RadioGraphics

Missed Breast Carcinoma: Pitfalls and Pearls[1]

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Mammography is the standard of reference for the detection of breast carcinoma, yet 10%–30% of breast cancers may be missed at mammography. Possible causes for missed breast cancers include dense parenchyma obscuring a lesion, poor positioning or technique, perception error, incorrect interpretation of a suspect finding, subtle features of malignancy, and slow growth of a lesion. Recent studies have emphasized the use of alternative imaging modalities to detect and diagnose breast carcinoma, including ultrasonography (US), magnetic resonance imaging, and nuclear medicine studies. However, the radiologist can take a number of steps that will significantly enhance the accuracy of image interpretation at mammography and decrease the false-negative rate. These steps include performing diagnostic as well as screening mammography, reviewing clinical data and using US to help assess a palpable or mammographically detected mass, strictly adhering to positioning and technical requirements, being alert to subtle features of breast cancers, comparing recent images with earlier mammograms to look for subtle increases in lesion size, looking for additional lesions when one abnormality is seen, and judging a lesion by its most malignant features.

Abbreviation: CAD = computer-aided detection

Index terms: Breast neoplasms, 00.32 • Breast neoplasms, radiography, 00.11 • Diagnostic radiology, observer performance

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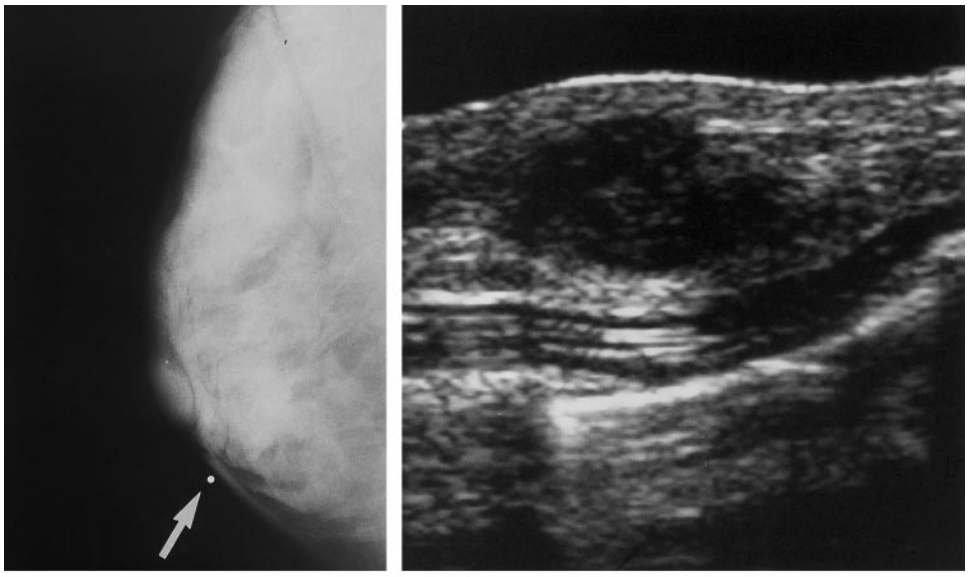


a. b.

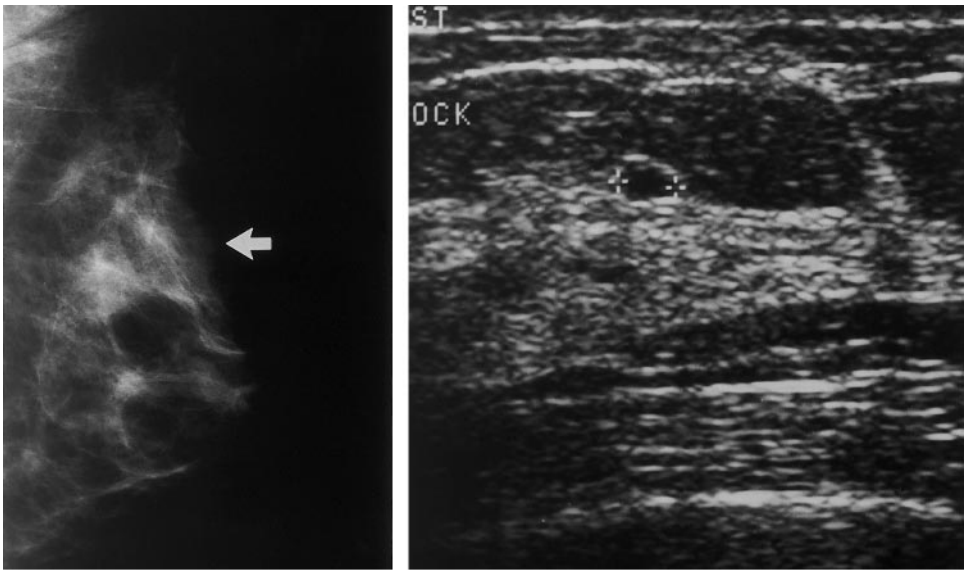
Figure 1. Invasive ductal carcinoma in a 36-year-old woman with dense breasts and a palpable mass. **(a)** Left mediolateral oblique mammogram demonstrates no finding that corresponds to a palpable mass (arrow). **(b)** US image obtained in the area of the palpable abnormality reveals a heterogeneous, hypoechoic mass with irregular margins. Although there is no acoustic shadowing and the mass is wider than it is tall, the hypoechogenicity and irregular margins are suspect for malignancy. Pathologic analysis demonstrated invasive ductal carcinoma.

Introduction

Mammography is the standard of reference for the early detection of breast cancer. Screening mammography is performed to detect an abnormality, whereas diagnostic mammography is used to further evaluate the abnormality or a clinical problem.

The purpose of screening mammography is simply to detect a potential cancer; therefore, the radiologist should not try to make a diagnosis on the basis of screening findings alone. Additional views are important in further assessing an identified abnormality and suggesting appropriate patient treatment. According to data from the Breast Cancer Detection Demonstration Project, the false-negative rate of mammography is approximately 8%–10% (1). After evaluating retrospective versus blinded interpretations of mammograms, others have concluded that the rate of missed breast cancers is as high as 35% (2). In a series of 150 mammograms (27 cancers) read by 10 radiologists, immediate work-up of the true cancers was recommended in 74%–96% of cases (3). Recent studies have emphasized the use of alternative imaging modalities to detect and diagnose breast carcinoma, including ultrasonography (US), magnetic resonance (MR) imaging, and nuclear medicine studies. However, high-quality mammography performed with meticulous attention to detail and positioning can significantly enhance the accuracy of image interpretation.

Breast cancers may be missed because of dense parenchyma that obscures a lesion (4), poor positioning or technique, lesion location outside the field of view, lack of perception of an abnormality that is present, incorrect interpretation of a suspect finding, subtle features of malignancy, or a slowly changing malignancy. Breast cancers are easily missed when they appear as focal areas of asymmetry or distortion (eg, invasive lobular carcinoma) or when their appearance suggests a benign cause (eg, medullary and mucinous [colloid] invasive ductal carcinomas, which usually manifest as mostly circumscribed masses) (5). Bird et al (6) found that 77 of 320 cancers (24%) in a screening population were missed, primarily due to dense breasts and a developing density that was not identified by the radiologist. Goergen et al (7) found that cancers missed at screening mammography were significantly lower in density and were more often seen on only one of two views than were detected cancers. In a review of interval cancers in the Malmo Screening Trial, Ikeda et al (8) found that 10 of 94 cases were missed due to observer error and 21 of 94 showed subtle signs of malignancy.



