Accuracy of combined mammography and breast ultrasound versus breast ultrasound alone in young women below 40 years.

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Abstract: Objective: To compare the accuracy of combined mammography and breast ultrasound versus breast ultrasound alone in evaluating young women below 40 years. **Patients and methods:** We retrospectively analyzed the electronic medical reports of all mammographic and sonographic breast imaging from November 2008 to December 2011 of young women, below the age of 40 years. Women presented to the breast imaging unit of Women and Fetal Imaging Center for screening and diagnostic purposes, were included in the study. Records were reviewed for sonographic or combined mammographic and sonographic findings together with Breast Imaging and Reporting Data System (BIRADS) assessment and histological results. Examintions rated as BIRADS categories; 1, 2, and 3 were considered negative, while 4 and 5 were considered positive. **Results:** A total of 256 patients were included in the study. Ninety eight patients (38.3%) were evaluated using breast ultrasound, while 158 patients (61.7%) were evaluated using both breast ultrasound and mammography. Palpable mass was the presenting symptom in 111 (43.4 %) of the cases. Biopsies were performed for 36 (14.1%) patients, while follow up for one year or more was done for 220 (85.9%)of patients. By either biopsy or follow up, 22 patients were malignant (8.6%) while 234 (91.4%) were benign. For the 98 cases evaluated with sonography, the sensitivity, specificity, positive predictive value (PPV) ,negative predictive value (NPV) and over-all accuracy were 87.5%, 100%, 100 % 98.9% and 89.8% respectively; While For the 158 cases evaluated with mammography and sonography, the sensitivity, specificity, PPV , NPV and over-all accuracy were 92.9% , 98.6% specificity, 86.7% , 99.3% and 98.1 % respectively. **Conclusion:** Among the study population, breast ultrasound alone accurately revealed the malignant cases that were present in our study group with 100% PPV, however performing combined mammography and sonography in suspicious cases may increase the sensitivity yet with no significant difference.
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Key words: Breast cancer, breast ultrasound, mammography

Abbreviations: BIRADS: Breast Imaging and Reporting Data System, FNAC: fine needle aspiration cytology, NPV: Negative predictive value, PPV:Positive predictive value

1. Introduction

Breast cancer in young women deserves special consideration as there are complex issues raised by cancer diagnosis at a young age. Breast cancer in these women may present differently to breast cancer in older women and may be more difficult to diagnose. For women under the age of 40, there are also particular concerns regarding pregnancy, fertility and contraception, sexuality and body image, as well as familial and genetic issues [(1).]

The diagnosis of breast cancer in young women has limitations in terms of recruitment of patients and how the imaging diagnostic technologies come to them. The low suspicion of malignancy in young women due to the lower prevalence of cancer and lack of patient stratification according to risk profiles often leads to delays in diagnosis or in the delivery of the most appropriate treatment strategies based on their individual characteristics. Overall, this fact contributes to the worse long-term outcomes observed in this patient group [(2).]

The ideal protocol for imaging the breast in a young woman is controversial. In response to the physiologic changes, breast density is increased, compromising the sensitivity of mammography [(3)]. However, in a small series of patients, it was found that the mammographic breast density of young women did not always change significantly and therefore did not negate the utility of mammography. Although some researchers suggest that mammography should be reserved for young women in whom malignancy has been proven or suspected [(4)], others argue that mammography is still helpful during this young age [(5)]. In contrast to the controversy that surrounds the utility of mammography, for young women younger with focal breast signs or symptoms, targeted ultrasound is the technique typically recommended for initial imaging evaluation [3,6,7].

Although mammography is a highly effective imaging method for detecting, diagnosing, and managing a variety of breast diseases especially cancer, It is an application where an emphasis on patient dose management and risk reduction is required. This is because of breast tissue has a relatively high sensitivity to some adverse effects of radiation, and second, mammography requires a higher exposure than other radiographic procedures (more than 0.03 mR) to produce the required image quality. The higher exposure, compared to other radiographic procedures, is because the breast is composed of soft tissue (no bones or air) and has very low contrast. Therefore, more radiation is required to produce visible images of both normal breast anatomy and signs of disease. Therefore, the barrier to the performance of mammography in a young woman is the perceived radiation risk [8].

