JMSCR Vol||05||Issue||12||Page 31890-31897||December 2017

www.jmscr.igmpublication.org
Impact Factor 5.84
Index Copernicus Value: 71.58
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v5i12.100

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Mammography Screening in Benign Breast Disease for Risk Stratification of Malignancy

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Abstract
Breast cancer is the most common female cancer worldwide. Although the widespread use of mammography screening has increased diagnosis of benign breast disease, no specific recommendations have been made for surveillance, except for women with atypias, who are usually recommended to undergo surgical excision. With the current advances in reporting by the use of BI-RADS, the standardization is achieved, but its accuracy in terms of histological correlation remains unanswered. This study will try to establish the same and also aid in improving the management of patients. Correlation between mammographic screening and histopathology among patients clinically diagnosed as benign breast disease were assessed for determining the accuracy of BI-RAD system mammography. On approval of Institutional Ethical Committee, 100 women between the age group 30-70 years were enrolled after obtaining written informed consent. Mammogram had100% sensitivity (95%CI=95.77, 100), 87% positive predictive value (95% CI=79.02, 92.24) and 87% diagnostic accuracy (95% CI=79.02, 92.24) as a screening tool in this study, which was statistically significant. Thirty-one to forty years age group constituted maximum percentage (65%), followed by 41-50 years (21%), >50 years age group (9%), 30 years (5%). Mean ± SD being 39.27 ± 7.22years. Majority of the women were multigravida (56%) and have breastfed baby (94%), which is statistically significant (p=0.001 and p= 0.005 respectively) using Pearson Chi-square test. Upper outer quadrant (35%) was the most common site of breast lump followed by lower inner (22.6%), upper inner (20.2%), central (11.7%) and lower outer (10.5%), which was statistically significant using Chi-square test (p=0.044). Three percentage mother and 1% sister had positive history of breast malignancy, which positively correlated with high-risk benign breast disease.
Keywords: *Breast, Mammography, BIRADS, benign, lump, malignancy.*

Introduction

Breast cancer has ranked number one cancer among Indian females of age adjusted rate as high as 25.8 per 100,000 women and mortality 12.7 per 100,000 women.[1] Breast cancer is the most common female cancer worldwide representing nearly a quarter (25%) of all cancers with an estimated 1.67 million new cancer cases

diagnosed in 2012. [1] There is a significant increase in the incidence and cancer-associated morbidity and mortality in Indian subcontinent as described in global and Indian studies. Earlier cervical cancer was most common cancer in Indian woman but now the incidence of breast cancer has surpassed cervical cancer and is leading cause of cancer death.[1] The main reasons for this observed hike in mortality is due to lack of inadequate breast cancer screening, diagnosis of disease at advanced stage and unavailability of appropriate medical facilities.[2] In India, majority of patients present at locally advanced or at metastatic stages at the time of diagnosis. According to various studies, majority of carcinoma breast cases in the west report in stages I and II of the disease, whereas in India 45.7% report in advanced stages. Disease presentation in such conditions results in increased mortality in India. [1] Although the widespread use of mammography screening has increased diagnosis of benign breast disease, no specific recommendations have been made for surveillance, except for women with atypias, who are usually recommended to undergo surgical excision. With the current advances in reporting by the use of BI-RADS, the standardization is achieved, but its accuracy in terms of histological correlation remains unanswered. This study will try to establish the same and also aid in improving the management of patients.

Objectives

The aim of the study is to evaluate the malignancy risk in benign breast disease using screening mammography. The objective is to assess the accuracy of BI-RAD system mammography in benign breast disease for evaluating the risk of malignancy, to find the correlation between mammographic screening and histopathology in diagnosis of malignancy among patients diagnosed clinically as benign breast disease and compare and contrast findings of breast lesions in BI-RADS categories 2 and 3 with histopathology and/or cytology. In addition, it is also compared with additional factors such as age, family history, parity, site of lump.

Methods

The study is a prospective study done in the Department of Radiology and General Surgery, Vinayaka Mission Medical College and Hospital, Karaikal from June 2016 to August 2017. The study is done after obtaining Institutional Ethical Committee clearance and informed and written consent from the patient. Female patients of age 30-70 years with clinical diagnosis of benign breast disease, family history of benign breast disease/family history of breast malignancy and histological and radiological studies suggestive of benign breast disease are included whereas patients with previous diagnosis of breast cancer, previous mastectomy (unilateral or bilateral) or breast reduction and those with biopsies with indeterminate histological classification are excluded from the study. Based on these criteria, a total of 163 patients who came to General Surgery Out-Patient Department, VMMC Karaikal were screened. From this, 125 patients who were clinically diagnosed with benign breast disease were further evaluated with mammography. Out of this, 25 were excluded. Thus, a total of 100 patients were included as the study population. A detailed history, clinical examination and investigations including mammography, histopathological examination in operated specimen are done. Data are entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. Chi-square test was used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation. p value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests. Statistical software: MS Excel, SPSS version 22 (IBM SPSS Statistics, Somers NY, USA) was used to analyse data.

