

MISSED MALIGNANCY IN MIXED BILATERAL BENIGN BREAST LESIONS- A CLINICAL STUDYSankararaman Balasubramanian¹, Bharathidasan Rajamanickam², Ambujam Govindasamy³, Raj Prakash Chandramohan⁴¹Associate Professor, Department of General Surgery, Private Clinic and Vinayaka Missions Medical College, Karaikal.²Associate Professor, Department of General Surgery, Private Clinic and Vinayaka Missions Medical College, Karaikal.³Professor and HOD, Department of General Surgery, Private Clinic and Vinayaka Missions Medical College, Karaikal.⁴Postgraduate Student, Department of General Surgery, Private Clinic and Vinayaka Missions Medical College, Karaikal.**ABSTRACT****BACKGROUND**

Though breast diseases even in benign status poses considerable anxiety and fear to the suffering woman and to her blood relatives, this leads to extensive investigative modalities in benign breast diseases including MRI and wire localisation of the impalpable lesion and biopsy to prove beyond doubt that it is not malignant. This paper is to enlighten the critical situation to which we were pushed in our analysis of 4 cases of bilateral benign cystic breast diseases who were diagnosed to have malignancy in one of the breasts during periodic followup, while they were on conservative treatment.

The interesting facts like- 1. Malignancy after wide excision for cystic lesions; 2. Incidence of malignancy in the family, 3 of the 4 patients; 3. Association of HER-2/neu oncogene positivity status in all the patients; 4. Demand and decision to do bilateral prophylactic mastectomy in patients even though the breast lesion proved to be benign.

MATERIALS AND METHODS

The study was conducted in Vinayaka Missions Medical College, Karaikal and Private Clinic in Thanjavur. A series of 320 cases of benign breast disease of varying ages from 20 to 60 years were studied for a period of 2 years. Diagnosis was made by means of histopathological examination and sonomammogram. Followup was done for a minimum period of 1 year.

RESULTS

320 cases of bilateral benign breast disease were studied, out of which 4 cases were found to be malignant during followup. The 4 cases were studied briefly and the results were as follows.

- 316 cases were found to be benign even after followup for a minimum period of 1 year.
- 4 cases were found to be malignant during followup.
- 3 out of 4 patients had family history of breast malignancy.
- 3 of 4 patients had ER +ve
 - PR +ve
 - HER-2/neu +ve
- 1- nulliparous unmarried.
- All four above the age of 40 years.
- High risk patients for developing malignancy.

CONCLUSION

High risk population must be screened routinely. The risk of malignancy is very high following benign breast disease. Other factors such as age, nature of discharge, parity and family history were taken into account and treatment was tailored according to the diagnosis.

KEYWORDS

Malignancy in Benign Breast Lesion, Bilateral Breast Lesion, Treatment.

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BACKGROUND

- The breast is a modified sweat gland composed of both epithelial and connective tissue elements. Therefore, neoplasms arising from these elements have to be classified separately.¹

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- Benign breast disease is the most common cause of breast problems; up to 30% of women will suffer from a benign breast disorder¹ requiring treatment at some time in their lives.
- The most important issue is to bear in mind that a patient complaining of breast symptoms can have breast cancer as well as a benign condition. When breast cancer is not treated early, median survival will be around 3 years.¹
- Both benign and malignant breast disorders can present with a palpable mass; skin dimpling, thickening or erythema; pain; nipple discharge and inversion or distortion or an abnormal screening mammogram with no clinical findings.²
- It is very important to collect as much information as possible prior to the definitive surgical treatment as the

approach to surgery in malignant and benign disease differs. With inadequate surgery, you may worsen the chances of your patient being cured and benefitted by the treatment instituted.

- Studies of benign breast disease can also clarify whether there is a continuum of breast alterations that culminates in breast cancer. However, it remains unclear which of the benign entities are actual precursors and which reflect a background of increased risk involving all breast tissue in a woman,³ but some conditions caution that they may pose a risk.
- Breast diseases even in benign status poses considerable anxiety and fear to the suffering woman and to her blood relatives.
- This leads to extensive investigative modalities in benign breast diseases including MRI and wire localisation of the impalpable lesion.
- Benign breast disease is an important risk factor for a later breast cancer, which can develop in either breasts.
- Important questions however include the degree of risk with the common non-proliferative benign entities, family history, etc. influencing.²
- The identification of benign breast disease has become more common as the use of mammography and sonomammogram has increased, and thus having accurate risk estimates for women who are diagnosed as benign is imperative.^{3,4}

MATERIALS AND METHODS

A prospective clinical study of 320 patients, among which 4 patients were presented briefly below. The chi-square test was used to analyse the values in the results. The standard deviation, p value and 't' score were computed and tabulated.

