RESEARCH ARTICLE

# The characteristics and risk factors of breast cancer patients trend distinctive regional differences: a cross-sectional study

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## Abstract

**Objective:** To determine the characteristics and risk factors of breast cancer patients in a tertiary care setting.

**Method:** The retrospective, cross-sectional study was conducted at the Sindh Institute of Urology and Transplantation, Karachi, and comprised data of all patients diagnosed with breast cancer from March 2017 to December 2021. Demographic characteristics, clinical presentation, stage of the disease and histopathological characteristics were noted. Data related to all the variables was not available in all cases. Data was analysed using SPSS 23.

**Results:** Of the 690 patients, 683(99%) were females and 7(1%) were males. The mean age at presentation was 49.3±13.5 years, while the mean duration of symptoms was 10.24±17.64) months. Most of the females were married 642(93%) and multiparous 484(70.9%), while 293(42.5%) had breastfed their children for >1 year, and 412(59.7%) had no history of contraception use. The most common stage at presentation was stage II (48.6%), and most patients had grade II 395(57.2%) invasive ductal carcinoma, with Luminal A molecular subtype noted in 287(41.6%) cases.

**Conclusion:** The characteristics of breast cancer in the sample had certain distinctions compared to other populations. It is important to integrate all datasets and develop guidelines appropriate to Pakistani population.

**Key Words:** Breast cancer, Risk factor, Clinical audits, Disease attribute, Medical oncology, Carcinoma.

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## Introduction

Breast cancer (BC) is the leading cause of mortality and morbidity worldwide. It is the most commonly occurring cancer in women and is the second most common cancer internationally, comprising 11.7% of all cancers.[1] In Pakistan, approximately 90,000 new cases are diagnosed every year, and 40,000 of them die.[2] There are no national cancer registries in Pakistan despite being the fifth most populous nation. Therefore, most of the figures are estimates based on data collected from small sections of the population. Based on the data from a local cancer registry from a district of Karachi, between January 1995 and December 1997, breast cancer made up approximately one-third of cancers in females. The data suggested that the women in the studied region of Karachi had the highest incidence of breast cancer in Asia.[3] This extraordinary information also raises concerns about data reliability and whether it truly represents attributes of the whole population.[2]

Studies have demonstrated differences in the epidemiological, clinical and histopathological characteristics among BC patients in different countries. For instance, approximately 50% of women with newly-diagnosed BC in the United States are age >63 years, while in developing countries, such women are aged 50 years.[4] Similarly, the in-situ disease is more common in the developed countries, while the locally advanced and metastatic disease is common at presentation in the developing countries [4]. This is most likely due to certain socioeconomic factors, including access to healthcare, varied genetic background, lifestyle, and aggressive tumour biology.[5,6] Due to the lack of reliable local statistics, the management of BC patients is based on Western recommendations. [7]

In the absence of a centralised database, there is a need to pool data from specialised centres for improving understanding of the disease dynamics nationally.

To make progress in this direction, the current study was planned to determine the characteristics and risk factors of BC patients in a tertiary care setting.

## Patients and Methods

The retrospective, observational study was conducted at the Sindh Institute of Urology and Transplantation (SIUT), Karachi, and comprised medical records of BC patients

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registered with the institutional Breast Clinic from March 1, 2017, to December 31, 2021. The sample was raised using consecutive non-probability sampling technique. Data of patients who were lost to follow-up after the first consultation and those consulting for a second opinion was excluded.

A priori sample size was calculated using using EpiInfo calculator with population >1 million, and 5% margin of error for unknown proportion (50%) with 95% confidence level. [8]

Data was collected using Google Forms, and included age, gender, residence, marital status, risk factors, age at menarche, menopause, parity, breastfeeding, contraception, family history, body mass index (BMI), clinical presentation, site and duration, stage of the disease, as well as histopathological characteristics, like tumour type, hormone receptor status, antigen Kiel-67 (Ki-67) and grade.

Data related too all these variables was not available for all the patients. However, the overall missing data did not represent significant proportion to affect the overall results.

