Subtle Finding Analysis in False Negative Results on Screening Mammogram and US: An Institute Study

Pornpim Fuangtharnthip, M.D.*, Naparat Viravan, M.D.*, Wilaiporn Bhothisuwan, M.D.*, Tamnit Augsusinha, M.D.**

*Department of Radiology, Faculty of Medicine Siriraj Hospital, **Thanyarak Breast Center, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

ABSTRACT

Objective: To determine the percentage and evaluate the subtle findings of false negative results on mammogram and ultrasonography (US) screening.

Methods: A retrospective study involved twelve breast cancer patients who had a negative result of malignancy on both the initial mammogram and US with an equal number of benign or negative cases mixed. One radiologist randomly reviewed all mammograms and US images without any knowledge of the final diagnosis, noting mammographic characteristics of breast density composition, lesion type, size, and morphology according to (BIRADS-LEXICON).

Results: The incidence of prospectively false-negative rates was 7.3% (7 of 9,582). The type of subtle findings characterized on the prior mammogram included a macrolobulated mass in one of seven lesions (14.3%), a macrolobulated mass with amorphous microcalcification in one (14.3%), amorphous microcalcification alone in one (14.3%), and asymmetrical breast density on one-view mammogram in two (28.6%). There were two of seven lesions with negative mammogram and positive US findings.

Conclusion: There is a small subset of breast cancer, called subtle findings, which can be perceptible but sometimes there are no definite malignant findings on the image interpretation. An understanding of the characteristics of subtle findings in false-negative screens may be a valuable aid in increasing the sensitivity of breast cancer detection.

Keywords: Subtle findings; False negative; Mammogram; Ultrasonography; Breast cancer

Mammography is so far the standard of reference for early detection of breast cancer; however, 10%-30% of breast cancer under going mammogram screening may not be detected. According to the data of the Breast Cancer Detection Demonstration Project, the false-negative rate of mammography is approximately 8%-10%.[1] After comparing a retrospective evaluation versus blinded interpretations of mammograms, it has been concluded that the rate of missed breast cancer is as high as 35%.[2] 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.[2-3] Subtle or indistinct features of malignancy are one of cancerous findings which are difficult to detect and interpret. These features include areas of architectural distortion, small groups of amorphous or punctated microcalcifications, focal asymmetrical breast density, and relatively well circumscribed masses. Recent studies have emphasized the use of alternative modalities such as ultrasonography (US) to detect and diagnose breast cancer, including the subtle findings. In our study, we defined "subtle features of malignancy" as the perceptible normal or benign findings on a screening mammogram and US where cancer later developed in the same areas. The purpose of our study was to determine the percentage and retrospectively review mammographic and ultrasonographic findings of subtle findings in false-negative results in the screening program.

MATERIALS AND METHODS

Screening mammogram and US records (9,582 records) from Thanyarak Breast Center from January 2000 to December 2002 were searched to identify patients with breast cancer. Among these, 17 cases were identified: a) proven-biopsy cases of breast cancer; b) had negative results of malignancy on an initial mammogram and US (BI-RADS categories 1 and 2); c) had completed mammogram (both craniocaudal (CC) and mediolateral (MLO) views) and US films on both the initial and subsequent studies; and d) had a subsequent mammogram or follow-up US at least 12 months between the initial and the latest mammogram. Five of the 17 cases were excluded from our study because of incomplete original mammographic and US films.

A radiologist of 4-year experience in breast imaging (P.F.) reviewed all mammographic and US images of twelve selected patients by mixing randomly negative or benign films on equal numbers of cases without limited reviewing time. The reviewer knew that half of the examinations had breast cancer and another half had benign or negative results without the awareness of histopathologic results. All cases were reviewed with the original mammographic and US films and the details of

TABLE 1. Seven cases with subtle findings on initial and subsequent mammogram and US based on BI-RADS categories and pathological results

