ORIGINAL ARTICLE

Association between Age of Patient and Grade of Breast Cancer

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ABSTRACT

Background: Breast Cancer is the most common cancer in women in most parts of the world. In developing countries, patients with breast cancer present for the first time in an advanced stage (stages 2 to 3).

Objective: The objective of this study was to investigate the distribution of histological grade and its association with age of breast cancer patients.

Methodology: This cross-sectional study was conducted in the Department of Medical Oncology at Jinnah Postgraduate Medical Center (JPMC) Hospital in Karachi. The study duration was July 2024 to December 2024. The study included women diagnosed with breast cancer between the ages of 18 and 80 years. The patients were categorized into different age groups, and tumor characteristics, including histological grade, tumor size, and lymph node involvement, were assessed. Statistical analysis was performed to identify significant associations between age and these characteristics, especially grade using Chi-square and Fisher's exact tests.

Results: A total of 120 patients were studied with a mean age at presentation for the participants was 47.3±12.63 years. Histological grading showed that 6 (5%) patients had grade I, 78 (65%) had grade II, and 36 (30%) had grade III cancer. No significant relationship was observed between age and histological grade (p=0.237). However, significant associations were found between age and axillary lymph node involvement (p=0.01) as well as TNM staging (p=0.03), with younger and older patients showing more advanced disease.

Conclusion: This study shows there is no significant association between the age of patients and the histologic grade of breast cancer. Further research with larger, multi-center studies is needed to validate these findings.

Keywords: *Breast cancer, age, tumor characteristics, lymph node involvement, TNM staging, prognosis, age-specific management.*

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer among women globally, though its occurrence varies significantly across different regions. It is most prevalent in Northern Europe and North America, moderately common in the Mediterranean and South America, and least common in Asia and Africa [1].

Breast cancer comprises 18% of all female cancers [2]. It is the second leading cause of death from cancer among women [3], affecting up to one in 11 women during life [4]. The American Cancer Society reports that approximately 1.3 million women are diagnosed with breast cancer each year worldwide, with an estimated 465,000 deaths resulting from the disease. In low-resource countries like Pakistan, even healthcare professionals such as nurses may lack sufficient knowledge about breast cancer, affecting early detection efforts [5]. Among every 1,000 women aged 50, about two are newly diagnosed with breast cancer, and around 15 have been diagnosed before reaching 50, indicating a prevalence rate of 2% [2]. Data from National Cancer Registries across various Asian countries show that the crude incidence rate of breast cancer ranges from 21.3 cases per 100,000 people in Jordan, 21.4 in Iran, 24.1 in Turkey, 34.86 in Malaysia, to 48 in Japan [1]. It accounts for 19-34% of all cancers in India [6] and 19.1% in Saudi Arabia [2].

The Karachi Cancer Registry, which is the only population-based cancer registry in Pakistan, identifies breast cancer as the most prevalent cancer among women, accounting for 34.6% of all female cancer cases. Between 1998 and 2002, the age-standardized incidence rate (adjusted to the world population) was 69.1 per 100,000, marking the highest reported breast cancer rate in Asia. Likewise, in Lahore—another major city in Pakistan—breast cancer is also the leading cancer among women [7]. International Association of Cancer Research, based in France, projected that there would be 250,000 cases of breast cancer in India by 2015 a 3% increase per year currently, and undoubtedly breast cancer will become an epidemic in India and Pakistan in another ten years [8].

Breast cancer incidence continues to rise until around the age of 80, peaks between 80 and 85 years, and then begins to decline. In Asian women, the disease tends to occur at a younger age, with the highest prevalence observed between 40 and 49 years, whereas in Western countries, the peak prevalence is typically seen between 50 and 59 years [1].

Many developed countries offer the National Breast Cancer Screening Programme, whereas in developing

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countries screening is assessed by individuals who can afford it [9]. The World Health Organization and experts recommend that countries with limited resources should focus their national breast cancer control programs on promoting early detection, particularly targeting women between the ages of 40 and 69 [10]. Third-world breast cancer is characterized by late presentation, advanced stage of disease with worse biological behaviors, and occurrence relatively at a younger age [11]. In developing countries, patients with breast cancer present for the first time in an advanced stage (stage 2 to 3) [12]. Various factors are thought to contribute to the delayed presentation of breast cancer, including psychosocial and cultural beliefs, lack of access to treatment facilities, low literacy rates, poverty, limited awareness about the disease, and fear of undergoing surgery [11]. Particularly in Islamic countries, generally, women abstain from touching their breasts, do not go for CBE (clinical breast examination), and feel embarrassed about undergoing mammography [13]. Trends in a change in age pattern has been noted in various studies. However, the association between age and grade of breast cancer has not been well studied.

