False negative mammograms: what can we learn from them?

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Learning objectives

A comprehensive mammography quality assessment program involves many steps and one of them is the evaluation of the accuracy of image interpretation. This is known as medical audit.

Providing radiologists direct feedback with audit results may result in better performance.

One important performance indicator is the number of false negative exams.

Our objectives are:

- Discuss the importance of medical audit in a Breast Imaging Center;
- Present the findings of our false negatives exams and discuss the possible causes of errors;
- Present the results of these cases discussions that could possibly have a impact in team performance in the future.
Background

The screening with mammography has already proved to help reduce breast cancer mortality.

However to achieve this goal, the cancer detection rate must be within acceptable ranges.

Recently, scientific papers have discussed issues related to errors in cancer diagnosis. Among the reasons are the harms related to these errors and the fact that missed breast cancer was one of the most frequent cancer-related diagnostic errors implicated in malpractice claims.

Studies revealed a large number of preventable factors, with mammography-related variables most frequently cited.

Trying to prevent these errors, one of the most important actions is to have a comprehensive mammographic quality assessment program, although sometimes it is not simple to implement it in a regular basis.

This kind of program involves many steps and one of them is the evaluation of image interpretation accuracy. This is known as medical audit.

There are many reasons for performing medical audits and one of the most important is that audits are the most meaningful way to demonstrate one’s success of failure in detecting otherwise occult breast cancer, the most important indicator of mammography performance. Therefore, auditing may be a very useful method to provide feedback to a mammography facility about its success in meeting performance benchmarks.

There have been only few reports of mammography practices using auditing results in an attempt to improve interpretative performance and even though radiologists receive limited feedback regarding their interpretive accuracy in mammography, arrangements for more extensive feedback about their performance in mammography could be useful.

For example, radiologists in the United Kingdom National Health Program attend routine breast disease-related meetings and receive personal and group audit reports that include data on cancer detection rate, recall rate, and proportion of all women recommended for biopsy after mammography (the Breast Imaging Reporting and Data System category 4 or 5) who are diagnosed with breast cancer. They also attend a multidisciplinary course with specialist training at high-volume mammography screening sites. Such activities have been cited in an increase in invasive cancer detection rate. Hence, direct feedback with audit results and focused training may result in better performance.
Therefore in the absence of specific scientific data, it is reasonable to assume that there is a beneficial effect on interpretive skills of auditing with feedback to participating radiologists.

One important performance indicator is the number of false negative exams. Also important is the discussion among team members once a false negative exam is presented. The goal of this kind of discussion must have educational purposes.

By definition, a false negative mammogram is the one with a negative result (BI-RADS 1 or 2) and the patient then develops a breast cancer within 12 months after this negative mammogram. This definition is not without ambiguity because a false negative exam can be due to:

A "true" false negative mammogram: when a woman with a biopsy-proven breast cancer detected either on the regular screening mammogram or clinically (before the next regular scheduled screening mammogram - interval cancer) has a previous negative exam even when judged retrospectively (Figure 1 and Figure 2).

A missed breast cancer: when a woman with a biopsy-proven breast cancer detected either on the regular screening mammogram or clinically has a previous exam prospectively interpreted as negative for tumor. In this situation, the detected cancer is judged retrospectively to be visible (initially missed) on the prior screening mammogram (Figure 3 and Figure 4).

Reviewing these false negative exams among the team members in a regular basis is very important because knowing the causes can possibly result in radiologist performance improvement.

In such meetings for example we compare the current exam (which contains the lesion proved to be cancer) with the previous one, which has a normal result.

According to data from the Breast Cancer Detection Demonstration Project, the false-negative rate of mammography is approximately 8%-10%. After evaluating retrospective versus blinded interpretations of mammograms, others have concluded that the rate of missed breast cancers is as high as 35%.

In general, the main causes of errors can be classified in preventable and non-preventable causes.

Among the preventable causes, some are related to radiologist performance and others to technical issues.

The main causes of missing cancers are dense breast, poor positioning or technique, lesions location outside the field of view (Figure 5), detection errors, interpretation errors, subtle features of malignancy and slow changing malignancy. Taking all these causes in consideration, cancers are easily missed when they appear as focal asymmetry, area of
distortion or when they have a benign appearance. It was also reported that missed breast cancers are more likely to be detected as developing opacities compared to cancers detected at screening.

