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Abbreviations:

BI-RADS = Breast Imaging Reporting
 and Data System
 DCIS = ductal carcinoma in situ

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Specificity of Mammography and US in the Evaluation of a Palpable Abnormality: Retrospective Review¹

PURPOSE: To determine the number of patients who received a diagnosis of breast cancer after having an area of clinical concern at presentation and combined negative mammographic and ultrasonographic (US) findings.

MATERIALS AND METHODS: During a 4-year period, 829 patients with a palpable abnormality at presentation and combined negative mammographic and US findings were identified. The number of women who went on to receive a diagnosis of breast cancer was determined retrospectively. The authors searched the breast imaging database and the pathology database, sent a contact letter to the referring physicians, and linked their data to the State Cancer Registry. They also analyzed the breast parenchymal density among all patients who had more than 2 years of follow-up.

RESULTS: Of the 829 women, 374 had follow-up information. Two-hundred thirty-three patients had negative imaging findings with more than 2 years of follow-up. The other 141 women were presumed to be cancer free, as they were not identified by the State Cancer Registry. Six (2.6%) of the 233 women had a diagnosis of breast cancer in the area of the palpable abnormality. The six cancers were diagnosed among the 156 women who had radiographically dense breast tissue (Breast Imaging Reporting and Data System category 3 or 4). Among the 77 women with predominantly fatty tissues, no cancers were diagnosed.

CONCLUSION: A negative mammographic and US finding of a palpable abnormality does not exclude breast cancer, but the likelihood of breast cancer is low, approximately 2.6%–2.7%. It may be higher if the breast tissues are dense and lower if they are predominantly fatty.

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A palpable abnormality should be further investigated even if the mammogram is negative (1–3). A focused ultrasonographic (US) examination has been promoted as an additional study to evaluate a palpable lump or thickening (2–5). Often, both mammography and US fail to demonstrate an abnormality. In this setting, we have always emphasized that the need for biopsy should be determined clinically. Although mammography and US of the breast individually cannot help exclude cancer, we sought to determine the accuracy of combined assessment. It was our anecdotal impression that the likelihood of cancer is low when both examination findings are negative. In retrospective studies, the pathologic findings in patients who underwent biopsy for a palpable abnormality were reviewed, but in no study to date, to our knowledge, has follow-up been attempted after initial negative examination findings (5). Consequently, we performed a retrospective review to determine the number of patients who developed breast cancer after having an area of clinical concern and combined negative mammographic and US findings.

MATERIALS AND METHODS

Our computerized database identified cases, from our 900-bed tertiary care center (Massachusetts General Hospital), in which the combined mammographic and targeted US

findings were negative in women who were referred with a clinically palpable abnormality, either a lump or thickening. Patients had been referred by internists, gynecologists, oncologists, or surgeons affiliated with our hospital. We were not able to determine their clinical impressions of the palpable findings. To ensure the use of modern mammography and US, we chose to review the data from January 1, 1995, through December 31, 1998. This period would also allow a 2-year follow-up for most patients. Our institutional review board allowed us to review patients' medical and pathology records and to contact the referring physicians without the need for informed consent.

Mammographic examinations in this study were performed with dedicated mammography units (DMR, 800T, GE Medical Systems, Milwaukee, Wis; Bennett Contour MAM-CP, Oldelft Benelux, Delft, the Netherlands; or the MAM-CP, Continental, Danbury, Conn). The mammographic examination consisted of at least the conventional two-view mediolateral oblique and craniocaudal projections of each breast. In addition, a spot compression "tangential view" of the area of concern as indicated by the patient was also obtained. Each study was interpreted by at least two board-certified radiologists (L.M., P.J.S., E.D.Y., K.A.M., D.H., M.S., E.A.R., D.B.K.) whose subspecialty is breast imaging. The mammogram was considered to be negative (ie, Breast Imaging Reporting and Data System [BI-RADS] category 1) if there was no evidence of a dominant mass, suspicious clusters of microcalcifications, or architectural distortion in the area of clinical concern.