Results

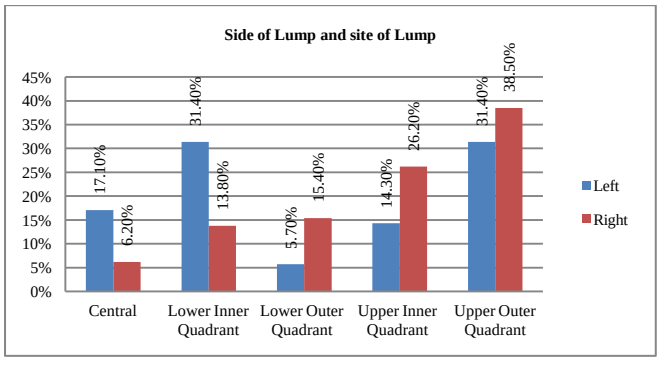
In the study majority i.e. 65% were in the age group 31 to 40 years, 21% were in the age group 41 to 50 years, 9% were in the age group >50 years and 5% were 30 years. The mean age was 39.27 ± 7.22 years. 12% of patients presented with Pain, 2% with Ulcer, 4% with Skin changes and 1% with Nipple discharge. Family history of benign breast disease was noted 3% in mother and 1% in sister. Majority didn't have a family history (96%). 6% of the subjects were nulliparous, 38% were primigravida and 56% were multigravida. In our study, 35% had lump on left side and 65% had on right side. Out of this, 31.4% had lump in upper outer quadrant and lower inner quadrant, 17.1% in central area, 14.3% in upper inner quadrant and 5.7% in lower outer quadrant on the left side. On the right side, 38.5% had lump in upper outer quadrant, 26.2% in upper inner quadrant, 15.4% in lower outer quadrant, 13.8% in lower inner quadrant and 6.2% in central area. There was significant difference in site of lump with respect to side of Lump (Table 1).

Table 1 Comparison between side of lump and site of lump

		Side			
		Left		Right	
		Number	%	Number	%
Site	Central	6	17.1%	4	6.2%
	Lower Inner Quadrant	11	31.4%	9	13.8%
	Lower Outer Quadrant	2	5.7%	10	15.4%
	Upper Inner Quadrant	5	14.3%	17	26.2%
	Upper Outer Quadrant	11	31.4%	25	38.5%

$\chi 2 = 9.81$, df = 4, p = 0.044*

Chart 1 Bar diagram showing Comparison between Side of Lump and site of Lump

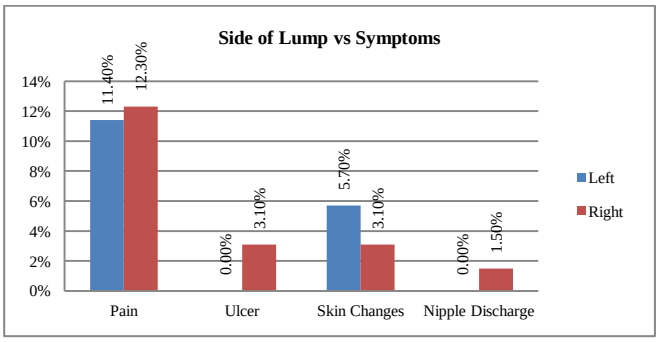


In subjects with left side lump, 11.4% had pain, 5.7% had skin changes and in subjects with right side lump, 12.3% had pain, 3.1% had ulcer and skin changes and 1.5% had Nipple discharge. There was no significant difference in symptoms with respect to side of Lump. (Table 2)

Table 2 Comparison between side of Lump and Symptoms at presentation

		Side				P value
		Left (n=35)		Right (n = 65%)		
		Number	%	Number	%	
Pain	Present	4	11.4%	8	12.3%	0.897
Ulcer	Present	0	0.0%	2	3.1%	0.295
Skin Changes	Present	2	5.7%	2	3.1%	0.521
Nipple Discharge	Present	0	0.0%	1	1.5%	0.461

Chart 2 Bar diagram showing Comparison between side of Lump and Symptoms at presentation