Grading of the tumours had been done using the Nottingham Modified Scarff-Bloom-Richardson system, while staging was based on the American Joint Committee on Cancer (AJCC) Anatomic Stage Groups[9] or which oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) levels were combined to create 4 categories; luminal A = ER+ and/or PR+, HER2-), luminal B = ER+ and/or PR-, HER2+), basal cell-like (BCL) or triple-negative = ER-, PR-, HER2-, and HER2-positive tumours = ER-, PR-, HER2+.[9]

In cases where immunohistochemistry (IHC) results showed equivocal results for HER2 status, fluorescent in-situ hybridisation (FISH) was used to confirm the receptor status. The Ki-67 index has been reported in three groups; up to 5%, 5-30%, and >30%. [10] Because of the cost involved, Ki-67 testing is ordered at SIUT in cases where postoperative histology is equivocal.

The data was managed using Microsoft Excel 2016, and analysed using SPSS 23. Mean ± standard deviation was calculated for continuous variables, while categorical variables were presented as frequencies and percentages.

## Results

Of the 12,083 patient interactions, including follow-up visits, during the study period, data was collected for 690(5.7%) patients who met the inclusion criteria (Figure).

**Table-1:** Demographic data and risk factors.

| Factor | N | Percent (%) |
|---|---|---|
| **Marital Status (n=690)** | | |
| Married | 642 | 93 |
| Single | 45 | 6.5 |
| Other | 3 | 0.4 |
| **Residence (n=690)** | | |
| Sindh | 650 | 94.2 |
| Punjab | 16 | 2.3 |
| Baluchistan | 17 | 2.5 |
| Khyber Pakhtunkhwa (KP) | 4 | 0.6 |
| Other | 3 | 0.4 |
| **Number of Children (n=683)** | | |
| Nulliparous | 99 | 14.5 |
| Uniparous | 41 | 6.0 |
| Multiparous | 484 | 70.9 |
| Not recorded | 59 | 8.6 |
| **Lactation History (n=690)** | | |
| Did not breastfeed | 30 | 4.3 |
| 6 months or less | 38 | 5.5 |
| 1 year | 61 | 8.8 |
| More than 1 year | 293 | 42.5 |
| Not applicable | 89 | 12.9 |
| Not recorded | 179 | 25.9 |
| **Contraception Use (n=690)** | | |
| Hormonal | 79 | 11.4 |
| Non-hormonal | 35 | 5.1 |
| None | 412 | 59.7 |
| Undisclosed | 164 | 23.8 |
| **Age at menarche (n=683)** | | |
| Less than 12 years | 23 | 3.3 |
| 12-14 years | 394 | 57.7 |
| More than 14 years | 71 | 10.4 |
| Patient unsure | 195 | 28.6 |
| **Menopausal Status (n=683)** | | |
| Premenopausal | 288 | 42.2 |
| Postmenopausal | 299 | 43.7 |
| Uncertain | 96 | 14.1 |
| **Family History of Breast Cancer (n=690)** | | |
| Yes | 119 | 17.2 |
| No | 490 | 71 |
| Unknown to the patient | 81 | 11.7 |
| **Family History of Other Cancers (n=690)** | | |
| Yes | 87 | 12.6 |
| No | 509 | 73.8 |
| Unknown to the patient | 94 | 13.6 |
| **Site (n=690)** | | |
| Left breast | 343 | 49.7 |
| Right breast | 336 | 48.7 |
| Bilateral breasts | 11 | 1.6 |

Of them, 683(99%) were females and 7(1%) were males. The mean age at presentation was 49.3±13.5 years, while the mean duration of symptoms was 10.24±17.64) months. The mean age at menarche was 13.22±1.29 years, and the mean age at menopause was 47.19±6.09