2. Patients and methods

Study Design

This retrospective study was conducted at breast imaging unit of the Fetal and Women Health Center, during the period between November 2008 till December 2011. Institutional review board approval was obtained before beginning this study. A written informed consent from each woman was not applicable due to retrospective nature of this study.

All mammograms and breast ultrasounds performed for young women below 40 years were collected .Electronic medical record for each patient was reviewed for the presenting complaint prompting diagnostic imaging .Then breast physical examination, sonographic and mammographic assessment, mammogram density, Breast Imaging and Reporting Data System (BIRADS categories), pathologic results of the biopsies taken, clinical follow-up and clinical outcomes.

Patients with biopsy-proven pathologic abnormality or more than 12 months of radiographic follow-up were included in this study; but those without pathologic diagnosis or with fewer than 12 months clinical follow-up were considered lost to follow-up.

For the screening cases, we were targeting women that had substantially increasedrisk of breast cancer, such as high breast density, or positive family history for breast cancer, this was to maximize the benefits and minimize the harms of screening this young age group[7].

Imaging and Image Interpretation

We followed the American College of Radiology practice guidelines [9, 10] for the performance of screening and diagnostic mammography and the ultrasound examination. In general, women younger than 40 years were first evaluated with ultrasound; mammography was performed if indicated by clinical symptoms or sonographic findings.The decision was mainly based on the radiologist opinion whether there was a need for further mammographic examination, either single or routine views (craniocaudal and mediolateral oblique). However, if indicated by the clinical situation, physicians had discretion to modify this protocol.

The study was interpreted by two consultant radiologists who had 10 and 15 years experience in breast imaging. For all patients, the mammographic and sonographic findings were described using the BIRADS lexicon. At the end of each examination, a final BIRADS category was reported. The BIRADS categories [9, 10] were: 1, negative; 2, benign findings; 3, probably benign findings, short-term follow-up recommended; 4, suspicious abnormality, biopsy recommended; and 5, highly suggestive of malignancy. BIRADS categories 1–3 were considered negative, and categories 4 and 5 were considered positive.

In addition to the BIRADS category assigned, breast parenchymal density was evaluated according to the American College of Radiology(ACR) (9) , (ACR 1) was categorized as almost entirely fat (less than 25% fibroglandular tissue); (ACR 2) was categorized as scattered fibroglandular densities (approximately 25% to 50% fibroglandular);(ACR3) was categorized as heterogeneously dense (approximately 51% to 75% fibroglandular); and ACR 4 was categorized as dense (more than 75% fibroglandular).

Ultrasonography

For all included women breast ultrasound examinations were routinely performed on both breasts with the regional lymphatic areas, by the same interpreting radiologist, using a real time,dynamic equipment (GE Voluson 730 pro, GE Healthcare, USA),which had a high resolution, phased- array transducer and a frequency that ranged from 7.0 to 12.0 MHz. Color and Power Doppler were available in the equipment. Basically in our institution, women with dense breasts (ACR categories 3 and 4) in screening mammograms were routinely examined with ultrasound and the final radiological diagnosis was interpreted using the BIRADS categories [10].

Mammography

Our protocol consisted of routinecraniocaudal and oblique mediolateral views for both breasts. All mammograms were performed using a dedicated mammography unit (Selenia, Hologic 2D Digital Mammography). Film processing optimized for mammography was used (Kodak, Rochester, NY). In our breast imaging unit, mammograms were viewed by the existing radiologist and immediate work –up for any required additional spot compression or magnificationviews was done in the same visit. Accordingly, no recalls were required for any additional views. The BIRADS assessments [9, 10] rendered at the time of imaging were used, without a retrospective second interpretation, for both sonographic and mammographic examinations.

Biopsy or follow up

Our golden standard was based on either performing biopsy or follow up for more than 12 months. 36 cases confirmed their diagnosis by percutanous biopsies, 25 out of 36 performed core

needle biopsy guide by sonography and the other 11 cases performed fine needle aspiration cytology (FNAC).All biopsies were guided by ultrasound and done by the same interpreting radiologist with a pathologiston site.

