simultaneously for the majority of the women, and the most recent mammogram had been obtained less than 2 months previously. All US examinations were performed by the same radiologists (M.S.B., W.K.M., J.M.C., H.R.K., W.H.K., N.C., A.Y., B.L.Y., S.H.L., M.Y.K., E.B.R., M.S.) who reviewed or interpreted the mammogram. US examinations were performed by radiologists who received specialty training in breast imaging (and who had 4–24 years of experience in breast imaging). They used high-resolution US equipment with a 14–16-MHz linear-array transducer (HDI 5000, Advanced Technology Laboratories, Bothell, Wash; LOGIQ 700, GE Medical Systems, Milwaukee,

Implication for Patient Care

- Supplemental screening with US can depict mammographically occult or subtle cancers that would not be depicted at mammography alone in women with dense breast tissue.

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Abbreviations:
ACRIN = American College of Radiology Imaging Network
BI-RADS = Breast Imaging Reporting and Data System
DCIS = ductal carcinoma in situ

Author contributions:
Guarantor of integrity of entire study, W.K.M.; 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, M.S.B., W.K.M., J.M.C., M.Y.K.; clinical studies, M.S.B., W.K.M., J.M.C., H.R.K., W.H.K., A.Y., B.L.Y., S.H.L., M.Y.K., E.B.R., M.S.; statistical analysis, M.S.B.; and manuscript editing, M.S.B., W.K.M.

Conflicts of interest are listed at the end of this article.

Wis). Mammograms were obtained by using dedicated digital mammography units (Senographe 2000D, GE Healthcare, Milwaukee, Wis; LORAD Selenia, Hologic, Bedford, Mass).

A retrospective review of our database revealed 356 consecutive women with 362 breast cancers detected at supplemental screening US during the study. The overall cancer yield was 3.4 cancers per 1000 women screened (362 of 106 856). Twenty-seven women were excluded, including 19 patients who had undergone mammography at an outside hospital and eight patients with contralateral cancers seen at mammography; 329 patients (median age, 47 years; age range, 29–69 years) were included in this study, with 335 US-depicted breast cancers (with six patients having bilateral breast cancers). Of the 335 cancers, 282 (84%) were invasive and 53 (16%) were ductal carcinoma in situ (DCIS) (Fig 1, Table 1).

All women underwent preoperative, sagittal dynamic contrast agent–enhanced MR imaging, and 204 (62%) of the 329 women underwent US-guided hook-wire localization. Mammograms that were obtained after wire localization, preoperative breast MR imaging, or both were used to determine the reference location of the cancer.

Mammography Review Design

The 329 mammograms were divided into three sets of approximately 110 mammograms each. Twenty mammograms were added to each case set: 10 mammograms showed subtle cancers seen at mammography, and 10 mammograms showed negative findings that were confirmed on the basis of at least one subsequent mammogram with a negative result during 2-year follow-up. The additional cases consisted of 30 women (median age, 54 years; age range, 38–70 years) with mammographically depicted subtle cancers (median tumor size, 1.7 cm; size range, 0.6–3.7 cm) and 30 women (median age, 57 years; age range, 41–73 years) with negative mammograms. In terms of mammographic breast density, 15 (25%) of 60 women had BI-RADS density type 2, 26 (43%) had BI-RADS density type 3, and 19 (32%) had BI-RADS density type 4. Even though women may have had BI-RADS breast density type 2 (scattered fibroglandular tissues ranging from 25% to 50% of the breast), some may have had dense breast tissue in at least one quadrant. In the ACRIN 6666 study, if women at elevated risk had dense parenchyma in at least one quadrant, they were eligible to participate in the study (5).

Three panels of radiologists (who had 4–16 years of experience in reading mammograms and who had read 1800–12 000 mammograms per year), each consisting of five members (three internal and two external radiologists), performed a retrospective review of the three case sets to determine whether the findings on the negative mammograms should be recalled. The radiologists were blinded to the study purpose and the case mix. The radiologists all had the same reading environment and reviewed the original mammograms on a high-resolution picture archiving and communication system monitor.

