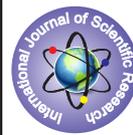


## Bilateral breast cancer: difference in histological and biological parameters in synchronous and metachronous presentation



### Oncology

**KEYWORDS:** contralateral breast cancer; Synchronous; metachronous; second primary cancer; metastatic

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### ABSTRACT

**Aim:** Bilateral breast carcinoma(BBC) is on the rise from past few decades, mainly because of the improved detection capabilities and increased overall survival times after primary breast cancer. The incidence of BBC

varies from 4–20%. The probability is between 0.5 to 1% per year with a cumulative incidence of 15% in patients with previous history of breast cancer.

**Methods:** We reviewed 52 bilateral breast cancer out of 6858 breast cancer patients treated at our hospital from 2006 to 2015. We analysed the significance of concordance of clinical and histological parameters among the synchronous(17) and metachronous groups(35).

**Results :** We had 17 patients of synchronous and 35 patients with metachronous BBC . The concordance rates of T stage, N stage and TNM stage were seen to be 47%, 53% and 47% respectively in synchronous cancers whereas they were 42%, 49% and 34% respectively in metachronous cancers. Histopathological subtype was same in 72% of patients in synchronous cancers while it was significantly more diverse in metachronous cancers (p=0.03). The concordance rates of histological grade were 53% in synchronous cancers and 38% in metachronous cancers(p=0.002). The concordance rate of estrogen receptor in synchronous cancers was 82% and in metachronous was 63 %(p=0.03). The concordance of progesterone receptor and cerbB-2 receptor expression among both groups was statistically insignificant.

**Conclusion :** We conclude that biological parameters can complement the histological factors in differentiating metastatic cancer from second primary cancer in synchronous and metachronous bilateral breast cancer cases.

### INTRODUCTION

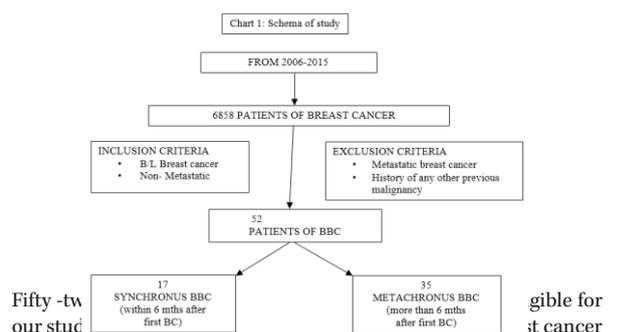
Globally, the incidence of bilateral breast carcinoma (BBC) is on the rise from past few decades, mainly because of the improved detection capabilities due to the introduction of mammography and increased overall survival times after primary breast cancer.[1] The overall incidence of BBC varies from 4–20%.[2] The risk factors associated with bilateral occurrence are: familial or hereditary breast cancer, young age at primary breast cancer diagnosis, lobular invasive carcinoma, multicentricity and radiation exposure.[3] The risk is 2-6 times higher in woman having a previous history of breast cancer for the development of second breast primary when compared to healthy populations. The probability is between 0.5 to 1% per year with a cumulative incidence of 15%.[4] Also the risk of primary contralateral carcinoma is constantly elevated in contrast to the risk of recurrence which decreases after 5-10 disease free years.[5]

Contralateral cancer is termed as either synchronous, i.e., developing within a specific time period from the development of first breast cancer which varies widely from one month to five years among different retrospective studies or metachronous meaning that the tumor manifestation occurs later than the time period of synchronous one.[6,7] However, this classification according to the length of the time is of little clinical value as it doesn't give information regarding the origin of second breast tumor. For the management purposes, the challenge in bilateral breast cancer is to find whether the second tumor is a new primary or a metastasis from the first carcinoma. Metastatic lesions will be histologically more closely related to the first carcinoma than second primary. Histological type, grading, presence of an in-situ component and steroid receptor status are the most commonly investigated factors.[8-10] In 1984, Chaudary et al described pathologic criteria based on which a

bilateral breast cancer can be considered as a second primary but the caveat is that a synchronous bilateral breast cancer most often is considered as a metastatic lesion and not a multifocal monoclonal lesion.[5] In the late 1990s the cDNA microarray-based comparative genomic hybridization (CGH) method has been employed to investigate the clonality of bilateral breast cancers and it showed higher DNA copy number changes in metachronous than in synchronous bilateral breast cancers.[11] However, this method is complicated, expensive and needs further validation for general use. This study was initiated to evaluate the difference in histological and biological parameters in bilateral breast cancers in synchronous & metachronous presentation and whether can they be used to differentiate a metastatic lesion from second primary in bilateral breast cancers.