Statistical analysis:

Data was revised for its completeness and consistency.Data were analyzed using SPSS® for Windows®, version 15.0 (SPSS, Inc, USA). Description of quantitative (numerical) variables was performed in the form of mean, range and standard deviation (SD). Description of qualitative (categorical) data was performed in the form of number of cases and percent. Analysis of categorical data was performed by using Chi-squared test. Diagnostic accuracy was assessed using the following terms: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio, negativelikelihood ratio and overall accuracy. A difference with*P*value <0.05 was considered statistically significant.

3. Results

A total of 256 women aged from 14-38 years, were finally analyzed , 98 cases (38.3%) were evaluated by breast ultrasound alone while 158 cases (61.7%) were evaluated by combined breast ultrasound and mammography .One hundred eighty two women (71.1%) were coming for diagnostic purpose and seventy four women (28.9%) were coming for screening .

Palpable mass was the presenting symptom in 111 (43.4%) women, followed by pain in 58(22.7%) women. Bloody nipple discharge was reported in eleven (4.3%) patients. Skin changes and other complaints represents (1.6%) of the cases. 91.8% of the studied young women were having benign condition by BIRADS while 8.2% were having a malignant lesion. Family history was positive in 33% of the cases. Biopsies were performed for 36 (14.1%) cases while follow up for one year or more was done for 220 (85.9%) of the cases. By either biopsy or follow up, 22 cases were proved malignant (8.6%) while 234 (91.4%) were benign .The study scheme and results were summarized in the flowchart (Figure 1).

