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General Surgery

Relation of Receptor Status and Tumor Grade with Menopausal Status in Patients of Carcinoma Breast

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| **Abstract** | **Original Research Article** |

Background: Carcinoma of the breast is the most common female cancer and its incidence is rapidly increasing over the last few decades. In Bangladesh, breast cancer is an issue of gaining concern. Receptor status and histological grade are two important prognostic factors of carcinoma breast. ***Aim of the study:*** To assess the relation and distribution of receptor status and tumor grade among pre and postmenopausal patients of carcinoma breast. ***Methods:*** This cross-sectional observational study was carried out in the Department of General Surgery, Bangabandhu Sheikh Mujib Medical University (BSMMU) Dhaka over a period of one year, a total of 59 admitted female patients with histologically proven carcinoma of the breast were divided into two groups included in this study. The premenopausal age group was considered as a group I (n=31) and the postmenopausal age group was considered as group II (n=28). Data regarding the tumor histopathological type, grading, and receptor status along with other variables were included in a pre-designed data collection sheet. After compiling data, Statistical analyses of the data were done with Statistical Packages for Social Sciences (SPSS- 22). ***Results:*** Sociodemographic variables and personal histories leading to a risk of breast cancer have no significant difference between pre and postmenopausal groups. Invasive ductal carcinoma (grade-II) was predominant in both groups. Estrogen and progesterone receptor-negative tumors were more frequent in premenopausal patients and estrogen and progesterone receptor-positive tumors were more frequent in a postmenopausal patient, but no statistically significant difference between the two groups. More than eighty percent of tumors were human epidermal growth factor-2 negative in both groups. The frequency of estrogen and progesterone receptor positivity gradually reduce from grade I to III in both groups and the frequency of estrogen and progesterone receptor negativity gradually increase from grade I to III in both groups. The frequency of human epidermal growth factor-2 negatively was more common in grade II tumors in the premenopausal group and human epidermal growth factor-2 receptor positively was more in grade I and III tumors in the postmenopausal group. ***Conclusion:*** Tumor histological type, grading has no difference in the two groups. Estrogen and progesterone receptor negativity were more in premenopausal women and estrogen and progesterone receptor positivity more in postmenopausal women. Human epidermal growth factor negativity was predominant in both groups.
Keywords: Breast Carcinoma, estrogen receptor, Progesterone Receptor, Human epidermal growth factor -2.

INTRODUCTION

Carcinoma breast is a major health problem throughout the world. It is the second most common cancer next to lung cancer and an incidence rate is about 11.6 % among all cancers. It remains the most common cancer of women. There are about 2.1 million newly diagnosed female breast cancer cases in 2018,