Each panel radiologist independently assessed approximately 130 cases in one session and categorized them according to the BI-RADS lexicon (23). Cases assigned a BI-RADS category of 1 or 2 were considered normal or benign, and those assigned a BI-RADS category of 0, 4, or 5 were considered abnormal. The location of abnormal findings was marked with an electric indicator, and the images were saved on a picture archiving and communication system. The marks were considered positive if they correctly indicated the corresponding mammographic location on at least one view. The use of BI-RADS category 3 was discouraged. Mammograms that were assessed by three or more of the five blinded radiologists as BI-RADS category 1 or 2 were considered negative, meaning that the findings required no immediate action. Cases that were assessed by the majority of the five radiologists as BI-RADS category 0, 4, or 5 were considered abnormal, meaning that the findings required immediate action. We assessed the sensitivity of the blinded radiologists for cancer detection in the 10 cases with subtle cancers added to each case set, and we tested the specificity of the blinded

Figure 1

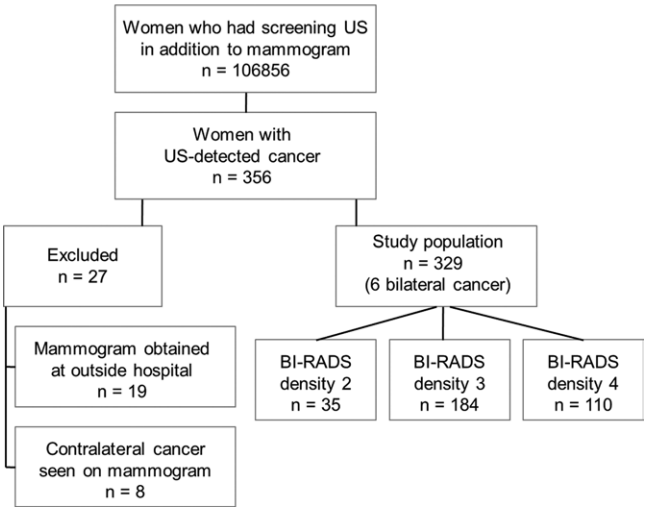


Figure 1: Flowchart shows the study population and excluded patients. Of 106 856 women who underwent screening breast US during the study, breast cancer was diagnosed in 356, and 27 were excluded from the study. A total of 329 women with 335 breast cancers were included in the study.

Table 1

Characteristics of 329 Patients with 335 Breast Cancers Detected with Screening US

Characteristic	No. of Patients or Cancers
Age (y)*	
<40	39 (12)
40–49	181 (55)
50–59	90 (27)
60–69	19 (6)
BI-RADS breast density type*	
2	35 (11)
3	184 (56)
4	110 (33)
Family history of breast cancer*	
Yes	17 (5)
No	312 (95)
Personal history of breast cancer*	
Yes	7 (2)
No	322 (98)
Histologic type†	
DCIS	53 (16)
Invasive cancer	282 (84)
Ductal	256 (76)
Lobular	20 (6)
Mixed	6 (2)
Invasive cancer size (mm)‡	
≤5	39 (14)
6–10	84 (30)
11–20	130 (46)
21–50	29 (10)
DCIS size (mm)§	
<20	31 (58)
20–50	19 (36)
50–70	3 (6)
Minimal cancer†‖	
Yes	176 (53)
No	159 (47)
Lymph node status‡#	
Negative	253 (90)
Positive	29 (10)
Stage†	
0 or I	283 (84)
II	52 (16)

Note.—Six patients had bilateral cancer. Data in parentheses are percentages.

* Data are numbers of patients. Percentages were calculated with a denominator of 329.

† Data are numbers of cancers. Percentages were calculated with a denominator of 335.

‡ Data are numbers of cancers. Percentages were calculated with a denominator of 282.

§ Data are numbers of cancers. Percentages were calculated with a denominator of 53.

‖ Minimal cancer was defined as invasive cancer 10 mm or smaller or DCIS.

Included only invasive cancer.

radiologists for the diagnosis of the 10 normal cases.