We routinely perform a focused US examination that is targeted to the area of clinical concern in every patient with a palpable lump or thickening at presentation. The US examination was performed by the same radiologist (L.M., P.J.S., E.D.Y., K.A.M., D.H., M.S., E.A.R., D.B.K.) who interpreted the mammogram, usually immediately after reviewing the mammogram. Therefore, each US examination was performed with the full knowledge of the clinical and mammographic findings. Each woman was evaluated with real-time US, with use of a high-frequency transducer, either a 10.0-MHz transducer (Diasonics Master Series, Milwaukee, Wis) or an 11-MHz transducer (Logic 400 MD, GE Medical Systems). All US examinations were performed with the patient in the supine position, with her ipsilateral arm raised

above her head. The breast tissues were flattened and thinned by shifting the patient into the appropriate oblique position with the help of an angled sponge placed beneath the patient. The sonogram was considered to be negative if there was no evidence of a cyst, mass, focal area of hypoechogenicity, focal area of hyperechogenicity, or architectural distortion. We do not perform color Doppler US on a routine basis.

In each patient's case record, the parenchymal density of the glandular tissue, risk factors, and imaging results were noted. Imaging results and demographic information were stored in a locally designed computer data management program that allows quick retrieval of the data. Each radiologist reviews the patient's records before a final BI-RADS assessment is made on the mammogram. With regard to the US examination, all of the just-mentioned information and all previous mammograms and sonograms were reviewed before the US examination. We do not grade the degree of clinical suspicion in our database and do not include other details of the clinical findings.

After we identified all patients with a palpable abnormality and combined negative mammographic and US findings, we then searched the computerized pathology database at our institution during the same period. This pathology database contains the results of all breast biopsies in the hospital and allows us to determine how many patients underwent surgery. Since it is possible that not all patients had their biopsies performed at our institution, we reviewed the radiology computer system to determine whether the patients had returned for any subsequent study and whether they had received a diagnosis of breast cancer.

To increase the number of cases with complete information, we sent a contact letter to their physicians to determine if any follow-up physical examination or surgery had been performed. We also linked our database with the State Cancer Registry to determine if any additional patients received a diagnosis of breast cancer outside our institution within 2 years of the negative imaging evaluation. This registry linkage was completed on November 1, 1999.

On the basis of the information obtained, we categorized negative findings from the combined imaging study as being true-negative or false-negative. The criteria for true-negative findings included a benign result from biopsy of the palpable abnormality (fine-needle aspira-

tion, core, or excisional biopsy) or a minimum of 2 years of negative follow-up results after the initial studies, and no evidence of tumor as per the State Cancer Registry. The criterion that we used for false-negative findings was if there was a positive result from biopsy of the palpable abnormality within 2 years of the combined studies with negative imaging findings.

All eight radiologists independently reviewed the false-negative mammograms for the parenchymal density of the glandular tissue and presence of a focal abnormality, and to determine if we agreed with the BI-RADS mammographic assessment. This evaluation was performed both blinded and then afterward with the knowledge of the patient's demographic information and the biopsy results. In addition, we also reviewed the pathology reports and staging at the time of surgery (type of cancer, size of the mass, and lymph node status).

We also analyzed the breast tissue pattern among those women with at least 2 years of follow-up to determine if the combined imaging was equally sensitive among patients with dense versus those with fatty breast tissue.

Statistical evaluation was performed by using the Fisher exact test to determine if there was a significant difference in the likelihood of breast cancer in dense versus fatty breast tissue. A *P* value of less than .05 was considered to indicate a statistically significant difference.

