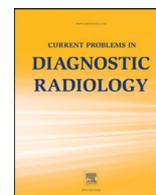




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Review of Subtypes of Interval Breast Cancers With Discussion of Radiographic Findings

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Interval breast cancers are those detected in the interim between regular screening examinations and are an unfortunate reality for breast cancer screening programs. However, their incidence can help gauge the success of breast cancer screening programs. There are four main categories of interval cancers, including true negative, false negative, minimal sign, and occult. The mammographic characteristics of each type of interval cancer are reviewed with example cases from an urban academic institution. Pitfalls and strategies to reduce interval cancers are discussed in detail.

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Background

The federally mandated Mammography Quality Standards Act (MQSA) of 1992 aims to improve breast cancer screening programs by requiring all breast imaging practices to run and review statistical analyses on every mammography examination and biopsy performed.¹ Each practice can then compare its data to benchmarks set by the American College of Radiology (ACR), the Agency for Healthcare Research and Quality (AHRQ), and Breast Cancer Surveillance Consortium (BCSC), in order to identify its strengths and weaknesses.²⁻⁴ One way to measure the success of a breast cancer screening program is to identify and analyze cases of interval breast cancers.

Screening mammography guidelines adopted by a breast cancer screening program will affect the incidence of interval breast cancers in that program, as the guidelines for screening mammography vary within the United States and internationally.⁵ Recommendations vary to include those for annual, biennial, and triennial screening. The ACR and American College of Obstetricians and Gynecologists recommend annual screening mammography beginning at age 40, while the U.S. Preventative Services Task Force and American Academy of Family Physicians recommend biennial screening beginning at age 50.^{2,6-8} Furthermore, the revised 2015 American Cancer Society guidelines recommend annual screening mammography between the ages 45 and 54 (with the choice to begin at age 40), then biennial screening starting at age 55.⁹ Guidelines remain inconsistent and controversial despite data that shows annual screening schedules are more successful in attaining the goal of early breast cancer detection, with fewer interval cancers. A review in which Houssami and Hunter

assessed the interval cancer rates by screening interval showed interval breast cancer rates of 14.7%, 17%–30%, and 32%–38% for the annual, biennial, and triennial screening groups, respectively.⁵

In addition to variability in screening guidelines, the categorization of interval breast cancers also varies by institution. This article describes four main interval cancer categories: true negatives, false negatives, minimal sign, and occult. True negative cancers are cancers that were not present on the most recent screening exam, but are visible on the current exam. False negative cancers are those that were present on the most recent prior screening mammogram, but assessed negative. Minimal sign cancers are cancers that develop from an equivocal finding on the prior screening mammogram. Occult cancers are those that are not visible mammographically, on either the most recent screening exam or the current diagnostic mammogram.

Interval breast cancers represent approximately 14.7% of all breast cancers in the screening population based on annual screening, at a rate of less than 8 in 10,000 screens.¹⁰ Patients with interval breast cancers can present either symptomatically or asymptotically. Symptomatic patients exhibit signs or symptoms of breast cancer, such as a palpable lump or skin thickening, and are detected by the patient or their clinician. Cancers in asymptomatic patients are detected incidentally on imaging studies performed for non-breast related symptoms, such as PET, CT, or MRI.

Once an area of breast concern is identified on self or clinical exam, or incidentally on another imaging study, the patient is evaluated with diagnostic breast imaging. This evaluation typically includes a mammogram and an ultrasound. The interpreting radiologist reads the new exam and compares it with the patient's prior mammogram, looking for interval change. If an interval breast cancer is diagnosed, the cancer can be categorized as one of the four interval cancer types. The radiologist does this by assessing whether the cancer is a new finding, or was seen on the prior screening mammogram. If neither scenario applies, the radiologist determines if the cancer developed from an equivocal finding on the prior screening mammogram, or if the cancer is ever seen mammographically. By performing this exercise and categorizing the interval breast cancer, the

Appropriate IRB approval was obtained for this retrospective clinical paper.

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radiologist may obtain more meaningful information which can be used for improved cancer detection.

In this review article, the four categories of interval breast cancers will be discussed, with case examples obtained at our urban academic institution. Our breast imaging program follows annual screening mammography guidelines, and all included examples presented within 365 days of the last screening mammogram. Emphasis will be on imaging characteristics and possible strategies to help reduce rates of interval breast cancers.

True Negative Interval Breast Cancers

True negative interval cancers are those that were not present on the most recent prior screening mammogram, but are detected on the current diagnostic mammogram, occurring in the interim before the next screening exam is performed. In other words, the most recent prior mammogram was a true negative.