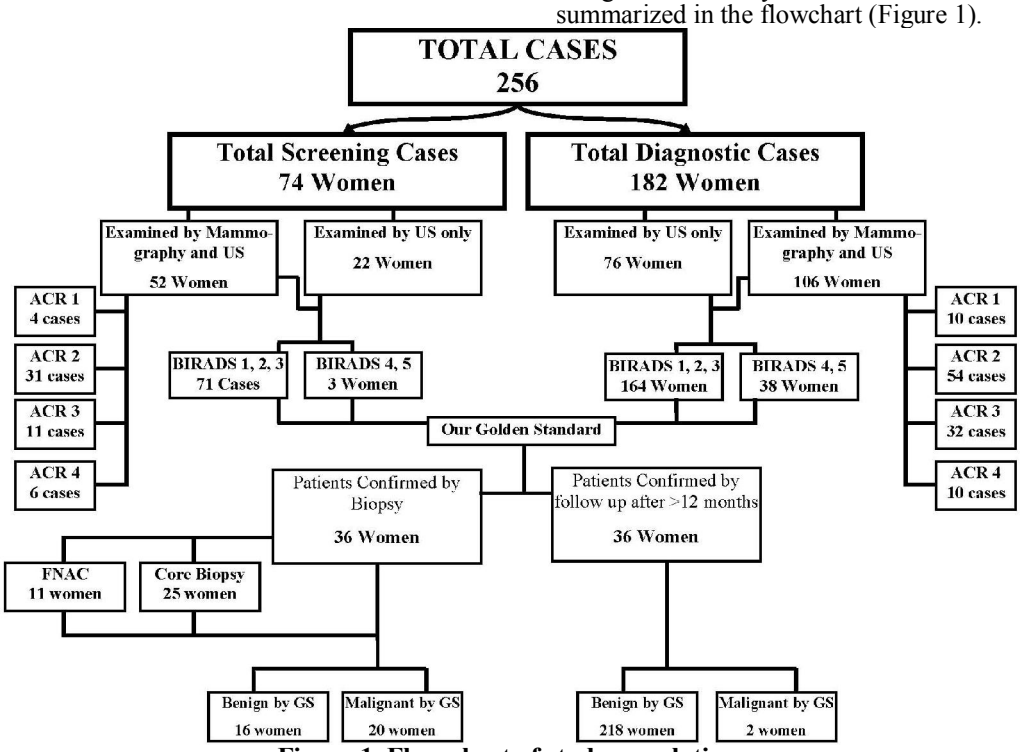

Figure 1. Flow chart of study population

Higher percentage of malignancy was noted among cases with palpable mass 15.6%, compared to other complaints (3.4%), and the difference was statistically significant. Women with positive history of contraception, higher gravidity and positive family history were having higher percentage of malignancy, however with no significant statistical difference observed. Distribution of BIRADS categories among the studied women compared with histological and clinical outcomes is shown in table 1. Higher percentage of heterogeneous density was detected among malignant cases confirmed by the golden standard compared to benign cases but the difference was not significant statistically (table 2). Most of the malignant cases were presented with focal asymmetry (10 cases) and micro-calcifications (6 cases) in the mammogram. Table 3 shows the diagnostic accuracy test among the studied women. No false positive cases were recorded by breast ultrasound with very high specificity, however higher overall accuracy was noted among cases examined by combined mammography and breast ultrasound.

Table 1: Distribution of BIRADS categories among the studied women compared with histological and clinical outcomes¶

Technique, BIRADS Category	Malignant by Biopsy	Benign by Biopsy	Malignant by Follow-up	Benign by Follow-Up	Total number (%)
Mammography and breast ultrasound (number =158)					
1 and 2	0	4	0	108	112 (70.9)
3	1	5	0	25	31 (19.6)
4-5	12	2	1	0	15 (9.5)
Total number (%)	13 (8.2)	11 (7)	1(0.6)	133 (84.2)	158 (100)
Breast ultrasound					
1 and 2	0	5	0	70	75 (79)
3	0	3	1	12	16 (15)
4 and 5	7	0	0	0	7 (6)
Total number (%)	7 (7.1)	8 (8.2)	1 (1.02)	82 (83.68)	98 (100)

¶Data are presented as numbers and percentage.
BIRADS: Breast Imaging and Reporting Data System.

Table 2: Comparison between golden standard test evaluation and breast density ¶

Number=158	Benign N=143		Malignant N=15		P¶¶
	N	%	No.	%	
Almost fat	13	9.1	1	6.7	0.1
Scattered fibroglandular tissue	79	55.2	6	40	
Heterogeneous	36	25.2	7	46.7	
Extremely dense	15	10.5	1	6.7	

¶ Data are presented as numbers and percentage
¶¶Analysis used chi-square test

Table3: Diagnostic accuracy tests among the studied women¶

	Breast ultrasound	Mammography and breast ultrasound
Sensitivity	87.5 %	92.9 %
Specificity	100 %	98.6 %
PPV	100 %	86.7 %
NPV	98.9 %	99.3 %
Accuracy	89.9 %	98.1 %
Positive Likelihood Ratio	0 %	67.32
Negative Likelihood Ratio	0.12	0.07

¶ Data are presented as numbers and percentage PPV positive predictive value
NPV negative predictive value

36 women [14.5% of the all included women (256)] confirmed their diagnosis by biopsy, 25 of them (69.4% of the biopsied cases) performed core needle biopsy and the other 11 cases (30.1%) performed fine needle aspiration cytology(FNAC), guided by ultrasound. 20 of the biopsied cases (55.6 %) were diagnosed as malignant findings (16 cases of the core biopsy and 4 cases of the FNAC) and all of the malignant percutanous biopsy cases were confirmed by the afterwards surgical intervention results. 16 of the biopsied cases (44.4%) were of benign results (9 core biopsy and 7 FNAC guided by US) and 11 of benign percutanous biopsy cases had been surgically intervened for benign lumpectomy due to their strong family history. Regarding the lymph nodes (LNs) involvement in malignant cases, 3 women showed positive malignant LNs by mammography, and an additional case, (total of 4 cases) were diagnosed with positive LNs when evaluated by breast ultrasound.

Forty-two (16.4%) of the 256 women were diagnosed as having fibroadenoma ,50 (19.9%) were having fibrocystic disease ,22 (8.2%) malignancy and 10 (3.9%) as inflammation or infection .Figures (2-7) show different images for malignant and benign masses examined by mammography and breast ultrasound .