In addition, three dedicated breast radiologists (M.S.B, W.K.M, W.H.K.; 5–24 years of experience) who did not participate in a blinded review re-reviewed the 329 mammograms by means of consensus to determine the possible reasons for nondetection by using the reference location. Breast density also was reviewed by means of consensus with the information of the original mammographic reading on the basis of the BI-RADS classification (23). Nondetection at mammography was attributed to one of four factors: *(a)* the presence of obscuring dense breast tissue, *(b)* interpretive error, *(c)* poor mammographic positioning, and *(d)* tumor location, which is not included in standard mammography, even though the positioning is appropriate (24,25). We defined as interpretive errors the subset of cancers recalled by more than three of the five blinded radiologists; we used the rationale that if a majority of radiologists in a blinded review interpreted the mammograms as abnormal, then the findings were visible (17). In the unblinded repeat review, findings that were judged abnormal by at least two of the three radiologists were considered subtle, and findings that were deemed abnormal by all three radiologists were considered evident. In addition, we assessed breast positioning for both mediolateral oblique and craniocaudal views by evaluating whether posterior breast tissues were included (26). For the cancers that were not included at mammography, one radiologist measured the distance from the nipple and the chest wall to the tumor margin at MR imaging.

Data and Statistical Analysis

The number of cancers recalled by the blinded radiologists was compared with the reasons for nondetection as determined by the unblinded radiologists. Reasons for nondetection at screening mammography were stratified for breast density (BI-RADS density type 2, 3, or 4), risk group (average vs high), size of invasive breast cancer (≤10 mm, 11–20 mm, or >20 mm) at pathologic examination, and cancer type (invasive vs DCIS). High risk was defined as a family history and personal history of breast cancer. Patients without a family or personal history of breast cancer were considered to be at average risk. The χ^2 or Fisher exact test was used to compare the proportions of the reasons for nondetection with breast density, risk group, invasive tumor size, and cancer type. All statistical analyses were conducted by using commercial software (SAS, version 9.2; SAS Institute, Cary, NC). A P value less than .05 was considered to indicate a significant difference.

Results

Blinded Mammographic Review

The blinded radiologists showed a median sensitivity of 90% (95% confidence interval range: 44.4%–69.2%, 97.5%–100%) based on the 10 cancer cases with subtle mammographic findings and a median specificity of 90% (95% confidence interval range: 35%–56%, 93%–100%) based on diagnosing the 10 normal cases. Three or more of the five blinded radiologists rated 272 (81%) of the 335 cancers as normal or benign on mammograms; these cancers required no immediate action. Of these 272 cancers, 131 (48%) were rated as normal by all five blinded radiologists, 82 (30%) were rated as normal by four of the five blinded radiologists, and 59 (22%) were rated as normal by three of the five blinded radiologists. Sixty-three (19%) of the 335 cancers were judged as having abnormal findings by

a majority of the blinded radiologists. Table 2 shows the number of cancers recalled by the five blinded radiologists along with the reasons for nondetection as determined by the unblinded radiologists.

Unblinded Mammographic Review

In the unblinded review, with knowledge of the location of US-depicted cancers, 263 (97%) of the 272 cancers were judged by the three unblinded radiologists to be mammographically invisible because of overlapping breast tissue (Fig 2). The remaining nine (3%) of 272 cancers were considered findings that were not included at mammography because of the difficult anatomic location of the cancer (n = 6) or poor mammographic positioning (n = 3) (Fig 3). Table 3 shows the clinicopathologic features, as well as the lesion locations, on the basis of MR imaging of the cancers that were not included at mammography. These cancers were located in the posterior portion of the breast and most frequently (six of nine cancers) in the immediate prepectoral region.

Sixty-three cancers were considered interpretive errors. Fifty-two (83%) of these 63 cancers were considered to have subtle findings, and 11 (17%) were confirmed to be evident by the three unblinded radiologists. Of the 52 cancers with subtle mammographic findings, 46 (88%) showed asymmetry at only one view, and six (12%) showed faint calcifications. Among the 11 cancers that were evident in retrospect, there were focal asymmetries in six (55%), clustered calcifications in four (36%), and architectural distortion in one (9%). Fifty-three (84%) of the 63 interpretive errors were mammographic findings without calcifications (Fig 4). These cancers contained no overlapping breast tissue, which was confirmed by means of the reference location.

