ORIGINAL RESEARCH

Diagnostic performance in detecting breast pathology on combined mammography and ultrasound

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Received: 12March, 2023 Accepted: 18April, 2023

ABSTRACT
Participants were women with no risk for breast cancer who presented for routine mammography and provided written informed consent. Each participant underwent mammography followed by ultrasound, both studies performed by the same Radiologist. 460 women underwent screening mammogram and adjunct ultrasounds were examined. 18 patients underwent tissue biopsies and histopathological correlation. Women had both ultrasound and mammography were part of the study. For the detection of all breast pathologies, the addition of ultrasound to mammography produced a statistically higher sensitivity with an improvement in sensitivity by 50%. However, this increased sensitivity is accompanied by a drop in specificity by 5%.
Keywords: Breast pathology, mammography and ultrasound

Introduction
Gonzaga *et al* in 2010 studied the use of ultrasound as an adjunct to mammography in assessment of breast tumors in 80 women, most women coming under the age group of 20 to 39. Of the 80 palpable breast masses, ultrasound correctly diagnosed the presence of masses in 74 cases; ultrasound had 100% sensitivity and 100% specificity for differentiating purely cystic masses from solid masses and 100% diagnostic accuracy for cystic masses nearly about 100 percent for fibroadenoma. The report concluded ultrasound being a relatively inexpensive and a more accessible modality for evaluating palpable breast masses should be the first line investigation especially in women below 30 years and as an adjunct to mammography in women over 30 years when mammography is available[1].

Ultrasound has been associated with increased false positive diagnoses.Corsetti V *et al* in 2004 reported that additional investigations or surgery due to false positive ultrasound in women with dense breasts was 5.5% which included 61 surgical biopsies in 0.84% of screens with benign outcomes. Surgical biopsy due to false positive ultrasound was 1% of screening examinations in women <50 years and 0.6% in women 50 years and older and benign surgical biopsies were seen in 4.5% and 0.9% of ultrasound detected lesions[2].

Berg *et al* in is study in 2006 concludedthat adding ultrasound as an adjunct to mammography increased the false positives from 4.4% to 10.4% PPV[3].

Ohlinger *et al* in 2006 reported that for ultrasound the false positive rate was 1.1% and 0.6% for mammography. When both methods were combined, the rate of unnecessary open biopsies was increased to 1.6%[4].

Nelson *et al* in 2009 suggested that false positive results due to mammography screening were 0.9 to 6.5%. The false negative results and biopsy rates were less among 40-49 years with 1 per thousand and 9.3 per thousand above 49 years; however use of additional imaging was highest with 84.3 per thousand. False positives for invasive and insitu breast cancer on screening mammography was between 0.07 to 0.73 per thousand women years[5,6].

Methodology
Study design: Prospective, observational study.

Study Population: 460.

Summary of Methodology

460 women underwent screening mammogram and adjunct ultrasounds were examined. 18 patients underwent tissue biopsies and histopathological correlation. Women had both ultrasound and mammography were part of the study. Mammography was performed with standard craniocaudal and medial lateral oblique views and a consultant radiologist would review the Images on 5 MP Barco monitor and then perform the ultrasound. A combined BIRADS was given at the end of both studies and retrospectively separate BIRADS were given on mammography and ultrasound with BIRADS 1 being normal, BIRADS 2 benign disease, BIRADS 3 atypical or intermediate but probably benign, grade 4 suspicious for malignancy and Grade 5 high suspicious for malignancy. Clinical and histopathological data was collected by reviewing the care 21 software and recorded on the excel sheet. Fine Needle Aspiration Cytology and excision biopsies were performed. For the purpose of the study any lesion which was given BIRADS 4 and 5 were taken as probability of cancer, BIRADS 3, 4 and 5 were considered as pathology, Lesions with BIRADS 3 were subjected to short interval follow up and few lesions had surgical excision. For easy understating of the data we have divided the radiological imaging according to the type of investigation (M= Mammography and U= ultrasound) and BIRADS grade (0 to 5). These were compared with follow up and final histopathological diagnosis. Statistical analysis was performed with 2 x 2 contingency table. Fisher's exact positivity test was used to know the association between mammography and ultrasound in breast cancer screening by using 2 x 2 contingency table.