Inclusion Criteria

1. Bilateral breast disease.
2. Clinically cystic disease of both the breasts with nipple discharge.
3. Sonogram/sonomammogram confirmation of bilateral cystic lesions.

Exclusion Criteria

1. Unilateral breast disease.
2. Previous history of breast malignancy treated in one breast.
3. Pregnant women.

Methods

Patients who were attending the OPD in Department of Surgery, VMMCH, Karaikal and also patients with breast lump attending the private clinic in Thanjavur with clinical suspicion of breast lump and proven with ultrasound or sonomammogram are taken in the study. A total of 320 patients were taken and out of which 4 cases which were proven to be malignant were discussed in detail. The chi-square test was used to analyse the values in the results. The standard deviation, p value and 't' scores were computed and tabulated.

Patient A- 45 yrs. old perimenopausal woman. She was operated one and a half years back for benign cystic disease-excision biopsy for proliferative breast disease.



Figure 1. Intra-op Picture of Benign Fibrocystic Lesion

She has a family history of breast carcinoma. Mammogram showed mass lesion with clustered microcalcification with ill-defined margin.

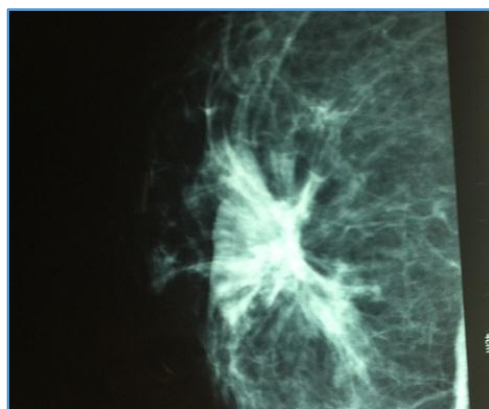


Figure 2. Satellite Mass with Clustered Microcalcification

Stellate mass with Clustered microcalcification.

Tru-cut biopsy showed as infiltrating ductal carcinoma following which MRM was done.

Patient B- 50 years old, post-menopausal, unmarried woman complains of swelling in both the breasts; 2 years back she was conservatively managed for benign fibrocystic disease. She gave a history of increase in size of the swelling.

Tru-cut biopsy- Invasive ductal carcinoma following which MRM was done.

Mammogram- Irregular mass with calcification.



Figure 3. Post-op Pic: Cystic component with Malignancy

Patient C- 46 years old perimenopausal unmarried woman, complains of swelling in both the breasts. She has a family history of breast CA. History of excision biopsy for sclerosing adenosis with dysplastic changes 1 year back. She has developed a swelling in the same breast.

During followup she was subjected to FNAC after mammogram with suspicious lesion and the result was infiltrating ductal CA. She had a lump on other side of breast, which was found to be benign. Revision MRM done on the left side. Prophylactic risk reduction mastectomy on the other side was done- patient demanded.



Figure 4. MRI - Showing Gadolinium Enhancement

Patient D- 40 yrs. old unmarried nulliparous woman had swelling in both the breasts for 2 yrs. One year back for benign fibrocystic disease- wide local excision done. On followup, she presented with hard and nodular lesion in same breast.

Tru-cut biopsy was infiltrating ductal carcinoma. During followup patient was advised surgery, but patient opted for surgery elsewhere.



Figure 5. Bilateral Mastectomy

RESULTS

320 cases of bilateral benign breast disease were studied, out of which 4 cases were found to be malignant during followup. The results were computed using chi-square test and tabulated. The 4 cases were studied briefly and the results were as follows.

Sl. No.	Total Patients	320
1.	Benign	316
2.	Malignant	4

Table 1

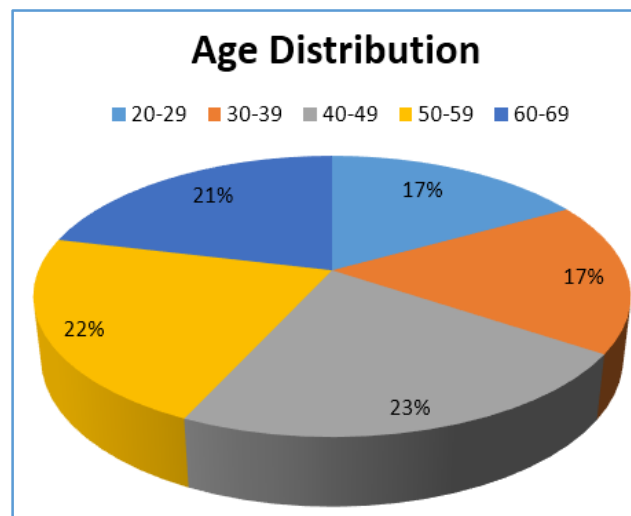
Age Wise Distribution

Sl. No.	Age (Years)	No. of Patients	No. of Patients- Proven Malignancy
1.	20 - 29	54	NIL
2.	30 - 39	56	NIL
3.	40 - 49	72	3
4.	50 - 59	70	1
5.	60 - 69	68	NIL