Although the mammographic manifestations of all interval breast cancers are variable, it has been reported in the literature that interval breast cancers most commonly present as masses.^{11–13} One study involving a cohort of over 647,000 women comparing screen-detected and interval cancers showed that most true negative interval cancers presented mammographically as masses (Fig 1), followed by architectural distortion, calcification, asymmetries (Fig 2), masses with calcifications, and others in decreasing frequency.¹⁴ In Hofvind et al, the average size of true negative interval breast cancers was found to be 18 mm and nearly 50% of interval cancers measuring less than 15 mm were true negative interval cancers.¹⁵

Multiple retrospective reviews have shown that the vast majority of interval breast cancers are in fact true negatives.⁵ In some studies, it has been found that all interval breast cancers are diagnosed at a more advanced stage than screen-detected cancers, and have an overall worse prognosis and survival rate compared to screen-detected cancers.^{5,16,17} One hypothesis is that cancers presenting during the short interval between screening exams rapidly proliferate.⁵ Studies have found that interval breast cancers, as a whole, are usually associated with nodal metastases, larger tumor size, higher histologic grade, and receptor profiles that are less amenable to treatment.⁵ However, among interval breast cancer categories, true negative interval cancers were less likely to be lymph node positive.¹⁵ Also, true negatives have been found to be relatively smaller than those of missed and minimal sign cancers.¹⁵ True negative cancers are an inevitable reality proving that cancer can develop in the time between regular screening mammograms.

False Negative Interval Breast Cancers

False negative cancers are also termed “missed” cancers and in retrospect were visible on the prior screening mammogram. It has been reported that between 10% and 30% of breast cancers are “missed.”¹⁸

False negative breast cancers may present as one-view asymmetries or slow growing masses (Fig 3).¹⁹ A recent review of false negative interval and screen-detected breast cancers on both screen film and digital mammography in two Norwegian counties found that a mass without calcifications was the most common mammographic finding associated with a false negative cancer, and represented 54% of all missed cancers.²⁰ The remaining 18% of false negative cancers on digital mammography included calcifications (with or without associated mass), asymmetry, and architectural distortion.²⁰ Another review by Hofvind et al found that up to half of all false negative cancers presented as a poorly defined mass and only one quarter showed calcifications.¹⁵ Hofvind et al demonstrated approximately 20% presented as calcification with an associated density or mass, 16% as architectural distortion, and 6% as calcifications alone.¹⁵

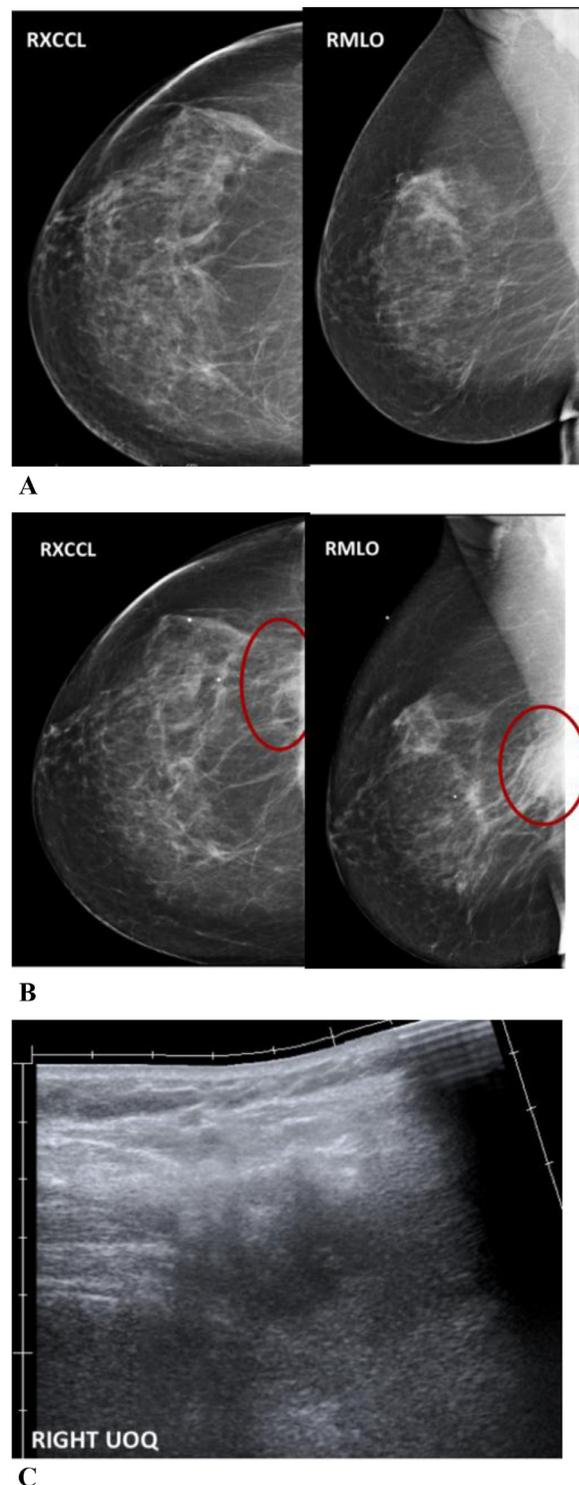
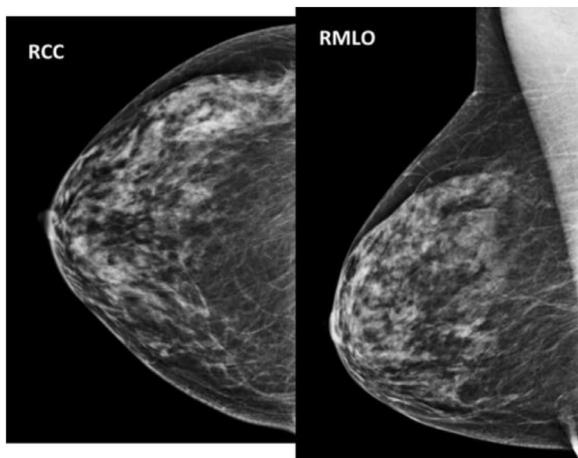
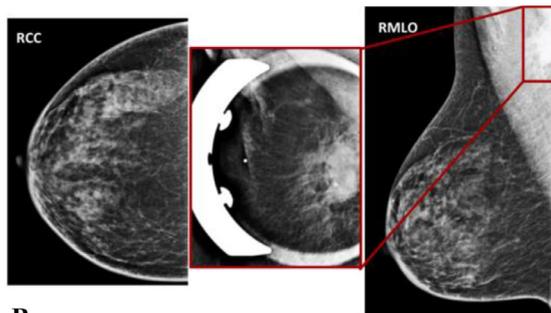


