

# Association of menopausal status with pathological features of tumor in stage I to III a breast cancer patients treated with upfront modified radical mastectomy

## Abstract

**Introduction:** Breast cancer is the commonest malignancy diagnosed among women worldwide. In Pakistan around 90,000 women are diagnosed with breast cancer every year. Lymphnode involvement, tumor size, receptor status, tumor grade, presence of LVI, age and ethnicity are well recognized prognostic factors for breast cancer. The aim of this study was to evaluate the relationship of menopausal status with pathological and prognostic features of tumor in patients with stage I to III A breast cancer treated upfront with modified radical mastectomy.

**Material and Methods:** This was a single institute observational retrospective study conducted at Nuclear Medicine Oncology and Radiotherapy Institute (NORI) Islamabad. A total of 381 patients with histopathologically proven diagnosis of Invasive ductal carcinoma after modified radical mastectomy were included from January 2009 to December 2013. Age, menopausal status, tumor site, tumor size, grade, lymphnode involvement, receptor status and presence of LVI were recorded on a particularly composed proforma. Statistical analysis for determining the association between menopausal status and pathologic features of tumor was performed using Chi-square test. P value < 0.05 was considered significant.

**Results:** The minimum age of study population was 24 years and maximum age was 80 years with a mean age +/- SD of 48.5 +/- 11.1 years. There was a statistically significant association between menopausal status and grade of tumor, lymphovascular invasion and HER2/neu overexpression (p < 0.05).

**Conclusion:** Grade of tumor, lymphovascular invasion and HER2/neu over expression in stage I to IIIA breast cancer has statistically significant association with menopausal status.

**Keywords:** breast cancer, premenopausal, postmenopausal, modified radical mastectomy

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**Humera Mahmood, Mohammad Faheem, Sana Mehmood**

Department of Oncology, Oncology & Radiotherapy Institute (NORI), Pakistan

**Correspondence:** Humera Mahmood, Consultant Oncologist, NORI Islamabad, Email hmfhaem02@gmail.com

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## Introduction

Breast cancer is the commonest malignancy diagnosed among women worldwide and ranks fifth as a cause of cancer related mortality.<sup>1</sup> According to Globocan 2012 report, it constitutes one in four of all cancers in women.<sup>2</sup> In 1990, the incidence of breast cancer was 59% in developed countries and 41% in developing countries whereas in 2012, it declined to 47% in developed countries and increased to 53% in developing countries. This shift of encumbrance encountered in recent years emphasizes that breast cancer is emerging as a major health problem for developing countries. Another concerning issue is the age at diagnosis. The median age of diagnosis in many Asian countries is 45-50 years and is approximately a decade lower than in most Western countries.<sup>3</sup> In Pakistan around 90,000 women are diagnosed with breast cancer every year which is about 2.5 times higher than that in neighboring countries like India and Iran.<sup>4</sup> Breast cancer represents 33% of all cancers in females reported at Nuclear Medicine Oncology and Radiotherapy Institute (NORI), Islamabad.<sup>5</sup> Despite the increase in awareness of cancer, approximately 71% women in Pakistan present either with locally advanced or metastatic disease which is in contrast to Western countries where only 10% patients present with stage III or IV disease.<sup>6</sup> Although early stage breast cancer is associated with improved survival, 20% patients still

die within 5 years because of disease. The high mortality risk noted in this subset is interrelated with triple negativity (ER, PR and HER2/neu negativity).<sup>7</sup> A number of prognostic and predictive factors have been implicated in the management of breast cancer. Prognostic factor is defined as a measurable variable that correlates with disease free or overall survival in the absence of systemic adjuvant treatment and thus with the natural history of disease. Lymphnode involvement, tumor size, receptor status, tumor grade, presence of LVI, age and ethnicity are well recognized prognostic factors for breast cancer.<sup>8</sup> Postmenopausal patients have better overall survival as compared to premenopausal patients.<sup>9</sup> The survival difference between post and premenopausal patients continues considerably even after adjustment for other prognostic factors like receptor status and nodal involvement.<sup>10</sup> Young patients present mostly with adverse pathologic features including high tumor grade, hormone receptor negativity, HER2/neu over expression and advanced stage. This accounts for a significantly higher mortality rate seen in patients younger than 40 years of age compared to older patients (18.3% vs 12.1%, P= 0.001).<sup>11</sup> The aim of this study was to evaluate the relationship of menopausal status with pathological features of tumor in patients with stage I to III A breast cancer patients treated with upfront modified radical mastectomy.

