Bahrain Medical Bulletin, Vol. 35, No. 1, March 2013

Dilemma of False Negative Mammograms in Breast Cancer Patients

Suhair Khalifa Al Saad, MB, ChB, FRCSI, CABS, CST*
Aicha Yamani, MB, ChB** Najeeb Jamsheer, MD, FRCR***

Background: Breast cancer is the most common cancer in women and the second cause of mortality after lung cancer. Mammography is an effective tool in detecting both clinically occult and palpable breast cancers. However, a good number of breast carcinomas may not appear on the mammogram. The false negative rate for conventional mammography worldwide is 10% - 30%[1]. There are very few studies addressing the results of mammography in Bahrain.

Objective: To estimate the incidence of false negative mammograms and the possible causes of false negative results in our group of breast cancer patients.

Setting: Salmaniya Medical Complex (SMC).

Design: Retrospective study.

Method: One hundred forty-six mammograms for breast cancer patients were reviewed from January 2000 to May 2011. The mammograms were divided into three groups according to the mammographic report, into malignant, suspicious and benign. Both malignant and suspicious (BIRADS 4, 5, & 6) reports were considered positive mammograms and were excluded from the study. The eleven mammograms, which were reported as benign (BIRADS 1, 2, & 3) and considered negative, were included in the study.

Result: The false negative mammograms were 11 (7.5%).

Conclusion: The incidence of false negative mammograms in this study is lower than international figures. False negative mammograms are more common in small sized tumors, located in upper outer quadrant, big breasts, single or un-experienced mammography reader and mostly in conventional than digital mammography.

Bahrain Med Bull 2013; 35(1):

---

* Assistant Prof. Arabian Gulf University & Consultant Surgeon
** Surgical Resident
*** Consultant Radiologist (Presently at Awali Hospital, BAPCO)
Departments of Surgery and Radiology
Salmaniya Medical Complex
Kingdom of Bahrain
Email: alsaadsuhair@gmail.com

Breast cancer is the most common cancer in women and the second cause of mortality after lung cancer[1]. It has been estimated that each year in North America, 40,200 deaths occur due to breast cancer and 239,300 new cases are diagnosed[2]. The incidence of advanced stage has decreased due to increased general awareness of the disease and early detection.

Mammography is an effective tool in detecting both clinically occult and palpable breast cancers. It has led to a dramatic improvement in breast cancer diagnosis and management since its introduction in 1970[2-4].

Although the mammogram can detect breast cancer in its early stages thus improving chances of successful treatment, there are still few breast carcinomas that may not be detected by mammogram.

BI-RADS is a breast imaging system for reporting; it is used by many radiologists including Bahrain. It was developed by the American College of Radiologists as a standard of comparison for rating mammograms and breast ultrasound images. The previously used systems lacked quantification and were not evidence-based. BI-RADS classification is very useful in the diagnosis of breast cancer[5].

A false negative mammogram is defined as the mammogram that is interpreted as normal, benign or probably benign (BI-RADS 1, 2 and 3) in a patient with cancer diagnosed by clinical evaluation and histopathological examination of the biopsy[6]. False negative mammograms are seen more with conventional mammograms. This incidence has decreased by more than one-third (from 30% to 19%) after the introduction of digital mammography[3,7].

The mammogram has a sensitivity that ranges from 70% to 90% and has been referred to as the best modality for breast cancer detection especially when combined with ultrasound[1,5]. Several randomized control trials demonstrated a significant decrease in breast cancer mortality when compared mammographically to non-mammographically screened women[8]. Unfortunately, there are few studies on the rate of false negatives and this makes it difficult to ascertain[9]. The accepted false negative rate worldwide is 10% - 30%, which may lead to delay in treatment and an increase in mortality and morbidity[1-3,10].

The aim of this study is to estimate the incidence and possible causes of false negative mammograms in our group of patients.