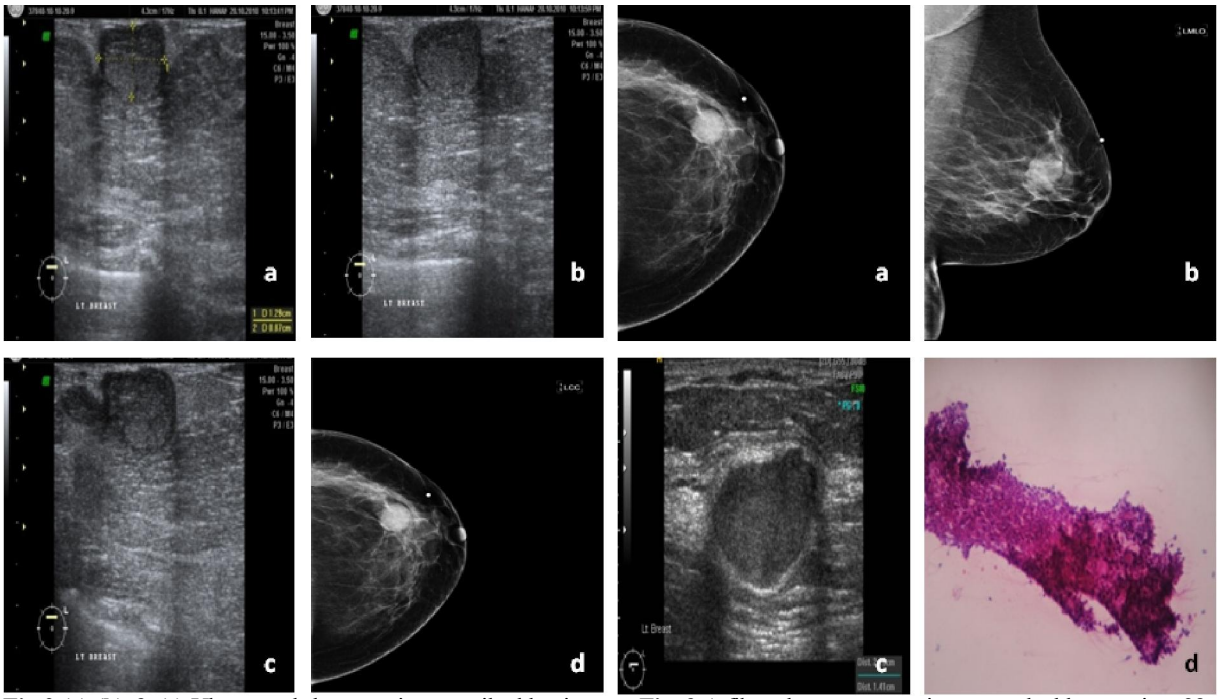

Fig 2,(a),(b) & (c) Ultrasound shows a circumscribed benign homogenous lesion noted at 12 o'clock position of the left breast, in lactating 30 years old woman. It measures 1.5x0.8 cm in diameter and consistent with a clinically felt lump, (d) A solitary mammographic benign lesion is shown. FNAC revealed galactocele. When Galactoceles are composed almost exclusively of milk, they mimic the US appearance of a benign solid tumor.

Fig. 3 A fibroadenoma presenting as a palpable mass in a 28-year-old woman. **(a &b)** Mammogram shows lobular mass with partially obscured borders.**(c)**Ultrasound shows corresponding solid oval isoechoic mass.**(d)** Cytology specimen from FNAC. Excisional biopsy confirmed the diagnosis of fibroadenoma.

