## Original Article

# CLNICO-PATHOLOGICAL SPECTRUM OF BREAST CARCINOMA - STUDY OF 1764 CASES

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## ABSTRACT

**Background:** Breast cancer is the second most common malignancy among women, next to Cervical cancer. Understanding the pathogenesis, morphological features and its risk-factors, including family history can help in the treatment, early detection and prevention of the disease. Data on the epidemiological profile of breast cancer patients from Pakistan is scarce due to the lack of systemic data collection systems and resources. Our Institute caters to patients from population of all strata and is a representation of cases at all hospitals in Armed Forces.
**Study design:** Descriptive cross sectional.
**Place & duration of study:** A retrospective audit of breast cancer patients presenting at a tertiary referral center (AFIP) from 2010 to 2015.
**Materials and Methods:** In an attempt to evaluate the clinico-morphological patterns of breast cancer patients, including their family history a detailed analysis of 1764 breast cancer cases diagnosed during the years 2010–2015 was carried out. Frequency, Mean and standard deviation were performed.
**Results:** Mean age of the patient at presentation was 47.4 years, ranging from 4–90 years. Among the various histo-morphological types, infiltrating duct carcinoma (IDC) was found to be commonest type i.e. in 1574 cases (89.2%), followed by infiltrating lobular carcinoma (ILC) in 47 cases (2.7%), Mucinous carcinoma 26(1.5%), Invasive papillary carcinoma 17(1%) and other types forming (0.9%). Recurrent carcinoma made up 35 (2%) of the cases. Lymph node positivity was observed in 540 cases (30.64%). Out of 1764 cases evaluated for presence of family history, 1163cases (65.9%) revealed positive family history of cancer. 64 cases (3.4%) were males while 1704 case (96.6%) were females.
**Conclusion:** Family history of breast cancer forms one of the major risk factor among the various determining factors for the development of breast cancer and for its early detection. It is important to take an appropriate history of cancers from the patients' relatives to identifying the high risk group. Mean age of initial presentation of carcinoma is also shifting to younger age groups due to better screening methods and awareness. Various morpholological subtypes of breast cancer have different prognostic and predictive implications. Educating the population about the risk factors would be helpful in early detection of breast cancer.
**Key words**: Invasive Ductal Carcinoma, Invasive Lobular Carcinoma, Mucinous Carcinoma, Recurrent Carcinoma.

## INTRODUCTION

Worldwide breast Cancer is the most frequent cancer in women with 1.05 million new cases every year and it represents over 20% of all malignancies among females [1]. Most of the incidence of breast cancer occurs in the developed world. High-risk areas include Europe and North America. The lowest rates are reported from Africa and Asia. However, it still ranks as the commonest cancer among women in these regions. Incidence of breast cancer is on the rise in most of the countries, inclusive of the areas, which have had previously low rates [2]. The data of cancer from the various parts of the country, has confirmed breast cancer as the leading cancer among women. At some stage of life, every 9th Pakistani women has a likelihood of breast cancer [3]. This malignancy accounts for 19 of all cancer cases among women nationally [4]. While the epidemiological studies for breast cancer carried out in the region have mainly focused on risk factors such as, age at menarche, menopause, religion and reproductive history, not much consideration has been given to the role of family history even though genetic predisposition is responsible for 5– 10% of all breast cancers [5]. It is a well-known fact that the hereditary factors play a far greater role in women for

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the development of breast cancer [6]. Several morphological and clinical parameters such as histological type of tumor, tumor grade, axillary lymph node involvement, bilaterality etc. have been confirmed in breast cancer patients as the predictors of tumor behaviour. These prognostic factors are indicators of the inherent aggressiveness of the tumor as well as of the extent of the disease and based on these factors, treatment decisions are being taken up by the clinicians. The association of these prognostic factors with familial cancers has not been documented. Population based cancer registries do not exist in the developing countries including Pakistan. Most of the available figures from these countries are estimates based on data from small sections of population. Hospital and Institution based data is therefore an important source of information in these regions. The present study attempts to describe some of the clinico-pathological features of the breast cancer being diagnosed at Armed Forces Institute of Pathology. The data has been analyzed by various parameters such as age, morphological patterns of tumor, lymph node status, familial history and gender.

## MATERIALS AND METHODS

The computer based hospital data maintained in Microsoft Excel format was obtained from year 2010 to 2015. This had some basic information about all the cancer cases registered in a year chronologically. The data was sorted depending on the "organ" of origin of cancer. The data of patients registered as "Breast" being the organ of

cancer was analyzed by applying descriptive statistics to further evaluate the clinical and pathologic features of breast cancer patients.