METHOD

One hundred forty-six mammograms for breast cancer patients were reviewed from January 2000 to May 2011. The mammograms were divided into three groups, according to the mammographic report, into malignant, suspicious and benign. Both malignant and suspicious (BIRADS 4, 5, & 6) reports were considered positive mammograms and were excluded from the study. The eleven mammograms, which were reported as benign (BIRADS 1, 2, & 3) and considered negative, were included in the study. They were evaluated regarding the type of mammogram done whether conventional or digital and the results of breast ultrasound, fine needle aspiration cytology, core biopsy if it was done and histopathology result of the surgical specimen. Details of the size, site, multifocality of the clinical lump and the presence of palpable axillary lymph nodes were also noted.

The patients were reviewed and evaluated for triple assessment (clinical evaluation by history and examination, radiological investigations by mammogram or breast ultrasound, FNAC or biopsy and histopathology). The patients had a breast lesion, which was either self-detected or reported as an abnormality on a screening mammogram.

Our radiologists used the **BI-RADS system,** which is a breast imaging system for data reporting for rating both mammograms and breast ultrasound images[7].

RESULT

Eleven (7.53%) mammograms were negative. Six of these patients were seen on or before year 2005 and five after 2005. Table 1 shows a detailed summary of the eleven patients: age, BI-RADS system report, possible cause for the mammographic findings, type of mammography, breast ultrasound, FNAC and histopathology.

Table 1: Summary of the Eleven Patients with False Negative Mammograms

Age	BI-RADS System	Possible Causes of false negative result	Mammogram	U/S Breast	FNAC	CORE BIOPSY	Histopathology
39	1	Very dense breasts with a lateral lesion within the axillary tail	Conven*	Not done	Mali**(C5)	Not done	Invasive ductal carcinoma (scirrhous)
44	2	Very dense big sized breasts	Conven*	Benign	Mali**(C5)	Not done	Invasive ductal carcinoma (NST)
32	2	Very dense breasts with lactational changes	Conven*	Not done	Mali**(C4)	Not done	Invasive ductal carcinoma with DCIS
41	2	Very dense breasts with retroglandular medial lesion	Conven*	Suspicious	Mali**(C4)	Not done	Invasive ductal carcinoma (NST)
43	2	Very dense breasts with a lateral lesion	Conven*	Not done	Mali**(C5)	Not done	Invasive ductal carcinoma (NST)
44	3	Tumor was lateral and the breasts were big & pendulous.	Conven*	Malignant	Mali**(C5)	Not done	Invasive ductal carcinoma (NST)
44	2	Dense breasts with well defined lateral small lesion	Conven*	Suspicious	Mali**(C4)	Not done	Invasive ductal carcinoma (NST)
63	1	Multifocal small central lesions missed due to improper compression technique	Conven*	Malignant	Mali**(C5)	Not done	Invasive ductal carcinoma (NST)
31	3	Very dense breasts	Digital	Benign	Mali**(C4)	B2 (benign)	Invasive Papillary carcinoma
54	1	Improper mammographic compression technique	Conven*	Malignant	Mali**(C5)	B5 (Mali**)	Invasive ductal carcinoma (NST)
53	2	Dense big sized breasts with multifocal retroglandular tumor	Conven*	Malignant	Mali**(C4)	B4 (Sus***)	Invasive ductal carcinoma (NST)

* Conventional ** Malignant *** Suspicious

NST: No special type, DCIS: Ductal carcinoma in situ, FNAC: C1: inadequate, C2: benign, C3: equivocal, C4: highly suspicious of malignancy, C5: malignant, **Core Biopsy**: B1: inadequate, B2: benign, B3: equivocal, B4: highly suspicious of malignancy, B5: malignant

Ten patients had conventional mammography and one had digital mammography. The BI-RADS system report is as follow: 1 (negative), 2 (benign) and 3 (probably benign). No microcalcification was found. Eight patients had breast ultrasound, two of which had negative ultrasound (benign) and the rest had either suspicious or malignant findings. All eleven patients had fine needle aspiration cytology (FNAC) and the results were in the range of C4 and C5. FNAC results were from C1 - C5. C1 means that the sample was inadequate to give an answer. C2 means benign and C3 probably benign, C4 means probably malignant and C5 is malignant[11].

Core biopsy was done only in three patients; two had malignant result and one was benign. The final histopathology was invasive ductal carcinoma in all patients except two; one had ductal carcinoma in situ and the other had invasive papillary carcinoma.

