

## DIVERSITY OF HISTOLOGICAL VARIANTS OF BREAST CANCER: A TERTIARY CARE HOSPITAL EXPERIENCE IN KARACHI, PAKISTAN

Shumyla Beg, Ghulam Haider, Ejaz Khan, Aisha Shahid, Paras Memon, Raja Rahul, Bhunisha Pavan, Kiran Abbas\*

Jinnah Postgraduate Medical Center, Karachi, Pakistan, \*Jinnah Sindh Medical University, Karachi Pakistan

### ABSTRACT

**Objective:** To determine the prevalence of histological subtypes of breast cancer and its association with age, molecular subtype, menopausal status, parity, obesity and tumor grade.

**Study Design:** Prospective, observational study.

**Place and Duration of Study:** The current study was conducted at Oncology Ward-4, Jinnah Postgraduate Medical Center, Karachi, Pakistan, from Apr 2018 to Sep 2019.

**Methodology:** Non-probability convenience technique was used for the sample selection. All patients with diagnosed breast cancer presenting at Oncology ward, Jinnah Postgraduate Medical Center were included in the study. Cases with a non-confirmed diagnosis of breast cancer or those with unknown histological subtype were excluded from the study. Statistical package for Social Sciences (SPSS version 25) was used to analyze the data. Chi-Square test was used to find the association of histological subtypes with age, molecular subtype, menopausal status, parity, obesity, grade of tumor among breast cancer patients.

**Results:** A total of 553 cases of breast cancer patients were reviewed in the study. The mean age of participants was  $46.75 \pm 10.852$  years. We found a frequency of 91.3% of Invasive Ductal Carcinoma (not otherwise specified) among women in our setting. The other rare types of cancer included invasive lobular carcinoma 2%, metaplastic 1.4%, and invasive micropapillary carcinoma 1%. Invasive ductal carcinoma (not otherwise specified). Invasive lobular carcinoma were significantly associated with luminal A type disease ( $p < 0.05$ ) while metaplastic was associated with basal type disease ( $p = 0.006$ ).

**Conclusion:** The most common histological subtype of breast carcinoma in our study population was invasive ductal carcinoma (not otherwise specified). However, various rarer variants of invasive ductal carcinoma were also reported. Histological subtypes play a pivotal role in predicting the behavior and clinical outcome of breast carcinomas.

**Keywords:** Breast neoplasm, Lobular carcinoma in Situ, Triple negative breast neoplasms.

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### INTRODUCTION

Breast cancer is a group of diseases that differ in many aspects including the clinical behavior that determines the characteristics, prognosis, and response to treatment. It is classified into several histological variants, based on their histological appearance which subsequently defines their clinical presentation and prognosis. Based on these variants, survival outcomes and best therapy is decided upon<sup>1</sup>.

Breast cancer is famously classified into two main groups: in situ carcinoma and invasive (infiltrating) carcinoma. The former is further sub-

stratified into invasive ductal or invasive lobular based on their growth patterns and histological features. Invasive ductal carcinoma is significantly more prevalent than invasive lobular carcinoma. Rarer forms of breast carcinoma include: mucinous, comedo, inflammatory, papillary and medullary carcinoma<sup>2</sup>. Ductal, lobular, mixed and metaplastic histologies are associated with aggressive disease whereas tubular, mucinous and papillary histologies are associated with favorable disease.

In Pakistan, incidence of breast cancer is highest among all Asian countries except Jews in Israel. The incidence is about 2.5 times higher than neighboring countries including India and Iran. In Pakistan, breast cancer prevalence is an

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**Correspondence:** Dr Kiran Abbas, Jinnah Sindh Medical University, Karachi Pakistan

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alarming 34.6% and a good percentage of these women present at a younger age as compared to the western countries<sup>3</sup>.

Primary data of mortality due to breast cancer is not available because of lack of follow-up in Pakistan due to poor or middle-class income. However, the Age Standardized Mortality Rate (ASMR) for Pakistan was 25.2/100,000. According to the study which was conducted at Liaquat National Medical College Karachi, Pakistan there were 8,291 registered breast cancer patients in hospital from 1994-2014<sup>4</sup>.

Breast cancer is a heterogeneous disease with each variant unique with respect to their clinical characteristics, behavior, and response to treatment regimes, patient survival, and overall prognosis. We evaluated the diversity of histological subtypes and assess the relationship between these subtypes and various tumor parameters.

Jinnah Postgraduate Medical Centre, Karachi is the only public sector medical oncology setup in the entire Sindh province. Our patient's epidemiological characteristics have almost never been studied before. So the importance of our study lies in the fact that it is one of its kind study highlighting the differences and variation in the frequency of histological variants of breast carcinoma its relation with age, menopausal status and grade of disease. These fundamental characteristics play a vital role in planning of treatment and prognostication.