## Material and methods

This was a single institute observational retrospective study. Apart from Rawalpindi and Islamabad, drainage area of NORI includes Upper Punjab, Northern areas, Kashmir and Gilgit Baltistan. A total of 381 patients with histopathologically proven diagnosis of Invasive ductal carcinoma after modified radical mastectomy were included from January 2009 to December 2013. The exclusion criteria were inadequate axillary dissection i.e. less than 6 axillary lymphnodes removed, microscopically positive or close resection margins, prior history of incisional/excisional biopsy, history of prior treatment, history of metastatic or recurrent disease, history of previous malignancy and coexisting second malignancy. The study was approved by Hospital Ethical Review Committee. Patients included in this study were those registered at outpatient department of Oncology at NORI hospital. Data were collected and entered into SPSS 20. Evaluation of estrogen (ER) and progesterone receptors (PR) and HER2/neu oncogene was accomplished using immunohistochemistry and in case of HER2/neu++ confirmation utilizing Fluorescent In situ Hybridization (FISH) technique was done. The criteria for explicating menopause were women 60 years or older, history of amenorrhea for 12 or more months in the absence of chemotherapy, hormonal treatment or ovarian suppression in women less than 60 years of age or serum Follicle Stimulating Hormone (FSH) and serum estradiol in postmenopausal range. Age, menopausal status, tumor site, tumor size, grade, lymphnode involvement, receptor status and presence of LVI were recorded on a particularly composed proforma. Descriptive statistics were calculated for both qualitative and quantitative variables. Statistical analysis for determining the association between menopausal status and pathologic features of tumor was performed using Chi-square test. P value < 0.05 was considered significant.

## Results

A total of 381 patients with the diagnosis of stage I to IIIA invasive ductal carcinoma of breast after modified radical mastectomy were enrolled in the study. The minimum age of study population was 24 years and maximum age was 80 years with a mean age +/- SD of 48.5 +/- 11.1 years. There were one hundred and eighty (47.2%) premenopausal and two hundred and one (52.8%) postmenopausal women. Majority of patients were ER and PR positive (67.2%), HER2/neu negative (67.7%), had tumor size between 2.1 cm to 5 cm (59.8%) and had grade 2 disease (65.4%). Clinicopathological features are given in Table 1.

**Table 1** Clinicopathological features

Age range 24-80 Years	
Mean age +/- SD	48.51 +/- 11.1 Years
Menopausal status	
Premenopausal	180 (47.2%)
Post menopausal	201 (52.8%)
Site of Tumor	
Right breast tumor	188 (49.3%)
Left breast tumor	193 (50.7%)
Stage	
T1	22 (5.8%)
T2	228 (59.8%)
T3	131 (34.4%)
N0	152 (39.9%)
N1	111 (29.1%)
N2	118 (31.0%)
Stage IA	9 (2.4%)
Stage IIA	103 (27%)
Stage IIB	119 (31.2%)
Stage III A	150 (39.4%)
Grade	
Grade I (Well differentiated)	10 (2.6%)
Grade II (Moderately differentiated)	249 (65.4%)
Grade III (Poorly differentiated)	122 (32%)
Receptor Status	
ER/PR positive	256 (67.2%)
ER/PR negative	125 (32.8%)
Her 2 neu positive	123 (32.3%)
Her 2 neu negative	258 (67.7%)
Lymphovascular Invasion	
LVI positive	179 (47%)
LVI negative	202 (53%)

There was a statistically significant association between menopausal status and grade of tumor, lymphovascular invasion and HER2/neu over expression. High grade tumors were 41.1% in premenopausal women and 23.9% in postmenopausal women; lymphovascular invasion was seen in 56.7% of premenopausal women vs 38.3% of postmenopausal women; HER2/neu oncogene was over expressed in 39.4% of premenopausal and 25.9% of postmenopausal women. Although not statistically significant premenopausal status was associated with larger tumors and N2 disease (Table 2).

**Table 2** Association of menopausal status with pathologic features of tumor. \*Group 1- ER,PR positive HER2/neu negative; Group 2- ER, PR and HER2/neu positive; Group 3 - ER,PR negative HER2/neu Positive; Group 4 - ER,PR and HER2/neu negative

Variable	Menopausal status		P Value	
	Premenopausal (N=180)	Postmenopausal (N=201)		
T stage	T1	8 (4.4%)	14 (7%)	0.073
	T2	100 (55.6%)	128 (63.7%)	
	T3	72 (40%)	59 (29.3%)	
N stage	N0	70 (38.9%)	82 (40.8%)	0.48
	N1	49 (27.2%)	62 (30.8%)	
	N2	61 (33.9%)	57 (28.4%)	
Stage group	IA	3 (1.7%)	6 (3%)	0.43
	IIA	43 (23.9%)	60 (29.8%)	
	IIB	58 (32.2%)	61 (30.3%)	
	IIIA	76 (42.2%)	74 (36.8%)	

Table Continued...