Table 2

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-Sided)
Pearson Chi-Square	7.233 ^a	4	.124
Likelihood Ratio	7.582	4	.108
Linear-by-Linear Association	.030	1	.863

Table 3



Graph 1

Age wise distribution shows a much increase in the incidence of risk of malignancy, as the age advances. In the age group 40 – 49, there are 3 patients out of 72 proved positive for malignancy. Out of 70 patients in the age group 50-59, one patient was tested positive for malignancy. Age wise distribution shows a non-significant ‘p’ value of 0.124. It was calculated using chi-square test. No significant interactions were observed between age and family history.

- 316 cases were found to be benign even after followup for a minimum period of 1 year.
- 4 cases were found to be malignant during followup.
- 3 out of 4 patients had family history of breast malignancy.
- 3 of 4 patients had ER +ve.
 - PR +ve.
 - HER-2/neu +ve.
- 1- Nulliparous unmarried.

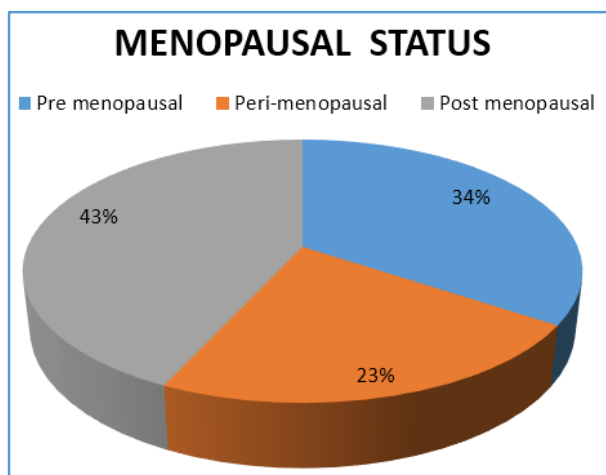
Menopausal Status

Sl. No.	Menopausal State	Age	Total	Malignancy
1.	Pre-menopausal	< 40 years	110	Nil
2.	Peri-menopausal	40 - 50 years	72	3
3.	Post-menopausal	> 50 years	138	1

Table 4

	Value	df	Asymp. Sig. (2-Sided)
Pearson Chi-Square	6.524 ^a	2	.038
Likelihood Ratio	6.133	2	.047
Linear-by-Linear Association	.134	1	.714

Table 5



Graph 2

The results in the menopausal status shows a statistically significant value of .036, which was calculated using chi square test. However, there was a significant interaction between the menopausal status, age and the risk of breast cancer.

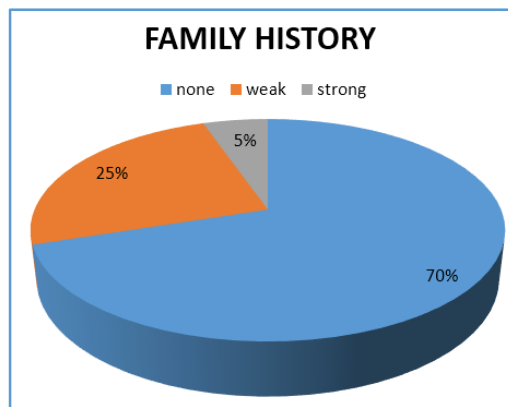
In the peri-menopausal age group, there is a high incidence of malignancy, i.e. the average menopausal age in the study group being 48 years. There are 3 out of 4 patients with malignancy observed within the age group of 40 - 50 years.

Family History of Breast Cancer

Sl. No.	Family History	No. of Patients
1.	None	238
2.	Weak	84
3.	Strong	18

Table 6

The family history shows a strong relation in 18 out of 320 patients. But there is a history either weak or strong in a total of 102 patients.



Graph 3

- All four above the age of 40 years.
- High risk patients for developing malignancy.