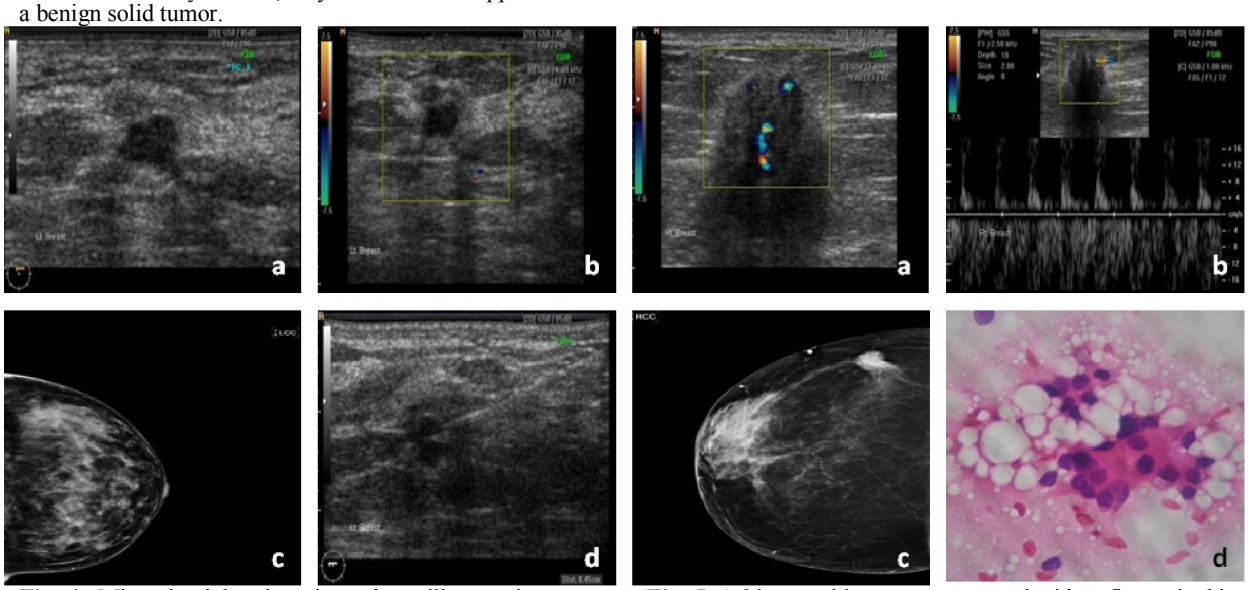

Fig 4. Microglandularadenosis and papilloma in a non lactating 33-year-old woman presented with positive family history **(a)** US image shows a 0.6 cm lobular lesion with hypoechoic echo texture noted at upper outer quadrant of the left breast (zone B), **(b)** no abnormal vascularity by Color Doppler US .(c) shows no corresponding mammographic features. FNAC guided by US.revealed intracystic papillary carcinoma versus infracted papilloma .

Fig. 5. A 30 year old woman presented with a firm palpable mass (a)Sonogram shows two oval shaped, inhomogeneous, ill-defined solid masses with posterior shadowing.(b) Colored Doppler US demonstrated abnormal neovascularity. (c) Mammogram shows a spiculated mass at UOQ of the right breast with few tiny microcalcification, the mass is well seen in mammogram due to fatty glandular parenchyma (ACR2). (D)Histopathology diagnosis revealed invasive ductal carcinoma

4. Discussion

A standard breast imaging protocol for the evaluation of young women below 40, has not been formally established, and previous studies that have described the accuracy of breast imaging in this population have included small numbers of patients or higher age group [11,12].

According to the American College of Radiology (ACR) Appropriateness criteria reviewed 2012 [13], breast ultrasound is the usually appropriate initial evaluation in young women, rating 9 = typically appropriate over mammography and magnetic resonance mammography. Also the recommendations of the International Atomic Energy Agency (IAEA) meeting on justification of medical exposure and appropriateness criteria, Vienna, 2009, noted that there is a significant and systemic practice of inappropriate radiological examination, leading to substantial radiation overuse and unnecessary exposure to stochastic effects of ionizing radiation. The stochastic effects occur by chance and often show up years after radiation exposure. They consist primarily of cancer and genetic effects and this makes it necessary to protect patients from potential harm [14].

In the previous studies, the comparison was usually done between mammography and combined mammo-graphyand sonography with little evaluation of the sonography alone which we need actually to evaluate its accuracy in such young age group. In our study the sensitivity of breast ultrasound alone was 87.5%, this was lower than the results published by Lehman *et al.*(95.7 %) in 2012 [15], and Hille*et al.*(92%) [16], and similar results to DevolliDisha[17]. Lehman *et al.*[15] worked on young women and DivolliDisha*et al.*[17] worked on dense breasts (usually in young women). While in combined sonography and mammography,our sensitivity was (92.9 %) which is slightly higher and within the range published [Ohushi*et al.*(86%) [18] and Corsetti*et al.*(86.7%) [19]], but their study were on women above 40 years,also Berg *et al.*(95%) [20], which was also conducted on elder age group.