Distribution of the Reasons for Nondetection at Mammography

The distribution of the reasons for nondetection at mammography differed significantly among the BI-RADS

Table 2

Comparison of Reasons for Nondetection as Determined by an Unblinded Review with the Number of Recalls Made by Five Blinded Radiologists

No. of Recall Radiologists	No. of Cancers	Reasons for Nondetection Determined at Unblinded Review		
		Overlapping Breast Tissue	Not Included at Mammography	Interpretive Error
0	131	125	6	0
1	82	80	2	0
2	59	58	1	0
3 or more	63	0	0	63
Total	335	263	9	63

Figure 2

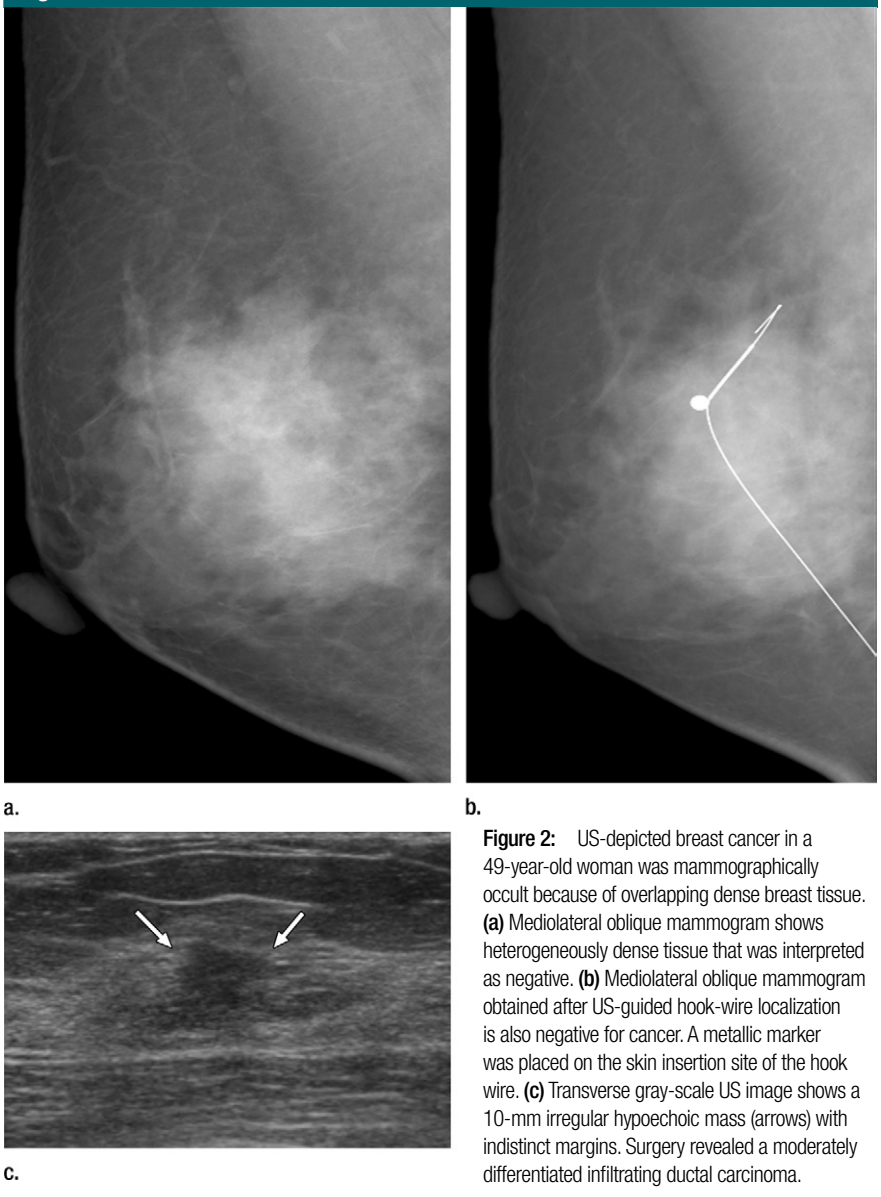


Figure 2: US-depicted breast cancer in a 49-year-old woman was mammographically occult because of overlapping dense breast tissue. **(a)** Mediolateral oblique mammogram shows heterogeneously dense tissue that was interpreted as negative. **(b)** Mediolateral oblique mammogram obtained after US-guided hook-wire localization is also negative for cancer. A metallic marker was placed on the skin insertion site of the hook wire. **(c)** Transverse gray-scale US image shows a 10-mm irregular hypoechoic mass (arrows) with indistinct margins. Surgery revealed a moderately differentiated infiltrating ductal carcinoma.