FIG 1. True negative. This patient presented with a palpable area of concern in the right breast 2 months after a negative screening mammogram (A). Diagnostic right exaggerated craniocaudal lateral (RXCCL) and right mediolateral oblique (RMLO) views (B) showed a developing asymmetry in the right upper outer quadrant (solid circles). Sonographic evaluation of the palpable area of concern (C) showed an irregular, hypoechoic mass, with microlobulated and angular margins. Image-guided biopsy returned invasive ductal carcinoma.

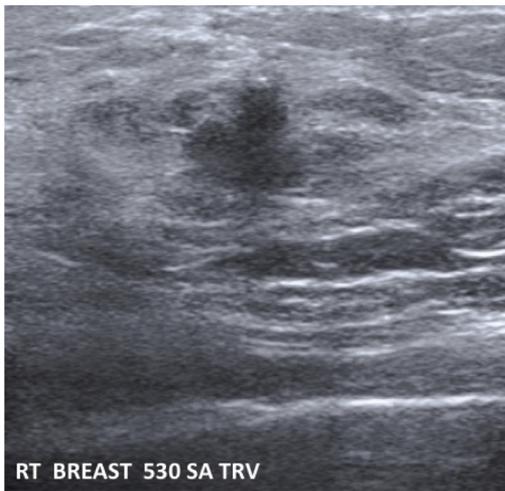
On digital mammography, up to 61% of masses less than or equal to 10 mm were missed, with a range of masses missed measuring from 4 to 18 mm.¹⁵ Hofvind et al reported that most false negative interval breast cancers had a slightly larger average size of 23 mm.¹⁵ The masses missed were equal density to the adjacent fibroglandular