accounting for almost 1 in 4 cancer-causing deaths among females which is about 24.2 %. Breast cancer is the most frequently diagnosed cancer for females in the vast majority of the countries (154 of 185) and also the leading cause of death in over 100 countries. The breast cancer incidence rate is highest in Australia /New Zealand and northern Europe [1]. According to GLOBCAN, in 2012[2] about 52.9 % of new breast cancer cases were diagnosed in developing countries in 2012, while the corresponding figure for 1980 was only 35 %. Ln Bangladesh the incidence rate of breast cancer is 21.4 per 100000 women, but this figure is likely to be an underestimate since many cases are missed due to lack of awareness, low level of education, misconceptions, poor socioeconomic status, insufficient access to health care and poor governance [3]. So, the prevalence of breast cancer is gradually rising in both developed and developing countries. Breast cancer is a multifactorial disease and positive associations of higher socioeconomic status, null parity, OCP user, early menarche and late menopause, lack of breastfeeding, and positive family history of breast cancer is almost established. Breast cancer is also a biologically heterogeneous disease and patients with the same diagnostic and clinical prognostic profile can have markedly different clinical outcomes [4]. Usually, the prognosis is related to a variety of clinical, pathological, and molecular features which include classical prognostic factors such that histologic type, grade, tumor size, lymph node status, and more recently receptor status [5, 6]. Estrogen receptor (ER) and Progesterone receptor (PR) are intracellular steroid hormone receptors that have received substantial attention since 1986. This hormone is released from the ovary and some extra ovarian sources also. These steroid hormones are necessary for normal breast development but an imbalance of them precipitates abnormal processes like epithelial hyperplasia, intraductal and invasive carcinoma.ER and PR expressions are the most important and useful predictive factors currently available for Breast carcinoma. A measurable amount of ER and PR are found in about (50-85) % of patients with breast cancer. Her -2 /Neu (Human epidermal growth factor -2) receptor status is another important biological prognostic and predictive factor for breast cancer. It is a member of the type 1 epidermal growth factor receptor family of receptor tyrosine kinases. Members of this family have intrinsic tyrosine kinase activity and are considered important mediators for cellular growth, differentiation, and survival[7]. Approximately, 20% of breast cancer patients have Her-2/Neu amplification which results in glycoprotein overexpression. This receptor status is associated with tumor aggressiveness and chemoresistance. A number of studies have been carried out throughout the world as well as in the Indian subcontinent to show the frequency and relation of ER, PR, and Her- 2/Neu status in breast cancer and their prognostic and predictive significance. Histological grading has also an important prognostic value. The most popular method of tumor grading uses three histologic grades, based on the degree of glandular differentiation, nuclear pleomorphism, and mitotic rate. A number of studies in-home and neighboring countries carried out regarding tumor histopathology, almost all studies show that most common tumors are invasive ductal carcinoma, most of the studies shown that higher prevalence of grade II tumor followed by grade III and grade I. Studies considering relation among tumor grade and hormone receptor status shown that tumor that is better differentiated are most likely to be ER, PR positive and has better prognosis [8, 9]. Studies considering tumor grade with age show that most breast tumors in the younger age group are usually higher grade and aggressive in nature with less survival rate. As breast cancer biology is influenced by hormones and there is a changing pattern of tumor histology and receptor status in different age groups. So, it is expected that menopausal status may be a demarcation of this changing biology. Some studies have shown a relation of tumor grade and receptor status with early and late age groups, but no study has shown the relation of tumor grade with the menopausal status of the patient as well as with receptor status. In this observational cross-sectional study, the distribution, as well as relation of tumor grade and receptor status with menopausal status, will be found out.

OBJECTIVES
General Objective
To assess the relation of receptor status and tumor grade with the menopausal status inpatient of carcinoma breast.

Specific objectives
- To assess the distribution of receptor status among carcinoma breast patients.
- To assess the distribution of histological grade among carcinoma breast patients.
- To assess any difference of receptor status between pre and postmenopausal patients of carcinoma breast
- To assess any difference of histological tumor grade in between pre and postmenopausal patients of carcinoma breast.

METHODOLOGY AND MATERIAL
This is a single-center cross-sectional observational study conducted in the Department of General Surgery, Bangabandhu Sheikh Mujib Medical University from February 2020 to March 2021. A total of 59 female patients with histologically proven carcinoma of the breast were admitted to the Department of General Surgery of BSMMU who fulfilled the eligibility criteria of the study recruited as the study population.

Inclusion Criteria
- Female patients with histologically proven

carcinoma of the breast.

Exclusion Criteria
- Recurrent carcinoma breast, who underwent surgery for breast cancer previously in the form of mastectomy or breast conservative surgery
- Patient who received neoadjuvant therapy.
- Patient with surgical menopause.

In this study among 59 patients, 31 were premenopausal (group-l) and 28 were postmenopausal (group-II) age group. In this study postmenopausal group defined those who reported no menstruation over the last twelve months. All the patients were enrolled by the purposive sampling technique. They were explained regarding the study and it was ensured to them that there will be no potential risk of this study, no experimental drug will be used to them. Prior to data collection both verbal and informed written consent were taken from every patient. Data regarding sociodemographic characteristics including age, education level, occupation, socioeconomic status were recorded. Data regarding the personal history of the patient including the age of menarche, menopausal status, OCP uses, number of children, breastfeeding, age at the time of delivery of the first child, and family history of breast cancer were also recorded. Data regarding the histological profile and receptor status of the tumor were recorded. Both of these investigations were done by the patient for their own treatment purpose, so no compensation was given to them. Histological profile was done by using a modified Bloom Richardson grading system. According to this grading score in between (3-5) is considered as grade-I (well-differentiated) tumor, score in between (6-7) is considered as grade-II (moderately differentiated) tumor and sore in between (8-9) is considered as Grade-III (poorly differentiated) tumor.