Figure 3

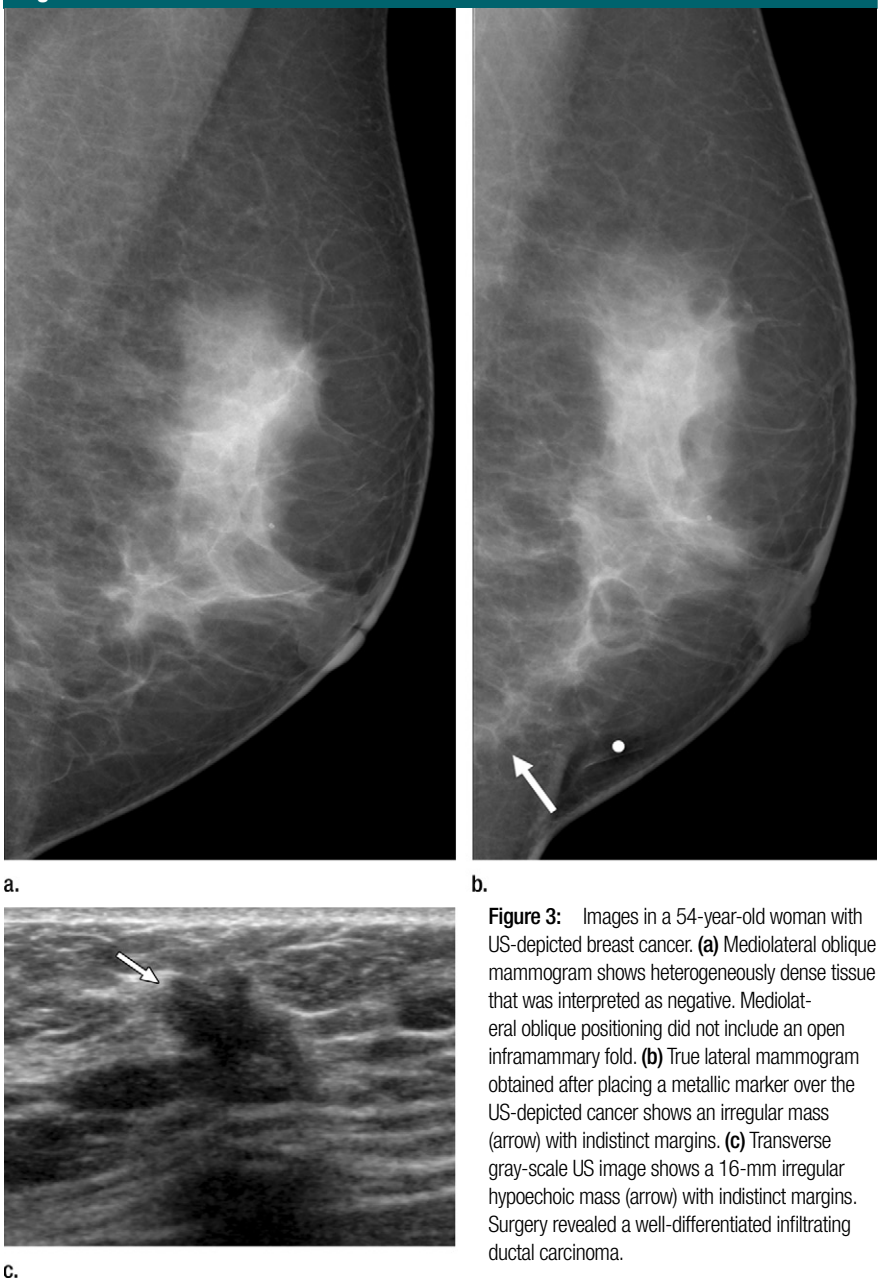


Figure 3: Images in a 54-year-old woman with US-depicted breast cancer. **(a)** Mediolateral oblique mammogram shows heterogeneously dense tissue that was interpreted as negative. Mediolateral oblique positioning did not include an open inframammary fold. **(b)** True lateral mammogram obtained after placing a metallic marker over the US-depicted cancer shows an irregular mass (arrow) with indistinct margins. **(c)** Transverse gray-scale US image shows a 16-mm irregular hypoechoic mass (arrow) with indistinct margins. Surgery revealed a well-differentiated infiltrating ductal carcinoma.

classification groups for breast density ($P < .001$); among invasive tumors 10 mm or smaller, 11–20 mm, or larger than 20 mm ($P < .001$); and between women at high risk and those at average risk ($P < .001$) (Table 4). However, there was no significant difference between DCIS and invasive cancer ($P = .866$). The percentages of overlapping breast tissue were 66% in patients with density type 2, 74% in those with density type 3, and 90% in those with density type 4. The percentages of interpretive errors were 31% in patients with density type 2, 23% in those with density type 3, and 7% in those with density type 4. In addition, the proportion of interpretive errors was higher in invasive tumors larger than 20 mm than in tumors 10 mm or smaller and tumors 11–20 mm (40% vs 14% and 18%, respectively; $P < .001$), whereas the proportion of overlapping breast tissue was lower in invasive tumors larger than 20 mm than in tumors 10 mm or smaller and tumors 11–20 mm (59% vs 82% and 80%, respectively; $P < .001$). The proportion of tumors not included at mammography was higher in the high-risk group than in the average-risk group (17% vs 2%, $P < .001$).

Discussion