Our specificity was 100 % for sonography alone which gives reliability for confirming the diagnosis, Hille*et al.*[16] reported (85%), while the specificity of combined sonography and mammography in our study was (98.6%), which means that adding mammography was not an add value for the specificity .These results were similar to Berg *et al.*(95 %) [20] . In addition, our NPV for sonography was (98.9 %) compared with Lehman et al. (99.9 %) [15], but the PPV was 100 % for sonography compared with (74.1%) in Ying *et al.*[21] study in 2012. The accuracy of sonography in our study was (89.9%) and for combined sonography and mammography (98.1 %). Hille*et al.*[16] accuracy result was 87 % but it was for evaluation of BIRADs 3-5 classification of breast ultrasound only.

The screening cost of sonography is lower than that of mammography alone , and we expect that it would result in better screening compliance because ultrasound requires less exposure to radiation than mammography and is available at most of the hospitals. However, economic evaluationsare needed to investigate whether ultrasound alone would be suitable as a national breast cancer screening strategy for a general population or for high-risk populations in developing countries [22,23].

On the other hand, the capacity of ultrasound to differentiate benign from malignant tumors has been claimed to lead to higher recall and biopsy rates, which brought about over diagnosis and overtreatment. Thus, the use of ultrasound alone as a screening method, for the general population,is not practical at present because of inadequate sensitivity and unsatisfactory accuracy rates [24].

The accuracy in our study was considerably higher in combined mammographyand sonography compared to sonography only. However, accuracy is not the only relevant factor in making a modality practical and beneficial for nationwide mass cancer screening. Other factors that need to be considered include the modality's likely effects on breast cancer mortality, financial cost, population selection, and Technical disparities, thus, several decades are needed to prove this modality's likely effects.

Most breast cancers in young women present with a palpable mass, whereas most cancers in women older than 40 years old are detected by screening mammography before becoming clinically evident [3].

Ultrasonography has proven effective in detecting clinically and mammographically occult cancers in the dense parenchyma of women before menopause [25- 27] and ultrasound is a useful tool for differentiating cystic lesions from solid tumors in the breast, potentially lowering the rate of unnecessary biopsies for benign lesions by up to 25% [27]. However, compared with mammography, the sensitivity of ultrasound depends more on the operator's experience and the equipment used[28, 29].

This suggests that additional cancer detection by ultrasound is likely to improve screening benefit in dense breasts, and supports the implementation of a randomized trial of adjunct ultrasound in women with increased breast tissue density. Screening sensitivity was 83.5% for mammography alone in low density breasts relative to 86.7% for mammography with ultrasound in high density breasts[19]. However, Lehman *et al.*[15], performed their study on a younger age group and concluded that breast imaging is warranted in women 30-39 years of age with focal signs or symptoms because of the small (1.9%) but real risk of malignancy. Ultrasound has high sensitivity (95.7%) and high NPV (99.9%) in this setting and should be the primary imaging modality of choice and the added value of adjunct mammography is low [15]. It was of profound importance to know the influence of negative mammography and breast sonography on the surgeons' decision over their clinical impression in suspicious cases.

The study has many strengths including that our screening protocol is standardized and computerized

and tracing the patients till the final diagnosis is accessible, also proper revision of our reports by experts yielded optimal interpretation.
The limitations of the study include the possible selection bias (single center), the small number of confirmed malignancy cases led to a lower statistical power of the study.

Conclusion:

Breast sonography accurately revealed malignancy and is considered an appropriate intial evaluation. It accurately revealed malignancy in young women and its advantages include radiation protection, easy, cheap, available, better compliance and specific with high PPV . Adding mammography to sonography in suspicious cases is accepted, it may increase the sensitivity yet with no significant difference.

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