Participants were women with no risk for breast cancer who presented for routine mammography and provided written informed consent. Each participant underwent mammography followed by ultrasound, both studies performed by the same Radiologist.

Inclusion criteria: Asymptomatic women 40 years of age and above coming for breast cancer screening

Exclusion criteria: Males, women < 40 years of age, symptomatic women with swelling/ discharge from the nipple, women unable to provide informed consent, women who cannot undergo adequate mammography, women unable to undergo a breast ultrasound, pregnant or breast-feeding women, women with known breast cancer or any other malignancy.

The proforma was filled after both mammogram and ultrasound reports were validated. Final histopathological diagnosis was obtained in 18 patients.

Study Sample

A total of 460 women who came for annual health screening and who satisfied both inclusion and exclusion criteria were enrolled.

Results:

Table 1: Diagnostic performance in detecting breast pathology on combined mammography and ultrasound

	Patients with breast pathology	Patients without breast pathology	Total
Breast pathologies detected on combined mammography and ultrasound	A=13=TP	B=2=FP	A+B=15
Breast pathologies not detected on combined mammography and ultrasound	C=3=FN	D=30 =TN	C+D=33
Total	A+C=16	B+D=32	A+B+C+D=48

Sensitivity = A/ (A+C) = 13/16=81.2% (95% confidence interval:0.53-0.95).
Specificity=D/ (B+D) =30/32=93.7% (95% confidence interval:0.77-0.98).
PPV= A/ (A+B) = 13/15=86.6% (95% confidence interval:0.58-0.97).
NPV=D/(C+D) =30/33=90.9% (95% confidence interval:0.74-0.97).
Accuracy= A+D/(A+B+C+D)=43/48=89.5.

Fisher's exact test

The two-tailed p value is less than 0.0001.

The association between rows (groups) and columns (outcomes) is considered to be extremely statistically significant

Table 2: Breast pathologies detected on combined mammography and ultrasound - in dense breasts

	Patients with breast pathology	Patients without breast pathology	Total
Breast pathologies detected on combined mammography and ultrasound	A=4=TP	B=1=FP	A+B=5
Breast pathologies not detected on combined mammography and ultrasound	C=0=FN	D=7=TN	C+D=7

Total	A+C=4	B+D=8	A+B+C+D=12

Sensitivity = A/ (A+C) = 4/4 =100% (95% confidence interval:0.39-1).
Specificity=D/ (B+D) =7/8=87.5% (95% confidence interval:0.46-0.99).
PPV = A/ (A+B) = 4/5=80% (95% confidence interval:0.529-0.98).
NPV= D/ (D+C) =7/7=100% (95% confidence interval:0.53-0.95).
Accuracy= A+D/ (A+B+C+D) =11/12=91.6.

The two-tailed p value equals 0.0101. The association between rows (groups) and columns (outcomes) is considered to be statistically significant.

Table 3: Breast pathologies detected on combined mammography and ultrasound - in fatty breasts

	Patients with breast pathology	**Patients without breast pathology**	**Total**
Breast pathologies detected on combined mammography and ultrasound	A=3=TP	B=1=FP	A+B=4
Breast pathologies not detected on combined mammography and ultrasound	C=1=FN	D =6=TN	C+D=7
Total	A+C=4	B+D=7	A+B+C+D=11

Sensitivity = A/ (A+C) = 3/4= 75% (95% confidence interval:0.21-0.98).
Specificity=D/B+D=6/7=85.7% (95% confidence interval:0.42-0.99).
PPV=TP/TP+FP= A/A+B =3/4=75% (95% confidence interval:0.21-0.98).
NPV= NPV=TN/TN+FN=A/D+C=3/9=85.5% (95% confidence interval:0.42-0.99).
Accuracy= TP + TN/ TP+TN+FP+FN= A+D/A+B+C+D=9/11=81.8.

The two-tailed p value equals 0.0879.
The association between rows (groups) and columns (outcomes) is considered to be not quite statistically significant.