### METHODS

We reviewed the medical records of 6858 breast cancer patients treated at our hospital from 2006 to 2015. [Chart 1]



and two patients with history of previous ovarian malignancy. Synchronous breast cancer was defined as development of second breast cancer within 6 months of diagnosis of first cancer and 17 patients were included in this group while 35 patients were having metachronous lesion which developed after 6 months of the primary.[2] Routine blood investigations including liver function tests, chest x-ray, ultrasonography abdomen & pelvis and bone scan when indicated were done to rule out distant metastasis. Contralateral breast lesions were diagnosed and confirmed by mammography/ ultrasono-mammogram and histopathological examination.

Cases were categorised into different histological subtypes using current WHO classification of breast cancer. Modified scarf-bloom-richardson staging was used for grading of ductal carcinoma.[12] For immunohistochemistry (IHC), deparaffinized sections were immunostained with primary antibodies to estrogen receptor, progesterone receptor and cerbB-2 oncoprotein. In estrogen and progesterone receptor stain, a 10% nuclear positivity rate was regarded as receptor positive. Strong complete membrane staining of >10% of tumor cells which correlates with '3+' score was taken as cerbB-2 positive. Cancer staging was done using AJCC 7<sup>th</sup> edition criteria.

Statistical analysis was done using SPSS software version 22. Student's t-test was employed for the analysis of group comparison with histologic and biologic parameters and Pearson's correlation was used to estimate correlation between variables. *p* value of 0.05 or less was taken as significant.

## RESULTS

We had 17 patients of synchronous BBC and 35 patients with metachronous BBC and all of them were female. Median age of presentation in synchronous group was 52(34-76) years. Metachronous group patients were having median age of 43(32-73) years at the time of index case presentation while 50(34-75) years for the second breast cancer. Median time interval between the development of first and second breast cancer in metachronous group was 23(7-92) months.[Table 1]

In both synchronous and metachronous groups, first breast cancer most commonly presented in stage III ( 53% & 54% respectively ) while stage II (41% & 43% respectively) was most common in second breast cancer presentation.[Table 1] The concordance rates of T stage, N stage and TNM stage were seen to be 47%, 53% and 47% respectively in synchronous cancers whereas they were 42%, 49% and 34% respectively in metachronous cancers.

Infiltrating ductal carcinoma was the most common histopathological subtype present in both the groups (76% in all).[Table 2]. Histopathological subtype was same in 72% of patients in synchronous cancers while it was significantly more diverse in metachronous cancers having concordance rates of 57% (*p*=0.03). Most of the cases of first cancer in both the groups had grade II tumor while in second cancer, grade III was most common in metachronous group where as grade II and III were equally common in synchronous cases. The concordance rates of histological grade were 53% in synchronous cancers and 38% in metachronous cancers.(*p*=0.002). Progesterone receptor was having concordance rate of 65% in synchronous and 66% in metachronous cancers. The concordance rate of estrogen receptor in synchronous cancers was 82% and in metachronous was 63 % which was statistically significant(*p*=0.03). In synchronous cancers, cerbB-2 expression was concordant in 88% of patients while in metachronous cancers the concordance rate was 60% which was not significant(*p*=0.23).[Table 3]

## DISCUSSION

The incidence of BBC in our study is 0.7% which is lower than the reported incidence of 4-20% in literature.[2] Longer survival times after the primary breast cancer has put more number of patients at risk of developing contralateral tumors. According to literature, the

contralateral breast is the most common site of second primary to develop in a patient of breast cancer.[5] Introduction of mammography has also resulted in the improved detection rate of the BBC.