RESULTS

In this study total, 59 patients were enrolled; they were divided into two groups among their menopausal status. In the premenopausal group (group-I) 31 patients and in the postmenopausal group (group-II) 28 patients. All were histologically proven female patients of carcinoma breast admitted to the department of general surgery, BSMMU over a period of fourteen months. The aim of the study is to find out the relation and distribution of histological grading and receptor status between pre and postmenopausal age groups.

Fig-I: Pie chart shows the distribution of patients in two groups

Table-1: Distribution of the study patients by age between two groups (n=59)

Age (years)	Premenopausal (n=31)		Postmenopausal (n=28)	
	n	%	n	%
<30	3	9.7	0	0.0
30-40	20	64.5	2	7.1
41-50	8	15.8	14	50.0
51-60	0	0.0	10	35.7
61-70	0	0.0	1	3.6
>70	0	0.0	1	3.6
Mean ± SD	37.61±6.59		51.68±7.19	
Range (min, max)	26,50		40,72	

Table 1 showed the distribution of the study patients by age between the two groups. It was observed that 64.5% of patients in group I belonged to the age group 30 to 40 years and 50% of group II belonged to the group to the age group 41 to 50 years of age. The mean age was 37.6 years in the premenopausal group and 51.9 years in the postmenopausal group.

Table-2: Distribution of the study patients by number of parity (N=59)

Number of parities	Group-I (n=31)		Group-II (n=28)		p-value
	n	%	n	%	
1	5	13.3	3	10.7	
2	16	53.4	12	42.9	0.595[ns]
>2	10	33.3	13	46.4	

Table 2 showed the distribution of the study patients by numbers of parity. It was observed that 53.4% of patients had parity two in group I and 46.4% of patients had parity >2 in group II. The difference was statistically not significant ($p>0.05$) between the two groups.

Table 3: Distribution of the study patient by the history of breastfeeding (N=59)

Breastfeeding (Minimum 2 Years)	Group-I (n=31)		Group-II (n=28)		p-value
	n	%	n	%	
Yes	30	96.8	26	92.9	0.494[ns]
No	1	3.2	2	7.1	

Table 3 showed the distribution of the study patients by the history of breastfeeding. It was observed that the majority of the patients had a history of breastfeeding which was 96.8% in group I and 92.9% in group II. The difference was statistically not significant ($p>0.05$) between the two groups.

Table-4: Distribution of the study patients by family history of breast cancer (N=59)

Family history of breast cancer	Group-I (n=31)		Group-II (n=28)		p-value
	n	%	n	%	
Yes	3	9.7	2	7.1	0.727[ns]
No	28	90.3	26	92.9	

Table 4 showed the distribution of the study patients by family history of breast cancer. Most of the patients had no family history of breast cancer which was 90.3% in group I and 92.9% in group II.

Table-5: Distribution of the study patients by histological type of cancer (N=59)

The histological type of cancer	Group-I (n=31)		Group-II (n=28)		p-value
	n	%	n	%	
Invasive Ductal Carcinoma	29	93.5	28	100.0	0.171[ns]
Invasive Lobular Carcinoma	2	6.5	0	0.0	

Table 5 showed the distribution of the study patients by histological type of cancer. It was observed that the majority of the patients had invasive ductal carcinoma. 93.5% in group I and 100.0% in group II suffered from invasive ductal carcinoma. The difference was statistically not significant ($p>0.05$) between the two groups.

Table-6: Distribution of the study patients by histological grading (N=59)

Histological Grading	Group-I (n=31)		Group-II (n=28)		p-value
	n	%	n	%	
Grade I	4	12.9	4	14.3	
Grade II	21	67.7	18	64.3	0.961ns
Grade III	6	19.4	6	21.4	

Table 6 shows the distribution of the study patients by grading. It was observed that the most common tumor grades for both groups were grade-II followed by Grade-III and Grade-I. The difference was statistically not significant (p>0.05) between the two groups.