## METHODOLOGY

This was a prospective, observational study conducted at Jinnah Postgraduate Medical Center, Karachi, Pakistan, from April 2018 to September 2019. A total of 553 patients with diagnosed case of breast carcinoma were included in the study. Ethics approval was obtained from Institutional Ethics Review Board (IERB) of Jinnah Postgraduate Medical Center with IRB registration number as RTMC No. ONC-2016-186-162. Sample size was calculated using 34.6% as the prevalence with 95% Confidence Level. Non-probability, consecutive sampling technique was used. Cases with a non-confirmed diagnosis

of breast cancer or those with unknown histological subtype were excluded from the study. Information about patient's demographics, tumor site, histological subtype, and other parameters were collected. SPSS-25 was used to analyze data. Chi-square test was used to find a significant association between different histological subtypes, age, molecular subtype, menopausal status, parity, obesity, grades of tumors in breast cancer patients.

## RESULTS

A total of 553 cases of breast cancer patients were reviewed in the present study. The mean age of participants was  $46.75 \pm 10.852$  years. The youngest patient was 18 years old while the oldest was 75 years old (table-I).

Out of 553 patients, only 4 (0.7%) patients had grade 1 breast carcinoma. Two hundred and eighty three (51.2%) of them had grade 2 while 262 (47.4%) patients had grade 3 breast carcinoma. On histological assessment, it was found that the most frequently occurring histological type of breast cancer was Invasive Ductal Carcinoma (not otherwise specified (IDC-NOS) with 505 (91.3%) cases reported in the present study. Other rarer types of breast cancers were Invasive mucinous carcinoma 3 (0.5%), Infiltrating Mixed D&L carcinoma, and IDC with focal micropapillary component 1 (0.2%) (table-I & fig-1).

Distribution of histological subtypes of breast carcinoma was assessed in three different subgroups i.e. subjects with age less than 35 years, subjects with age between 35 to 50 years, and subjects who were older than 50 years. Majority i.e. 318 (57.5%) belonged to the age group between 35 to 50 years. Invasive ductal carcinoma was the most prevalent subtype in all three age groups. 92.8% out of these 318 in the age group 35-50 years, 94.6% out of 56 in the age group less than 35 years, while 90% out of 179 in the age group older than 50 years was diagnosed as invasive ductal carcinoma. On applying the chi-square test, it was found that the age was not significantly correlated with histological subtypes ( $p=0.422$ ).

The most prevalent molecular subtype was luminal A followed by basal type. Among the aggressive histologies IDC (NOS) and invasive lobar carcinoma (ILC) were associated with luminal A type disease ( $p=0.01$ ) while metaplastic

**Table-I: Demographic and clinical profile of patients with breast cancer.**

Variables	n (%)
<b>Age Groups</b>	
<35 years	56 (10.1%)
35-50 years	318 (57.5%)
>50 years	179 (32.4%)
<b>Menstrual Status</b>	
Premenopausal	333 (60.2%)
Postmenopausal	220 (39.8%)
<b>BMI</b>	
Underweight (<18.5 kg/m <sup>2</sup> )	32 (5.8%)
Healthy Weight (18.5-24.5 kg/m <sup>2</sup> )	213 (38.5%)
Overweight (25-29.9 kg/m <sup>2</sup> )	166 (30%)
Obese ( $\geq 30$ kg/m <sup>2</sup> )	142 (25.7%)
<b>Parity (Number of Children)</b>	
None	32 (5.8%)
1-3 children	213 (38.5%)
4-6 children	166 (30%)
>6 children	142 (25.7%)
<b>Histological Variants of Breast Cancer</b>	
Invasive ductal carcinoma (IDC-NOS)	509 (92%)
IDC with Paget's Disease	4 (0.7%)
IDC bifocal carcinoma	3 (0.5%)
IDC with focal micropapillary component	1 (0.2%)
IDC with Mucinous differentiation	6 (1.1%)
IDC with papillary pattern	2 (0.4%)
IDC with focal squamous differentiation	3 (0.5%)
Invasive micropapillary carcinoma	1 (0.2%)
Invasive Lobular Carcinoma (ILC)	11 (2%)
Invasive mucinous carcinoma	3 (0.5%)
Metaplastic	8 (1.4%)
Infiltrating Mixed D&L carcinoma	2 (0.4%)

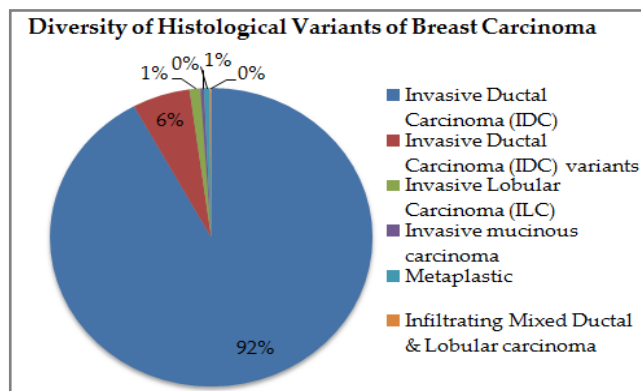
was associated with basal type disease ( $p=0.006$ ). Among the favorable histologies IDC with mucinous differentiation was also associated with luminal A type while 1 case of papillary was her2/neu enriched and the other was basal type as shown in table-II.