Our review of the mammograms of breast cancers detected at screening US revealed that 263 (78%) of 335 tumors were obscured by overlapping breast tissue, 63 (19%) were misread owing to interpretive errors, and nine (3%) were not included owing to difficult anatomic location or poor positioning. The population in our study differs from populations in prior studies of false-negative mammographic findings because we focused on the possible reasons for nondetection at mammography in US-depicted breast cancers. Approximately 80% of cancers showed no mammographic findings that required immediate action by three or more of the five blinded radiologists. The unblinded repeat review was used to confirm the cancer cases that were recalled by the blinded radiologists and identify the cancers that were not included at standard mammography.

Prior investigators reported the nonspecific findings of prior negative mammograms in women with breast cancer detected at follow-up mammography (17–19). Ikeda et al (18) showed that a subset of cases was interpreted as normal or benign by a majority of blinded radiologists and that 80% of these cases also were deemed normal or benign by an unblinded repeat review. They concluded that there is a subset of breast cancers that display nonspecific mammographic findings that do not warrant recall and that this subset is mostly composed of noncalcified findings, such as focal islands of fibroglandular tissue or densities.

Table 3

Demographics and Lesion Locations at MR Imaging in Patients with Breast Cancers Not Included at Mammography

Patient No./Age (y)	Risk Factor	Size* (mm)	Pathologic Finding	Lymph Node Status	Lesion Location Quadrant	Distance from Nipple (cm)	Distance from Chest Wall (cm)	Reason
1/39	Personal history	10	IDC	Negative	Lower outer	5.0	0.1	Prepectoral location
2/55	None	4	IDC	Negative	Lower outer	4.5	0.2	Prepectoral location
3/38	Family history	7	DCIS	Negative	Upper outer	4.0	0.5	Prepectoral location
4/54	None	16	IDC	Negative	Lower outer	5.5	1.0	Poor positioning
5/38	Family history	7	IDC	Negative	Upper outer†	6.5	0.6	Prepectoral location
6/44	None	20	IDC	Negative	Upper inner	4.0	0.5	Prepectoral location
7/50	None	10	IDC	Negative	Upper inner	5.5	0.1	Prepectoral location
8/60	None	18	IDC	Negative	Lower outer	4.5	1.0	Poor positioning
9/45	Family history	32	IDC	Positive	Upper outer†	6.5	1.5	Poor positioning

Note.—IDC = invasive ductal carcinoma.