Table-7: Distribution of the study patients by hormone receptor status (N=59)

Hormone receptor status	Group-I (n=31)		Group-II (n=28)		p-value
	n	%	n	%	
ER+, PR+	10	32.3	15	53.6	0.172[ns]
ER-, PR-	17	54.8	12	42.9	
ER+, PR-	4	12.9	1	3.5	

Table 7 shows the distribution of the study patients by hormone receptor status. It was observed that 54.8% of patients had ER-, PR- in the group, I, and 53.6% patients had ER+, PR+ in group II. The difference was statistically not significant (p>0.05) between the two groups.

Table 8: Distribution of the study patients by Her/2 Neu status (N=59)

Her/2 status	Group-I (n=31)		Group-II (n=28)		p-value
	n	%	n	%	
Her/2 Neu+	6	19.4	5	17.9	0.882[ns]
Her/2 Neu-	25	80.6	23	82.1	

Table 8 shows the distribution of the study patients by hormone receptor status. It was observed that 80.6% of patients were Her/2 Neu - in group I and 82.1% were group II. The difference was statistically not significant (p>0.05) between the two groups.

**Table-9: Distribution of the receptor status and tumor grade among pre and postmenopausal age groups (N=59)**

	Grading											
	Group I						Group II					
	Grade I (n=4)		Grade II (n=21)		Grade III (n=6)		Grade I (n=4)		Grade II (n=18)		Grade III (n=6)	
	n	%	n	%	n	%	n	%	n	%	n	%
Hormone receptor status												
ER+, PR+	3	75.0	7	33.3	0	0.0	3	75.0	11	61.1	1	16.7
ER-, PR-	1	25.0	12	57.1	4	66.7	1	25.0	6	33.3	5	83.3
ER+, PR-	0	0.0	2	9.5	2	33.3	0	0.0	1	5.6	0	0.0
Her/2 Neu status												
Her/2 Neu +	2	50.0	3	14.3	1	16.7	0	0.0	5	27.8	0	0.0
Her/2Neu -	2	50.0	18	85.7	5	83.3	4	100.0	13	72.2	6	100.0