RESULTS

Between January 1, 1995, and December 31, 1998, a total of 92,897 breast imaging examinations were performed in 41,644 patients at our institution; 4,501 patients had a palpable abnormality at presentation. Of these, 1,708 patients were evaluated only with US targeting the palpable abnormality because they were younger than 28 years (our age threshold for diagnostic mammography). Since these patients did not have a mammogram, they were excluded from our study. There were 2,793 women older than 28 years who were evaluated with mammography and real-time US. In most women, US was performed at the same visit as the mammographic examination. All the US examinations were performed within 5 days of mammography. These patients were the subjects of our study. The mean age of this cohort of patients was 46 years (median age, 52 years; age range, 29–82 years).

Among the 2,793 women, we identified 912 palpable lesions in 829 patients whose imaging findings were negative at mammography and US. Some patients had more than one palpable abnormality at presentation.

In 455 (55%) of the 829 patients, the initial imaging studies were performed after November 1, 1997, and therefore, these patients did not have the full 2 years of follow-up after the initial imaging study. As a result, these patients cannot be fully classified. As of November 1, 1999, we had follow-up information on the remaining 374 women. Two hundred thirty-three patients had been followed up for at least 2 years at our institution. The other 141 women were lost to follow-up but were presumed to have a benign cause to explain their palpable abnormality because the State Cancer Registry did not identify them. The Registry linkage was performed to identify any cancers that might have occurred within 2 years of the negative imaging findings among the women in our review. The State Cancer Registry estimated that less than 5% of the study patients may not have been captured because of underreporting to the tumor registry or because the patients moved out of the state.

Demographics and Risk Factors

Of the 829 patients in our study, 480 (58%) had dense breast tissue, BI-RADS category 3 or 4. No noteworthy risk factor could be identified in our cohort. Twelve percent (99 patients) had a family history of breast cancer, less than 2% (16 patients) had a strong family history of breast cancer (premenopausal first-degree relative). Ten percent (83 patients) had a history of prior benign breast biopsy results. Fifty-four percent (447 patients) were postmenopausal, and 28% (232 patients) were receiving hormone replacement therapy.

Among the 374 women who had 2 years of follow-up or who underwent biopsy, the mean age was 48 years (median age, 51 years; age range, 30–85 years). Nine percent (33 patients) had a family history of breast cancer, less than 1% (3 patients) had a strong family history of breast cancer (premenopausal first-degree relative). Ten percent (37 patients) had a history of prior benign breast biopsy findings. Fifty-eight percent (216 patients) were postmenopausal, and 32% (119 patients) were receiving hormone replacement therapy.

True-Negative Results

Two hundred twenty-seven (97%) of the 233 patients were classified into the true-negative category. Thirty (83%) of 36 women who underwent biopsy had a benign result, most commonly fibrocystic changes (22 [73%] of 30) or fibrosis (eight [27%] of 30). Among these 30 patients, eight underwent fine-needle aspiration, four underwent core biopsy, and the remaining 18 patients underwent excisional biopsy. One hundred ninety-seven patients had at least 2 years of follow-up with either mammography, US, or repeated physical examinations, with documentation in the patient's chart and no evidence of malignancy.

False-Negative Results

Six (2.6%) of 233 patients received a diagnosis of breast cancer in the area of the palpable abnormality despite combined negative mammographic and US findings. The State Cancer Registry Data did not identify any additional patients with a diagnosis of cancer outside our institution. Among the 233 women, our retrospective review identified 36 patients (15%) who underwent a biopsy despite the initial negative imaging work-up. Six (17%) of 36 patients who underwent biopsy had a diagnosis of breast cancer in the region of the palpable abnormality based on a biopsy soon after the initial imaging studies (range, 0–42 days; mean, 18 days). At the time of the initial negative imaging work-up, one abnormality was palpated by the patient only, two abnormalities were detected by the referring physicians only, and three abnormalities were detected by both the referring physicians and the patients. All six cancers represented solitary findings.