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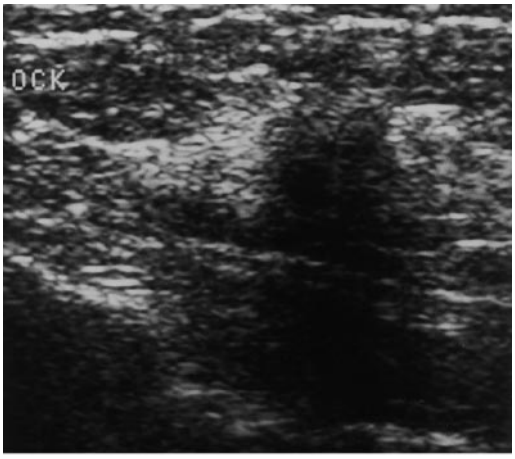

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Figure 2. Invasive lobular carcinoma in a 40-year-old woman with dense breasts. **(a)** Right mediolateral oblique screening mammogram shows a small, oval obscured mass superiorly (arrow) that was not seen on the craniocaudal view. **(b)** US image of the mass demonstrates a simple cyst. **(c)** US image reveals an incidentally detected irregular mass with acoustic shadowing in the lower outer quadrant. Pathologic analysis demonstrated invasive lobular carcinoma.

In this article, we discuss and illustrate the aforementioned pitfalls that can lead to missed breast cancers and provide guidelines to help reduce the false-negative rate of mammography.

Causes of Missed Breast Cancers

Dense Parenchyma

Breast parenchyma that is inherently dense compromises the ability to detect a mass, especially a noncalcified, nondistorting lesion. The radiologist must be particularly attentive in searching for areas of architectural distortion or faint microcalcifications. Magnification views are used to evaluate the morphologic features of suspect or faint microcalcifications. Because architectural distortion may be the only sign of malignancy in a dense breast, the tissue must be intensely evaluated for any areas of tethering or disruption of orientation of normal parenchymal elements. Unless it is documented as a postsurgical scar, an area of architectural distortion must be further evaluated with additional views (eg, spot compression, magnification, off-angle). US may also be helpful in determining the presence of a solid mass that corresponds to an area of distortion.

Any patient with dense breast parenchyma, a palpable mass, and negative mammographic findings should undergo US for further evaluation of the mass (Fig 1). US is very important in the evaluation of mammographic abnormalities, being useful in characterizing palpable masses in dense tissue and circumscribed isodense masses (Fig 2). US can be especially helpful in the evaluation of asymmetric densities seen at mammography because it can help identify the density as either breast tissue or a true mass. Soo et al (9) and Skaane (10) found the negative predictive value of US with mammography for a palpable lesion to

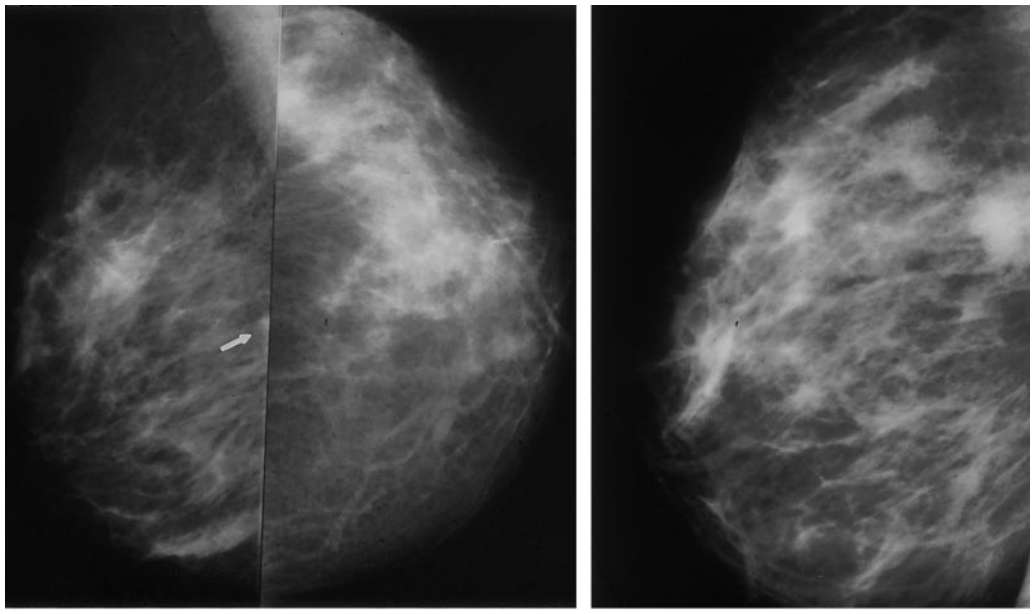

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Figure 3. Proper positioning. **(a)** Left mediolateral oblique (left) and craniocaudal (right) mammograms obtained with improper positioning demonstrate poor visualization of the posterior tissue. The margin of a mass is barely perceptible at the edge of the mediolateral oblique image (arrow). **(b)** On a left mediolateral oblique mammogram obtained with improved positioning, a cancer is seen near the chest wall. An exaggerated craniocaudal view may also help demonstrate such a mass.

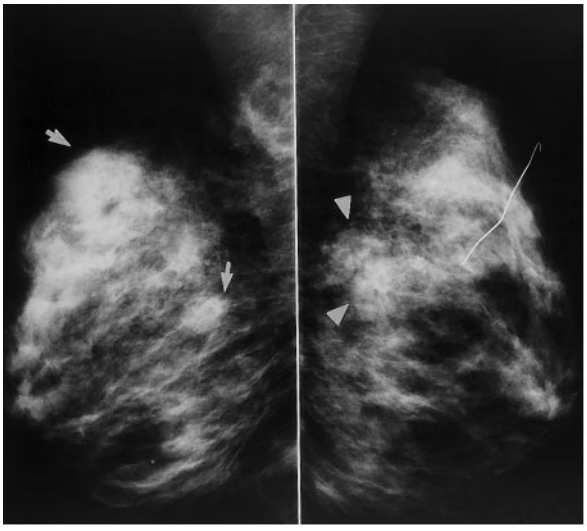
be 99.8% and 100%, respectively. Moy et al (11) found the negative predictive value of US with mammography for a palpable mass to be 97.4%. However, a palpable mass that appears solid at US warrants further evaluation with biopsy.

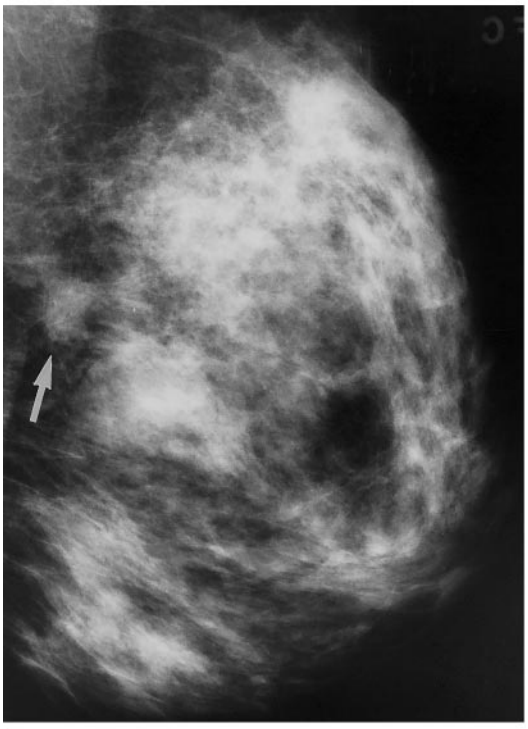
Poor Positioning

Proper positioning and image contrast are absolutely necessary in all aspects of radiology, but especially in mammography. The technologist must adhere to the positioning standards to maximize the amount of tissue included on the image (12). Findings on the mediolateral oblique view that indicate proper positioning include visualization of the pectoralis muscle to the level of the nipple, a convex appearance of the pectoralis major muscle, complete visualization of posterior breast tissue, breast tissue that is well compressed and positioned in an up-and-out orientation, and an open inframammary fold (Fig 3). At craniocaudal imaging, the technologist should verify that the breast is pulled straight forward and not exaggerated laterally, and that the breast tissue is well compressed. The difference between the posterior nipple line measurement on the mediolateral oblique and craniocaudal views should not exceed 1 cm. Emphasis on the upper outer quadrant, which demonstrates the greatest proportion of breast cancers, is necessary. However, the technologist must use the craniocaudal view as a complement to the mediolateral oblique view to visualize the medial tissue as well.