## RESULTS

During the 5-year period from 1st January 2010 to 31st December 2015, a total of 1764 patients were diagnosed as having breast carcinoma. Majority of patients were residents of upper part of Pakistan as they have easy access to AFIP. The mean age of the patients with breast cancer was 47±14 years and the age ranged from 11 to 90 years. The median age was 47 years and mode was 40 years. Peak age of incidence was 40-60 years followed by 21-40 years. [table3]. Among the various histo-morphological types, infiltrating duct carcinoma (IDC) was found to be commonest type i.e. in 1574 cases (89.2%), followed by infiltrating lobular carcinoma (ILC) in 47 cases (2.7%), Mucinous carcinoma 26(1.5%), invasive papillary carcinoma 17(1%). Recurrent carcinoma made up 35 (2%) of the cases and other types forming (0.9%) [Table-1]. Among the other rare types of lesions 4 cases were of NLH,3 were of neuroendocrine carcinoma and 2 were of leiomyosarcoma [Table-2]. Lymph node positivity was observed in 540 cases (30.64%). Out of 1764 cases evaluated for presence of family history, 1163 cases (65.9%) revealed positive family history of cancer while 601 (34.1) had no history of breast carcinoma. 64csaes (3.4%) were males while 1704 case (96.6%) were females. [Table-4] Among patients categorized as other types of breast carcinoma, their distribution is shown in table [Table-3].

**Table-1: Various types of breast malignancy and their mean age and percentage.**

| Hisrtopathological types | Mean Age | N | Std. Deviation | Percent |
|---|---|---|---|---|
| Invasive ductal carcinoma | 47.5432 | 1574 | 14.83172 | 89.2 |
| Invasive lobular carcinoma | 45.5957 | 47 | 17.77964 | 2.7 |
| Invasive papillary carcinoma | 51.2941 | 17 | 13.44324 | 1.0 |
| Medullary carcinoma | 46.1111 | 9 | 20.11495 | .5 |
| Metaplastic carcinoma | 55.0000 | 7 | 13.12758 | .4 |

| | | | | |
|---|---|---|---|---|
| Mixed ductal and lobular carcinoma | 46.5000 | 16 | 12.14359 | .9 |
| Mucinous carcinoma | 47.0385 | 26 | 15.82525 | 1.5 |
| Other carcinoma | 44.1250 | 16 | 18.23870 | .9 |
| Paget's disease | 43.2857 | 7 | 12.48618 | .4 |
| Recurrent invasive ductal carcinoma | 46.1143 | 35 | 9.89287 | 2.0 |
| Tubular carcinoma | 45.4000 | 10 | 15.63614 | .6 |
| **Total** | **47.4444** | **1764** | **14.85268** | **100.0** |

**Table-2: Other types of breast malignancy.**

| | **Frequency** | **Percent** |
|---|---|---|
| Leiomyosarcoma | 2 | 12.5 |
| MALT Lymphoma | 1 | 6.3 |
| myelois sarcoma | 1 | 6.3 |
| Neuroendocrine carcinoma | 3 | 18.8 |
| NHL Diffuse large B cell type | 4 | 25.0 |
| Small round blue cell tumour | 1 | 6.3 |
| Solitary fibrous tumour | 1 | 6.3 |
| Spindle cell lesion | 1 | 6.3 |
| synovial sarcoma | 1 | 6.3 |
| Undiffrentiated malignant neoplasm | 1 | 6.3 |
| **Total** | **16** | **100.0** |

**Table-3: Age distribution of breast malignancy.**

| | | AGE | | | | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Invasive ductal carcinoma | Invasive lobular carcinoma | Invasive papillary carcinoma | Medullary carcinoma | Metaplastic carcinoma | Mixed ductal and lobular carcinoma | Mucinous carcinoma | Other carcinoma | Paget's disease | Recurrent Invasive ductal carcinoma | Tubular carcinoma | |
| **Age** | 1-20 | 57 | 5 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | **66** |
| | 21-40 | 476 | 12 | 2 | 3 | 1 | 4 | 7 | 9 | 4 | 12 | 5 | **535** |
| | 41-60 | 773 | 22 | 12 | 3 | 3 | 10 | 15 | 4 | 2 | 20 | 3 | **867** |
| | 61-90 | 268 | 8 | 2 | 2 | 3 | 1 | 3 | 3 | 1 | 3 | 2 | **296** |
| **Total** | | **1574** | **47** | **17** | **9** | **7** | **16** | **26** | **16** | **7** | **35** | **10** | **1764** |