Figure 1 shows the locations of breast lesions on craniocaudal and oblique mammographic views.

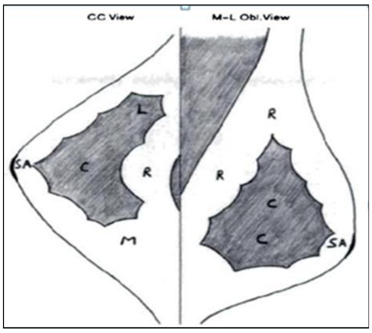

Figure 1: Key to Location of Lesions on Craniocaudal (left) and Mediolateral Oblique (right) Views of the Breast (L=Lateral, R=Retroglandular, M=Medial, SA=Subareolar, C=Central)

The possible causes of false negative mammograms in our patients were as follows: dense breasts in 8 (72.7%) patients and improper imaging technique in 3 patients. The latter was due to either poor quality, blurred images or big breasts and tumor being peripherally located and either partially or completely not included in the image, see table 1, figures 2, 3 and 4.

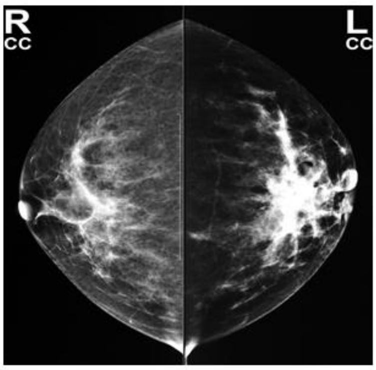

Figure 2: Bilateral Digital Mammographic Cranio-Caudal Views Showing Cancer of Left Breast, which Was Obscured by Dense Parenchymal Tissue. Histopathology Was Invasive Papillary Carcinoma

Figure 3: Poor Quality Mammographic Oblique View, Improper Compression. The Palpable Lump on the Left Was Overlooked

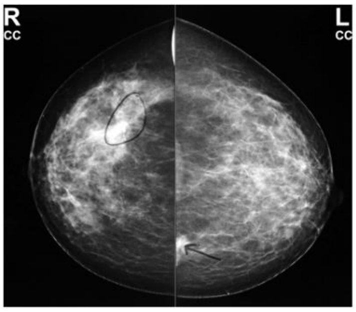

Figure 4: Bilateral Mammographic Cranio-Caudal Views in Big Dense Breasts. Right Breast Lesion (Circle), Left Posterior (Retro-glandular) Lesion (Arrow). Second Reading and Biopsy of the Overlooked Left Breast Lesion Confirmed Malignancy

Table 2 shows the site, size, multifocality of the tumor and lymph node status. It shows 6 (54.5%) patients had tumors less than or equal to 2 cm (T1). Four (36.4%) had tumor size between 2.5 cm and 4 cm. In 6 (54.5%) patients, the tumor was located in the lateral aspect of the breast (5 in UOQ, and 1 in LOU), 2 in the medial aspect (UIQ) and in 3 central (1 subareolar and 2 retroglandular). Three patients had positive axillary lymph nodes on histopathology. Multifocality on histopathology was positive in three patients. In five (45.5%) patients, the breasts were very big (weight approximately >1 kg each).

Table 2: The Size, Site of the Tumors, Lymph Node Status and Multifocality

Tumor Size	**Site of the Tumor (See figure 1)**	**Lymph Node Status**	**Multifocality**
2cm	Left UOQ (lateral)	Negative	Negative
4cm	Right UOQ (lateral)	Positive	Negative
1cm (all lesions)	Left UlQ (medial)	Negative	Positive
2cm	Right UIQ (medial)	Negative	Negative
> 5cm	Right UOQ (lateral)	Negative	Negative
1cm	Right UOQ (lateral)	Positive	Negative
1.5 cm	Right UOQ (lateral)	Negative	Negative
1 cm (4 lesions)	Left central (retroglandular)	Negative	Positive
4 cm	Left central (subareolar)	Negative	Negative
2.5 cm	Right LOQ (lateral)	Positive	Negative
3 cm (the main lesion)	Left central (retroglandular)	Negative	Positive

UOQ: upper outer quadrant, UlQ: upper inner quadrant, LOQ: lower outer quadrant

DISCUSSION

Although breast imaging has been performed since the 1920's, modern mammography has existed since 1970[12].