A



B

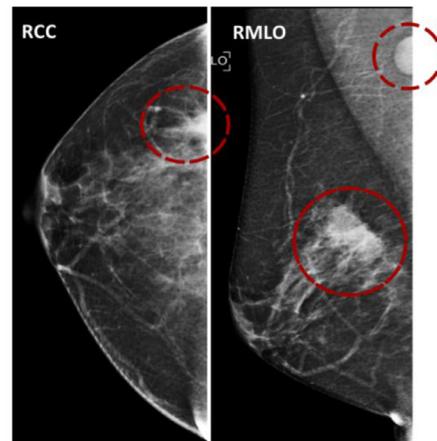


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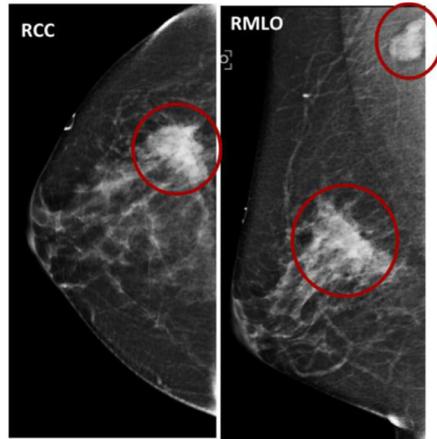
FIG 2. True negative. One year after a negative screening mammogram (A), this patient presented with a palpable area of concern in the right axilla. A one view asymmetry was identified superiorly and posteriorly in the palpable area, as marked by a metallic BB, on the RMLO diagnostic projection (B). Targeted sonographic evaluation of the palpable area was performed and showed an abnormal lymph node in the palpable area (not shown). Whole breast ultrasound revealed an irregular, hypoechoic mass with microlobulated and angular margins in the subareolar tissues at 5:30 (C). Biopsy of the subareolar mass and palpable axillary lymph node revealed invasive ductal carcinoma with metastatic axillary lymphadenopathy.

tissue, irregularly shaped, with most demonstrating indistinct margins and a minority demonstrating spiculated margins.²⁰ Mass detection was not typically a perceptual dilemma. Instead, errors of misinterpretation arose if findings were incorrectly assessed as benign.¹⁵

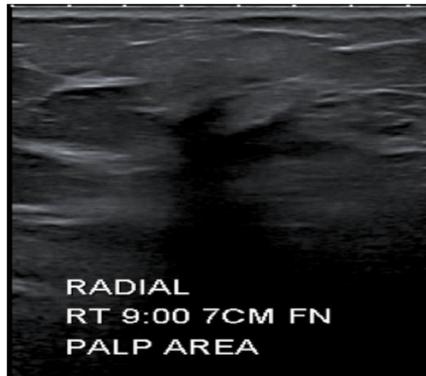
False negative cancers have the worst prognosis among all interval breast cancer subcategories, but make up the minority of interval breast cancers.⁵ They present a challenge in determining what led to



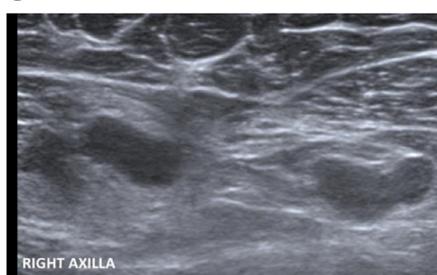
A



B



C



D

FIG 3. False negative. A patient presented 5 months after a screening exam assessed as negative (A) with a palpable right upper outer quadrant breast mass, which corresponded to an area of focal asymmetry (solid circles) on the diagnostic CC and MLO projections (B). The diagnostic RMLO projection also demonstrated a partially included abnormal axillary lymph node (B). In retrospect, the focal asymmetry was present on the screening exam (dashed circles). Sonographic evaluation of the right upper outer quadrant demonstrated an irregular mass with angular margins and posterior

a false negative assessment on the screening mammogram. As in all of radiology, there are multiple contributing factors that can lead to a missed finding. These factors may be technical or patient-related, but missed findings can also be related to interpretive or perceptual errors by the radiologist.

While the specifics of all factors leading to a false negative mammogram are beyond the scope of this review, a few common technical factors should be emphasized. It is essential for technologists to maximize the amount of breast tissue imaged by following positioning standards.²¹ Optimal patient positioning for a screening mammogram is imperative for interpretation. Positioning considerations must abide by the ACR Mammography Quality Control Manual.²² Radiologists must be aware of adequate patient positioning standards to assess if an exam is of diagnostic quality for interpretation. Proper positioning can be evaluated using the posterior nipple line (PNL), which is a line drawn from the nipple perpendicular to the chest wall on both craniocaudal (CC) and mediolateral oblique (MLO) views.²³ The PNL measured on both views should be within 1 cm of each other, to ensure adequate breast tissue coverage.²³ Proper positioning of the breast on the MLO view should include visualization of the pectoralis major to the level of the nipple with the anterior margin of the muscle either straight or convex.²⁴ The axilla, axillary tail, and the inframammary fold must also be included.²⁴ Another positioning and technologist-related issue is to ensure as much breast tissue as possible was imaged. The standard two views in the MLO and CC projections may exclude additional breast tissue and supplemental views can be included for the screening exam. Exaggerated CC views include more of the posterolateral breast tissue and can be performed on screening exams in which the posterolateral breast tissue is incompletely included.¹⁸ One final way to ensure optimal imaging technique to reduce missed cancers is to ensure the nipple is seen in profile and centered on at least one view.²⁴