Contralateral breast cancer can either be synchronous or metachronous. Synchronous BBC was first defined based on the simultaneous diagnosis of tumors in both breasts by Kilgore in 1921.[14] Later, a time interval between the diagnosis of the tumors was introduced which varies widely among different retrospective studies, i.e., From being 1 month, 2 months, 3 months, 6 months or even 1 year.[15-19] We chose the time interval of 6 months for our study as most of the comparative studies have chosen the same criteria. The incidence of synchronous bilateral cancer (both cancers diagnosed within six months) is approximately 1% to 2% and of metachronous cancer 5% to 10%.[18,20] In our study, the incidence is 0.2% & 0.5% for synchronous and metachronous BBC, respectively.

For treatment purposes, the dilemma is whether we are treating one disease or two? It is important to differentiate between second primary breast cancer and metastasis from primary breast lesion as the management of the two differs. Second primary breast cancer can be offered radical management while metastatic lesion will go for palliative treatment. First attempt to this was made by Chaudary et al[5] in 1984 when he described following pathologic criteria for the diagnosis of second primary breast cancer – 1. there must be in situ change in the contralateral tumor. 2. the tumor in the second breast is histologically different from the cancer in the first breast. 3. the degree of histological differentiation of the tumor in the second breast is distinctly greater than that of the lesion in the first breast. 4. there is no evidence of local, regional or distant metastases from the cancer in the ipsilateral breast. Despite the arrival of newer methods such as cDNA microarray-based CGH.[11] Chaudary's criteria is still most commonly used because of its ease of clinical applicability. Among synchronous BBC patients, 8 had the same TNM staging in both the cancers while in metachronous group 14 patients retained the same. The concordance rate of T stage, N stage & TNM stage was 47%, 53% & 47% respectively in synchronous group and 42%, 49% & 34% respectively in metachronous patients but none of them was statistically significant. Selvakumar et al[21] also didn't find it significant, but Gong et al[22] in his study of 41 bilateral breast cancer patients found statistically significant (*p*=0.03) concordance rate of 64% and 32% for synchronous and metachronous lesions respectively. The concordance rate of histopathologic type was 72% and 57% of synchronous and metachronous cancers, respectively which was statistically significant (*p*=0.03). This signifies that synchronous cancers are more clonally related compared to metachronous cancers. Same significant result was obtained by Gong et al[22] where the concordance rate was 93% and 59% for synchronous and metachronous cancers respectively(*p*=0.02). Selvakumar et al[21] found the result to be insignificant. In synchronous group, 53% cases had same grading in both first and second cancer while in metachronous group, the same grading was present only in 38% cases (*p*=0.002).None of the other studies we compared, found this result significant. Also to note was the fact that 62% patients had their grading increased to higher grade in metachronous cases while the same was in only 30% patients in synchronous group. Thus, according to Chaudary's criteria, metachronous group had higher number of second primary than metastatic lesions. The presence of intra-ductal component in the contralateral tumor is one of the factor studied in literature and as reported by Intra et al, implies second primary and rules out metastatic origin.[10] Since our treatment records were inconsistent regarding the presence or absence of intra-ductal component, we didn't consider this factor for analysis.

Steroid receptor expressions have been evaluated by many authors, but the significance of concordance rates has been different in different studies. In our study, the concordance rate of estrogen receptor was significantly higher in synchronous cases (82%) than in metachronous cases(63%). Concordance rates of progesterone and

Her-2-neu receptors were insignificant in our study. Diaz et al[23] in his study over 58 patients also found the concordance rate of estrogen receptors significant ( $p=0.04$ ) while Gong et al[22] found the concordance rate of progesterone receptors significant ( $p=0.03$ ). Neither of them were significant in Selvakumar et al study.[21] The concordance rate of Her-2-neu expression was not significant in any of the study we compared.

Our study had a few limitations, first being the low number of patients involved. Second, we didn't do any genetic testing for familial breast carcinoma, which has a high incidence of bilateral breast cancer with specific phenotypes. Third, most of the patient in metachronous cases had received tamoxifen as adjuvant therapy, which is known to affect the development of contralateral breast carcinoma.