Patient no.	On screens			On Diagnosis	Interval		Pathologic	
	Mammogram	US		Mammogram	US		Time (months)	Result
		Findings	Size (mm.)		Findings	Size (mm.)		
1	Asymmetrical breast density	Negative	-	Architectural distortion	Ill-defined low echoic mass	4x3	16 m	IDC,W
2	Asymmetrical breast density	Negative	-	Spiculated mass + Pleomorhpic micro Ca+	Ill-defined low echoic mass+Ca*	3.5x3	16 m	IDC,M
3	Amorphous Ca*	Negative	-	Amophous microCa+	Ill-defined low echoic mass (T>W)	8x6	15 m	IDC,M
4	Macrolobulated mass	Macrolobulated Oval low mass	6x6	Spiculated mass	Irregular low echoic mass (T>W)	10x5	14 m	IDC,W
5	Negative	Oval low echoic mass	4x2	Pleomorhpic clustered microCa + increased density mass	Irregular low echoic mass	9x8	13 m	IDC,P
6	Negative	Oval low echoic mass	3.6x3.9	Negative	Irregular low echoic mass	9.1x5.7	14 m	IDC,W
7	Macrolobulated mass with amorphous microcalcification	Oval low echoic mass+ Ca+	10x9	pleomorphic clustered microCa + increased density mass	Irregular low echoic mass+ Ca+	10x9	18 m	IDC,M

NOTE: IDC, W= Invasive ductal carcinoma, well-differentiated: IDC, M= Invasive ductal carcinoma, moderately-differentiated: IDC, P= Invasive ductal carcinoma, poorly-differentiated: Ca+= calcification

examination were assessed with a magnifying lens. All lesions were categorized according to the American College of Radiologist Breast Imaging Reporting and Data System [BI-RADS][4] for masses and calcifications into BI-RADS category 0-6. BI-RADS categories 1 and 2 indicated normal or benign findings and categories 4, 5 and 6 indicated abnormal findings. The use of category 3 (probably benign) was discouraged. However, the data showed no case of category 3 on the prior mammograms.

The rationale was that the findings were negative of malignancy on prospective screening but they were interpreted retrospectively by a radiologist that they required immediate work-up which were called false-negative results or missed cancer.[4] Seven of twelve cases were classified as prospectively false-negative reports; these cancers can be visible in retrospect on the prior screening mammogram. Five of twelve cases were excluded from our study. Three cases were excluded because they were classified as the interval cancer (n=3) which cannot be seen on the screening mammogram even retrospectively but defined as cancer in patients presented with clinical findings before the next scheduled mammogram. The other two cases were excluded because of having suspicious findings (BI-RADS 4) with negative pathologic results for malignancy (n=2) on the first biopsy and positive malignancy on the re-biopsy. The perceptible findings on the prior mammogram were analyzed according to the finding type, diameter, location and depth within the breast. Breast density composition was also recorded. Each finding was categorized by using the BI-RADS lexicon for masses and calcification and BI-RADS category 3-5.[5] All visible findings on the prior mammogram in seven prospectively false-negative reports were defined as subtle findings of malignancy on data analysis.

To assess all lesions, the data of the patient age, lesion location, breast tissue composition, mammographic and ultrasonographic findings (bases on ACR BI-RADS classification) and pathological results (cancer type and grade) were collected. All malignant cases were proven by biopsy with cancer type and grading.

The quality of film such as exposure and position was subjectively evaluated as poor, fair or good.

RESULTS

The incidence of a prospectively false negative rate in our study was 7.3% (7 of 9,582). The mean age of seven detectable-cancer patients was 47.8 years old [ranged 44-63 years old], with four (44.4%) patients aged 40-49 years, two (22.2%) aged 50-59 years, and one (11.1%) aged 60 years or older.

Breast density (on the basis of BI-RADS classification) showed scattered fibroglandular breasts in three (42.8%); heterogenously dense breasts in three (42.8%); and, extremely dense breasts in one (14.3%).

Table 1 shows types of lesions characterized on the prior mammogram including one mass (14.28%); two cases of asymmetrical breast density on one-view mammogram (28.8%) (Fig. 1); one case of mass with microcalcification (14.3%); one microcalcification alone (14.3%) (Fig. 2), and another two cases of negative mammogram (28.8%); four of seven patients (57.1%) had extremely dense and heterogenously dense breasts.

Regarding the morphology and distribution characteristics of the masses, the margin and shape of all seen masses (n=2) on the mammogram were well-defined and macrolobulated.

Regarding the characteristics of microcalcification on the initial mammogram, the morphologic pattern of all lesions were amorphous microcalcification (n=2) with clustered distribution patterns.

The mean interval between mammographic examinations was 15.14 months [ranged 12-18 months].