Motion artifact or blur can obscure abnormalities or subtle areas of architectural distortion leading to missed cancers.²⁵ Among the patient-related artifacts in full-field digital mammography (FFDM), motion artifact, and skin lines predominate.²⁵ Techniques to reduce motion artifact include instructing the patient to remain still during imaging, increasing compression, increasing kilovolt peak (kVp), or using a rhodium target rather than a molybdenum target.²⁵

Radiologists can be the source of error leading to a false negative mammogram. Perfection is not possible, but there are factors to consider for optimal screening mammography interpretation. The reality is that radiological errors are common across all radiology subspecialties, with a reported day-to-day error rate ranging from 3% to 5% and retrospective error rate up to 30%.²⁶ In a review on errors and discrepancy in radiology, Brady summarized that system issues can be a leading cause of errors.²⁷ Cognitive biases also plague radiologists when interpreting studies and include anchoring bias, framing bias, satisfaction of search, or premature closure, among others.²⁷ These biases can influence radiologist interpretation and result in incorrect or missed diagnoses.^{28,29}

Errors in perception occur when an abnormality is present, but not detected by the interpreting radiologist. They are the number one error made by radiologists and have been reported to be as high as 60%–80%.²⁵ Perceptual errors are more often associated with “one-view” findings, small nonspiculated masses, low-density lesions, developing asymmetries, and subtle calcifications.¹⁹ By viewing mammograms as mirror images utilizing the “masking technique,” identifying abnormalities on two views and avoiding “satisfaction of search,” errors in perception can be reduced.^{25,30}

Another way to reduce errors of perception, and thereby to reduce false negative interval cancers, is through double reading

– having two radiologists review the mammogram, which has been found to increase cancer detection by up to 15%.^{31,32} Shaw et al found that consensus review, in which double read screening exams with discordant assessments were subsequently reviewed by a group of three to five breast imagers, resulted in an increased cancer detection rated by 7.3%.³³ They found that disagreement was highest with masses, asymmetries, and architectural distortion. Disagreement was lowest with calcifications, which accounted for up to two-thirds of ductal carcinoma in situ (DCIS) cases and nearly one-third of all “consensus” cancers – those that underwent consensus review. Overall, there was a decrease in both false negative and false positives.

Interpretive or cognitive errors are those that occur when an imaging finding is made, but its significance is incorrectly assessed. They can be reduced through experience and targeted continuing medical education, batch reading, and comparison of new and old mammograms.^{34–37} It is important when interpreting a screening mammogram to have multiple prior screening mammograms to use as comparisons.³⁸ This enables the radiologist to identify developing abnormalities or stable benign findings. Batch reading helps to reduce interpretive errors due to distraction, distraction free, uninterrupted time to interpret screening mammograms.³⁶ Furthermore, frequent interruptions can lead to loss of concentration and result in failure to detect abnormalities.²⁷

Minimal Sign Cancers

Minimal sign cancers are those that develop from an equivocal imaging finding that is not characteristically benign or malignant. The criteria for minimal sign are inconsistent due in part to the subjectivity of what is considered “minimal sign”.³⁹ In review of the published literature, some have combined the incidence of minimal sign cancers with that of false negative cancers.

Examples of minimal sign cancers may include a mass (Fig 4), mass with microcalcifications, asymmetric density (Fig 5), architectural distortion, asymmetric density with microcalcifications, or only microcalcifications.^{11,39} Broeders et al found that architectural distortion yielded a more positive outcome if detected early.¹¹ Around 17% of interval cancers that presented mammographically as an area of increased density without microcalcifications occurred in an area of architectural distortion when the prior screening was retrospectively reviewed, thus reinforcing architectural distortion as a “precursor sign” for breast cancer.¹¹ Bansal and Thomas found that the most common minimal sign interval breast cancer associated with a more advanced stage, requiring a more aggressive treatment approach, were those that presented as a mass or asymmetry associated with microcalcifications.³⁹

The same contributing factors that can lead to a false negative cancer can also lead to a minimal sign interval cancer. As previously discussed under technical factors, optimal patient positioning and imaging as much breast tissue as possible is essential for an adequate exam. With the goal of reducing radiologist error and increasing interpretive accuracy, many breast centers have begun to offer screening mammography with breast tomosynthesis (DBT) or 3D mammography.