DISCUSSION

Risk Factors

1. Age and Gender- 1 in 233 from ages 30 to 39 years, 1 in 69 from ages 40 to 49, 1 in 42 ages 50 to 59, 1 in 29 from ages 60 to 69 and 1 in 8 by age 80 years.⁵
2. Personal History of Breast Cancer.
3. Histologic Risk Factors- LCIS, ADH and ALH (Proliferative lesions with atypia).^{3,6,7}

Histological Risk Factors for Development of Breast Cancer	
Histological Diagnosis	Estimates, RR
Proliferative Disease	1.0
Proliferative Disease without Atypia	1.3 - 1.9
Proliferative Disease with Atypia	3.7 - 4.2
Strong Family History	4 - 9
Lobular Carcinoma in Situ	> 7

Table 7

4. Family History and Genetic Risk Factors- First-degree relatives 2-fold to 3-fold excess risk.⁸
5. Genetic factors are estimated to be responsible for 5% to 10% of all breast cancer cases, but they may account for 25% of cases in women younger than 30 years.^{9,10}

Because the risk for development of breast cancer is high in carriers of a BRCA gene mutation, the use of prophylactic surgery is considered to be the most rational approach.¹¹

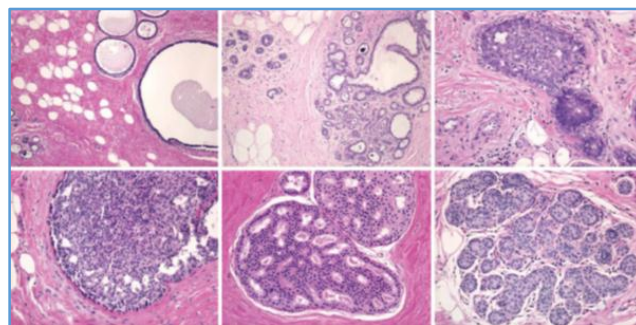


Figure 6. Histopathological Appearance of Benign Breast Disease (Haematoxylin and Eosin)¹²

Panel A shows non-proliferative fibrocystic changes: the architecture of the terminal-duct lobular unit is distorted by the formation of microcysts associated with interlobular fibrosis. Panel B shows proliferative hyperplasia without atypia. This is adenosis, a distinctive form of hyperplasia characterised by the proliferation of lobular acini, forming crowded gland-like structures. For comparison, a normal lobule is on the left side. Panel C also shows proliferative hyperplasia without atypia. This is moderate ductal hyperplasia, which is characterised by a duct that is partially distended by hyperplastic epithelium within the lumen. Panel D again shows proliferative hyperplasia without atypia, but this is florid ductal hyperplasia: the involved duct is greatly expanded by a crowded, jumbled-appearing epithelial proliferation. Panel E shows atypical ductal hyperplasia: these proliferations are characterised by a combination of architectural complexity with partially formed secondary lumens and mild nuclear hyperchromasia in the epithelial-cell population. Panel F shows atypical lobular hyperplasia: monotonous cells fill the lumens of partially distended acini in this terminal-duct lobule.

6. Reproductive Risk Factors- onset of menarche before 12 years of age, first live childbirth after age 30, nulliparity and menopause after age 55 years.¹³
7. Exogenous Hormone Use- Therapeutic or supplemental oestrogen and progesterone increases the risk of development of breast cancer.

Prophylactic Mastectomy

Prophylactic mastectomy- reduce the chance of developing breast cancer in high-risk women by 90%.

Several groups have reported on prospective studies in BRCA1 and BRCA2 mutation carriers with prophylactic mastectomy prevent breast cancer.^{13,14}

More recently, results of Risk-Reducing Mastectomy (RRM) and Risk-Reducing Salpingo-Oophorectomy (RRSO) were reported in BRCA1 and BRCA2 mutation carriers.¹⁵

CONCLUSION

- High risk population must be screened routinely.^{3,7,11}
- The risk of malignancy is very high following benign breast disease.
- Unless it is obviously benign, only histology may rule out breast cancer.¹²
- When performing surgery beware when operating on the lesion- include larger or smaller margins according to the findings and do not remove the whole breast tissue.
- Our study shows that histologic features, the age at biopsy and the degree of family history are major determinants of the risk of breast cancer after the diagnosis of benign breast disease.
- Any infection needs close monitoring, care and enough patience for healing.^{16,17}
- Understanding the risk associated with benign breast disease is important, because the increasing use of mammography has increased the frequency of breast biopsies, most of which yield benign findings.¹⁸
- In a retrospective study of women undergoing annual mammographic screening, Elmore et al. found that 18.6 percent of women underwent a biopsy after 10 screening mammograms. The use of hormone therapy may also affect

the frequency of breast biopsies. Chlebowski et al reporting for the Women's Health Initiative investigators found that relatively short-term therapy with oestrogens plus progesterone increased the percentage of women with abnormal mammograms, a major indicator for breast biopsy.^{17,19}

Summary

Our study shows that histologic features, the age at biopsy and the degree of family history are major determinants of the risk of breast cancer after the diagnosis of benign breast disease.²⁰ We found no increased risk among women with non-proliferative lesions, unless a strong family history was present. No significant interaction between atypia and family history was apparent. The excess risk of cancer in the ipsilateral breast in the first 10 years after the diagnosis of benign breast disease, especially in women with atypia points to the presence of precursors in some women.

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