We reviewed these patients' mammograms. All patients with a diagnosis of cancer had heterogeneously dense breast tissue at mammography (BI-RADS tissue pattern 3 or 4). In five patients, a focal abnormality could not be identified, even in retrospect (Fig 1). In one patient, a subtle mass on the mammogram may have been present (Fig 2). These patients ranged in age from 38 to 67 years (mean age, 47.6 years). The pathologic findings were invasive ductal carcinoma in one patient, pure ductal carcinoma in situ (DCIS) in two patients, invasive lobular carcinoma in one patient, and invasive ductal carcinoma with associated DCIS in two patients. In the two cases of pure DCIS, it was not an incidental finding. The Table gives the stage of the cancers at the time of surgery.

Dense versus Fatty Breast Parenchymal Density

In the subgroup of 233 patients in our review with known 2-year follow-up results, 156 (67%) had dense breast tissue at mammography, and all six false-negative cases were in this group. Therefore, if only women with dense breast tissues were included, the actual false-negative rate was somewhat higher (3.8% [six of 156 patients] vs 2.6%). Among women with fatty tissues, the combined examination appeared to be more accurate at excluding cancers, but the numbers are smaller (zero of 77; 95% CI: 0, 0.048).

Clinical Breast Examination

As stated earlier, we were not able to collect data regarding the referring physicians' clinical impressions of the palpable abnormalities. We also did not collect data regarding the patients' histories and the specific characteristics of the palpable findings. In the contact letter we sent to the referring physicians, in 24 patients, the palpable abnormality resolved. These patients were followed up with close physical examination. None of these patients have yet developed breast cancer.

DISCUSSION

The primary reason for performing mammography in a woman with a palpable mass is to screen the ipsilateral and contralateral breast for occult cancer (1–3,6,7). A woman with a palpable breast mass is often referred for diagnostic mammography to evaluate the palpable abnormality and to determine its appropriate management (1,6,7). There are essentially four possibilities: First, the palpable finding is not visible with mammography; second, the finding is visible with mammography but is indeterminate; third, the finding is visible and clearly benign (calcified fibroadenoma, hamartoma, oil cyst); or fourth, the finding is suspicious for malignancy. US is most valuable for determining whether the palpable abnormality is cystic or solid (8–11). It is not uncommon for the mammogram to be negative and to have a lesion visible on the sonogram, especially in the setting of dense breast tissue.

Interestingly, no breast cancers were found among women with fatty breast tissue compared with those with dense tissue. We suspect that if the tissues are fat at mammography, US probably has little to offer because mammography is highly sensitive in the group of patients with fatty breasts. Many have the anecdotal