Variable	Menopausal status		P Value	
	Premenopausal (N=180)	Postmenopausal (N=201)		
Grade	G1	5(2.8%)	5 (2.5%)	0.001
	G2	101 (56.1%)	148 (73.6%)	
	G3	74 (41.1%)	48 (23.9%)	
LVI	Present	102 (56.7%)	77 (38.3%)	0
	Absent	78 (43.3%)	124 (61.7%)	
ER/PR status	Positive	118 (65.6%)	138 (68.7%)	0.296
	Negative	62 (34.4%)	63 (31.3%)	
Her 2 Neu oncogene	Positive	71 (39.4%)	52 (25.9%)	0.003
	Negative	109 (60.6%)	149 (74.1%)	
*Receptor gp	Group 1	77 (42.8%)	112 (55.7%)	0.025
	Group 2	41 (22.8%)	26 (12.9%)	
	Group 3	30 (16.7%)	26 (12.9%)	
	Group 4	32 (17.7%)	37 (18.4%)	

## Discussion

Breast cancer is on rise in many Asian countries particularly Pakistan.<sup>12</sup> This study was designed to determine the association of menopausal status with prognostic features of tumor. Our main assumption was that premenopausal patients usually present with adverse prognostic factors as compared to postmenopausal women. Age at diagnosis differs noticeably among different populations. The mean age of diagnosis in our study was 48.51 years which is in accordance with that reported in other Asian countries; whereas in the US the mean age for breast cancer is 61 years.<sup>13</sup> The ratio of postmenopausal to premenopausal breast cancer observed in this report was 1.11:1. The percentage of premenopausal breast cancer is considerably higher in developing countries as compared to developed countries (47.3% vs.18.5%) and has been attributed to distinct hereditary and environmental risk factors.<sup>1</sup> Lymphovascular invasion (LVI), a well recognized prognostic marker is defined as tumor emboli present within a vessel in the vicinity of invasive carcinoma. The presence of LVI predicts nodal and distant spread and is used by oncologists for risk stratification and decision of adjuvant treatment.<sup>14,15</sup> Our demonstrated a statistically significant association between menopausal status and LVI. Premenopausal women had an increased incidence of LVI (p= 0.000). This observation is also supported by a study conducted by G Gurleyik et al.<sup>16</sup> Although the authors couldn't unearth a close relationship between the presence of LVI and menopausal status, they noted a trend towards higher frequency of LVI in premenopausal patients.<sup>16</sup> Another marker envisaging tumor assertiveness is histologic grade. Higher grades are linked with lower long term survival. The 10 year overall survival is 90-94% for low grade tumors and 30-78% for high grade tumors.<sup>17</sup> We discerned that 41.1% premenopausal and 23.9% postmenopausal women had grade 3 tumors (p=0.001). A meta-analysis was led by Anders et al.<sup>18</sup> to provide further insight into breast cancer emerging in premenopausal women. The results were indistinguishable with earlier reports indicating that breast cancers in premenopausal women are usually of higher grade.<sup>18</sup>

Breast cancer exhibits widespread molecular and clinical heterogeneity. HER2/neu proto-oncogene is amplified in 20-30% of breast cancers and is allied with aggressive phenotype of tumor cells, resistance to treatment and lower overall survival. A study performed by Singhai et al.<sup>19</sup> revealed that over expression of Her2neu oncogene was related to age but not to menopausal status.<sup>19</sup> Conversely, another

study by Faheem et al.<sup>20</sup> showed a strong association between menopausal status and HER2/neu positivity (p=0.000).<sup>20</sup> The present study also illustrated a strong relationship between menopausal status and HER2/neu positivity. Thirty nine percent premenopausal women and twenty six percent postmenopausal women had tumors over expressing HER2/neu respectively (p= 0.003). ER, PR and HER2/neu status not only provide prognostic information but also predict response to treatment. Breast cancer is best characterized by combined expression of these receptors than by single receptor status alone. Studies have shown that tumors over expressing HER2/neu are usually ER and PR negative and present at younger age with aggressive tumor biology.<sup>21</sup> Patients who are ER/PR positive and HER2/neu negative are more likely to be older, have early stage disease and have decreased incidence of lymphnode involvement.<sup>22</sup> This was evident in our results; 43% of premenopausal women as compared to 56% of postmenopausal women were ER/PR positive HER2/neu negative (Group 1) (p=0.025).

Tumor size and lymphnode involvement are markers of outcome in patients with breast tumors. Studies have revealed an extra 6% chance of death with each positive lymphnode and an additional 1% chance of death with each millimeter of tumor diameter.<sup>23</sup> Nevertheless, we did not find a statistically significant association between menopausal status and tumor size, lymphnode involvement or stage. A study comprising of 258 patients carried out by Ali EM et al also failed to illustrate a significant correlation between axillary lymphnode status and patient's age, age groups or menopausal status.<sup>24</sup> Apart from these pathologic features various molecular markers and treatment factors may also be related with menopausal status. Additionally, as the tumor characteristics differ in both premenopausal and post menopausal women robust population based studies with longer follow up are required to determine its impact on outcome and thus survival.

## Conclusion

Grade of tumor, lymphovascular invasion and HER2/neu over expression in stage I to IIIA Breast cancer have statistically significant association with menopausal status whereas ER/PR status, tumor size and nodal involvement are not significantly related with menopausal status.

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## Conflicts of interest

The authors declare that there is no conflict of interest.

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