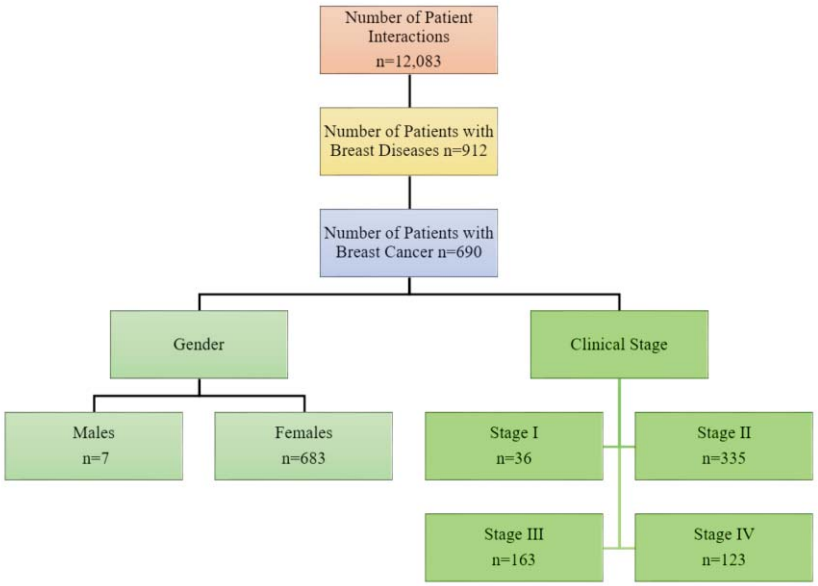


**Figure:** Study flow-chart with demographic and clinical distribution.

**Table-2:** Tumour characteristics.

| Characteristic | N | Percent (%) |
|---|---|---|
| **Histopathology Diagnosis** | | |
| IDC | 610 | 88.4 |
| ILC | 29 | 4.2 |
| DCIS | 12 | 1.7 |
| Other | 39 | 5.6 |
| **Grade** | | |
| I | 34 | 4.9 |
| II | 395 | 57.2 |
| III | 220 | 31.9 |
| Not applicable | 21 | 3.1 |
| **Not reported[a]** | 20 | 2.9 |
| Receptor Status | | |
| Luminal A | 287 | 41.6 |
| Luminal B | 83 | 12 |
| Triple-Negative | 169 | 24.5 |
| HER2 Positive | 54 | 7.8 |
| **Not reported[a]** | 97 | 14.1 |
| Ki-67 Index | | |
| Less than or equal to 5% | 5 | 0.7 |
| Between 5% and 30% | 247 | 35.8 |
| More than or equal to 30% | 211 | 30.6 |
| Not checked | 227 | 32.9 |
| **Stage** | | |
| Stage 0 | 33 | 4.8 |
| Stage I | 36 | 5.2 |
| Stage II | 335 | 48.6 |
| Stage III | 163 | 23.6 |
| Stage IV | 123 | 17.8 |

IDC: Invasive ductal carcinoma, ILC: Invasive lobular carcinoma, DCIS: Ductal carcinoma in-situ, HER2: Human epidermal growth factor receptor 2, Ki-67: Antigen Kiel-67. a: Proportion of patients had partial treatment or diagnostic workup done at other institutions and some of these variables were not recorded.

years. The mean BMI was 28.4±5.89 kg/m$^2$ at presentation. Most of the females were married 642(93%) and multiparous 484(70.9%), while 293(42.5%) had breastfed their children for >1 year, 79(11.4%) had a positive history of contraception use, 119(17.2%) had a family history of BC, and 87(12.6%) patients had family history of some other cancer (Table 1).

The right breast was affected in 336(48.7%) cases and the left breast in 343(49.7%). Invasive ductal carcinoma (IDC) was found in 610(88.4%) cases395(57.2%) tumours were grade II409(59.3%) were ER+ and 469(68%) were HER2-. Molecular subtype categorisation showed luminal A in 287(41.6%) patients. Most of the patients presented with stage II disease (48.6%) (Table 2).