Creative positioning may be necessary to include areas of palpable abnormalities on the images. Radiopaque markers should be placed on palpable areas, with repositioning of the marker between projections as needed to keep the marker superimposed on the palpable finding. In addition, a spot compression view obtained over a palpable mass with the skin in tangent can reveal an underlying mass and demonstrate overlying skin thickening or retraction. Creative positioning may also be helpful in patients who are tense, who have suffered a stroke, or who have shoulder problems or other debilitating factors that limit visualization of the posterior breast on standard mediolateral oblique views.

Off-angle or step oblique views are very helpful in the evaluation of densities or abnormalities seen in only one projection (13). Densities seen on the craniocaudal view alone may be further characterized and localized with use of spot compression and rolled craniocaudal views. If a lesion rolls medially when the top of the breast is rolled medially, it is located superiorly; if it rolls laterally, it is located inferiorly. The technologist should label the image with the orientation in





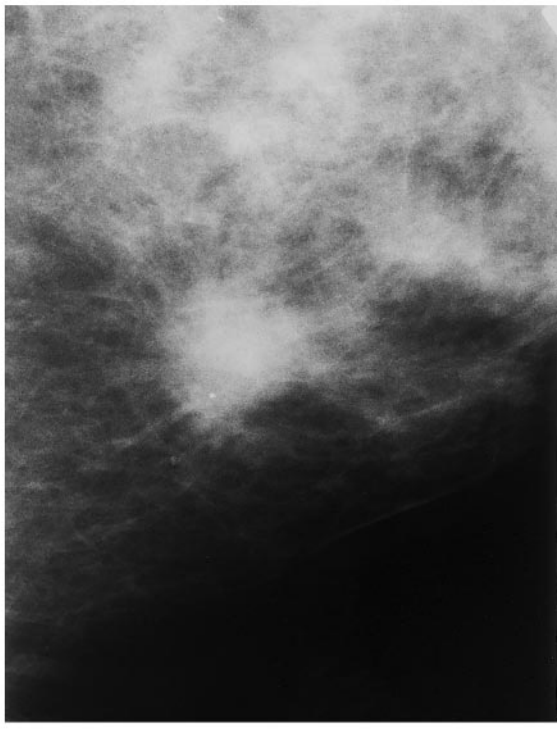
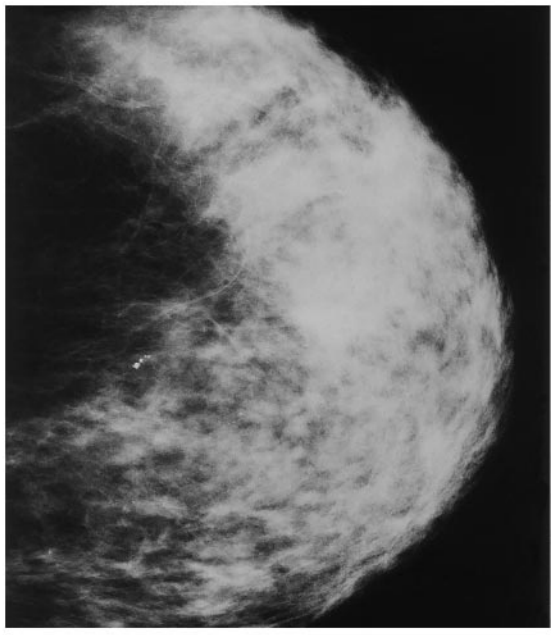


Figure 4. Creative positioning for lesion detection. **(a)** Bilateral mediolateral oblique mammograms show dense parenchyma with well-defined masses (arrows) and a focal irregular density superoposteriorly on the right side (arrowheads). The well-defined masses proved to be cysts at US. **(b)** On a right lateromedial mammogram, the irregular density (arrow) has moved upward, a finding that indicates a medial location. At lateromedial mammography, the medial aspect of the breast is closer to the film and can therefore be better evaluated. **(c)** Spot magnification mammogram (right cleavage view) demonstrates a spiculated mass. Pathologic analysis revealed invasive ductal carcinoma.

which the top of the breast was rolled (eg, *craniocaudal RL* = "craniocaudal rolled laterally"). If a density is seen only on the mediolateral oblique view, a mediolateral view is required to locate and further evaluate the lesion (Fig 4). In such a case, a medial lesion will move superiorly on the lateral view, whereas a lateral lesion will move inferiorly. This concept of triangulation is extremely important in identifying the actual position of a lesion. Off-angle or step oblique views, like standard views, are most helpful when the lesion is superimposed over fat and not dense tissue. Exaggerated craniocaudal views may be helpful in demonstrating a posteriorly located lesion that is seen on the mediolateral oblique view only. US may also be helpful in verifying the location of a mass that is clearly seen on only one view.

Poor Technique

The technologist must optimize image contrast to avoid obtaining over- or underpenetrated images. Proper positioning of the photocell is necessary to achieve correct optical density on the image. Careful attention to daily processor quality control is also necessary to optimize contrast. The technologist should always review the images



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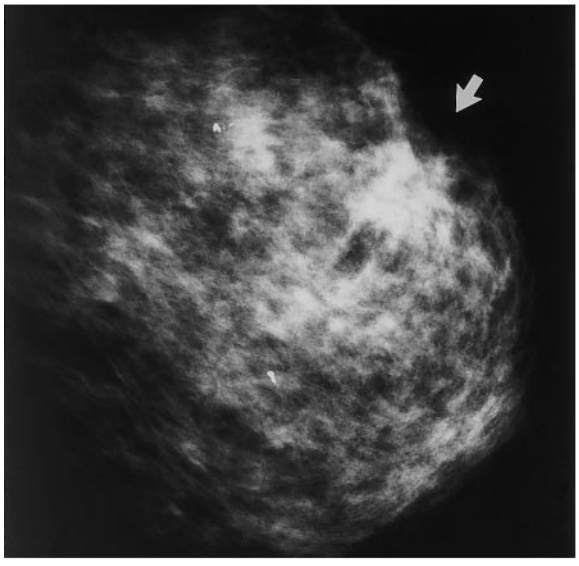