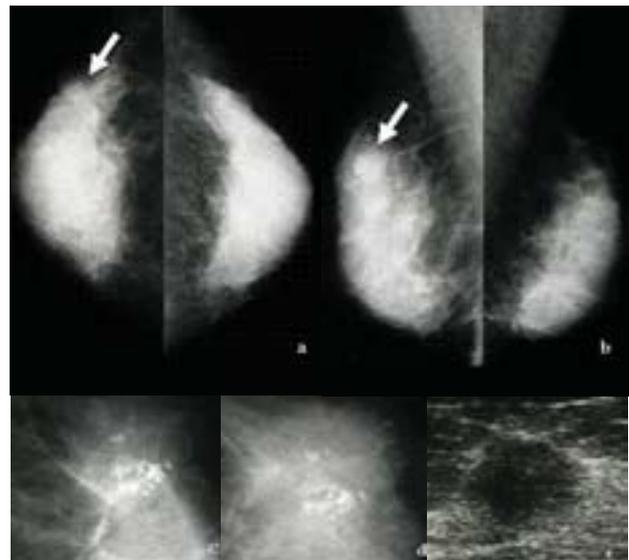The mean maximal lesion size on the prior US
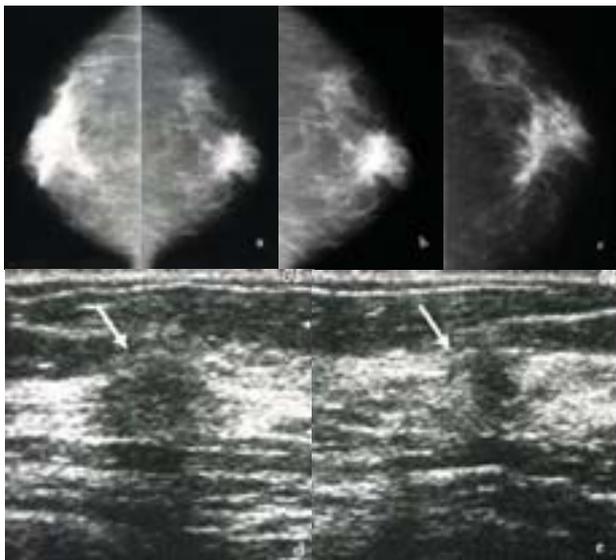
Fig 1. Subtle finding: asymmetric density: Bilateral craniocaudal (a.) mammogram demonstrates asymmetrical density (arrow) at 10 o'clock on the left breast on the prior mammogram and (b) changes to an architectural distortion (arrow) 16 months later; (c); a finding that become more evident with mirror image interpretation. The ultrasonographic finding was an ill-defined low echoic mass (d, e (arrow)) and the biopsy reveals invasive ductal carcinoma, well-differentiated.

Fig 2. Subtle findings:a 51-year-women with amorphous microcalcification on the screening mammogram: Bilateral craniocaudal (a) and mediolateral (b) mammograms show amorphous microcalcification (arrow) at 1 o'clock on the right breast (spot magnified view: c) changing to pleomorphic microcalcification (spot magnified view: d) 18 months later. The ultrasonographic finding was negative on the initial US which became an ill-defined low echoic mass (e) and the biopsy reveals invasive ductal carcinoma, moderately-differentiated.

was 3.41 mm (ranged 0-10 mm: negative US =3). The mean maximal lesion size on the subsequent US was 7.6 mm (ranged 3.5-10 mm). As for the initial ultrasonographic findings, the most common pattern was small oval well-defined low echoic masses (n=4) which became enlarged and ill-defined margins on the diagnostic mammogram. All hard-copy films were good in position and exposure.

DISCUSSION

Most publications reported variable rates of missed cancer on screening mammogram up to the optimized images based on different techniques of mammogram on average of 10 to 58 %[2-8] which means using only mammogram for the detection of breast cancer is incomplete. Recent studies have emphasized the use of ultrasonography (US). Not only that it helps the detection and diagnosis of breast cancer especially in dense breast composition,[9-12] but it also predicts the possibility of malignancy in a well-circumscribed mass, and to make decisions or take an intervention such as a biopsy or planning a short-term follow-up time on the suspicious masses. US is also helpful in to evaluate asymmetric densities seen in mammography, as it can identify the density whether it is a breast tissue or a true mass. In our study, we studied both the mammogram and US and found an incidence of missed breast cancer (= 7.3%) which was less than in some previous studies,[2-8] which were performed only on screening mammograms. Also we found that US is very helpful in characterizing the mammographic abnormality, especially asymmetrical density seen on only one view. One reason for the less missed cancer rate in our study was that we always use adjunctive US because of higher percentage of dense breast tissue composition in Thai women. However, we cannot strongly conclude that the additional US reduces the rate of missed cancer, since we found only one positive case on US that is negative on

the diagnostic mammogram. However, we still believe that any patient with dense breast parenchyma, palpable mass and negative mammographic findings should undergo US for further evaluation of the mass.