DBT has been found to increase cancer detection and reduced recall rates compared with routine 2D screening mammography.⁴⁰ DBT is superior at detecting architectural distortion, when used as an adjunct to routine screening mammography.^{38,41} Up to 74% of cases of architectural distortion and 26% of masses occult on 2D mammography were detected with DBT.^{38,41} The addition of DBT to screening mammography may help improve the accuracy of interpretation, as architectural distortion can be a precursor sign of breast cancer and masses are the most common interval cancer finding.

shadowing at 9:00 (C). Axillary ultrasound (D) showed sonographically abnormal lymph nodes with cortical thickening. Biopsy of both the mass and axillary lymph node under ultrasound guidance was performed and returned invasive ductal carcinoma with metastatic axillary lymphadenopathy.

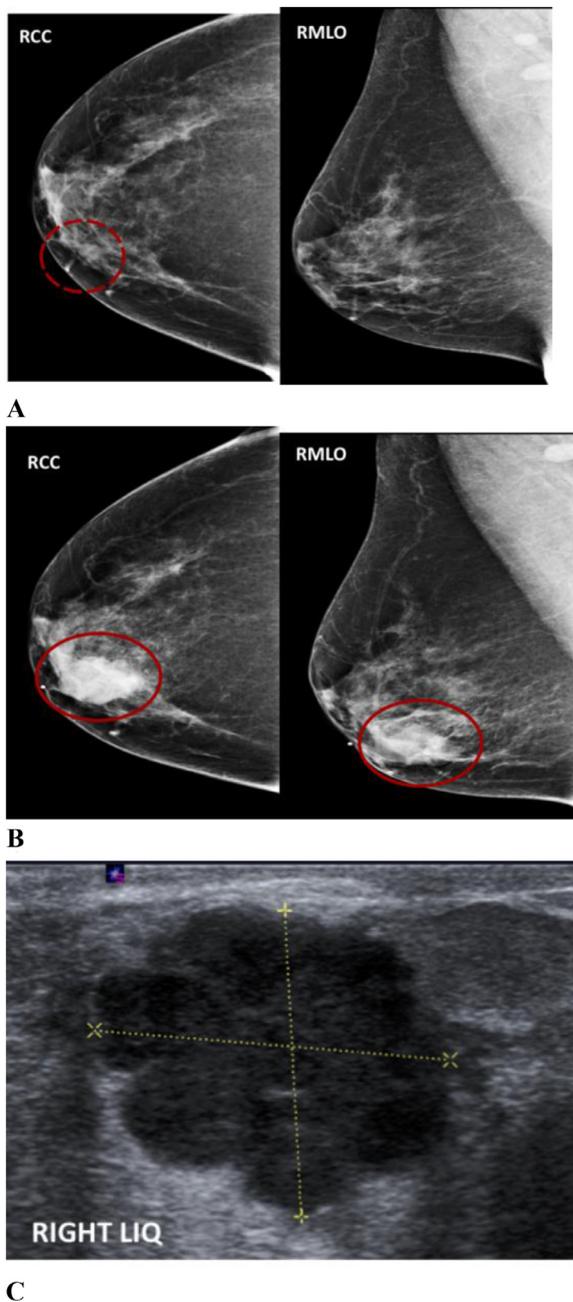


FIG 4. Minimal sign. Ten months after a screening exam with a *minimal sign* (dashed circle), that was assessed as negative, (A), the patient presented with a palpable area of concern in the right breast. The diagnostic mammogram (B) showed an irregular, high density, microlobulated mass in the lower inner quadrant (solid circles) and in the area of the *minimal sign*, as seen in retrospect on the screening CC projection. The mammographic mass correlated with an irregular, hypoechoic mass, with microlobulated margins on grayscale sonography (C). Ultrasound-guided core needle biopsy returned invasive ductal carcinoma.

Occult Interval Breast Cancers

Occult interval breast cancers are those which cannot be seen mammographically and represent anywhere from 7% to 32% of all interval breast cancers based on reported literature.⁵ They present after a negative screening mammogram and remain mammographically occult at the time of presentation (Figs 6 and 7).

One possible explanation is that the cancer is in a location not included on standard mammographic views, such as far medially or inferiorly in the breast. However, another known possibility is that the cancer is obscured by dense breast tissue.⁴²