The team members must try to understand the reasons for the normal result in the previous exam (false negative): was the lesion visible; was the exam technically correct (technical errors account for 6% to 17% of the cases); was the lesion interpretation correct; what could be done to avoid this situation to repeat.

After these brainstorms, in many times actions are taken that have a positive impact in the daily practice, trying to improve the team performance.

If technical errors are omitted from analysis, false negative mammograms may basically be secondary to one of three factors that each constitute a third of the cases:

1. No mammographic features of malignancy ("true" false negative exam) (Figure 6 and Figure 7);
2. Subthreshold features of malignancy. Such findings have been termed nonspecific examples of which include mammographic findings suggesting normal islands of fibroglandular tissue, a few benign-appearing and/or slow growing lesions (cases difficult to judge even retrospectively) (Figure 8, Figure 9 and Figure 10);
3. Observer error, which mainly, results from detection error and interpretation error (missed lesions).

After reviewing the cases, we realized that microcalcifications evaluation is an important issue in our practice, since the majority of false negative exams observed involve this kind of finding. Not only we faced some misdetections especially small clusters in very dense breast tissues (Figure 11) but also misinterpretations particularly in slow growing lesions.

Comparing to exams older than the most recent one is very important because this can help detect slow growing lesions; malignant calcifications have been reported to be stable at mammography as long as 63 months (Figure 12).

Also we learned that changes after breast surgical procedures (mainly skin thickening and distortion) must be checked with special attention and again, it is mandatory in these patients to compare with previous exams older than the most recent one; sometimes with exams from 3 or 4 years earlier trying to detect slow growing lesions (Figure 13).

Because there is Radiologic Technologist Continuing Education Program on a regular basis in our facility, we do not find technical problems frequently.

To avoid errors related to technical issues, it is important to assure that not only a proper image is obtained, but also the additional images whenever needed. For example:

Magnification to evaluate microcalcifications;
Spot compression plus magnification to evaluate the margins of a nodular lesion.

To avoid errors related to medical performance, some additional important steps are mandatory:

Concordance of mammography and other diagnostic imaging methods like sonography and MRI;

Sometimes, the evaluation of a specific mammographic finding may distract the observer from noticing other significant areas of concern. This is referred to as satisfaction of search. Such pitfalls emphasize the importance of reviewing all breast tissue during each study as a screening exercise (Figure 14);

Also important is to have precise clinical information related to that specific exam and correlate it with the imaging findings (Figure 15);

Double reading of mammograms has been shown to increase the detection rate for breast cancer by up to 15%. Computer-aided detection (CAD) 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%.
Fig. 1: This 48 years old patient presented with a palpable lump in the left axillary tail. The current mammogram showed a faint focal asymmetry (A) and the sonography depicted a small hypoechoic mass with a hyperechoic halo (B). Biopsy result: Invasive Ductal Carcinoma. In the previous exam (performed 11 months earlier) an even fainter focal asymmetry was present but it was not noticed also because at that time the patient was asymptomatic (C). This case shows the important role of the clinical exam in elevating subthreshold mammographic findings to threshold. Without the clinical information probably the focal asymmetry would not be noticed.

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Fig. 2: This 43 years old patient presented with a small cluster of pleomorphic calcification in the left breast UOQ during a screening exam (B). The final assessment for this case was considered BI-RADS 4. Biopsy result: High Grade DCIS. In the previous exam performed 7 months earlier (A), no abnormal findings were noticed. Although no abnormal findings were visible in the previous exam, by definition, it is a false negative exam. It is not considered an interval cancer because it is still clinically occult.

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**Fig. 3:** This 61 years old patient presented with a spiculated mass in the UOQ of the right breast during a screening exam (A). Biopsy result: Invasive Ductal Carcinoma. In the previous mammogram (performed 11 months earlier) the mass could already be seen (B). This was considered a case of missed cancer. It was assumed that the lesion was partially obscured by the dense breast parenchyma, but still detectable. As we know, dense breast parenchyma lowers the sensitivity of mammography and sonography can sometimes improve cancer detection in this kind of breast tissue.