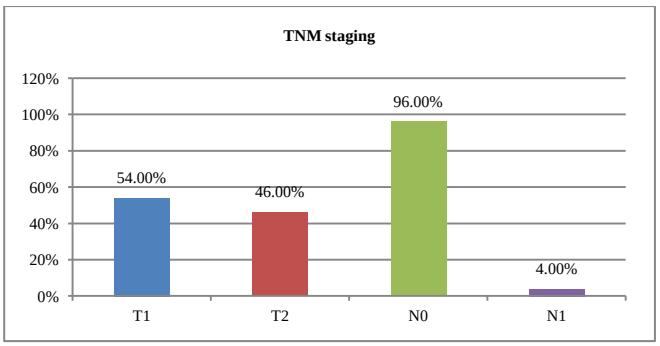


TNM staging of the lumps showed that 54% had T1 staging and 46% had T2 staging, 96% had N0 staging and 4% had N1 staging. (Table 3)

Table 3 TNM staging of tumour in the study

		Number	%
Tumour	T1	54	54.0%
	T2	46	46.0%
Node	N0	96	96.0%
	N1	4	4.0%

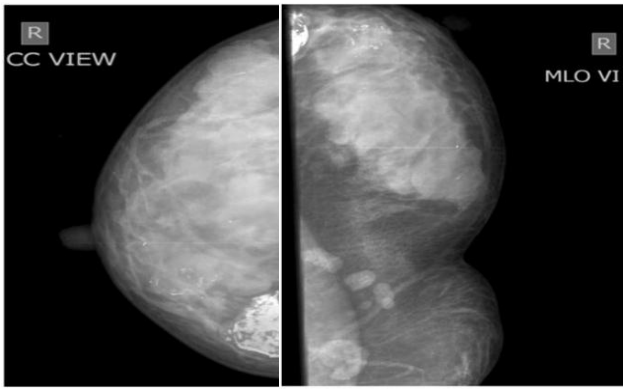
Chart 3 Bar diagram showing TNM staging of tumour in the study



Clinically, 67% fibroadenoma, 19% breast lump, 5% fibroadenosis, 3% breast abscess, 3%

phylloids tumour, 2% breast lipoma and 1% mastitis were diagnosed. Figure 1 shows a case of fibroadenoma.

Figure 1 A case of fibroadenoma, with complaints of lump in right breast since 3 months. Mammogram shows multiple fibroadenomas in varying degree of calcifications noted on right side

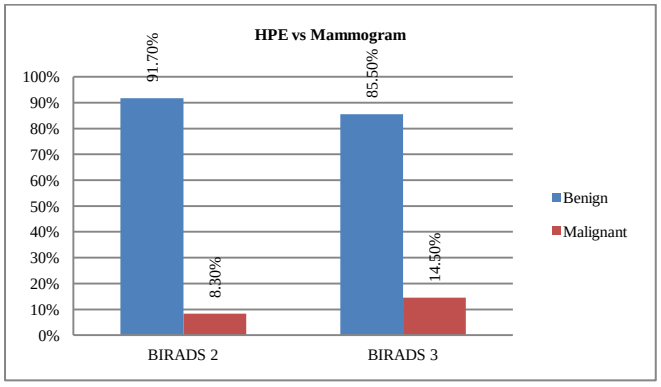


On correlating the histopathological and mammogram findings, out of the 24 subjects with BIRADS 2, 91.7% were benign and 8.3% had malignant lesions and among 76 subjects with BIRADS 3, 85.5% were benign lesions and 14.5% had malignant lesions, thus showing no significant association between the two. (Table 4)

Table 4 Comparison between HPE and Mammogram findings among subjects

		Outcome			
		Benign		Malignant	
		Number	%	Number	%
Mammogram	BIRADS 2	22	91.7%	2	8.3%
	BIRADS 3	65	85.5%	11	14.5%

Chart 4 Bar diagram showing Comparison between HPE and Mammogram findings among subjects



Out of all the 100 subjects who were diagnosed to have benign lesion in mammogram, correlation with histopathological examination showed 87% to be benign and 13% to be malignant lesions. (Table 5)

Table 5

		Outcome			
		Benign		Malignant	
		Number	%	Number	%
Mammogram	Benign	87	87%	13	13%

Thus, the sensitivity, positive predictive value and diagnostic accuracy of the study was found to be 100%, 87% and 87% respectively.