In conventional mammography, images are recorded on X-ray film. The radiologist views the film using a "light box". On the other hand, the digital mammography is captured using an electronic X-ray detector, which converts the image into a digital picture which is reviewed on a computer monitor. On digital mammography, magnification, modification, orientation, brightness and contrast could be done to help the radiologist see certain areas clearly[7,13,14]. In few studies, it was found that false negative results are higher in conventional than digital mammography[3,7].

In our group; ten had conventional mammography and one had digital mammography. Digital mammography was introduced in 2009; it might lower the false negative cases in SMC hospital in the future.

Dense breasts appear white on mammogram similar to malignant lumps and that makes breast density the strongest predictor of failure of mammogram[15]. The absence of mammographic abnormalities is also related to the small size of the tumor, histological characteristics, lack of microcalcifications and absence of desmoplastic reaction particularly in dense breasts[9].

Small malignant opacities within non-uniformly dense breasts might be mistaken for normal parenchyma or benign lesions[16]. Symptomatic patients with false negative mammograms are usually of young age and the lesion is often in the upper outer quadrant[17]. In our group of patients, eight were below 50 years of age and seven had dense breasts, which might explain why such tumors were missed. Early stage small cancers might be detected by US even in patients below 50 years of age and in those with dense breasts on mammography[18].

One study on 2,809 patients concluded that the diagnostic accuracy of mammography and US combined is more than mammography alone (0.91 versus 0.78)[19]. Cancer detection rate of US, if performed after mammography increases from 4.16% to 5.5%[20].

Postmenopausal women, on the other hand, have less dense breasts due to the breast aging process where fibroglandular tissue is replaced by fatty tissue. In these patients, mammography is able to detect malignant lumps appearing as white patches against the dark fatty tissue[15]. In Bahrain, women 50 years and above continue to have dense breasts which can contribute to difficult reading of mammograms.

The second possible cause of a false negative mammogram is faulty or improper imaging technique (figure 3)[21-25]. The tumor is located very peripherally (very lateral or superior) in the breast that it is not included in the tissue being compressed for imaging. Lesions in the posterior area are also frequently overlooked[16]. Figure 1 illustrates the areas of the breast seen on mammography. In our study, one patient had bilateral breast tumors; the tumor on the left was overlooked due to its location in the posterior area against the chest wall (figure 4).

Technical factors, such as parallel-plate compression distributes the thickness of breast tissue to improve image quality and prevent motion blurr[26]. The radiographer also has to make sure the entire breast is compressed between the film plates to avoid missing a possible peripheral malignant lump[27]. This may explain the cause of missing tumors in our patients number 8 and 10.

If the breasts were big and were not compressed evenly like in our patient number 2, 6 and 8, lateral or posteriorly located tumors will be missed.

False negative and false positive rates varied widely depending on the radiologist's experience, years and volume of work[28].

The rate of breast cancer detection increases when the mammograms are read by two radiologists. The second radiologist may detect abnormalities that have been either overlooked or misinterpreted by the first radiologist and vice versa[16,29]. Cancer detection has increased by 5% - 15% with independent double interpretation of the mammogram while sensitivity has increased by 5%[1,2,3,23,30,31]. Other studies recommended triple or even quadruple reading of screening mammograms[32].

A study evaluated breast MRI as a screening tool, which showed that it rarely identifies occult cancer and could be reported false negative in patients with suspicious findings on mammogram and US[33].

Another study showed that combining mammogram, US and MRI improves cancer detection for high-risk women[8].

A false negative screening mammogram result may lead to delay in diagnosis and further treatment of the affected women. Triple assessment includes teamwork between the breast surgeon, the radiologist and the cyto-histopathologist[34].

In this study, all patients were reevaluated by triple assessment. The mammographically reported BI-RADS 1, 2, or 3 were malignant by clinical evaluation and by FNAC or histopathology reports.

In a study, the combined test of mammography and core biopsy was more sensitive than any single test. It identified breast cancer in 9% compared with mammography[35].