Table 9 shows the distribution of the receptor status and tumor grade with menopausal status. It was observed that in group I, ER+, PR+ was found 75.0% in grade I, ER-, PR- was found 57.1% and 66.7% in grade II and III respectively. In group II, ER+, PR+ were found 75.0% i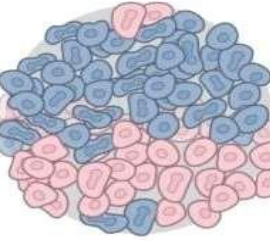n grade I, 61.1% in grade II, and ER-, PR- were found 83.3% in grade III. In group, I, Her/2 Neu- was found 50.0% in grade I, 85.8% in grade II, and 83.3% in grade III. In group II, Her/2 Neu - were found 100.0% patients in grade I, 72.2% in grade II, and 100.0% in grade III.
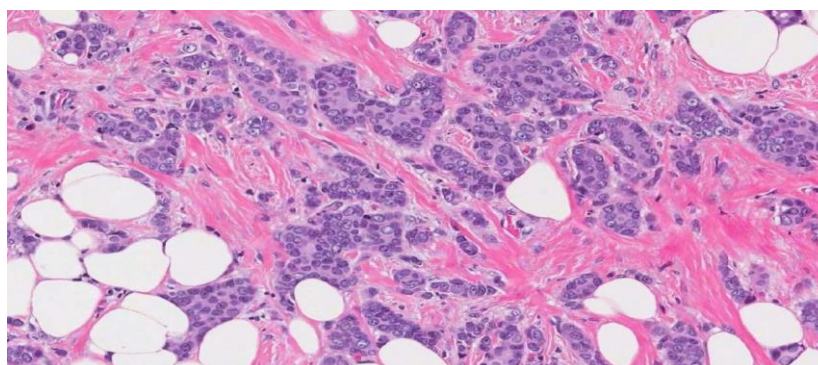
Fig-II: Microscopic slide view of invasive ductal carcinoma, NOS, moderately differentiated
(Source-Department of Pathology, BSMMU)
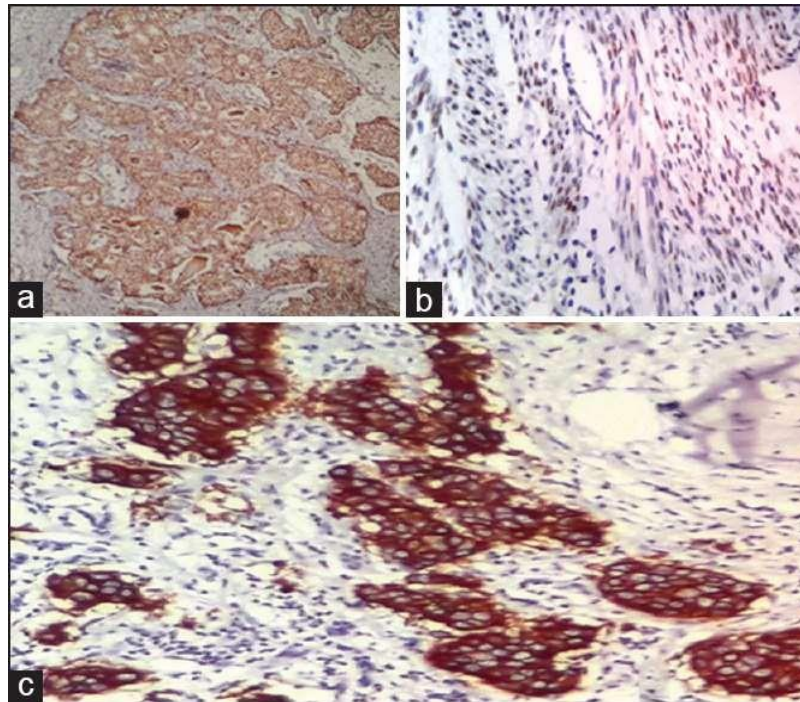
Fig-III: Photomicrography of immunohistochemistry showing a) Estrogen receptor-positive, b) Progesterone receptor-positive and c) Human epidermal growth factor-2 receptor-positive.
(Source-Department of Pathology, BSMMU)

Fig-IV: Bloom -Richardson scoring system
[*]Source: https://pathology.jhu.edu/breast/staging-grade

DISCUSSION

Carcinoma of the breast is the most common malignancy diagnosed among women worldwide. In Bangladesh, breast cancer is an issue of gaining concern that causes high mortality. This cross-sectional observational study was carried out with an aim to assess the distribution and relation of different histological grades and receptor status among the

carcinoma breast patients in between pre and postmenopausal age groups. Distribution of study patients in between two groups and that about 52.6 % of patients were in the premenopausal age group. This distribution is similar to another study. Hossain *et al.,* 2014 [3] also found that among breast cancer patients in Bangladesh about 56 % were in the premenopausal age group. Gupta *et al*., 2015[10] also found a similar result. The distribution of the study patients by age between two groups observed that 64.5% patients belonged to age (30-40) years in premenopausal group and 50 % patients belonged to age (41-50) years in postmenopausal group. The mean age was 37.61±6.59 years in the premenopausal causal group and 51.68±7.19 years in the postmenopausal group. Iqbal., *et al*. 2014 [11] found mean age for the premenopausal age group was 37.5 years which is very close to this study observation. Mostafa *et al.,* 2010[12] found an overall mean age of 45.5 years irrespective of menopausal status. But no study was available in one to find out the mean age of postmenopausal patients with carcinoma breast in our country. In this study, it was observed that 100.0% of patients were housewives in the premenopausal group and 85.7% in the postmenopausal group. The differences were statistically not significant (p<0.05) between the two groups. In this study, it was observed that 45.2% of patients were OCP users in the premenopausal group and 53.6% in the postmenopausal group. The difference was statistically not significant (p>0.05) between the two groups. 47.0 % of a breast cancer patient has a history of taking OCP according to Afroz *et al*., 2017 [13] and 49 % according to Jabeen *et al*., 2013 [14] which is comparable to our result. In this study, it was observed that more than half (53.4%) of the patients have double parity in the premenopausal group and 42.9% in the postmenopausal group. Parity more than two was found 33.3% and 46.4% in respectively in pre and postmenopausal group. Single parity was found 13.3% and 10.7% in respectively in pre and postmenopausal groups. The differences were statistically not significant (p>0.05) between the two groups. Iqbal *et al*., 2015 [15] showed mean parity of 2.2 among breast cancer patients. Lack of breastfeeding is a risk factor of breast cancer is possibly not justifiable for our country because our culture is mostly in favor of breastfeeding. In this study, it was observed that 70% delivered their first child less than 20 years of age in the premenopausal group and 60.6% in the postmenopausal group. Breast cancer incidence risk in relation to positive family history has been assessed in multiple published studies [16-19]. In this study, it was observed that 9.7 % of patients have a positive family history of breast cancer in premenopausal and 7.1% in the postmenopausal age group. So, from the above discussion, we found that the above mention sociodemographic variables and risk factors of breast cancer have no significant difference between pre and postmenopausal groups. In this study, it was observed that 93.6% of patients were suffering from invasive