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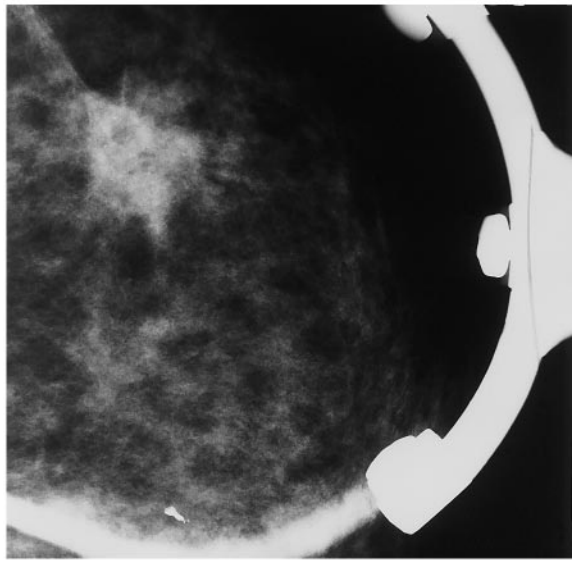

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Figure 5. Proper imaging technique. **(a)** Right craniocaudal screening mammogram obtained in a 65-year-old woman demonstrates underpenetration. **(b)** Right mediolateral oblique mammogram reveals an irregular density (arrow) that was obscured on the craniocaudal view. **(c)** Right craniocaudal spot magnification mammogram demonstrates an irregular mass with microcalcifications. At pathologic analysis, the mass proved to be invasive ductal carcinoma.

under proper mammographic viewing conditions to assess the adequacy of imaging technique (Fig 5). Image blur is problematic, particularly in the assessment of microcalcifications. Rosen et al (14) found that in 62% of cancers that manifested as microcalcifications and were incorrectly followed up with imaging rather than biopsy, image blur on magnification views compromised image quality.

Lack of Perception

Two major causes of missed breast cancers are related to radiologist error. The first of these causes is lack of perception. Perception error occurs when the lesion is included in the field of view and is evident but is not recognized by the radiologist. The lesion may or may not have subtle features of malignancy that cause it to be less visible. Small nonspiculated masses, areas of architectural distortion and asymmetry, and small clusters of amorphous or faint microcalcifications may all be difficult to perceive.

To avoid perception error, images should be reviewed as mirror images, with mediolateral oblique images placed together and craniocaudal images placed together (Figs 6, 7). The radiologist should compare like areas on the side-by-side images to identify any focal asymmetric density or low-density mass. Identification of a focal density should prompt a search for this density on the corresponding view in the same arc from the

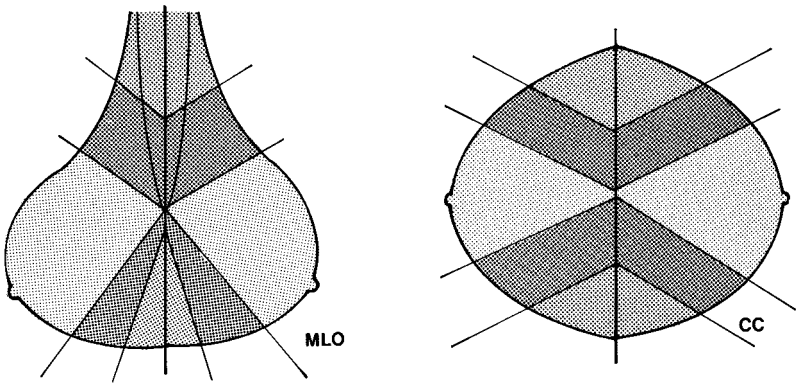

Figure 6. Drawings illustrate useful search patterns in mirror image interpretation. *CC* = craniocaudal, *MLO* = mediolateral oblique.

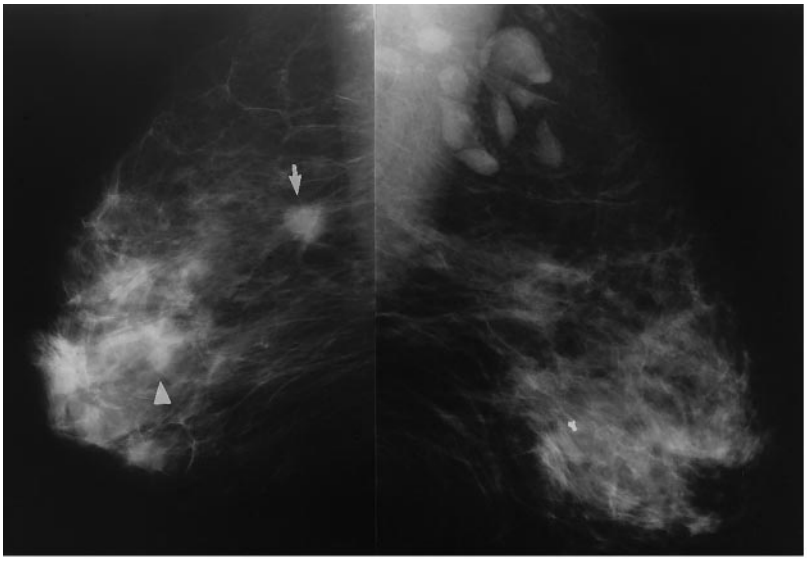

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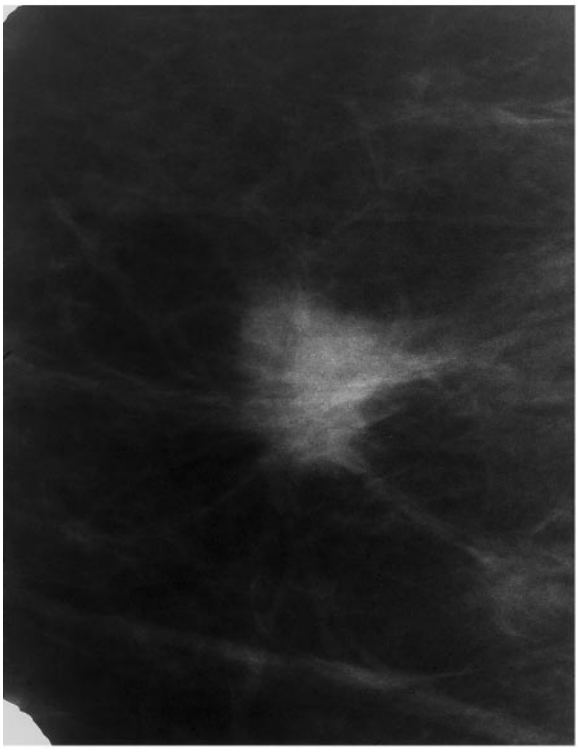
Figure 7. Mirror image interpretation. **(a)** Bilateral mediolateral oblique mammograms reveal an irregular mass posteriorly on the left side with a highly suspect appearance (arrow). In addition, a subtle distortion is noted more inferiorly (arrowhead), a finding that becomes more evident with mirror image interpretation. **(b, c)** On left craniocaudal spot compression mammograms, the posterior **(b)** and anterior **(c)** lesions demonstrate a spiculated appearance (arrowhead in **c**). Pathologic analysis demonstrated multicentric invasive ductal carcinoma.