Discussion

Developed in the early 1990s, the BI-RADS scoring method has been used extensively as a surrogate to histo-pathological reporting of breast cancer. In BI-RADS mammograms are categorized from 0 – 6, with category 0 requiring further investigation and category 6 being biopsy proven malignancy. Categories 1 to 5 are further broken down into negative, benign finding, probably benign finding, suspicious and highly suggestive of malignant lesion respectively. Prior to implementation of BI-RADS there was a lack of uniformity in reporting of mammography findings and this often resulted in varied reporting and management strategies. This ambiguity had also led to increased difficulties in establishing performances standards across settings. This had been the main impetus in developing the BI-RADS system and several research studies have shown the scoring system to be useful in predicting the likelihood of cancer [3, 4, 5]. These results are also seen in my study and hence further show the value of BI-RADS in effective management of breast cancer.

In the world, breast malignancy is the leading cause of deaths next to carcinoma lung. Current scenario is that there is a slight decline in breast cancer mortality due to the success of early detection and advancement in treatment. For many decades there had been a dramatic increase in the incidence of invasive breast cancer. Currently the incidence of invasive breast cancer has been reduced significantly, but the number of in situ

cancer specially ductal carcinoma in-situ has increased due to usage of screening mammography.[1]

In India, in females, breast cancer is the leading cause of mortality. Infiltrating ductal carcinoma is the commonest histological type. Certain unknown factors, habits and customs prevalent in the community are noted differences in the incidence of breast cancer. [1]

This study was conducted for assessing the risk of malignancy in women coming to out-patient department of General Surgery, Vinayaka Missions Medical College Karaikal who were diagnosed clinically with benign breast disease and further evaluated with mammography. The total study population consisted of 100 women. It was found that there was a significant increase in malignancy who were diagnosed clinically as benign breast disease.

Benign breast disease was seen commonly among young age group. As age increases risk of malignancy increases.

Chandanwale et al (2017) [6] noted that fibrocystic change is the most common disease in which precancerous lesions are seen. The most common age group of these lesions is 31–40 years. This was similar to the present study. Benign breast lesions with associated precancerous breast lesions must be separated from pure benign breast lesions and need future evaluation and follow-up. Miglioretti et al (2012) [7] concluded that women aged 40 to 49 years with a 2-fold increased risk have similar risk-benefit ratios for every two year screening mammography as average-risk women aged 50 to 74 years. Threshold RRs required for favorable risk-benefit ratios vary by screening method, interval, and outcome measure.

Das N et al (2014) [8] conducted a study matching with the present one and found that commonest presentation of benign breast diseases was breast lump followed by nodularity of breast. The commonest presentation was breast lump which comprised 69 (69%) cases followed by nodularity of the breast (17%) and breast pain (13%). In the study conducted by Prajapati et al (2014) [9] it was noted that breast lump was the presenting complaint in 550(82.8%) of 664 patients, the lump was painless in 458(83.3%), associated with pain and breast ulcer in 59(10.7%) and 33(6.0%) patients respectively. This was significant statistically.

Webb et al (2002)[10] confirmed that the major risk factor for breast cancer is having a first-degree family history of the disease. Among women with proliferative disease, those with a family history of breast cancer were almost 3 times as likely to have atypia (prevalence odds ratio = 2.72, 95% CI 1.23-5.89) than those with no family history. In conclusion, women with a family history of breast cancer appear to be at increased risk of being diagnosed with BBD, in particular the high-risk types of BBD associated with a greatly increased risk of breast cancer. This link adds weight to the belief that BBD with atypia is a precursor or marker lesion for breast cancer. Ashbeck et al (2007) [11] found that women with low-risk diagnoses and a family history of breast cancer had an age-adjusted HR of 2.33 (95% CI, 1.68-3.22), whereas women with a low-risk diagnosis and no family history of breast cancer had an age-adjusted HR of 2.14 (95% CI, 1.88-2.44). The number of women with a family history of breast cancer is inadequate for further analyses of possible risk modification in the specific low-risk categories.

On correlation with the site of lump, significant difference in site of lump with respect to side of lump ($p = 0.044$) was noted in the present study. According to literature as upper and outer quadrant contains bulk of mammary tissue, lumps (benign and malignant) are commonest in that position. Shantha Kumar et al (2017)[12] in their study in Government Vellore Medical College and Hospital, Vellore, Tamilnadu reaffirmed that the upper and outer quadrant was the commonest site of the lump in our patients (55 patients), while the upper inner quadrant was involved in 37, the lower and outer in 15 and the lower and inner quadrant in 9. Hussain, in his series had 29 patients (58%) with the lump in the upper and

outer quadrant. Both studies showed the upper and outer quadrant to be the dominant quadrant to have a palpable lump. These findings were very similar to the present study. Srivastava et al (2017) [13] revealed that lesion was most commonly present in upper outer quadrant 33 cases (27.5%) and in lower outer quadrant there were 18 cases (15%).