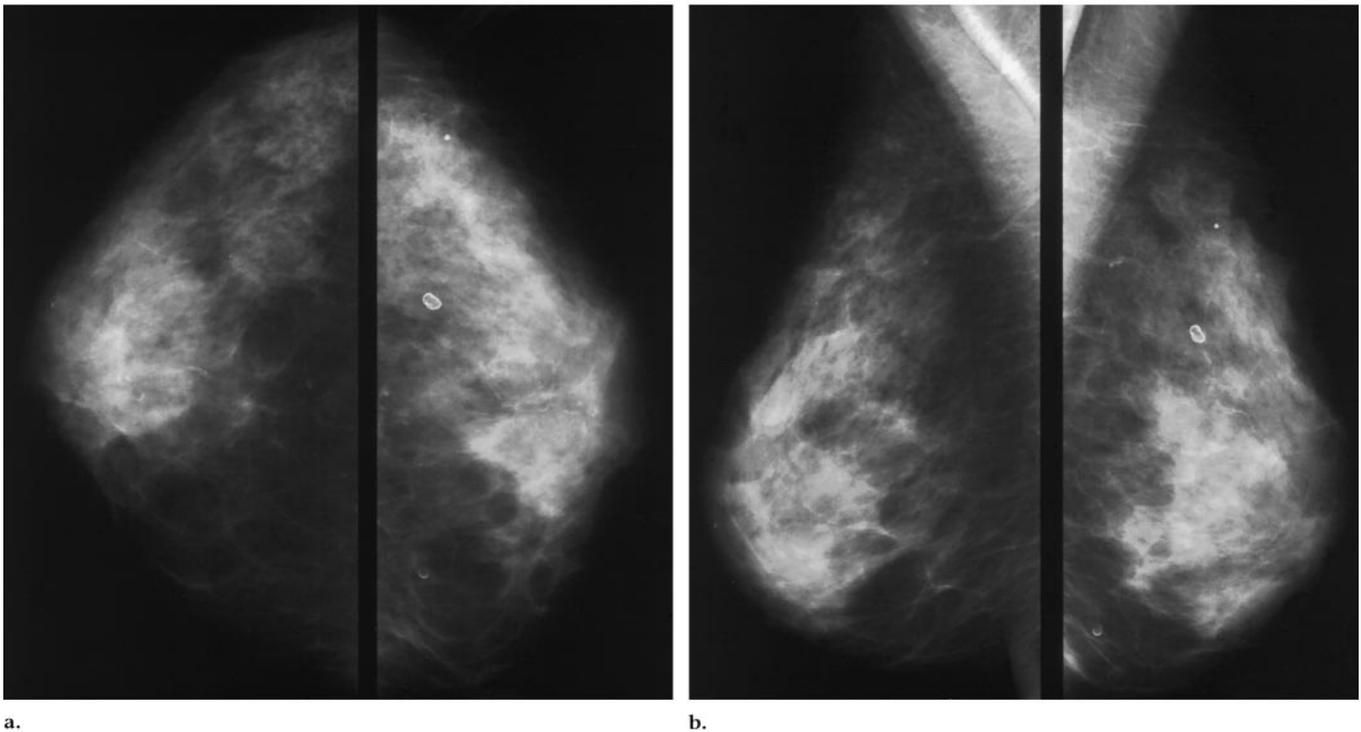


Figure 1. Mammograms in a 38-year-old woman with a lump at the 4-o'clock position in the right breast. (a) Craniocaudal and (b) mediolateral oblique mammograms of both breasts. The glandular tissue was considered to be of high density, without a focal abnormality in the area of clinical concern. The pathologic diagnosis was high-grade DCIS.

total impression that cancer is unlikely if there is only fat on the mammogram; however, this has never been shown scientifically. Our study supports this impression; all six cancers were detected in women with dense breast tissue (BI-RADS category 3 or 4).

We have always stressed that the management of a palpable breast mass should be directed primarily by the findings at clinical breast examination because mammography cannot help exclude the presence of malignancy, particularly in the setting of a palpable breast mass (6,7,10). The palpable breast mass may not have a mammographic correlate, despite the use of additional specialized views. Overall, approximately 10%–15% of all detectable malignancies will be mammographically occult (12–14). Thus, a normal mammographic examination should not preclude biopsy of a clinically suspicious finding.

Nevertheless, one could not infer that mammography is useless in evaluating the palpable mass, only that its role is complementary to that of a skilled clinical breast examination. This role is not surprising. Mammography and clinical breast examination help evaluate different properties of breast tissue. The two techniques are complementary; findings

of one examination are used only rarely to negate the findings of the other examination (6).

We made three interesting observations regarding clinical breast examinations from our data review. First, only a minority of patients with negative mammograms and sonograms actually underwent biopsy of the palpable abnormality. The yield of breast cancer among those who underwent biopsy was what might be expected based on clinical examination alone. Second, most patients underwent biopsy soon after the initial studies (mean, 18 days later); therefore, the clinical suspicion was high and correct. Third, some patients' palpable abnormalities spontaneously resolved, and these patients were followed up with close physical examination. None of these patients had developed breast cancer.