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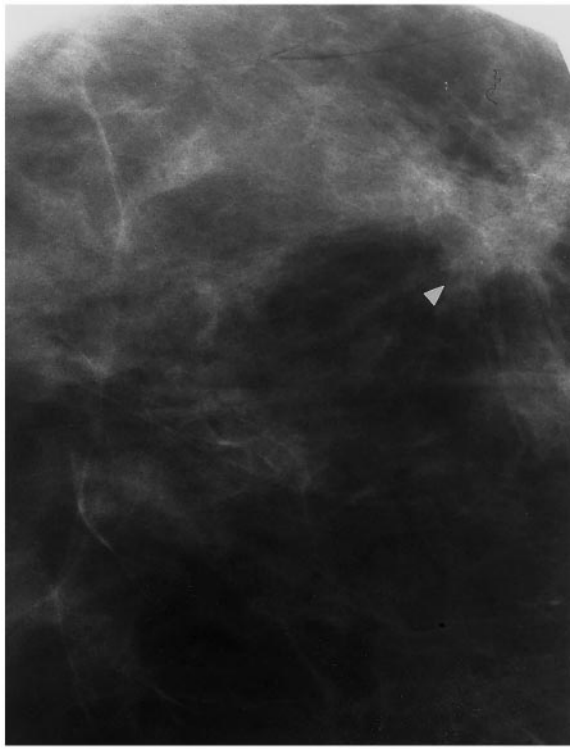

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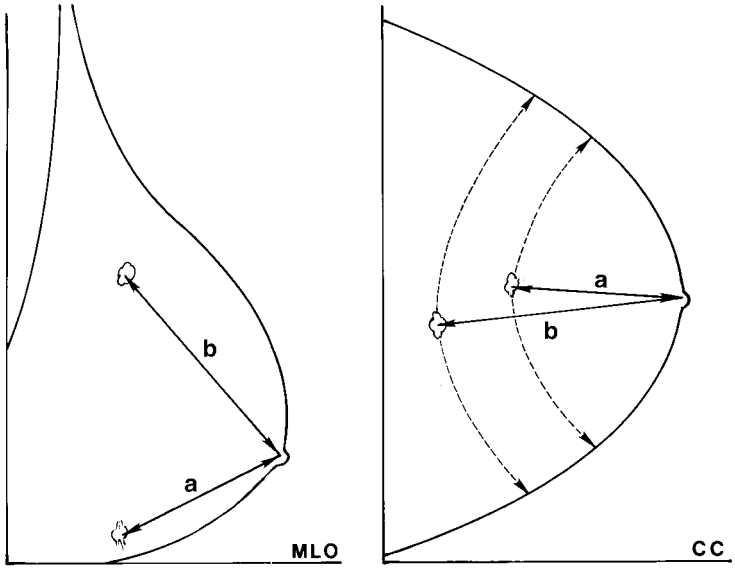


Figure 8. Diagrams illustrate nipple-to-lesion arc measurements used to determine lesion depth. *a* = distance from nipple to anterior lesion, *b* = distance from nipple to posterior lesion, *CC* = craniocaudal, *MLO* = mediolateral oblique.

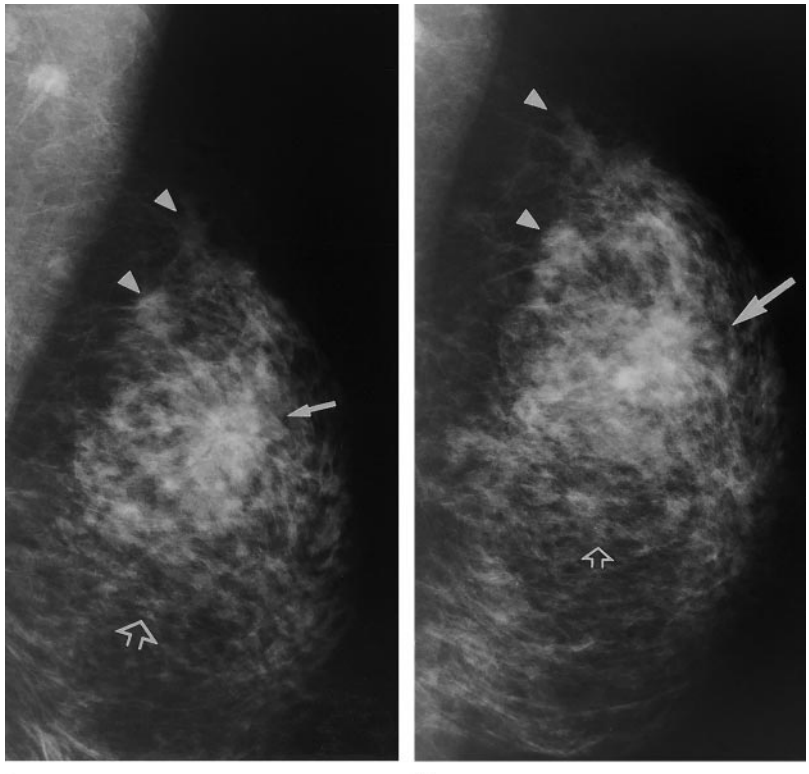
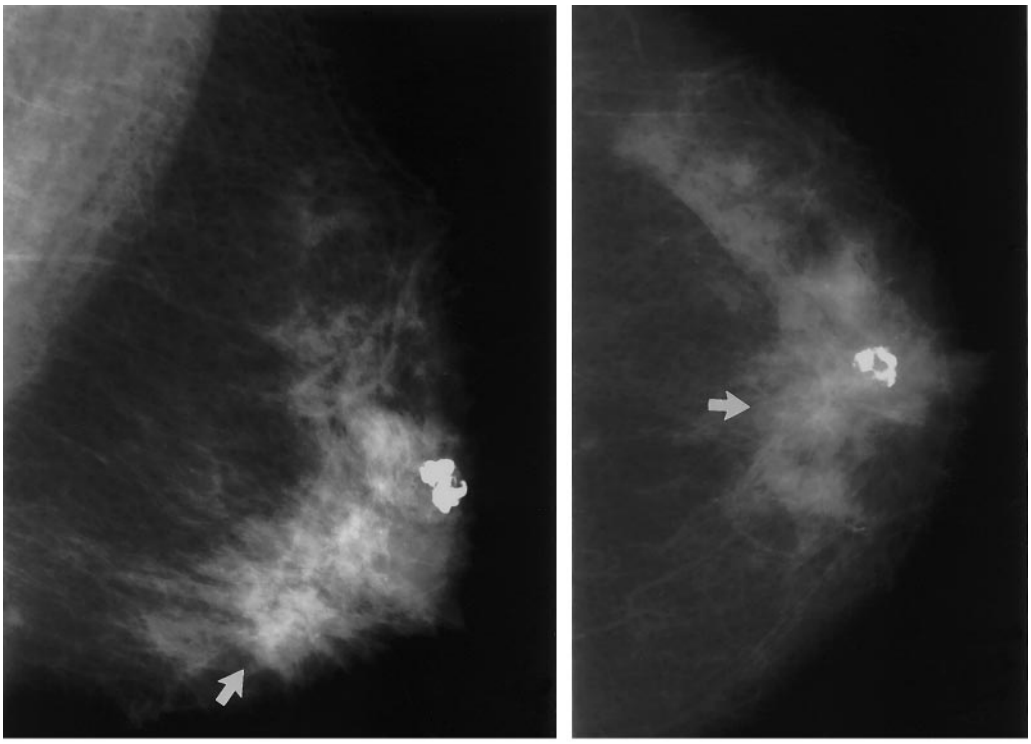


Figure 9. Multicentric breast cancer in a 63-year-old woman. Right mediolateral oblique **(a)** and right exaggerated craniocaudal lateral **(b)** screening mammograms show a prominent area of architectural distortion at the 10 o'clock position (solid arrow). Note also the two small, indistinct masses in the axillary tail (arrowheads) and the linearly arranged microcalcifications at the 7 o'clock position (open arrow). An indistinct high-density node is also seen in the axilla and proved to be malignant at surgery. Pathologic analysis demonstrated multicentric invasive ductal carcinoma and ductal carcinoma in situ.



a. b.