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**Fig. 4:** This 47 years old patient presented with a small cluster of pleomorphic microcalcifications in the UOQ of the left breast during a screening exam (B). Biopsy
result: DCIS The previous mammogram performed 9 months earlier already showed some faint pieces of pleomorphic calcifications (A), but this small cluster was not noticed by the interpreting physicians. Although the number of calcifications has increased during this 9 month period, this is probably a slow growing tumor. It is important to keep in mind that if the morphology of the microcalcifications is suspicious, a biopsy is mandatory even if it is stable because it can be a slow growing tumor. The team members considered this a case of missed cancer.

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**Fig. 5:** This 77 years old woman, presented for screening exam. She has previous benign breast biopsies. The current exam shows a small nodular lesion with spiculated margins in the inferior and very posterior aspect of the left breast (A and B). The cytological result was Carcinoma. In the previous exam (performed 11 months earlier) the lesion, although subtle, could already be seen (C and D). This anatomic area (near the inferior mammary fold) is difficult to image routinely and most of the time needs additional tailored images. Errors due to technical issues accounts for 6 to 17% of problems.

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**Fig. 6:** This 47 years old patient presented with a small cluster of pleomorphic microcalcifications in the right breast during a screening mammography (B). Biopsy result: Microinvasive Ductal Carcinoma. The previous exam performed 11 months before did not show any suspicious microcalcifications (A). This is a "true" false negative exam, which means that no missed lesion is noted even during a retrospective analysis.

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**Fig. 7:** This 42 years old patient presented with an abnormal PET-CT scan showing a nodular lesion with high SUV in the left breast. Because of this finding, she performed a mammogram which showed a nodular lesion with irregular margins in the lower quadrants of the left breast (A and B). Biopsy result: Invasive Ductal Carcinoma The previous mammogram performed 6 months earlier was considered normal by the team members even in a retrospective analysis (C and D). Therefore it is a "true" false negative exam.

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Fig. 8: This 59 years old patient presented with a spiculated mass in the inferior aspect of the right breast during a screening mammography (A, B and C). She had had plastic surgery many years before. Biopsy result: Tubulolobular Invasive Carcinoma. The previous exam performed 10 months earlier showed only the architectural distortion due to plastic surgery (D, E and F). Even though in the current exam the lesion is clearly seen, it is not obvious that the lesion was present in the previous exam. It is possible that the lesion was already there but the architectural distortion due to plastic surgery could have lead to a misinterpretation.

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Fig. 9: This 58 years old patient presented with an architectural distortion in the right breast UOQ (A). Although during the spot compression (B) the lesion seems to disappear, it was considered suspicious based on its appearance on the MLO view. Biopsy result: Invasive Ductal Carcinoma. In the previous mammogram (performed 6 months earlier) a possible suspicious finding was considered at the same location in the MLO view and a spot compression was made but no lesion was seen after the additional image (C and D). The team members considered that no lesion was present in the previous exam. This final conclusion was enforced by the fact that a spot compression was made in the same location as the now visible current lesion. Only in retrospect we can say where the lesion probably was. Probably this is an example of subthreshold features of malignancy where this lesion appears to be a normal island of fibroglandular tissue.
Fig. 10: This 50 years old patient presented with a cluster of pleomorphic microcalcifications in the UOQ of the left breast during a screening exam (B). She has a positive family history of breast cancer. Biopsy result: Invasive Ductal Carcinoma. The previous mammogram performed 5 months earlier already showed three tiny pieces of microcalcifications at the same location (A). By definition according to BI-RADS, a cluster of microcalcifications must have at least 5 pieces of microcalcifications. Therefore, the team members considered that the previous exam did not have abnormal findings although a very important lesson was learned: sometimes one should consider short term follow up (BI-RADS 3) for "clusters" with less than three pieces of calcifications, especially if the calcifications are new and without a clearly suspicious morphology. If the morphology is suspicious, then a biopsy is mandatory even if there are less than 5 pieces of microcalcifications.

Fig. 11: This 49 years old patient presented with at least four small clusters of pleomorphic microcalcifications in the inferior aspect of the right breast during a screening mammography (B). Biopsy result: DCIS. The previous exam performed 11 months earlier showed three clusters of microcalcifications only after a retrospective analysis (A). These calcifications were fainter and within dense breast tissue, therefore they were not detected. The team considered this a difficult case to judge because even though the
microcalcifications were seen in a retrospective analysis, it is not clear that they would be seen during a prospective analysis.