False-negative findings on screening mammograms contribute to increased breast cancer mortality rates.[4-8] Bird et al.[13] found that 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.[14] found that cancers missed at screening mammography were significantly lower in density and more often seen on only one of two views than detected-cancers. In a review of false-negative cancers in Malmo Screening Trial, Ikeda et al.[15] found that 10 of 94 cases were missed due to observer's error and 21 of 94 showed subtle signs of malignancy. The subtle or indistinct features of malignancy are one of the most challenging breast cancers to diagnose and most often leads to interpretation errors. These subtle findings include areas of architectural distortion, tiny groups of amorphous or punctated microcalcifications, focal asymmetric densities, dilated ducts, and relatively well circumscribed masses.[1,16] Sickles found that only 39% of nonpalpable cancer showed classic signs, including spiculate masses and linear microcalcifications.[17] In our study, the subtle findings of most breast cancers were classified in asymmetrical breast density on one view; however, no additional view was done on the screens. Others are amorphous microcalcifications and macrolobulated well-defined masses. Asymmetrical breast density on one view is one of the problematic findings to differentiate real tumor and summation breast tissue. Pearson et al. recommended step-oblique mammography to help the assessment of the noncalcified density and grouped microcalcifications identified on only one standard mammographic projection.[17] The spot compression and rolled views are helpful to characterize and localize the densities seen on the craniocaudal view alone. Also, any areas of microcalcifications should be evaluated with

magnification views to accurately define their morphologic features as well as their number and distribution. Although the usefulness of US in verifying the location of a mass seen on only one view of the mammogram is found, US cannot detect all abnormalities because of some sonographically nonvisible cancerous tumors; even some lesions can be mammographically detected. However, US is helpful in predicting the possibility of malignancy in a well-circumscribed mass. On the basis of an US evaluation, simple cysts seen on US are benign findings. Solid lesions that are smooth, elliptic and wider than their height are probably benign. However, masses that have irregular margins, are markedly hypoechogenic and taller than their width are suspiciously malignant.[18] A nonpalpable circumscribed mass on mammography that is likely a benign solid feature on US may be reevaluated at a short interval time.[19] If, however, the mass is seen on US as a solid lesion with worrisome features, such as a "taller-than-wide" shape or irregular margins, biopsy is indicated.[19] Moreover, any increase in the size of a circumscribed, noncystic mass should also prompt further evaluation with a biopsy. We believe that not only US will help radiologists to characterize the mass but also help us to determine the benignity of the suspicious masses in the follow-up of the US findings. For example, any circumscribed, noncystic mass with an increase in size in the follow-up US should prompt further evaluation with a biopsy; any stable circumscribed, noncystic mass in the follow-up US should be classified as benign. As we know, even an additional US can depict an additional tumor, there are some groups of cancer which supplement US alone without mammography was problematic such as intraductal cancer (DCIS) and no value in fatty breasts. In our opinion, the use of combined US and mammography was of higher value in the detection of breast cancer, especially in problematic cases and dense breast tissue composition.

Invasive lobular carcinoma accounts for approximately 8%-10% of breast cancers and it is easily missed because it is commonly manifested as a focal asymmetric density, an area of architectural distortion, and negative mammographic findings.[20] 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. Fortunately, we did not find any invasive lobular carcinoma in our cases. However, negative US findings at the site of a suspect asymmetric density should not preclude biopsy.

Another subtle finding which can give false negative results is dilated ducts infrequently associated with malignancy. Patterns of ductal dilatation that suggest malignancy include a unilateral solitary dilated duct and dilated ducts associated with micro calcifications or in a nonsubareolar location.[21-23]

Lack of perception is one of the major causes of missed breast cancers related to radiologist error which occurs when the lesion is included in a standard mammogram but not recognized by the radiologist. Many subtle findings causing a lack of perception, due to less visible lesions and difficult to perceive, are small nonspiculated masses, areas of architectural distortion and asymmetry, and small clusters of amorphous or faint microcalcifications. To avoid perception error, images should be reviewed as mirror images, with mediolateral oblique and craniocaudal images placed together and comparing like areas on the side-by-side images to identify any focal asymmetric