The absence of benign breast lesions using histology (gold standard) testing in this study implies that it is not feasible to calculate specificity of BIRADS for diagnosing breast cancer in the current study. The increasing trend of malignant lesion on histopathological examination of benign disease may be due to inter and intra observer variability. Larger longitudinal studies done by Orel S. G et al (2003) used over a 1000 patients to look at Positive Predictive Value for each BI-RADS categorization and its predictive usefulness for malignancy.[14] Showing effectiveness of placing mammographic lesions into BI-RADS categories, the study further highlighted the varying Positive Predictive Value values amongst the BI-RADS categories. In another related study, Lieberman et al (2000) found that the standardized terminology of the BI-RADS lexicon does allow quantification of the likelihood of malignancy for various lesions. [15] In that study, the features with the highest Positive Predictive Value were spiculated margins, irregular shape, linear morphology of micro calcifications, and segmental or linear distribution of micro calcifications. The predictive accuracy in these two categories is large enough to encourage more active utilization of BI-RADS. Fisher et al (1978) noted that one mammographic designation for each breast based upon the greatest-risk pattern disclosed a similar inconsistency in correlation with corresponding histopathologic features. [16]

Limitations

The reporting of the mammogram needs a darkened room with dark filterson the view-box to block out unnecessary light. These measures ensure the reporting of an image with better contrast. Also additional equipment such as a magnifying glass will be utilized to scrutinize the images better. The format of the mammographic report however was not standardized. The diversity in the readings of the mammogram themselves used to result in doubts on the findings, interpretation and recommendation of breast cancer management. In many instances, reports could not be clearly categorized as either positive or negative.[17] As multiple radiologists were used to interpret the images, we were not able to effectively capture inter and intra-rater reliabilities. This study only included biopsy-proven lesions. Hence the study does not inform on predictive value of BI-RADS on benign-appearing lesions that were interpreted as definitely benign or were recommended for follow-up only (BI-RADS 2 and 3). Although problems persist with the system, including the issues of inter- and intraobserver variabilities, multiple studies have validated the efficacy of the descriptors and assessment categories. There is no other system available currently that accomplishes what BI-RADS has done. Continued auditing, research, refinement and revisions of the BI-RADS lexicon are to be expected and will lead to continued improvement and better patient care.

Recommendations

The use of the standardized BI-RADS lexicon among radiologists involved with breast imaging should be encouraged. The referring physicians should be further educated about the BI-RADS assessment categories and the correlation between the various categories and outcome so that tissue diagnosis is reserved for those lesions that are indeterminate (BI-RADS category 3). Strict short interval follow up of patients categorized BI-RADS 3 as a means of surveillance of malignancy with additional investigations like FNAC, Trucut biopsy, MRI etc should be advised. This would require forming a patient database with regular updated contacts and collaboration with referring physicians. With regard to radiography in the

hospital, although the standards were high a few recommendations are listed below:

1. A true oblique should be taken routinely in all patients. The advantages of this view are enumerated elsewhere, but because most lesions were found to occur in the upper outer quadrant, the use of this view is even further warranted.
2. The use of grids in larger and dense glandular breasts has been discussed. It is a very useful addition to the sonography.
3. All the exposures were taken using an automatic photo timer. It is preferable to use manual settings because they can be varied according to breast size and density.
4. It was noted, with concern, that very few patients (especially those in the high risk age groups) visited the hospital on their own accord. In Western countries all women above the age of 40 are recommended to have yearly mammograms. This should be encouraged in our region also and the onus lies on doctor and healthcare providers to increase patient awareness of the benefits of early detection of breast -cancer.
5. The fact that breast cancer appears to affect younger age groups in our environment further emphasises the need for screening patients for non-palpable cancers.

Conclusion

Women who are clinically diagnosed with benign breast disease underwent mammography and further histopathological examination, thereby determining the accuracy of BI-RAD system mammography as screening technique and risk stratification. Benign breast disease is commonly seen in younger age group. Commonest presentations are lump in breast and mastalgia. Even though correlation between family history with breast malignancy is not statistically significant, there is a greater risk of developing high-risk types of benign breast disease in families with history of breast cancer. There is statistically significant increased prevalence of benign breast disease in multigravida women and positive history of breastfeeding. Upper outer quadrant is the most common site of benign breast lump, which is statistically significant. Even though BI-RADS 2 and 3 in mammography showed majority of benign lesions, there is increased trend of malignancy in higher BI-RADS criteria, on further histopathological examination. Sensitivity, positive predictive value and diagnostic accuracy are very high for mammographic screening.

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