Figure 10. Satisfaction of search. Right mediolateral oblique **(a)** and craniocaudal **(b)** mammograms demonstrate subtle architectural distortion (arrow) behind an obvious calcified fibroadenoma. The first interpreting radiologist noted the fibroadenoma but missed the distortion, which proved to be invasive ductal carcinoma.

nipple (Fig 8). Additional views may be needed to verify the presence of a true lesion.

Failure to diagnose multifocal and multicentric breast cancers can directly affect patient treatment. Multifocal breast cancer is defined as two or more cancers in the same quadrant, whereas multicentric breast cancer is defined as two or more cancers in different quadrants (Fig 9). In multicentric disease, breast conservation therapy is contraindicated. These disease entities may not be perceived owing to "satisfaction of search," in which observation of an obvious finding misleads the radiologist into not looking carefully for other lesions (Fig 10). Careful attention must also be paid to the contralateral breast after observation of a suspect lesion because contralateral synchronous cancers have been reported in 0.19%–2.0% of patients (15) and may actually be seen in 9%–10% of patients at MR imaging (16). Satisfaction of search can also occur in cases of an obvious benign lesion with a subtle cancer. The radiologist must not be satisfied with finding just one lesion, but must search carefully for others, whether benign or malignant.

Another special circumstance that can present a perception problem involves a patient with a palpable node in the axilla that is evaluated with biopsy and represents metastatic adenocarcinoma, likely of breast origin. The primary breast cancer may be occult and either not observed or very subtle at mammography. Careful attention

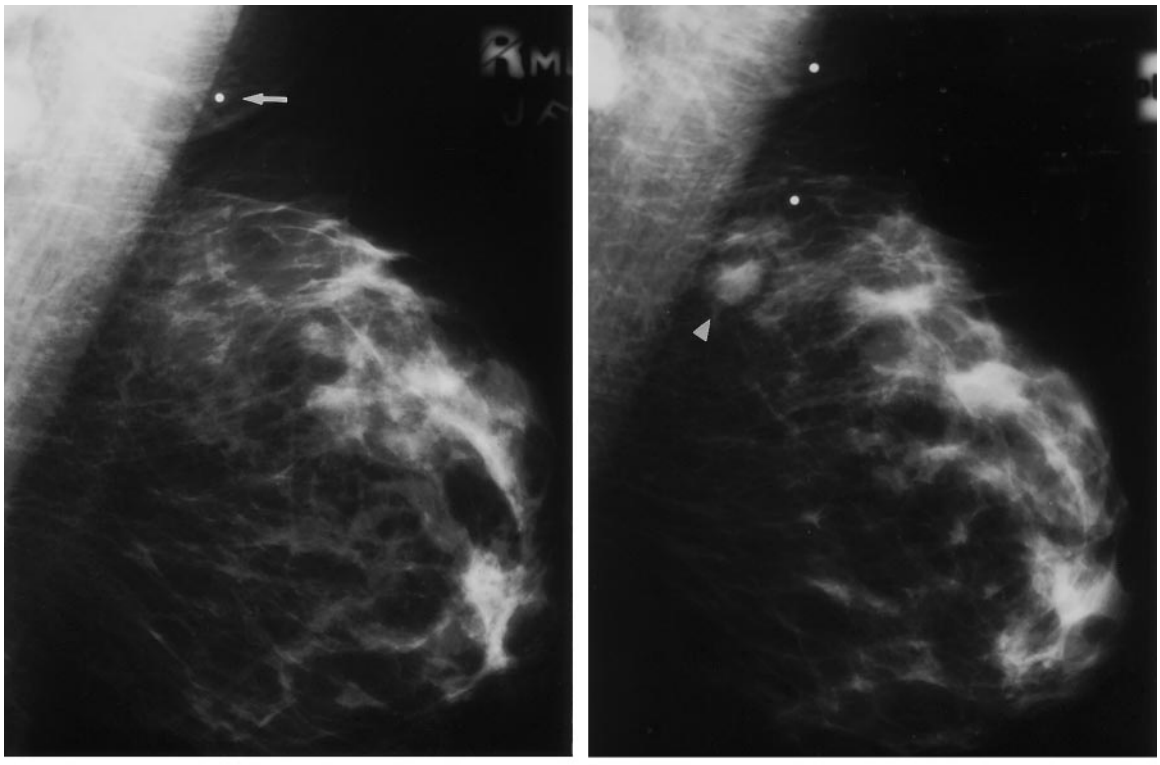


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Figure 11. Occult cancer with metastases in a 36-year-old woman. **(a)** Right mediolateral oblique mammogram that was thought to be otherwise negative reveals an enlarged axillary node (arrow) that was palpable. **(b)** On a right mediolateral oblique mammogram obtained 3 months later while the patient was being evaluated for adenopathy, the previously occult cancer in the 11 o'clock position (arrowhead) became visible. Pathologic analysis demonstrated invasive ductal carcinoma with metastasis to the axilla.

to mirror image abnormalities or focal asymmetric densities is important in identifying the primary lesion (Fig 11). MR imaging has been useful in identifying the primary carcinoma when a metastatic node is found in the axilla and mammographic findings are negative (17).

US may be helpful (like MR imaging and, occasionally, scintimammography) in the search for occult breast malignancy in special circumstances, such as those involving patients with multicentric cancer or with metastases to the axilla and no obvious breast lesion (18,19). Berg and Gilbreath (20) found preoperative whole breast US to be complementary to mammography in patients with known breast cancer and in whom breast conservation was planned. MR imaging is becoming increasingly important in demonstrating the local extent of disease in patients with breast cancer.

Incorrect Interpretation

The second major cause of missed breast cancers that is related to radiologist error is incorrect interpretation of a lesion, which occurs when an abnormality with suspect features is observed but is misinterpreted as being definitely or at least probably benign. Several factors may lead to misinterpretation, such as lack of experience, fatigue, or inattention. Misinterpretation may also occur if the radiologist fails to obtain all the views needed to assess the characteristics of a lesion or if the lesion is slow growing and prior images are not used for comparison. The radiologist may erroneously judge the abnormality by its most benign features and miss important malignant features that necessitate biopsy (Fig 12).

The margins of masses are best evaluated with spot compression imaging. A mass that appears relatively smooth may be indistinct or microlobulated on spot compression images. Therefore, margins should not be characterized on the basis