ductal carcinoma in the premenopausal group and 100.0% in the postmenopausal group. The differences were statistically not significant (p>0.05) between the two groups. Sharma *et al*., 2019[20] found in their study that invasive ductal carcinoma is the most common histopathology accounting for 96.1% followed by invasive lobular carcinomas (2.8%) and medullary carcinomas 1.1% respectively similar to other Indian studies which are closely resembled with the present study [21-23]. In our country, invasive ductal carcinoma incidence was about 94.6 % according to Mostafa *et al*., 2010 [12]. Histological grading has an important prognostic value in breast cancer. The most popular method of tumor grading is the modified Bloom-Richardson grading system. In this present study, it was observed that 67.7% of patients had grade II in the premenopausal group and 64.3% in the postmenopausal group. Tumor grade I was found 13% in the premenopausal group and 14.3% in the postmenopausal group. Tumor grade III was found 19.3% and 21.4% in pre and postmenopausal groups respectively. The differences were statistically not significant (p>0.05) between the two groups. In this study, it was observed that 54.8% of patients have ER -, PR- tumors in the premenopausal group and 42.9% in the postmenopausal group. ER +, PR + were found 32.2% and 53.6% in there and postmenopausal groups respectively. ER +, PR - was found 13% in the remise menopausal group and 3.6% in the postmenopausal group. The differences were statistically not significant (p>0.05) between the two groups. Sofi *et al*., 2012 [24] found ER, PR positivity was 65 % in the patient above fifty years and the result is consistent with my postmenopausal age group. A study by Mostafa *et al*.,201012 showed among the Bangladeshi breast cancer patient 67%was ER+, PR+, 25.7 % is ER-, PR- and 2% is ER+, PR-. This result is consistent with my postmenopausal group result, but they do not compare their result between pre and postmenopausal age groups. Her /2 Neu receptor status is an important biological prognostic and predictive factor for breast cancer. In this present study, it was observed about 80% of patients were Her/2 Neu- in both groups. The differences were statistically not significant (p>0.05) between the two groups. In this study for both premenopausal and postmenopausal age groups the frequency of ER+, PR+ was gradually reduced grade I to grade III tumor, which was 75 %,33.8%, 00 % for premenopausal and 75 %, 61.1% 16.7% for postmenopausal age group respectively. On the other hand, the frequency of ER-, PR- were gradually increase from grade I to grade III for both groups, which was25%, 57.1%,66.7% for premenopausal, and 25%, 33.3%, 83.3% for the postmenopausal group respectively. Regarding the Her/2 Neu status in this study, it was observed that premenopausal group Her/2 Neu - were found 50.0% in grade l, 85.8% in grade II, and 83.3% in grade III tumor. In the postmenopausal group, Her/2 Neu - were found 100.0% patients in grade I and grade III, 72.2% in grade II. In this study, in

both pre and postmenopausal groups the frequency Her/2 Neu status did not follow the tumor differentiation.