**Conclusion**

Our study shows that synchronous cancers are more closely related to the primary tumor than the metachronous lesions. We conclude that biological parameters can complement the histological factors in differentiating metastatic cancer from second primary cancer in synchronous and metachronous bilateral breast cancer cases. However, a large scale validation study is required to define their role for this purpose because of varied results present in different studies.

**Acknowledgment**

We gratefully acknowledge Prof M Vijaykumar for his guidance for preparation of manuscript. We also acknowledge Department of Medical Record.

**Abbreviation**

- BBC: bilateral breast carcinoma
- CGH: comparative genomic hybridization
- DNA: Deoxy ribonucleic acid
- WHO: world health organization
- IHC: Immunohistochemistry
- AJCC: American Joint Committee of Cancer
- IDC: intra ductal component

**Tables**

**Table 1:** Patient characteristics of bilateral breast cancer

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Variables	Synchronous (n=17)		Metachronous(n=35)	
	1 <sup>st</sup> breast cancer	2 <sup>nd</sup> breast cancer	1 <sup>st</sup> breast cancer	2 <sup>nd</sup> breast cancer
Age at diagnosis	52(34-76)	43(32-73)	50(34-75)	
Time interval of	0	23 (7-92)		
<b>Stage</b>				
0	0	2	3	2
I	0	2	2	7
II	6	7	11	15
III	9	4	19	7
IV	2	2	0	4
Same	47%		34%	
Different	53%		66%	
$\chi^2=3.076$ , df=1.000, p= 0.32				

**Table 2:** Histological parameters in bilateral breast cancers

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	Synchronous		Metachronous	
	1 <sup>st</sup> breast cancer	2 <sup>nd</sup> breast cancer	1 <sup>st</sup> breast cancer	2 <sup>nd</sup> breast cancer
<b>Histology</b>				
Infiltrating ductal carcinoma	13	10	29	27
DCIS	0	2	3	2
Medullary	0	1	1	2
Lobular	2	2	1	0
Tubular	0	0	0	1
Mucinous	1	0	0	1

Papillary	1	2	1	2
Same	72%		53%	
Different	28%		47%	
$\chi^2=11.34$ , df=1.000, p=0.03				
<b>Histological Grade</b>				
I	3	2	2	3
II	6	4	15	7
III	4	4	12	17
Same	53%		38%	
Different	47%		62%	
$\chi^2= 13.78$ , df=1.000, p=0.002				

**Table 3:** Steroid receptor and cerbB-2 expression in bilateral cancers

Table 3 Steroid receptor and cerbB-2 expression in bilateral cancers		
Variables	Synchronous (n=17)	Metachronous(n=35)
<b>Estrogen receptor</b>		
Both (+)	8(47%)	15(43%)
Both (-)	6(35%)	7(20%)
(+)→(-)	-	5(14%)
(-)→(+)	-	8(23%)
Same	14(82%)	22(63%)
Different	3(18%)	13(37%)
$\chi^2=9.318$ , df=1.000, p=0.03		
<b>Progesterone receptor</b>		
Both (+)	6(35%)	6(17%)
Both (-)	5(30%)	17(48%)
(+)→(-)	-	8 (23%)
(-)→(+)	-	4(12%)
Same	11(65%)	23(66%)
Different	6(35%)	12(34%)
$\chi^2= 2.003$ , df=1.000, p=0.79		
<b>cerbB-2</b>		
Both (+)	4(23%)	3(9%)
Both (-)	11(65%)	18(51%)
(+)→(-)	-	6(17%)
(-)→(+)	-	8(23%)
Same	15(88%)	21(60%)
Different	2(12%)	14(40%)
$\chi^2=2.975$ , df=1.000, p=0.23		