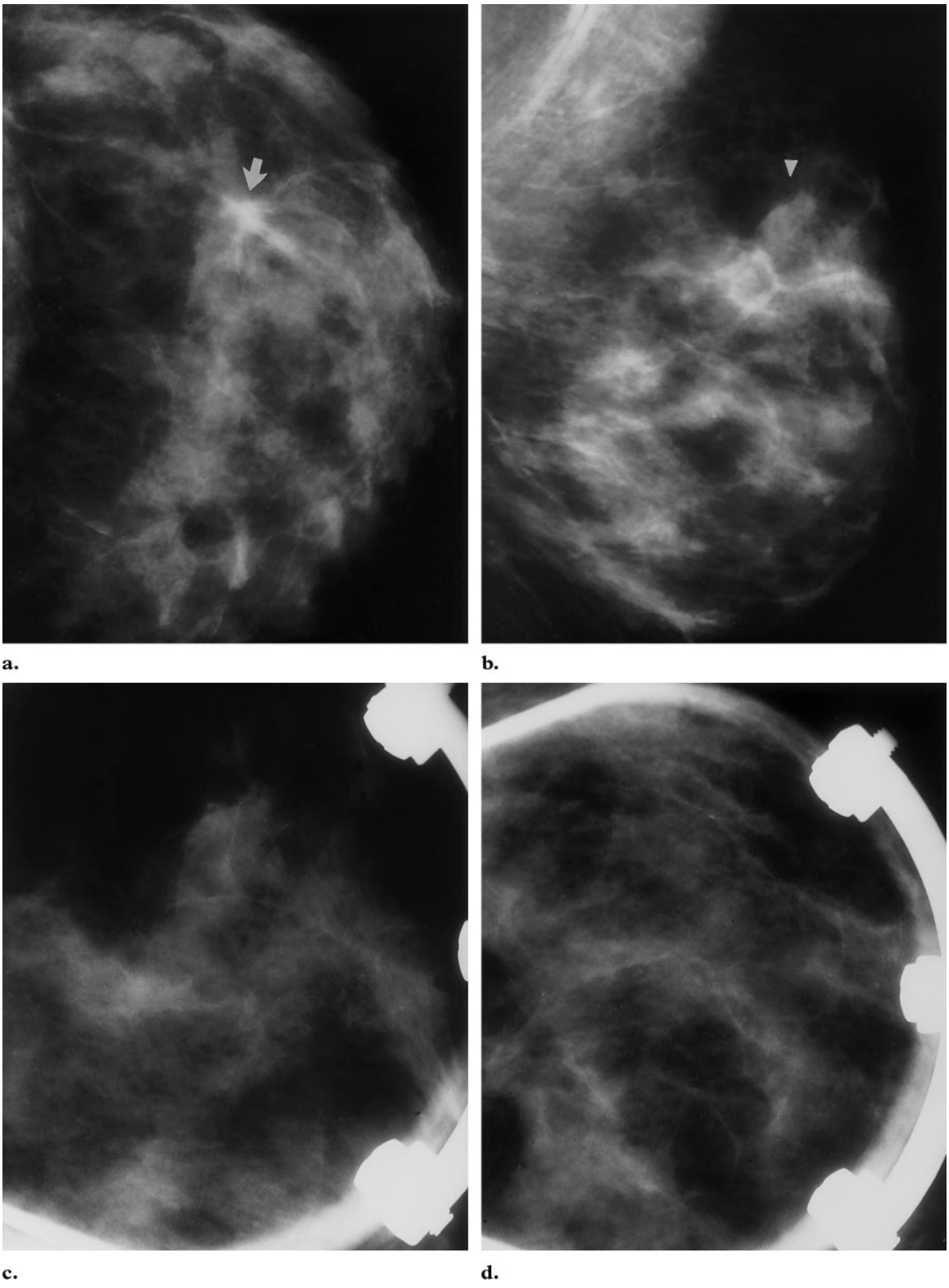


Figure 12. Apparent lesion thinning at spot compression mammography. **(a, b)** Right craniocaudal **(a)** and mediolateral oblique **(b)** mammograms demonstrate focal architectural distortion (arrow in **a**) that may correspond to a superiorly located lesion (arrowhead in **b**). **(c, d)** Mediolateral oblique **(c)** and craniocaudal **(d)** spot compression mammograms show a persistent but less prominent area of distortion. At 6-month follow-up mammography, the area appeared more prominent, and biopsy was performed. Pathologic analysis demonstrated invasive ductal carcinoma. Rolled craniocaudal views were also obtained and helped confirm the persistence of the lesion.

of a screening study alone. Any areas of microcalcifications should be evaluated with magnification views to accurately define their morphologic features as well as their number and distribution. Characterization of a lesion that is identified at screening mammography should be based on diagnostic mammographic findings and not on screening findings alone.

Subtle Signs of Malignancy

The cancers that are the most challenging to diagnose and that most often lead to interpretation errors are those with subtle or indistinct features of malignancy. These features include areas of architectural distortion, small groups of amorphous or punctate microcalcifications, focal asymmetric densities, dilated ducts, and relatively well circumscribed masses. In a study of nonpalpable cancers, Sickles (21) found that only 39% manifested with classic signs, including spiculated masses and linear microcalcifications.

Although well-circumscribed cancers are relatively uncommon, they do exist (22). Medullary, colloid (mucinous), and papillary carcinoma commonly manifest as well-circumscribed masses (Fig 13). Invasive ductal carcinoma not otherwise specified is usually not circumscribed; however, because it occurs frequently, it accounts for the majority of circumscribed cancers. Spot compression magnification of a seemingly circumscribed mass that proves to be a cancer will often demonstrate some area of indistinctness or microlobulation of the margin.

US is helpful in predicting the likelihood of malignancy in a circumscribed mass. Simple cysts seen at US constitute a benign finding. Solid lesions that are smooth, elliptic, and wider than they are tall are probably benign. However, masses that have irregular or angulated margins, are markedly hypoechogenic, and are taller than they are wide are probably malignant (23). A nonpalpable circumscribed mass at mammography that demonstrates what are likely benign solid features at US may be reevaluated at an early interval (24). If, however, the mass is seen at US as a solid lesion with worrisome features such as a "taller-than-wide" shape or irregular margins (23), biopsy is indicated. Any increase in the size of a circumscribed, noncystic mass should prompt further evaluation with biopsy.

Asymmetric densities are frequently seen at mammography. These findings in isolation have a low positive predictive value for malignancy; however, when they are associated with microcalcifications or architectural distortion, the risk of malignancy is increased (Fig 14). In a retrospective review of interval cancers, Ikeda et al (8) found that 21 of 94 cases (22%) showed subtle signs of malignancy, mostly asymmetric densities. Other worrisome features associated with focal asymmetric densities include interval enlargement, a new asymmetric density, a nonhormonal finding at mammography, and a palpable mass. Clinical history is important in evaluating focal areas of asymmetry. In the absence of tumor or infection, focal developing densities should prompt further assessment and, usually, biopsy. Rosen et al (14) found that 10 of 12 malignant areas of asymmetry (83%) were new, yet were incorrectly followed up by the radiologist. Hormonal changes are typically diffuse and bilateral, although a focal developing density can result from hormone replacement therapy. A developing density that is thought to be hormonally related calls for discontinuation of therapy for 3–4 weeks, followed by repeat mammography.

Invasive lobular carcinoma accounts for approximately 8%–10% of breast cancers and is easily missed because common manifestations in-