CONCLUSION

This study was undertaken to assess the relation of receptor status and tumor grade with menopausal status in patients with carcinoma breast. The risk factors were almost alike between the two groups. Invasive ductal carcinoma with grade II differentiation was the most common tumor in both groups. ER-, PR- was most common in premenopausal women, and ER+, PR+ tumor was most common in postmenopausal women. More than 80% of women had Her/2– tumors in both groups. Tumor histologic type, grading, and receptor status have no significant difference between the two groups. Considering the relation of receptor status with tumor grade, frequency of ER+, PR+ gradually reduce from grade I to grade III tumor and frequency of ER-, PR - gradually increase from grade I to grade III tumor in both groups. On the other hand, Her/2- tumors were common in grade II in premenopausal women and more common in grade I and III in postmenopausal women.

LIMITATION

The study was a single-center study so the results of the study may not reflect the exact picture of the whole country. The sample size was very small; result from such a small sample may not reflect the actual difference between the two groups. The present study was conducted at a very short period of time that was insufficient to find out an exact picture of the disease biology. Some reports have been done outside the pathology department of BSMMU also accepted, so there is a possibility of variation of reports among different laboratories. Differences in the duration of tissue fixation and difference of experience of technician and pathologist may be the reason. Report both from core biopsy sample as well as specimen sample were accepted, so there is a possibility of specimen-related variation of the report. The difference in tissue quantity and quality may be the cause of variation in the report.

RECOMMENDATION

Patients of the premenopausal group suffer from a more aggressive type of tumor as most of the tumors are hormone receptor-negative compared to the postmenopausal group. So, they need more active and careful measures. Most of the tumors in our country are Her/2 receptor-negative in both groups. So, immunotherapy against the Her/2 receptor has a limited role. The further study recommended finding out the other biological parameter including p53, Ki-67 proliferation index to obtain the complete biological profile of the disease. Further studies can be undertaken by including a large number of subjects involving multiple centers throughout the country to obtain a better picture of the biological profile of breast cancer in pre and postmenopausal age groups.

REFERENCES

1. Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer J Clin*, *68*(6), 394-424.
2. Databases/Iarc-Cancerbases/GLOBOCAN-2012-Estimated-Cancer-Incidence-Mortality-And-Prevalence-Worldwide-In-2012-V1.0-2012
3. Hossain, M.S., Ferdous, S., & Karim-Kos, H.E. (2014). Breast cancer in South Asia: a Bangladeshi perspective. *Cancer epidemiology*, *38*(5), 465-470.
4. Munjal, K., Ambaye, A., Evans, M.F., Mitchell, J., Nandedkar, S. and Cooper, K. (2009). Immunohistochemical analysis of ER, PR, Her2 and CK5/6 in infiltrative breast carcinomas in Indian patients. *Asian Pac J Cancer Prev*, *10*(5), 773-778.
5. Ahmad, A., Bano, U., Gondal, M., & Khan, A. (2009). Her-2/neu gene overexpression in breast carcinoma and its association with clinicopathological characteristics of the disease. *J Coll Physicians Surg Pak*, *19*, 297-299.
6. Rastelli, F., & Crispino, S. (2008). Factors predictive of response to hormone therapy in breast cancer. *Tumori Journal*, *94*(3), 370-383.
7. Ishaque, N. (2014). Her 2 Overexpression in Breast Carcinoma; Its Significance and Association with Age and Tumor Grade. *Ann Pak Inst Med Sci*, *10*, 54-56.
8. Maynard, P.V., Blamey, R.W., Elston, C.W., Haybittle, J.L., & Griffiths, K. (1978). Estrogen receptor assay in primary breast cancer and early recurrence of the disease. *Cancer Res*, *38*(11 Part 2), 4292-4295.
9. Hilf, R., Feldstein, M.L., Gibson, S.L., & Savlov, E.D. (1980). The relative importance of estrogen receptor analysis as a prognostic factor for recurrence or response to chemotherapy in women with breast cancer. *Cancer*, *45*(8), pp.1993-2000.
10. Gupta, D., Gupta, V., Marwah, N., Gill, M., Gupta, S., Gupta, G. (2015). Correlation of hormone receptor expression with histologic parameters in benign and malignant breast tumors. *IJP*, *10*(1), 23-34.
11. Iqbal, J., Abukhatir, M., Shafi, A.A., Alyahya, G.M., & Alharthi, B.N. (2014). Hormone receptor status of breast cancer in patients of different age groups, lymph node status histological type and tumor grade, an experience at King Fahad Medical City, Riyadh. *Pak J Surg*, *30*(4), pp.296-300.
12. Mostafa, M.G., Larsen, M.T., & Love, R.R. (2010). Estrogen receptor, progesterone receptor, and Her-2/neu oncogene expression in breast cancers among Bangladeshi women. *J Bangladesh Coll Phys Surg*, *28*(3), 157-162.