Triple test which we are using in our assessment was also evaluated by many different studies and all showed that clinical evaluation, mammography, US, and FNAC or core biopsy were more accurate when combined than any single test alone[36-38].

CONCLUSION

The incidence of false negative mammograms in our study (7.53%) is lower than international figures (10%-30%).

Triple assessment is mandatory in breast lump evaluation to improve breast cancer detection.

Author contribution: All authors share equal effort contribution towards (1) substantial contributions to conception and design, acquisition, analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; and (3) final approval of the manuscript version to be published. Yes

Potential conflicts of interest: No

Competing interest: No. **Sponsorship**: No.

Submission date: 28 January 2012 **Acceptance date**: 29 December 2013.

Ethical approval: Research Committee, SMC, Ministry of Health.

REFERENCES

1. Brem RF, Baum J, Lechner M, et al. Improvement in Sensitivity of Screening Mammography with Computer-aided Detection: A Multiinstitutional Trial. AJR Am J Roentgenol 2003; 181(3): 687-93.
2. Destounis SV, DiNitto P, Logan-Young W, et al. Can Computer-aided Detection with Double Reading of Screening Mammograms Help Decrease the False-Negative Rate? Initial Experience. Radiology 2004; 232(2): 578-84.
3. Majid AS, de Paredes ES, Doherty RD, et al. Missed Breast Carcinoma: Pitfalls and Pearls. Radiographics 2003; 23(4): 881-95.
4. Brem RF, Hoffmeister JW, Rapelyea JA, et al. Impact of Breast Density on Computer-Aided Detection for Breast Cancer. AJR Am J Roentgenol 2005; 184(2): 439-44.
5. Berg WA, Blume JD, Cormack JB, et al. Combined Screening with Ultrasound And Mammography vs Mammography Alone in Women at Elevated Risk of Breast Cancer. JAMA 2008; 299(18): 2151-63.
6. Yankaskas BC, Schell MJ, Bird RE, et al. Reassessment of Breast Cancers Missed during Routine Screening Mammography: A Community-Based Study. AJR Am J Roentgenol 2001; 177(3): 535-41.
7. What is DMIST? Available at: www.cancer.gov/clinicaltrials/noteworthy-trials/dmist/what-is-dmist. Accessed on 12.6.2011.
8. D'Orsi CJ, Newell MS. On the Frontline of Screening for Breast Cancer. Semin. Oncol 2011; 38(1): 119-27.
9. Murphy IG, Dillon MF, Doherty AO, et al. Analysis of Patients with False Negative Mammography and Symptomatic Breast Carcinoma. J Surg Oncol 2007; 96(6):457-63.
10. Smith LF. Palpable Cancer of the Breast and Negative Mammography: The Ongoing Dilemma. J Surg Oncol 2007; 96(6):451-2.
11. Kocjan G, Bourgain C, Fassina A, et al. The Role of Breast FNAC in Diagnosis and Clinical Management: A Survey of Current Practice. Cytopathology 2008; 19(5): 271-8.
12. Benefits and Risks of Mammography. Available at: www.imaginis.com/breast-health/benefits-and-risks-of-mammography. Accessed on 10.6.2011.