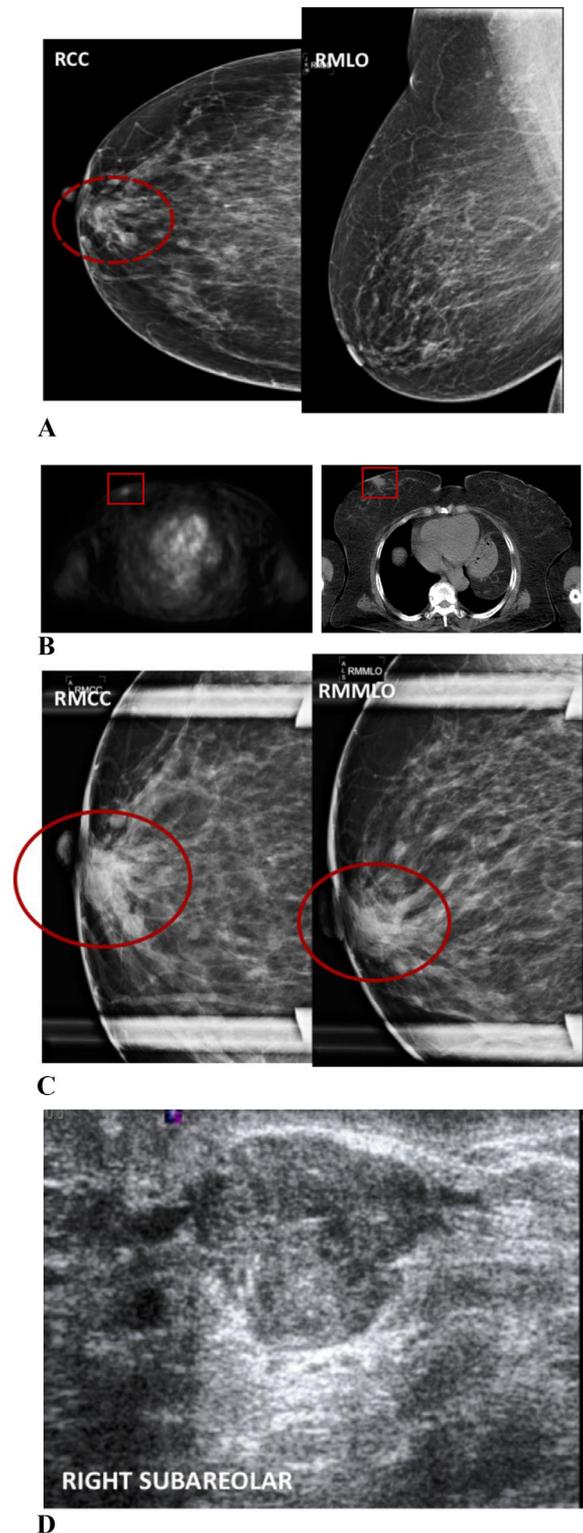
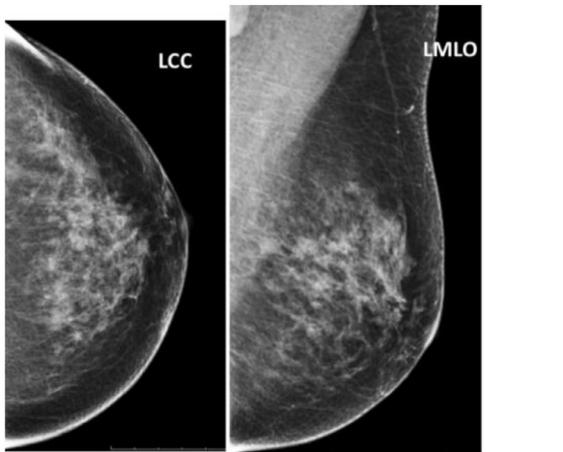


FIG 5. Minimal sign. Patient diagnosed with PET-detected breast cancer, 6 months after a screening mammogram with a *minimal sign* that was assessed negative (A). PET-CT was performed for surveillance of the patient's endometrial cancer and an incidental focus of FDG avidity in the right breast (square) was noted (B). The finding correlated with an obscured subareolar mass on the diagnostic spot magnification CC and MLO views (solid circle) (C). A subareolar asymmetry was present in hindsight on the CC view of the screening mammogram (dashed circle), but was interpreted as normal fibroglandular tissue. An irregular, antiparallel, hypoechoic subareolar mass was found on targeted ultrasound (D). Ultrasound-guided core needle biopsy returned invasive ductal carcinoma and papillary-type ductal carcinoma in situ.