Discussion

In our study, combined use of mammography and ultrasound increased the false positive rate by 4%, (from 4% to 8% with the addition of ultrasound). The literature shows a wide variation in the change in false positive rate by the addition of ultrasound. Berg *et al* showed increase from 4.4% to 10.4%, while Nelson *et al* showed a large 12-fold increase from 6.5% to 84.5%[3] and Ohlinger *et al* showed a marginal decrease from 1.1% to 0.6%[4].Corsetti V *et al* reported that additional investigations or surgery due to false positive ultrasound in women with dense breasts occurred in 5.5%.Surgical biopsy due to false positive ultrasound was 1% of screening examinations in women <50 years and 0.6% of screening examinations in women 50 years and older and benign surgical biopsies were caused in 4.5% and 0.9% of ultrasound detected lesions[2].

When identifying all breast pathologies, we found the sensitivity was 31.2% on mammography alone and 81.2% on combined mammography and ultrasound with improvement in sensitivity by 50%. A significant improvement in sensitivity was also found by Gonzaga *et al* in 2010 who studied the use of ultrasound as an adjunct to mammography in assessment of breast tumors in 80 women, more than half of whom were in the 20 to 39 age group. Of the 80 palpable breast masses, ultrasound diagnosed the presence of masses in 74 cases; ultrasound had 100% sensitivity and 100% specificity for differentiating purely cystic masses from solid masses and 100% diagnostic accuracy for cystic masses, closely followed by fibroadenoma. The report concluded that ultrasound is a relatively inexpensive and a more accessible modality for evaluating palpable breast masses and should be the first line investigation especially in women below 30 years and as an adjunct to mammography in women over 30 years when mammography is available[7].In our study, however, specificity droppedmarginally from 96.8% to 93.7%.

When identifying allbreast pathologies in dense breasts, we foundsensitivity was 25% on mammography alone and 100% on combined mammography and ultrasound, with a significant improvement of 75%. Literature also shows that the sensitivity of adjunct ultrasound mammography is especially increased in dense breasts.Van Gills *et al*studied 19,152 participants with 258 screen detected and145 interval cancers on mammography alone.[8] The positive predictive value was lower (29%) in women with dense breasts compared those with lucent breasts (52%). Also, it was observed that the survival rate was less for those with dense breasts and concluded that high breast density had an unfavorable prognosis on screening performance. Leong LC, *et al* screened141 asymptomatic women between 2002 to 2004 with negative mammograms and dense breasts with mean age of 45.1 years with ultrasound[9]. The breast cancer detection rate was 1.4%. Sensitivity was 100% and specificity was 88.5%. The positive predictive value was 14.3% and the negative predictive value was 100%. Attam *et al* found that for women with breast density of 50% or more, the breast cancer risk rose by two-fold as compared to women with breast density of < 10%[10]. However, for premenopausal women, breast density of 50% or more raised risk by 3.86 times compared to however for women > 47 years the association was not as consistent. He further suggested that breast density does not identify all women who will develop breast cancer because the study found many cancers in low density breasts on mammography (< 50%)[10]. Navneet Kaur *et al* studied 115 cases and 127 controls and found that there was a significant increase in breast cancers in dense breasts and less risk of breast cancer in fatty breasts[11].

When identifying allbreast pathologies in fatty breasts, we found a sensitivity of 25% on mammogram alone and 75% on combined mammography and ultrasound for fatty breasts respectively with a significant improvement in sensitivity by 50% for all breast pathologies. The difference in specificity, positive predictive value, negative predictive value and accuracy was not statistically significant. Unlike other studies, Locate *et al* showed that the non-dense breast areas are associated with an increased breast cancer risk. The study postulated that the total breast area is larger on the MLO view and the interpretation is subjective on MLO whether subcutaneous fat or actual breast tissue and hence an increase in body mass index and subcutaneous tissue increased the risk of breast cancer[12].

Conclusion

- For the detection of all breast pathologies, the addition of ultrasound to mammography produced a statistically higher sensitivity with an improvement in sensitivity by 50%. However, this increased sensitivity is accompanied by a drop in specificity by 5%.
- For the detection of all breast pathologies in dense breasts, the addition of ultrasound to mammography produced a statistically higher sensitivity with an improvement in sensitivity by 75%.

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