Grade II disease was most prevalent followed by grade III disease. All the cases of metastatic carcinoma were grade III. All cases of grade I were IDC (NOS), table-III.

Majority of patients were premenopausal. ILC and metaplastic histologies were seen in postmenopausal women while all the cases of Paget's disease reported were recorded in premenopausal women ( $p$ -value = 0.01).

**DISCUSSION**

According to the WHO, there are over 20 histological subtypes of breast carcinoma. Out of these, IDC is the most common type, with a global prevalence of 40-70%<sup>5</sup>. These diverse subtypes differ significantly with respect to their behavior, hence, affecting the prognosis and response to therapy<sup>6-8</sup>.



**Figure-1: Diversity in histological subtypes of breast carcinoma among participants n=553.**

In the current study, over 550 diagnosed cases of breast carcinoma were analyzed. The mean age of patients was  $46.75 \pm 10.85$  years. 56 (10.1%) patients were younger than 35 years 318 (57.5%) were in between 35 to 50 years of age, while 179 (32.4%) were older than 50 years.

Various studies have also shown a similar age patterns among the Asian countries like India/Pakistan i.e. younger age groups are more prevalent in breast carcinoma as compared to older age groups<sup>9-12</sup>. Shams *et al*, reported that 77.2% breast cancer patients were found to be younger than 60 years of age<sup>11</sup>.

The mean age of patients with breast carcinoma in the western countries is 54 years with region as reported by Kakarala, the average age was 46 years which is almost 10 years younger

**Table-II: Association of histological subtypes & molecular subtypes of breast cancer.**

Histological Type	Triple Negative	Triple Positive	*ER/PR +ve Her2 -ve	*ER/PR -ve Her2/neu +ve
Invasive ductal carcinoma (IDC-NOS)	128	62	149	107
IDC with Paget's Disease	-	-	-	3
IDC bifocal carcinoma	-	-	1	1
IDC with focal micropapillary component	-	-	1	-
IDC with Mucinous differentiation	1	-	4	-
IDC with papillary pattern	1	-	-	1
IDC with focal squamous differentiation	2	-	-	-
Invasive micropapillary carcinoma	-	-	1	-
Invasive Lobular Carcinoma (ILC)	-	-	7	2
Invasive mucinous carcinoma	1	-	1	-
Metaplastic	7	-	1	-
Infiltrating Mixed D&L carcinoma	-	-	2	-
<i>p</i> -value	0.006	0.87	0.01	0.18

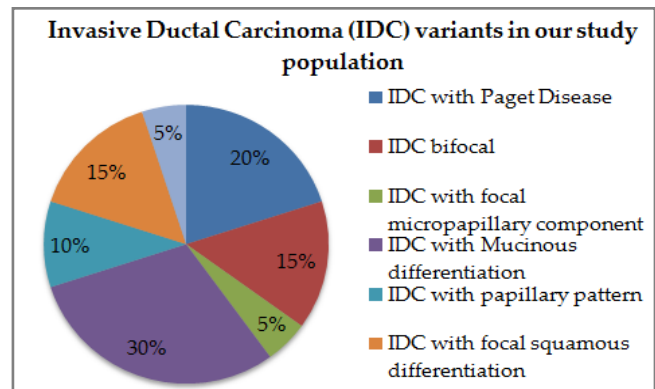
\*ER/PR = Estrogen Receptor / Progesterone Receptor  
Her2/neu =

**Table-III: Histological subtypes & grade of breast cancer in our patients.**

Histological Type	Grade I	Grade II	Grade III
Invasive ductal carcinoma (IDC-NOS)	5	261	243
IDC with Paget's Disease	-	1	3
IDC bifocal carcinoma	-	1	2
IDC with focal micropapillary component	-	-	1
IDC with Mucinous differentiation	1	5	-
IDC with papillary pattern	-	2	-
IDC with focal squamous differentiation	-	1	2
Invasive micropapillary carcinoma	-	-	1
Invasive Lobular Carcinoma (ILC)	-	8	3
Invasive mucinous carcinoma	-	3	-
Metaplastic	-	-	8
Infiltrating Mixed D&L carcinoma	-	2	-

a postmenopausal status ensued while, in our

when compared to the western world<sup>9</sup>. In this study majority of the patients were pre-menopausal. There could be some environmental and modifiable risk factors involved such as diet, carcinogens, pollution, etc. that contributes to a younger age at diagnosis in our population.