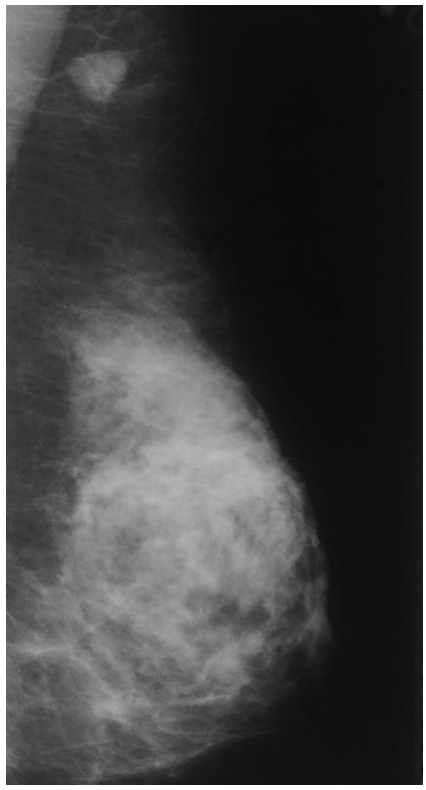
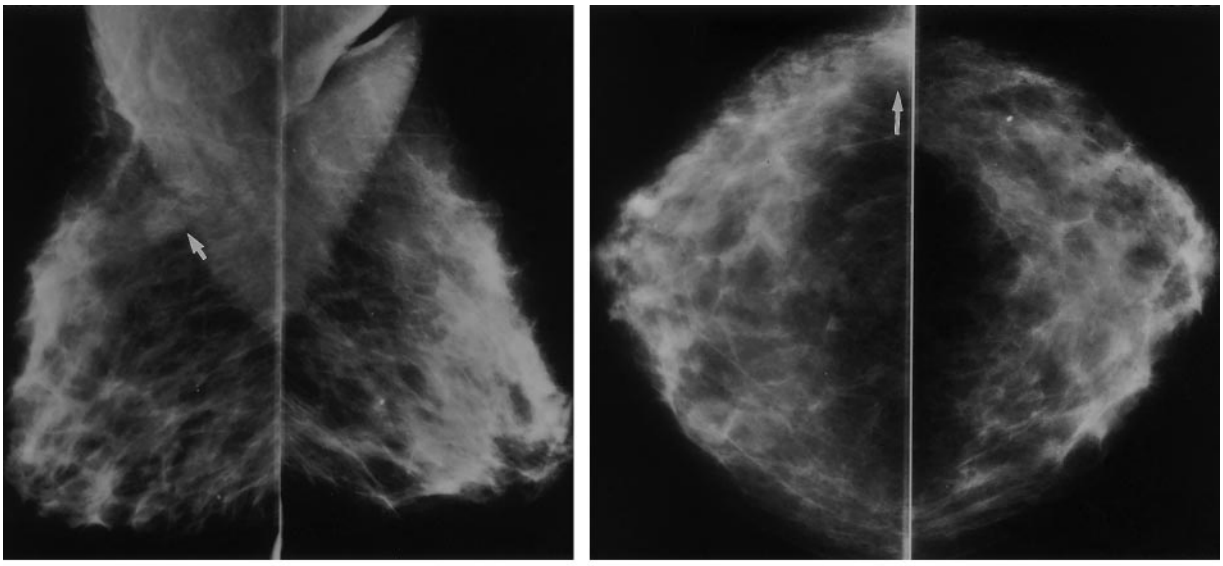
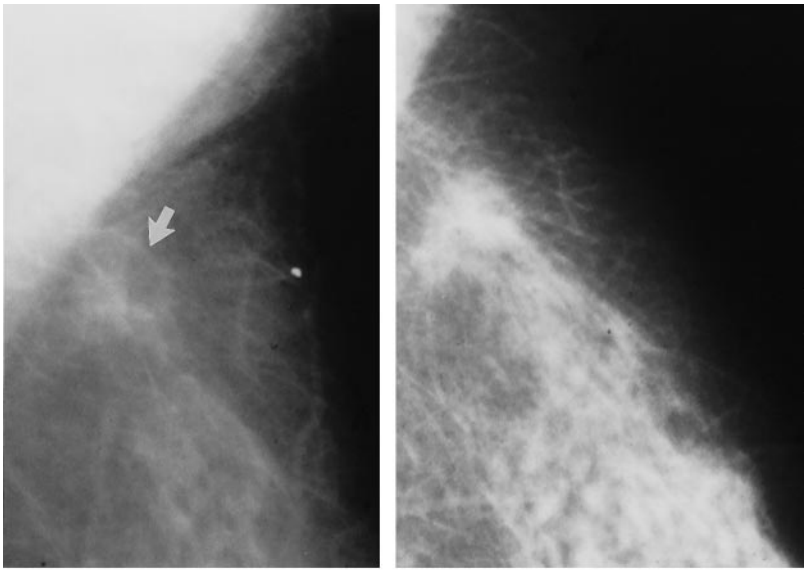


Figure 13. Circumscribed cancer in a 63-year-old woman. Right exaggerated craniocaudal lateral mammogram demonstrates a nonpalpable mass in the axillary tail. The mass is lobulated and circumscribed and has high density. Spot compression mammography would help verify the characteristics of the margins. Pathologic analysis demonstrated mucinous carcinoma.



a. b.

Figure 14. Asymmetric density. Bilateral mediolateral oblique **(a)** and craniocaudal **(b)** mammograms demonstrate a new focal asymmetric area in the left axillary tail (arrow), a finding that becomes more evident with mirror image interpretation. Biopsy revealed infiltrating lobular carcinoma.



a. b.

Figure 15. Slow-growing cancer. **(a)** Right mediolateral collimated mammogram shows focal architectural distortion superiorly (arrow). The area was not noted on subsequent images because it had changed imperceptibly. **(b)** Right mediolateral collimated mammogram obtained 8 years later demonstrates interval growth of the lesion. Biopsy was performed, and pathologic analysis demonstrated tubular carcinoma.

clude a focal asymmetric density, an area of architectural distortion, and negative mammographic findings (25). US may demonstrate prominent focal shadowing.

The work-up of a focal asymmetric density includes a clinical examination; additional mammography (spot compression and off-angle views) and US may also be helpful. However, negative US findings at the site of a suspect asymmetric density should not preclude biopsy. Dilated ducts are infrequently associated with malignancy. Patterns of ductal dilatation that suggest malignancy include a unilateral solitary dilated duct (21) and dilated ducts associated with microcalcifications or in a nonsubareolar location (26).

Slow-growing Cancers

The doubling time for breast cancers has been reported to range from 44 to 1,869 days (27). However, malignant calcifications have been reported to be stable at mammography for as long as 63 months (28). Low-grade malignancies may not undergo obvious change between annual interval screenings. Therefore, a slowly changing cancer may go undetected if the radiologist fails to compare findings with those on older images (Fig 15). A lesion with features that strongly

suggest malignancy but that has been stable for 1–2 years still requires biopsy because it may represent a slowly changing cancer. In particular, caution should be used in evaluating stable masses or lesions with suspect morphologic features that decrease in size in patients who are receiving tamoxifen. Tamoxifen is used to treat breast cancers and to prevent the development of breast cancer in high-risk women, but it can also be used to check the growth of occult malignancies.

Role of Double Reading

Double reading of mammograms has been shown to increase the detection rate for breast cancer by up to 15% (29,30). Computer-aided detection (CAD) represents a relatively new technology that has been implemented in some mammography facilities for double reading. Clinical studies have shown that CAD increases the sensitivity of breast cancer detection by radiologists by up to 20% (31,32). The sensitivity of the CAD systems is greater for detecting calcifications than for detecting masses (33). In a study of 115 cancers retrospectively judged to merit recall on the screening mammogram prior to the mammogram on which they were diagnosed, 77% of lesions were identified with CAD (34). In all, 86% of 35 missed areas of calcifications and 73% of 80 missed malignant masses were detected with CAD. We may continue to see increasing use of both CAD and a second radiologist for double reading of screening mammograms.

Conclusions

Although mammography is the standard of reference for the detection of early breast cancer, as many as 30% of breast cancers may be missed. To reduce the possibility of missing a cancer, the radiologist should take the following steps when interpreting mammographic findings:

1. Do not rely on screening views alone to diagnose a detected abnormality; complete the evaluation with diagnostic mammography.
2. Review clinical data and use US to help assess a palpable or mammographically detected mass.
3. Be strict about positioning and technical requirements to optimize image quality.
4. Be alert to subtle features of breast cancers.
5. Compare current images with multiple prior studies to look for subtle increases in lesion size.
6. Look for other lesions when one abnormality is seen.
7. Judge a lesion by its most malignant features.

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