13. Afroz, S., Rahman, S.S., & Hossain, M.M. (2017). A Study Survey on Risk Factors associated with Breast Cancer in Bangladeshi Population. *J Cancer Sci*, *9*(5), 463- 7.

14. Jabeen, S., Haque, M., Islam, M.J., Hossain, M.Z., Begum, A., & Kashem, M.A. (2013). Breast cancer and some epidemiological factors: a hospital-based study. *Journal of Dhaka Medical College*, *22*(1), pp.61-66.

15. Iqbal, J., Ferdousy, T., Dipi, R., Salim, R., Wu, W., Narod, S.A., Kotsopoulos. (2015). Risk factors for premenopausal breast cancer in Bangladesh. *I J B C*, *2015*, 1- 7

16. Anderson, H., Bladström, A., Olsson, H., & Möller, T.R. (2000). Familial breast and ovarian cancer: a Swedish population-based register study. *Am J Epidemiol*, *152*(12), 1154-1163.

17. Hemminki, K., Granström, C., & Czene, K. (2002). Attributable risks for familial breast cancer by proband status and morphology: a nationwide epidemiologic study from Sweden. *IJC*, *100*(2), 214-219.

18. Figueiredo, J.C., Ennis, M., Knight, J.A., McLaughlin, J.R., Hood, N., O'Malley. (2007). Influence of young age at diagnosis and family history of breast or ovarian cancer on breast cancer outcomes in a population-based cohort study. *Breast Cancer Res Treat*, *105*(1), 69-80.

19. Colditz, G.A., Kaphingst, K.A., Hankinson, S.E., &d Rosner, B. (2012). Family history and risk of breast cancer: nurses' health study. *Breast Cancer Res Treat*, *133*(3), 1097-1104.

20. Sharma, T.D., Sinam, N., & Bhaumik, A. (2019). Evaluation of Hormone receptor status in patients with operable breast cancer: a retrospective study at a Regional Cancer Centre in Northeast India, *JMSCR*, *7*(01), 1020-1027.

21. Jain, S. A., Aggrawal, L., Ameta, A., Nadkarni, S., Goyal, A., Ranjan, D., & Gaur, K. (2014). Study of ER, PR and HER-2/NEU reactivity pattern in the patient of Breast Cancer in northern part of India. *IOSR-JDMS*, *13*, 9-19.

22. Shrivastava, N., Gupta, R., & Gaharwar, A. P. S. (2016). Clinico pathological presentation of carcinoma of breast at tertiary care centre in Vindhya region, Rewa, Madhya Pradesh, India. *International Surgery Journal*, *3*(3), 1156-1162.

23. Bogarapu, C. B., Vayalapalli, M. R., Bendi, H., & Mantra, S. (2016). A retrospective study on the incidence of breast carcinoma in a tertiary care hospital. *International Journal of Contemporary Medical Research*, *3*, 1714-1716.

24. Sofi, G. N., Sofi, J. N., Nadeem, R., Shiekh, R. Y., Khan, F. A., Sofi, A. A., ... & Bhat, R. A. (2012). Estrogen receptor and progesterone receptor status in breast cancer in relation to age, histological grade, size of lesion and lymph node involvement. *Asian pacific journal of cancer prevention*, *13*(10), 5047-5052.