Fig. 12: This 64 years old patient presented with a small cluster of pleomorphic microcalcifications in the upper quadrants of the right breast during a screening exam (D). Biopsy result: High Grade DCIS The previous mammogram performed 11 months earlier already showed some calcifications, but probably due to the presence of scattered benign calcifications throughout the breast and its stability since 2008, this small cluster was not noticed (C). The team members considered this a difficult case to judge. Only during a retrospective analysis and after comparing with older exams it is possible to
clearly depict this cluster of calcification and realize that it had been changing since 2008 (A and B). It is important to remember though that, even in cases with multiple scattered calcifications, the radiologist must try to find specific clusters with suspicious morphology. Also, it is important to compare with exams older than the most recent one trying to detect subtle changes.

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Fig. 13: This 66 years old patient had a previous surgery due to benign lesion, 4 years before. In the current exam she presented with a palpable lump in the right breast UOQ, which turns out to be the same location of the previous surgery. The mammogram shows an architectural distortion associated with skin thickening (C). Biopsy result: Invasive
Lobular Carcinoma. Although subtle, in the previous mammogram (performed 7 months earlier) some important findings could already be seen. Compared with the previous exams, it is possible to notice that the skin thickening has been increasing since 2009 (A and B); a finding that in this clinical setting should had been taken into consideration, even though no sonographic changes were noticed at those times. It is well known that lesion detection in patients with previous breast surgery sometimes can be challenging due to the presence of architectural distortion secondary to the surgery. Our team concluded that this false negative exam was a case of misinterpretation because the architectural distortion and the skin thickening were considered to be related to the previous surgery, even though these findings have been worsening during the years.

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Fig. 14: This 73 years old patient presented for screening. She has a personal history of cancer in the left breast 6 years earlier and was treated with mastectomy and reconstruction on the left breast and a plastic surgery on the right. On the current exam we can see an irregular mass with spiculated margins in the posterior aspect of the outer quadrant of the right breast (A). In the left breast there is a large mass with coarse dystrophic calcification due to fat necrosis (A). Right breast biopsy result: Invasive Lobular Carcinoma. On the previous exam performed 6 months earlier, the lesion, although smaller, was already seen (B) but some issues must be considered in this particular case: First, there is a diffuse architectural distortion in the right breast especially in the posterior aspect, where the lesion is located, due to the plastic surgery and this finding lead to a misinterpretation. The lesion was in fact considered as part of the scar tissue. Second, there is a large distracting lesion in the left breast. This is often referred to as satisfaction of search, when a specific mammographic finding may distract the observer from noticing other significant areas of concern.

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Fig. 15: This 47 years old patient presented with a palpable lump in the UOQ of the right breast. The current mammography showed a dense breast parenchyma and only the spot compression depicted an architectural distortion (A). The sonography (not presented here) showed not one, but two suspicious hypoechoic irregular masses in this same location. A breast MRI (not presented here) was then performed and showed a third irregular mass in the superior aspect of this breast, which was only depicted during a second look ultrasound. Biopsy result: Invasive Ductal Carcinoma (All three lesions). The previous exam performed 10 months earlier did not show any suspicious finding. This is a case of interval cancer. This kind of lesion (architectural distortion) within a dense fibroglandular tissue sometimes is difficult to detect and the clinical finding is crucial.

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Imaging findings OR Procedure details

Between January 2011 and August 2012 our facility performed 20308 mammography exams. Eighty one patients with breast cancer diagnosed were selected. All of them had previous exams also made in our facility.

Among these patients, 18 had negative previous mammography and/or sonography exams (BI-RADS 1 or 2) done less than 12 months relative to the current exam.

The findings of the exams considered to be false negative were retrospectively analyzed and discussed among the team members.

The findings were classified as:

1. The lesion was not visible;
2. The lesion was visible, but it was not detected by the radiologist;
3. The lesion was detected by the radiologist, but the interpretation was incorrect.
Conclusion

To improve the standard of care in any Breast Imaging Center it is mandatory to have a comprehensive mammographic quality assessment program. In such program, some key performance indicators must be measured.

False negative mammograms are one of these indicators. It is important to know not only the number of false negative exams, but also the reasons of those events to occur because among these lesions, missed cancers will be found. Knowing the causes of missed lesions will guide the corrective actions.

The team members must be deeply involved, must have a professional and mature behavior to understand that the final goal is to improve the medical performance as well as patient care.

A Breast Imaging Center that does not collect and analyze those data cannot take appropriate steps to prevent those events to repeat.
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