## Discussion

BC, despite its wide prevalence among women worldwide, presents dissimilarities among population groups. In Pakistan, the reported age at BC diagnosis is lower than the European and North American populations[4]. In the current study, the mean age at diagnosis was 50.34±12.69 years (range: 21-90 years). This is similar to earlier data from across Pakistan [10-13]. Regionally, a study from northern India also indicated similar age at presentation (47.88 years).[7] The mean age at presentation for Iraqi women was 49.4 years compared to 61.7 years for British women.[6] Similarly, the median age of BC patients at diagnosis in the US was 61 years. [5]

It has been suggested that the young age of the population along with lower life expectancy in developing countries are the reasons for evidently younger age at presentation compared to the developed countries. [2,15] Another explanation may relate to the higher frequency of consanguineous marriages in these countries, which is a known risk factor for genetic mutations. [12] Unfortunately, there is no large genetic study from Pakistan analysing this element due to resource constraints. An alternative way to determine genetic association is to consider familial distribution. Interestingly, there was a positive family history of BC in 17.2% of the patients in the current study. Similar results (16.9% and 18.2%) reported earlier. [16,14] In contrast, this proportion was reported 11% in a US study.[17] There appears to be a trend towards a higher proportion of first-degree relatives with BC among Pakistani cohort.

However, due to the lack of genetic testing, such conclusions cannot be verified.

The most common histopathological type in tye current study was IDC (88.4%). This was similar to other studies conducted in Pakistan. [11,12,16] In contrast, the incidence of invasive lobular carcinoma (ILC) was low in Pakistan compared to Western data (15%) [2,14, 4,18-20]. The reason for this distinction may be the presence of certain protective factors in the Pakistani population that were also noted in the current study, including multiparity (70.9%), prolonged lactation for >1 year (42.5%), younger age at birth of the first child, low prevalence of hormone replacement therapy (HRT) and younger age at disease presentation. [2,13,18-20]

The current study found 1.7% prevalence of ductal carcinoma in-situ (DCIS) cases which was relatively higher than other studies from Pakistan. [2,14] The data is remarkably lower compared to 51% reported DCIS cases in the US.[3] The lack of population-based mammographic screening programmes in Pakistan may be the reason for the low incidence of in-situ BC. This relates to the lack of awareness of the disease and the importance of screening not only among women and primary healthcare workers, but the social taboos related to the diagnosis, and the limited availability of mammography machines.

There are similarly conspicuous differences noted in stage distribution of BC patients at presentation. The current study found that most of the patients presented with stage II disease (48.6%). Of the remaining, 4.8%, 5.2%, 23.6% and 17.85% presented with stage 0, stage I, stage III and stage IV disease, respectively. Other studies from 63% and 58% patients with stage III and IV at diagnosis [3], with only 10% presenting with stage I and <1% with stage 0 [2]. A study reported 46% stage III and 16% stage IV at diagnosis, and 9% stage I at presentation [13]. Regionally, majority of the patients reportedly presented with stages III and IV disease in India and Iraq. [7,21] In contrast, in the IS, approximately 4.89% patients presented with stage IV disease, and 48.84% with stage I. [22] A United Kingdom study showed 60.8% patients presenting with stage I disease, and only 2.3% and 0.7% with stage III and stage IV disease at diagnosis. [6] This difference between the clinical stages of the disease is attributed to several factors common in the developing world, including the lack of screening programmes, delay in seeking medical treatment, low socioeconomic status, lack of proper healthcare and education system, and lack of knowledge about the disease, leading to ignorance, fear and fatalistic attitudes. This was evident by the mean duration of symptoms 10.24 ± 17.64 (range: 1-300) months in the current study.

There appeared to be a higher incidence of triple negative in the current study (24.5%) compared to earlier studies from Pakistan that showed 14-30.8%. [22,23] In regional countries, like India and Iraq [6,7,14], the percentages were quite similar. In comparison, literature from Britain reported only 5% of patients with triple-negative subtype.[6] Since the triple-negative subtype is associated with poor prognosis, it can be one of the reasons for high mortality seen, and this should prompt further research into the risk factors for triple-negative BC in different populations.

The current study has limitations, representing a small subset of population. Besides, there was missing data in the records. The results, as such, are nor generalisable to the whole country.

## Conclusion

Younger age and later stage at presentation among BC patients was noted. There is a clear need of developing a centralised cancer-based registry in the country.

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**Author's Contributions**

**BS:** Conceptualization, methodology, resources, writing, review and Editing, Supervision, Project administration
**MN:** Methodology, validation, formal analysis, investigation, data Curation, writing original Draft, review and editing, visualization
**MAK:** Validation, formal analysis, resources, writing, review and Editing, visualization.