A prospective study to analyze the influence of more detailed information such as greater refinement as to the type of palpable abnormality, whether or not it was a discreet finding, its clinically estimated size, who actually discovered it, and whether the mass was unchanged in size, enlarging, or fluctuating over time might help to refine the questions. Nevertheless, the conclusion that some cancers are not evident at combined mam-

mographic and US examinations remains unchanged.

A potential limitation of our review is the length of the follow-up for the study cohort. It is possible that there may be more women with false-negative findings. We had 2 years of follow-up information for 233 (62%) of 374 women. We found no entries of our patients in the State Cancer Registry for the 141 women who did not return to our institution for further evaluation. Although no additional patients were identified through the State Cancer Registry, we do not know how complete the registry is; also, it is possible that some women moved out of state. We acknowledge that there is a lag time for all clinically diagnosed cancers to be entered into the tumor registry database.

Knowing how to deal with women who are lost to follow-up is always difficult. For example, it is possible (although highly unlikely), that a large number, if not all of these women, actually have cancer. The other possibilities are that no patients had a diagnosis of breast cancer, or a different percentage than that in the study group have breast cancer or, the same percentage as that in the study group have breast cancer. Most investigators accept that their follow-up results are

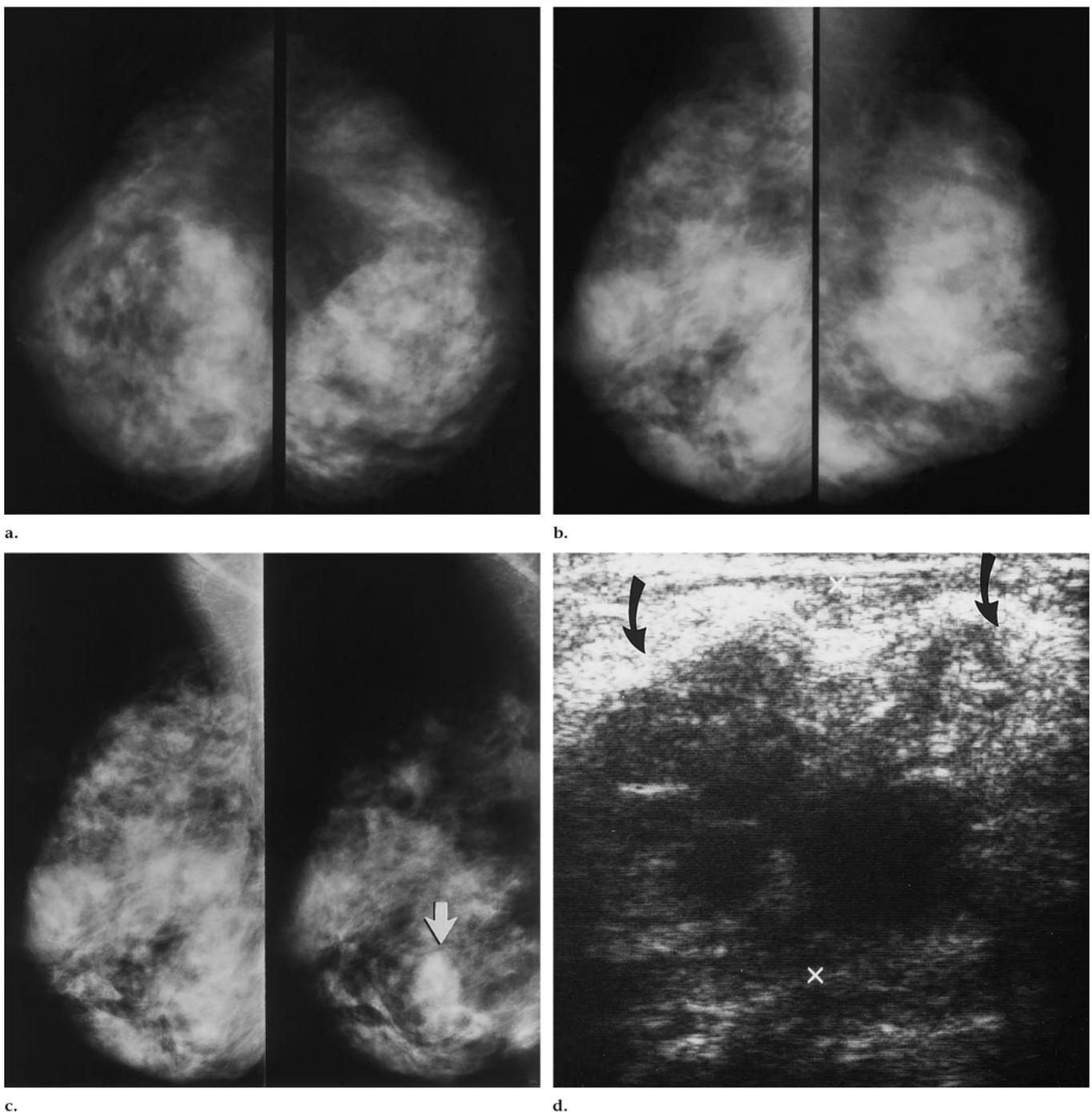


Figure 2. Mammograms and a sonogram in a 57-year-old woman with a lump at the 5-o'clock position in the left breast. (a) Craniocaudal and (b) mediolateral oblique mammograms of both breasts. The glandular tissue was considered to be of high density. A subtle mass may have been present on the initial mammogram, best seen on the mediolateral oblique projection. (c) Initial mediolateral oblique mammogram (left) and mediolateral oblique mammogram obtained 4 months later (right). An ill-defined mass (arrow) is seen in the inferior left breast. (d) Transverse sonogram in the lateral lower quadrant demonstrates an ill-defined hypoechoic 4.5-cm mass. The arrows delineate two lobulations within the mass. The crosshairs depict the anteroposterior dimension (2.9 cm) of the mass. The histopathologic diagnosis was stage T3 invasive lobular carcinoma.