* Tumor size was measured as the greatest dimension at pathologic examination.

† Tumors were included in only one mammographic view.

Table 4

Reasons for Nondetection at Screening Mammography

	BI-RADS Breast Density*			Risk Group*		Invasive Tumor Size (mm)*			Cancer Type†	
Reason	Type 2 ($n = 35$)	Type 3 ($n = 184$)	Type 4 ($n = 110$)	Average ($n = 305$)	High ($n = 24$)	≤10 ($n = 123$)	11–20 ($n = 130$)	>20 ($n = 29$)	Invasive ($n = 282$)	DCIS ($n = 53$)
Overlapping breast tissue	23 (66)	136 (74)	99 (90)	241 (79)	17 (71)	101 (82)	104 (80)	17 (59)	222 (79)	41 (77)
Interpretive error	11 (31)	43 (23)	8 (7)	59 (19)	3 (12)	17 (14)	24 (18)	11 (38)	52 (18)	11 (21)
Not included at mammography	1 (3)	5 (3)	3 (3)	5 (2)	4 (17)	5 (4)	2 (2)	1 (3)	8 (3)	1 (2)

Note.—Numbers in parentheses are percentages.

* $P < .001$.

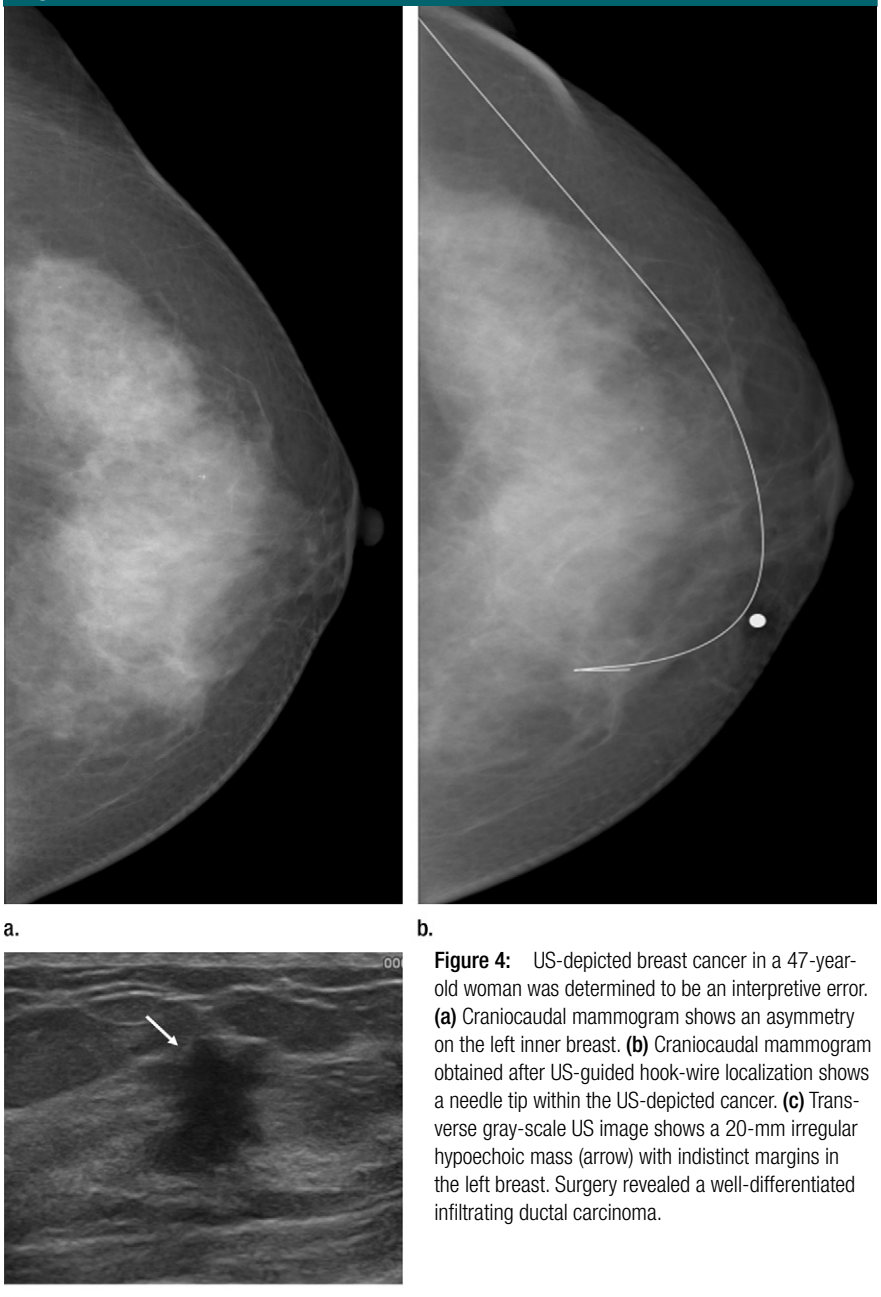
† $P = .866$.