A



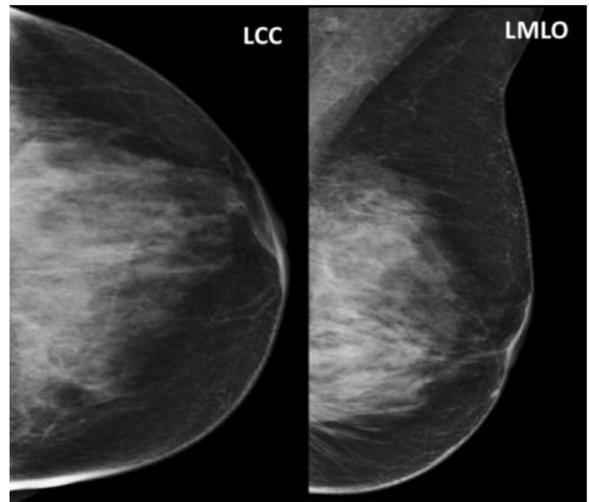
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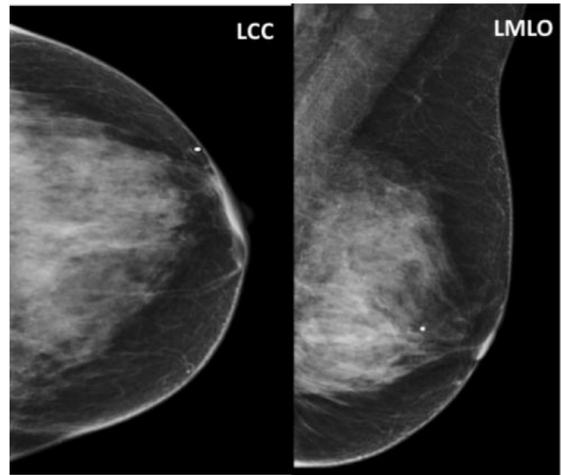
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FIG 6. Occult. Four months after a negative screening mammogram (A), the patient presented to an outside hospital with new palpable right supraclavicular and left axillary masses, which prompted a CT of the chest. Representative axial and coronal CT images demonstrated multiple bilateral pathologically enlarged right supraclavicular and left axillary lymph nodes suspicious for metastatic disease (solid circles) (B). Left axillary ultrasound (C) demonstrated morphologically abnormal axillary nodes with prominent eccentric cortical thickening and near loss of the fatty hila. Ultrasound guided core biopsy of one of the axillary nodes returned metastatic invasive ductal carcinoma. Breast MRI was subsequently performed (not shown) and showed segmental non-mass enhancement encompassing nearly the entire left upper inner quadrant.

The sensitivity of screening mammography declines from as much as 80% in mostly fatty breasts to as low as 30% in women with dense breast tissue.⁴² This is largely due to the masking effect in which dense fibroglandular tissue camouflages a cancer that would otherwise be detected. Dense breast tissue also confers an increased relative risk of breast cancer the exact extent of which is currently unknown.⁴²



A



B



C

FIG 7. Occult. A patient presented nine months after a negative screening mammogram (A) with a new palpable mass in the left breast, labeled with a BB on diagnostic CC and MLO projections (B). Targeted ultrasound of the palpable area (C) showed two adjacent irregular, hypoechoic masses with indistinct margins. Ultrasound-guided core needle biopsy returned invasive ductal carcinoma with ductal carcinoma in situ.

The knowledge of the potential pitfalls of screening mammography in women with dense breasts has not only raised awareness to the general public and radiologists of the increased risk of interval breast cancers, but has also led a call-to-action across state legislatures on breast density notification. Currently 31 states and the District of Columbia have passed various forms of a

law mandating inclusion of breast density in the mammography report and notification of breast density to patients. Another 5 states have introduced legislation at the time of this publication. Taking into account personal risk factors and provided information on breast density, women and their providers are better suited to make informed decisions regarding screening supplementation with breast ultrasound or MRI.

Conclusion

Interval breast cancers represent approximately 14.7% of all breast cancers in the screening population based on annual screening, at a rate of less than 8 in 10,000 screens.⁹ Current literature supports that interval breast cancers are diagnosed at a more advanced stage and have an overall worse prognosis compared to screen-detected breast cancers.⁵ Interval breast cancers are a reality for any radiology practice that interprets breast imaging studies. As such, auditing for interval breast cancers and analyzing factors which led to the cancer being diagnosed after a negative screening exam can result in imaging protocol or interpretation changes which may help decrease interval cancer occurrence.

We reviewed the four main subcategories of interval breast cancers: true negatives, false negatives, minimal sign, and occult. The majority of interval breast cancers are true negatives and the minority are false negatives, or “missed” cancers.^{5,11} The existence of interval cancers, and understanding their imaging manifestations, allows radiologists to address possible pitfalls and employ strategies which may help avoid an interval cancer in the future. It is always good practice to adhere to quality assurance measures, including MQSA guidelines. Interpreting radiologists should also consider their own limitations to minimize errors of interpretation and perception. Practicing by current standard of care, as related to breast density legislation, can help ensure women and their providers make informed decisions on screening for women with dense breasts. Although interval breast cancers are inevitable, reviewing why they occur and identifying ways to reduce their occurrence should be an ongoing goal of radiologists who interpret mammograms.

Declarations of Interest

None.

Supplementary data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1067/j.cpradiol.2018.08.010>.

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