13. Lewin JM, D'Orsi CJ, Hendrick RE, et al. Clinical Comparison of Full-field Digital Mammography and Screen-film Mammography for Detection of Breast Cancer. AJR Am J Roentgenol 2002; 179(3): 671-7.
14. Digital Mammography. Available at: www.southtownsradiology.com/digital-mammography.html. Accessed on 1.6.2011.
15. Berg WA, Gutierrez L, NessAiver MS, et al. Diagnostic Accuracy of Mammography, Clinical Examination, US, and MR Imaging in Preoperative Assessment of Breast Cancer. Radiology 2004; 233(3): 830-49.
16. Bird RE, Wallace TW, Yankaskas BC, et al. Analysis of Cancers Missed at Screening Mammography. Radiology 1992; 184(3): 613-7.
17. Murphy IG, Dillon MF, Doherty AO, et al. Analysis of Patients with False Negative Mammography and Symptomatic Breast Carcinoma. J Surg Oncol 2007; 96(6): 457-63.
18. Corsetti V, Houssami N, Ferrari A, et al. Breast Screening with Ultrasound in Women with Mammography-negative Dense Breasts: Evidence on Incremental Cancer Detection and False Positives, and Associated Cost. Eur J Cancer 2008; 44(4): 539-44.
19. Berg WA, Blume JD, Cormack JB, et al. Combined Screening with Ultrasound and Mammography vs Mammography Alone in Women at Elevated Risk of Breast Cancer. JAMA 2008; 299(18): 2151-63.
20. Pistolese CA, Perretta T, Cossu E, et al. Value of the Correct Diagnostic Pathway through Conventional Imaging (Mammography and Ultrasound) in Evaluating Breast Disease. Radiol Med 2011; 116(4): 584-94.
21. Huynh PT, Jarolimek AM, Daye S. The False-negative Mammogram. Radiographics 1998; 18(5): 1137-54; quiz 1243-4.
22. Meeson S, Young KC, Wallis MG, et al. Image Features of True Positive and False Negative Cancers in Screening Mammograms. Br J Radiol 2003; 76(901): 13-21.
23. Birdwell RL, Ikeda DM, O'Shaughnessy KF, et al. Mammographic Characteristics of 115 Missed Cancers Later Detected with Screening Mammography and the Potential Utility of Computer-aided Detection. Radiology 2001; 219(1): 192-202.
24. Buist DS, Porter PL, Lehman C, et al. Factors Contributing to Mammography Failure in Women Aged 40-49 Years. J Natl Cancer Inst 2004; 96(19): 1432-40.
25. Mandelson MT, Oestreicher N, Porter PL, et al. Breast Density as a Predictor of Mammographic Detection: Comparison of Interval - and Screen-detected Cancers. J Natl Cancer Inst 2000; 92(13): 1081-7.
26. Kavanagh AM, Cawson J, Byrnes GB, et al. Hormone Replacement Therapy, Percent Mammographic Density, and Sensitivity of Mammography. Cancer Epidemiol Biomarkers Prev 2005; 14(5): 1060-4.
27. Mawdsley GE, Tyson AH, Peressotti CL, et al. Accurate Estimation of Compressed Breast Thickness in Mammography. Med Phys 2009; 36(2): 577-86.
28. Woodard DB, Gelfand AE, Barlow WE, etal. Performance Assessment for Radiologists Interpreting Screening Mammography. Stat Med 2007; 26(7): 1532-51.
29. Hukkinen K, Kivisaari L, Vehmas T. Impact of the Number of Readers on Mammography Interpretation. Acta Radiol 2006; 47(7): 655-9.
30. Harvey SC, Geller B, Oppenheimer RG, et al. Increase in Cancer detection and Recall Rates with Independent Double Interpretation of Screening Mammography. AJR Am J Roentgenol. 2003; 180(5): 1461-7.

31. Thurfjell EL, Lernevall KA, Taube AA. Benefit of Independent Double Reading in a Population-Based Mammography Screening Program. Radiology 1994; 191(1): 241-4.
32. Elmore JG, Brenner RJ. The More Eyes, the Better to See? From Double to Quadruple Reading of Screening Mammograms. J NatlCancer Inst 2007; 99(15): 1141-3.
33. Yau EJ, Gutierrez RL, DeMartini WB, et al. The Utility of Breast MRI as a Problem-Solving Tool. Breast J 2011; 17(13): 273-80.
34. Jan M, Mattoo JA, Salroo NA, et al. Triple assessment in the diagnosis of breast cancer in Kashmir. Indian J Surg. 2010; 72(2):97-103.
35. Jensen A, Rank F, Dyreborg U, et al. Performance of Combined Clinical Mammography and Needle Biopsy: A Nationwide Study from Denmark. APMIS 2006; 114(12): 884-92.
36. Ahmed I, Nazir R, Chaudhary MY, et al. Triple Assessment of Breast Lump. J Coll Physicians Surg Pak 2007; 17(9): 535-8.
37. Beattie A. Detecting Breast Cancer in a General Practice – Like Finding Needles in a Haystack? Aust Fam Physician 2009; 38(12): 1003-6.
38. Coolen A, Leunen K, Menten J, et al. False-negative Tests in Breast Cancer Management. Neth J Med 2011; 69(1): 324-9.