These findings are consistent with those in our study, which showed that 78% of US-depicted cancers were obscured by overlapping normal breast tissue. Breast cancer can be obscured by surrounding dense tissue at mammography because tumors and fibroglandular tissues have similar densities (27). Screening breast US may enable earlier detection of mammographically occult cancers that would not be detected at mammography alone.

In our study, 63 (19%) of 335 US-depicted cancers were misinterpreted at mammography and were placed by a majority of the blinded radiologists in a group that would require recall. The percentage of interpretive errors was significantly higher in women with less dense breasts or with a larger (>20 mm) invasive tumor ($P < .001$). In the ACRIN 6666 screening protocol, a retrospective review in which investigators were blinded to other imaging and pathologic data showed that 19 (28%) of 67 cancers were missed at mammography and 15 (21%) of 71 cancers were missed at US because of interpretive errors (15). The errors in our study with respect to interpretation of mammograms are similar to those in the ACRIN study and other review studies on mammographically missed cancers (20,28,29). We also found that nine (3%) of 335 US-depicted cancers were not included at mammography. These undetected cancers more frequently were located at the immediate prepectoral region in women at high risk. This finding is consistent with the findings of Schrading and Kuhl (30) who reported that the posterior location was observed more frequently in women at high risk for breast cancer and women with *BRCA* mutations. Thus, breast positioning during mammographic examinations should be optimized to include the posterior tissues, particularly in women at high risk with dense breasts.

In our study, radiologist-performed handheld screening US demonstrated a cancer detection rate of 3.4 cancers per 1000 women screened, which is consistent with findings from other screening US studies (5,6,8–13,31). The population in our study consisted

Figure 4



a. b. c.

Figure 4: US-depicted breast cancer in a 47-year-old woman was determined to be an interpretive error. **(a)** Craniocaudal mammogram shows an asymmetry on the left inner breast. **(b)** Craniocaudal mammogram obtained after US-guided hook-wire localization shows a needle tip within the US-depicted cancer. **(c)** Transverse gray-scale US image shows a 20-mm irregular hypoechoic mass (arrow) with indistinct margins in the left breast. Surgery revealed a well-differentiated infiltrating ductal carcinoma.

mainly of women who had either heterogeneously dense or extremely dense breasts. Moreover, 7% of women with US-depicted cancer had a familial or personal history of breast cancer. Our data support the idea that screening US can improve cancer detection in women with dense breasts who are at increased or normal risk.

This study had several limitations. First, women with BI-RADS breast density type 2 were included in our study population even though they were not considered to have dense breasts. Second, this study was retrospective, and we did not review older mammograms for comparison with prior normal mammograms. Third, for digital image quality, we evaluated only image positioning, and false-negative mammograms could have been influenced by other image deficiencies, such as compression and exposure. Finally, the false-negative or false-positive rate of US was not determined. Handheld screening US is controversial because it may be time-consuming and relatively low in positive predictive value for biopsies, and there is no proved mortality benefit (32).

In conclusion, most breast cancers detected at screening US were not identified at mammography, even in retrospect, owing to the presence of overlapping dense breast tissue. However, 19% of cancers showed errors in mammographic interpretation, and another 3% of cancers were not included at standard mammography.

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