**Table-4: Histopathological types of breast malignancy and its correlation with gender and history.**

| History | | | Invasive ductal carcinoma | Invasive lobular carcinoma | Invasive papillary carcinoma | Medullary carcinoma | Metaplastic carcinoma | Mixed ductal and lobular carcinoma | Mucinous carcinoma | Other carcinoma | Paget's disease | Recurrent invasive ductal carcinoma | Tubular carcinoma | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Present** | Gender | Male | 14 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | **15** |
| | | Female | 519 | 17 | 3 | 4 | 1 | 4 | 8 | 9 | 4 | 12 | 5 | **58** |
| | Total | | 533 | 17 | 3 | 4 | 1 | 5 | 8 | 9 | 4 | 12 | 5 | **50** |
| **Absent** | Gender | Male | 40 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | **45** |
| | | Female | 1001 | 29 | 14 | 4 | 5 | 10 | 18 | 6 | 3 | 23 | 5 | **1118** |
| | Total | | 1041 | 30 | 14 | 5 | 6 | 11 | 18 | 7 | 3 | 23 | 5 | **53** |
| **Total** | Gender | Male | 51 | 1 | 0 | 1 | 1 | 2 | 0 | 1 | 0 | 0 | 0 | **60** |
| | | Female | 1520 | 46 | 17 | 8 | 6 | 14 | 26 | 15 | 7 | 35 | 10 | **1704** |
| | Total | | **1574** | **47** | **17** | **9** | **7** | **16** | **26** | **16** | **7** | **35** | **10** | 1764 |
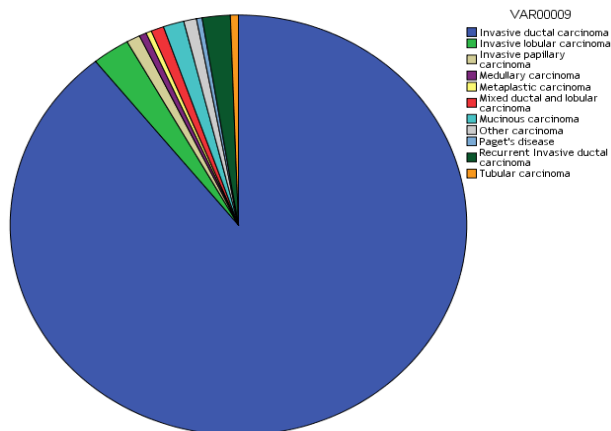


**Figure-1: Graphical presentation of various types of breast malignancies.**

## DISCUSSION

In the US, most common female cancer is the breast cancer, it is also the second most common cause of cancer death in women [7]. Approximately 232,620 new cases of invasive breast cancer are expected to be diagnosed in the United States in 2011, and 39,970 will die from the disease. The lifetime probability of developing breast cancer is one in six overall (one in eight for invasive disease) [7].

Breast cancer is the most common cancer in women in urban areas of developing countries. Because of the lack of awareness on early detection and barriers to health services, most women with breast cancer are diagnosed in late stages in low- and middle-income countries [8]. The greatest rise in the incidence of breast cancer has been in Asian countries.

From Pakistan studies, have consistently shown breast cancer to be the most frequent cancer of the women [9]. Data from various institutes of the country including Karachi Institute of Radiotherapy and Nuclear Medicine (KIRAN) [10] and Jinnah hospital Lahore have also shown breast cancer to be the commonest cancer of women accounting for 38% of all. In the developed countries like United Kingdom, Australia and USA the percentage of patients of breast cancer among all female cancers are 30%, 27% and 26% respectively [11].

Breast cancer has a complex etiology, possibly with interplay of many causal factors including hormonal, genetic and environmental factors operating over a long period. The interactions

of the various etiological factors are yet to be completely understood, although several risk factors have been well defined, Moreover, analysis of newer parameters like family history could be helpful in screening high risk women for developing breast cancer, followed by planning of future, preventive and treatment modalities.

Age of the cancer patient is an important factor both for occurrence and management of the case. In the present study, the average age of the breast cancer case at presentation was found to be 47 years. Similarly, in various population-based registries located in different parts of the region the average age of breast cancer patients has been found to be 50 to 53 years [7, 12]. Amongst US white females the average age of occurrence of breast cancer has been reported to be 61.0 years [12]. The average age of occurrence of the breast cancer in India reveals that the disease occurs a decade earlier, as compared to western countries. The reason for early age of occurrence amongst Indian females is not very clear. A similar viewpoint has been put forward in the Czech population by a study conducted by Borovanova [13]. In their study, they found a shift of cancer more towards younger women.