**References**

1. Holmberg L, Adami HO, Ekblom A, Bergstrom R, Sandstrom A, Lindgren A. Prognosis in bilateral breast cancer. Effects of time interval between first and second primary tumours. Br J Cancer 1988;58:191-4.
2. Dawson LA, Chow E, Goss PE. Evolving perspectives in contralateral breast cancer. Eur J Cancer 1998;34:2000-9.
3. Chuba PJ, Hamre MR, Yap J, et al. Bilateral risk for subsequent breast cancer after lobular carcinoma in-situ: analysis of surveillance, epidemiology, and end results data. J Clin Oncol 2005;23:5534-41.
4. Heron DE, Komarnicky LT, Hyslop T, Schwartz GF, Mansfield CM. Bilateral breast carcinoma: risk factors and outcomes for patients with synchronous and metachronous disease. Cancer 2000;88:2739-50.
5. Chaudary MA, Millis RR, Hoskins EO, et al. Bilateral primary breast cancer: a prospective study of disease incidence. Br J Surg 1984;71:711-4.
6. Abdalla I, Thisted RA, Heimann R. The impact of contralateral breast cancer on the outcome of breast cancer patients treated by mastectomy. Cancer J 2006;6(4):266-72.
7. Bloom ND, Daluovoy RV, Ceccarelli F, Degenshein GA. Bilateral mammary carcinoma; immunologic implications. New York state J Med 1980;80(6):908-10.
8. Dawson PJ, Maloney T, Gimotty P, Juneau P, Ownby H, Wolman SR. Bilateral breast cancer: one disease or two? Breast Cancer Res Treat 1991;19:233-44.
9. Coradini D, Oriana S, Mariani L, et al. Is steroid receptor profile in contralateral breast cancer a marker of independence of the corresponding primary tumour? Eur J Cancer 1998;34:825-30.
10. Intra M, Rotmensz N, Viale G, et al. Clinicopathologic Characteristics of 143 Patients with Synchronous Bilateral Invasive Breast Carcinomas Treated in a Single Institution. Cancer 2004;101:905-12.
11. Seo MY, Rha SY, Yang SH, et al. The pattern of gene copy number changes in bilateral breast cancer surveyed by cDNA microarray-based comparative genomic hybridization. Int J Mol Med 2004;13:17-24.
12. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology 1991;19:403-10.
13. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A III. AJCC Cancer Staging Manual, 7th ed. New York: Springer; 2010. p347-76.
14. Kilgore AR. The incidence of cancer in the second breast. JAMA 1921;77:454-7.
15. Gollamudi SV, Gelman RS, Peiro G, et al. Breast conserving therapy for stage I-II

- synchronous bilateral breast carcinoma. *Cancer* 1997;79:1362-9.
16. Fritz A, Ries L (eds). *The SEER Program Code Manual*. 3rd Edi. Bethesda, Md: National Cancer Institute; 1998 (updated January 2003).
  17. Hartman M, Czene K, Reilly M, et al. Incidence and prognosis of synchronous and metachronous bilateral breast cancer. *J Clin Oncol* 2007;25:4210-6.
  18. de la Rochefordiere A, Asselain B, Scholl SM, et al. Simultaneous bilateral breast carcinomas: A retrospective review of 149 cases. *Int J Radiat Oncol Biol Phys* 1994;30:35-41.
  19. Al-Jurf AS, Jochimsen PR, Urdaneta LF, Scott DH. Factors influencing survival in bilateral breast cancer. *J Surg Oncol* 1981;16:343-8.
  20. Donovan AJ. Bilateral Breast cancer. *Surg Clin North Am* 1990;70:1141-9.
  21. Selvakumar VP, Garg S, Siddiqui K, Goel A, Kumar K, Kumar R. Tailored approach to management of bilateral breast cancer in Indian women. *Asian J Oncol* 2015;1:97-100.
  22. Gong SJ, Rha SY, Jeung HC, Roh JK, Yang WI, Chung HC. Bilateral breast cancer: Differential diagnosis using histological and biological parameters. *Jpn J Clin Oncol* 2007;19:592-60.
  23. Diaz R, Munarriz B, Santaballa A, Palomar L, Montalar J. Synchronous and metachronous bilateral breast cancer: a long-term single-institution experience. *Medical oncology* 2012;29(1):16-24.