unknown and cannot be determined, and the women are excluded from the review with the assumption that they have the same experience as those with known follow-up results. In most studies, they are simply removed from the anal-

ysis. A reasonable assumption might be that this group has the same percentage of breast cancer as those for whom we have follow-up results. Given this assumption, among the 141 women who were not identified by the State Cancer

Registry, 137 (97.4%) of 141 women are tumor free. The true-negative rate is then 97.3% (364 of 374).

In conclusion, we sought to determine whether the combination of a negative mammogram with a negative sonogram

Stages of the Six Cancers Not Diagnosed with Mammography and US

Date of Study*	Date of Surgery*	Cancer Stage	TNM Stage	Comments
06/23/97	10/02/97	I	T1N0M0	0.9-cm mass
06/11/96	06/27/96	I	T1N0M0	1.1-cm mass
09/05/97	11/12/97	IIA	T1N1M0	1.5-cm mass, one positive node
06/25/96	07/15/96	IIA	T2N0M0	2.4-cm mass
07/09/97	02/14/98	IIB	T2N1M0	2.5-cm mass, three positive nodes
05/27/97	10/06/97	IIIA	T3N1M0	5.2-cm mass, four positive nodes

*Dates are in month/day/year format.

can accurately exclude breast cancer. We believe that a negative mammogram and sonogram do not exclude breast cancer, but the likelihood of breast cancer is very low, approximately 2.6%–2.7%. This increases to 2.6%–3.8% if the patient has radiographically dense breast tissue. The fact that we have not identified any cancers in breasts that are predominantly fat, for which mammography is most sensitive, is not surprising. In fatty breast, mammography is highly sensitive and the benefit from US is small. However, because of the small number of patients in this cohort, we cannot reliably suggest that the combined examination can help exclude cancer. We believe that clinical assessment remains important in evaluating a palpable abnormality, even if the mammogram and sonogram are negative. However, the combined examina-

tion can reinforce the clinical impression if the suspicion is low.

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