**Figure-2: Invasive ductal carcinoma variants in our population.**

On assessment of different subtypes of breast carcinoma, we found that IDC-NOS with 505 (91.3%) was the most common type reported in our population. Other rarer types of breast cancers included 8 variants of IDC (fig-2). Our findings were in consistence with another study conducted in Karachi, Aga Khan University

Hospital in 2000, where they found IDC prevalence of 81.99%<sup>10</sup>. The second most common subtype was ILC with a prevalence of 2%, followed by metaplastic type with a prevalence of 1.4%. However, in the year 2000 it was reported by Siddiqui *et al*, that, ductal carcinoma in situ was the second most commonly seen breast cancer after IDC with a prevalence of 16.25%, followed by mucinous carcinoma (0.52%), infiltrating lobular carcinoma (0.34%) and papillary carcinoma (0.17%)<sup>11</sup>.

Similarly, in another study conducted in 2017 in Pakistan, it was reported that IDC was the most common subtype seen with 106 (84.8%) cases in patients over the age of 60 years<sup>12</sup>. However, in this study patients with age 60 years or older were assessed, so we could not compare our results in younger age groups. Nevertheless, Shams *et al*, reported that mixed ductal and lobular type cancers were only seen in 1.4% of cases. In our study, only 2 cases were observed with the same subtype.

In our study, the prevalence of IDC (NOS) turned out to be 505 (91.3%). However, we also reported the occurrence of other variants of IDC including, IDC with PD, IDC bifocal, IDC with focal micropapillary component, IDC with Mucinous differentiation, IDC with papillary pattern, and IDC with focal squamous differentiation. Many of these special subtypes have favorable prognosis and better outcome than the IDC (NOS). Researchers like Shams & Zhou have shown that IDC with PD and invasive micropapillary carcinoma have a poorer outcome than their conventional IDC counterpart<sup>13-15</sup>.

In the present study, we reported that the majority of the cancers in the young age group between 18-35 years had IDC-NOS subtype with an alarming frequency of 94.6%. This was in concordance with WHO breast cancer facts and figures 2017-2018, where an increasing trend in both in-situ and invasive breast cancer has been seen since the 1980s. This rise can be explained by the increase in mammography screening, rising incidence of obesity, smoking, and use of meno-

pausal hormones, all of which are associated with breast cancer risk<sup>16</sup>. Younger patients are more susceptible to aggressive forms of breast cancers. Germ line mutational analysis is highly recommended with strong family history of breast/ovarian carcinoma in order to identify women who can benefit from risk reduction strategies. Certain molecular and histological types of breast cancer are associated with specific mutation, for example ILC in conjunction with a family history of diffuse gastric carcinoma indicates mutation in E cadherin CDH1<sup>17-21</sup>.

We reported a high incidence of IDC with mucinous differentiation in the group between 35-50 years (5 out of 6 cases) this was in contradiction to the study reported by Al-Zawi, *et al* showing a frequency of 3 (1.76%) in women older than 75 years<sup>22</sup>. Patients with favorable histologies can be offered treatment de-escalation, as chemotherapy post-surgery can be omitted and endocrine therapy would suffice provided, they are Estrogen receptor positive, further highlighting the significance of histological subtype<sup>23</sup>.

Majority of Invasive Lobular Carcinoma (8 out of 11 cases) and metaplastic carcinoma (4 out of 8 cases) were reported in the elderly age group of more than 50 years, this finding was similar to internationally published data where Chen, *et al* reported the frequency of ILC to be 63.4% in patients over the age of 60 ( $p < 0.005$ )<sup>24</sup>. Moreover, metaplastic histology was also associated with grade III disease and almost all cases were basal type further adding to the aggressiveness<sup>25</sup>. Our study reported that incidence of metaplastic carcinoma in our population is 1.4% and majority occurs in postmenopausal women. Al Syed *et al* also reported similar findings with a median age of 48 years (range, 14-58)<sup>21</sup>.

Breast cancer is usually suspected in older women with a positive family history. However, this is contradictory to our current findings as we had prevalence of younger and middle aged women as well. Along with age and tumor subtype, many other factors also play a huge role in determining the clinical course of the disease.

Therefore, we recommend that clinicians should always assess these parameters along with the histological subtype of the tumor to provide the best health-care possible.

## CONCLUSION

The most common subtype of breast carcinoma in our population found was invasive ductal carcinoma (IDC-NOS). However, we also reported frequency of some of the rare subtypes of IDC. Histological subtypes play a pivotal role in predicting the behavior and clinical outcome of breast carcinomas. The study highlighted our population's demographic and epidemiological variations.

## CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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