density or low-density mass on the corresponding view in the same arc from the nipple. The additional views may be needed to verify the presence of a true lesion. We believe that even though all images are reviewed as mirror images with additional views on the suspicious lesions, one of the important things to reduce the rate of lack of perception is a careful attention to mirror image abnormalities or focal asymmetric densities to identify the lesion. The characterization of the detected lesion may help the radiologists to place them on the actual lexicon BI-RADS classification such as evaluation of margin of mass. The spot compression image is one of the best techniques of imaging to evaluate the margins of the mass. A mass that appears relatively smooth may be indistinct or microlobulated on spot compression images. Characterization of any lesions that is identified on screens should be carefully evaluated based on diagnostic mammographic findings and not on screening findings alone. In our opinion, though we did not analyze the causes of missed breast cancer, worrying about observer's error and incorrect interpretation in mammographers will reduce the rate of missed cancer and increase the sensitivity of detection and accuracy of breast cancer diagnosis

In summary, it is very important for both referring physicians and women who undergo mammography to understand that neither mammograms nor the experts who interpret mammograms are perfect. Although an understanding of the characteristics of subtle findings in false-negative screens may be of valuable aid in increasing the sensitivity of breast cancer detection. There is a small subset of breast cancers, called subtle findings, which can be perceptible but sometimes have no definite malignancy findings on image interpretation. Nevertheless, we believe that failure to identify the subtle findings prospectively does not guarantee these interpretations below the reasonable standard of care.

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บทคัดย่อ

การวิเคราะห์ลักษณะภาพความผิดปกติในผู้ป่วยมะเร็งเต้านมที่มีผลการคัดกรอง ทั้งจากแมมโมแกรม และอัลตราซาวน์เป็นผลลบลวง

พรพิมพ์ เฟื่องธารทิพย์ พ.บ.*, นภารัตน์ วีรวรรณ พ.บ.*, วิไลพร โพธิสุวรรณ พ.บ.*, ธรรมนิตย์ อังศุสิงห์ พ.บ.**

*ภาควิชารังสีวิทยา, คณะแพทยศาสตร์ศิริราชพยาบาล, **ศูนย์กันยรักษ์, โรงพยาบาลศิริราช, มหาวิทยาลัยมหิดล, กทม. 10700, ประเทศไทย*

จุดประสงค์: เพื่อประเมินความชุกและวิเคราะห์ลักษณะภาพความผิดปกติในผู้ป่วยมะเร็งเต้านมที่มีผลการคัดกรอง ทั้งจากแมมโมแกรม และอัลตราซาวน์เป็นผลลบลวง

วิธีการ: การศึกษาย้อนหลังในผู้หญิง 7 คน (จากการศึกษาใน 9,582 คน) ที่มีผลการคัดกรองมะเร็งเต้านมโดยทั้งแมมโมแกรมและอัลตราซาวน์เป็นผลลบลวง ภายในช่วงเวลาไม่เกิน 18 เดือน ก่อนที่จะตรวจพบมะเร็งเต้านม แต่หลังจากที่นำภาพแมมโมแกรมและอัลตราซาวน์มาวิเคราะห์อีกครั้ง พบลักษณะความผิดปกติ โดยผลการตรวจทางแมมโมแกรมและอัลตราซาวน์จะอ้างอิงตาม Breast Imaging Reporting and Data System โดยแบ่งเป็น Category 0 - 6 ข้อมูลเกี่ยวกับวิธีการตรวจพบ ผลทางพยาธิวิทยา และขนาดของก้อนเนื้อ ได้ถูกนำมาวิเคราะห์

ผลการศึกษา: อุบัติการณ์การเกิดผลลบลวง ในสถาบันของเราเท่ากับ 7.3% ในการศึกษานี้พบผู้หญิงไทยมีผลลบลวงทั้งหมด 7 คน โดยมีลักษณะความผิดปกติในแมมโมแกรมเป็นแบบ Macrolobulated mass 1 คน, Macrolobulated mass with amorphous microcalcification 1 คน, amorphous microcalcification 1 คน, asymmetrical breast density 2 คน และไม่พบความผิดปกติจากแมมโมแกรม แต่อัลตราซาวน์ผิดปกติ 2 คน

สรุป: มะเร็งเต้านมบางชนิด สามารถแสดงลักษณะภาพความผิดปกติ แต่ลักษณะภาพของความผิดปกติของมะเร็งอาจไม่ชัดเจนทั้งในแมมโมแกรมและ/หรืออัลตราซาวน์ ดังนั้น ความรู้และความเข้าใจเกี่ยวกับลักษณะความผิดปกตินี้จะมีประโยชน์ และสามารถช่วยเพิ่มอัตราการตรวจพบมะเร็งเต้านมได้