Breast carcinoma is primarily classified by its histological appearance, originating from the inner lining epithelium of the ducts or the lobules that supply the ducts with milk. For the morphological study of breast carcinoma, two main questions need to be answered: is the tumor limited to the epithelial component of the breast (in situ carcinoma) or has invaded the stroma to become invasive carcinoma and does the tumor arise from the duct (ductal carcinoma) or from the lobule (lobular carcinoma)? Both tumor types arise from the same segment of the mammary gland which is TDLU. The cytoarchitectural features should be used for diagnostic purposes in daily histopathological

practice, to determine the tumor to be ductal or lobular, rather than its precise location within the breast tissue.

The various histologic types of breast cancer have prominent prognostic clinical, and biological features. Invasive ductal carcinoma (IDC) is the most frequent followed by invasive lobular carcinoma (ILC) and some rare variants. The 89.2% frequency of IDC in our patients is higher and 2.7% frequency of ILC is lower than that found in the studies from other developed countries. About 70% to 80% patients had IDC and 5% to 15% had ILC in the developed countries [14] while 90% to 92% IDC and 1% to 3% ILC has been reported from Pakistan [15]. These differences can be due to the reproductive practices such as (early age at birth of first child, prolonged lactation and high parity), low frequency of hormone replacement therapy and early peak age of breast cancer incidence of the local women, as all these factors are known protective factors for ILC [14].

Invasive ductal carcinomas are breast cancers having malignant ductal proliferation along with stromal invasion in the presence or absence of DCIS, apart from their relative proportion. IDCs are a heterogeneous group of tumors classified according to cytoarchitectural features, as they have wide scope of morphological variation. Some of them have enough distinctive features and particular behavior to be classified as special subtypes, while the majority, which constitute about 75% of IDC, fail to exhibit sufficient morphological features to be classified as specific histological types and are designated as IDC not otherwise specified (NOS). Also "no special type" (NST) is used to emphasize the distinction from specific-type tumors, which is internationally accepted [16].

IDC no specific type (NST) is the most common type of IDC that constitutes about 40%–75% of all mammary invasive carcinomas in the published series [17]. This subtype shows a wide scope of

morphological variation and clinical behaviors, such as tumor size, grade, relative proportion of tumor cell and stroma, and types of margins. The tumor also has a heterogeneous type of growth, including diffuse sheets, nests, cords, or singly distributed cells with variable amount of ductal differentiation. The amount of ductal differentiation ranges from more than 70% of tumor tissue to complete absence. The areas of necrosis and calcification can be detected in 60% of cases. Foci of squamous metaplasia, apocrine metaplasia, or clear cell changes are sometimes present [18]. In the current study 89.2% of the cases were classified is IDC NST.

Invasive lobular carcinoma (ILC) is the second major biologically distinct invasive mammary carcinoma other than IDC. It constitutes 5%–15% of invasive breast carcinoma and usually affects older age group women affected by conventional IDC [16]. ILC tumor cells are typically round, small, relatively uniform, and noncohesive and have characteristic growth pattern with single-file infiltration of the stroma. The diagnosis of ILC can be made in the presence of these cytoarchitectural features even in the absence of in situ component. The incidence of ILC appears to be increasing, particularly in postmenopausal women, and this finding may, at least partly, be related to hormone replacement treatment. Inactivation of E-cadherin by mutation, loss of heterozygosity, or methylation are characteristic molecular changes in ILC, particularly the pleomorphic subtype. ILC has five distinct histological variants. The classic type of ILC expresses the typical cytoarchitectural features of ILC; typically, the presence of small uniform tumor cells distributed singly in the stroma, forming Indian file pattern and surrounded by the lobules in a concentric (targetoid) pattern [18]. In our study 2.7 % of the cases were diagnosed as ILC.

Tubular carcinoma is a rare, distinct, well-differentiated special type of breast carcinoma with an excellent prognosis, constituting about 2% of IDC in published series. Tubular carcinoma is more common in elderly women and is less likely to have lymph node metastasis [19]. Microscopically, it is characterized by the proliferation of angulated, oval, or elongated tubules with haphazard arrangement and has open lumina lined by a single layer of epithelium without supporting the outer layer of myoepithelial cell and basement membrane, with multifocal invasion of the stroma and fat at the periphery of the tumor. Percentage of tubular carcinoma was 0.6% in the current study.

Mucinous carcinoma is a rare, special subtype of breast carcinoma associated with good prognosis, it is a disease of elderly patient, over 60 years, and usually occurs in postmenopausal women. It accounts for only 2% of total breast carcinomas. Other terms that are used to identify this tumor include gelatinous carcinoma, colloid carcinoma [17]. Microscopically, the tumors comprising small clusters of uniform epithelial tumor cells with mild nuclear atypia float in abundant mucus. These cell clusters are arranged as solid, acinar structures. The mucin is almost entirely extracellular [6]. In the current study 1.5 % of the cases were mucinous carcinoma.

Medullary carcinoma is a rare, special subtype of breast cancer presented by a well-defined tumor mass and anaplastic morphology; nonetheless, it has favorable prognosis and better outcome than the common IDC. It affects women about 50 years of age. It is particularly common in carriers of *BRCA*1 mutations [17]. It accounts for less than 5% of mammary carcinomas in most series, but frequency as high as 7% has also been reported [16] .The gross appearance can easily be mistaken for a fibroadenoma. Microscopically, it is a "well-circumscribed carcinoma composed of poorly differentiated cells with scanty stroma and prominent lymphoid infiltration" and the borders are always of

the *pushing* type [18]. Percentage of medullary carcinoma was 0.5% in the current study.

Invasive papillar carcinoma is a very rare subtype of breast carcinoma with better prognosis than classic IDC, mostly affecting the postmeno-pausal women and is more common among white women. It comprises less than 1%–2% of invasive breast cancers [18] Most papillary carcinomas of the breast are predominantly intraductal lesions. The invasive papillary carcinoma should have a predominantly papillary morphology not less than 90% in the invasive component [19]. In the current study 1% of the cases were Invasive papillar carci-noma.

Neuroendocrine carcinoma of the breast is a rare, special subtype of breast cancer representing about 2% of breast carcinoma. It exhibits morphological and immunohistochemical features similar to those of neuroendocrine tumor (NET) of both gastrointestinal tract and lung and has more than 50% of tumor cells that express the neuroendocrine markers. Conventional invasive breast carcinoma NOS and some special variant exhibiting focal neuroendocrine differentiation are not uncommon features. We found 3 cases of neuroendocrine carcinoma in the current study.

Metaplastic carcinoma is an aggressive invasive beast carcinoma, characterized by the dominant component of metaplastic differentiation (squamous, spindle, and mesenchymal). It represents less than 1% of all invasive breast carcinomas. It affects postmenopausal women with an average age of 55 years, and in it, metastases to axillary nodes are relatively uncommon [17]. Percentage of medullary carcinoma was 0.4% in the current study

The clinical appearance of the Paget's disease is usually a thickened, sometimes pigmented, erythematous weeping or crusted lesion with irregular borders. Mammary Paget's disease

(MPD) is almost always associated with an underlying breast cancer in 92–100% of cases. Approximately 50% of this patient present with an associated palpable mass in the breast [20]. 0.4% of the cases had Paget's disease in the current study.

Recurrent breast cancer is breast cancer that comes back after initial treatment. Although the initial treatment is aimed at eliminating all cancer cells, a few may have evaded treatment and survived. These undetected cancer cells multiply, becoming recurrent breast cancer. 2% of the patients had recurrent breast disease in the current study

Breast cancer can also occur in men and children. Breast carcinoma in males make for less that 1% of all breast cancer cases, and the cancers may be either invasive or in situ. The breast cancers in men can be very similar to those seen in women, and most cases are composed of invasive ductal carcinoma with positive estrogen receptor (ER) expression. But the most common breast lesion in males is not breast cancer but is rather gynecomastia, or breast enlargement, which may either involve one breast (unilateral) or both breasts (bilateral). In the current study incidence of carcinoma in males was 3.4 % which is higher than that reported in western studies.

## CONCLUSION

In conclusion, the profile of breast cancer patients in Pakistan follows a pattern similar to that of other developing countries with earlier peak age and advanced disease stage at presentation. Higher frequency of breast cancer among all cancers is registered at local hospitals. Very few women are diagnosed at Stage 0 having DCIS. Limited availability of mammography machines in local hospitals is the main reason. The local women have higher frequency of Invasive Ductal Carcinoma and lower frequency of Invasive Lobular Carcinoma. This difference is attributed to the low prevalence of the risk factors for ILC in the local population. Incidence

of male breast cancer is twice that of the world in general. Introduction of hospital information systems in the local cancer hospitals and population based cancer registry at the national level is required for accurate and reliable local cancer data base. Various morpholological subtypes of breast cancer have different prognostic and predictive implications. Promotion of breast health awareness and better facilities for earlier diagnosis and appropriate

treatment is required to improve the present clinical scenario.

## AUTHORS CONTRIBUTION

**Shoaib Naiyar Hashmi:** Gave the main idea of the study.

All authors worked in Histopathology Department AFIP Rawalpindi and dealt with the patients` samples which were included in the study.

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