Pakistan is a developing country with limited resources. Early detection of breast cancer plays a crucial role in preventing premature death, physical complications, and emotional suffering in women. Promoting awareness about screening is highly encouraged, as breast cancer cases are increasing and high mortality rates are often linked to late diagnosis and a lack of public awareness. Knowing the grade of cancer and its association with different age groups will be helpful in the management of breast cancer in various age groups. Background lacking, theoretically, young patients have high-grade tumors as compared to older age patients according to several studies and reports.

The present study aimed to determine the association between the age of the patient and the grade of breast cancer.

MATERIALS AND METHODS

The study was a cross-sectional survey conducted in the Department of Medical Oncology at Jinnah Postgraduate Medical Center (JPMC) Hospital in Karachi. The study spanned six months from 1st July 2024 to 31st December 2024 following the Institutional Review Board (IRB) approval.

A previous study reported that histological grade I was seen in 18.2% of patients [14]. Using p=18.2% at 95% confidence interval and 7% margin of error, a sample size came out to be 117 patients. Sample size calculation was performed using the online available calculator Open-Epi.

Participants were selected based on the following inclusion criteria: women aged 18 to 80 years who were diagnosed with breast cancer according to operational definitions, had a cancer duration of 24 weeks, and represented all stages of breast cancer. Exclusion criteria included patients unwilling to participate, patients with a history of breast trauma, and pregnant or lactating women.

Before enrollment, the study was explained in detail to each eligible participant, and written informed consent was obtained. Baseline demographic and clinical details, including age, residence, education, marital status, height (measured using a wall-mounted scale in centimeters), weight (measured using a digital weighing machine with light clothing), and BMI (calculated as Weight in Kg / Height in m^2), were recorded in a predesigned proforma.

Each participant underwent screening for breast carcinoma, which included immunohistochemical staining and histological grading based on a histopathology report. The histological grading of breast cancer was performed using the Scarff-Bloom-Richardson grading system.

To minimize bias and confounders, strict adherence to the exclusion criteria was maintained, ensuring that only relevant data were included in the analysis. Data were entered and analyzed using SPSS version 24.0. Descriptive statistics, including the mean ± SD or median (IQR), were calculated for continuous variables such as age, weight, height, BMI, and family monthly income. Categorical variables like residential status, marital status, educational level, diabetes mellitus, hypertension, family history of breast cancer, and breast cancer grades were summarized using frequencies and percentages.

The association between breast cancer grades and age was analyzed using the Chi-square test or Fisher's exact test, as appropriate. To control for confounding variables (age groups, BMI, residential status, marital status, educational level, diabetes, hypertension, family history of breast cancer, and family income), stratification was applied. Post-stratification, Chi-square or Fisher's exact tests were conducted, with a p-value ≤ 0.05. Bar graphs and pie charts were used to present the graphical representation of the data, ensuring a clear visualization

RESULTS

The mean age at presentation for the participants was 47.3±12.63. The mean age at menarche was 12.72±1.64 years (**Table 1**). The age distribution of the participants was as follows: <30 years, 9 (7.5%); 30-50 years, 75 (62.5%); 51-70 years, 34 (28.3%); and >70 years, 2 (1.7%). Marital status showed that 102 (85%) were married and 18 (15%) were unmarried. Regarding parity,

92 (76.7%) had children and 28 (23.3%) did not. Ethnic distribution included Sindhi, 32 (26.7%); Urdu, 54 (45%); Punjabi, 22 (18.3%); Pashto, 5 (4.2%); Balochi, 3 (2.5%);and Other, 4 (3.3%).

Family history of cancer was reported in 49 (40.8%) participants, while 71 (59.2%) had no family history. A family history of breast cancer was present in 42 (35%) participants, and absent in 78 (65%). Menopausal status was almost evenly split, with 63 (52.5%) being premenopausal and 57 (47.5%) postmenopausal. Body Mass Index (BMI) showed the following distribution: <18, 4 (3.3%); 18-23, 4 (3.3%); 23-25, 62 (51.7%); 25-30, 45 (37.5%); and >30, 5 (4.2%). Lastly, 92 (76.7%) participants had a history of lactation, while 28 (23.3%) did not.

Table 1: Sociodemographic variables of participants.

Variables	Mean (SD)	
Age at presentation	47.3 (12.63)	
Age at menarche	12.72 (1.64)	
Variables	**Frequency**	**Percentage**
Age Group		
<30 years	9	7.5
30-50 years	75	62.5
51-70	34	28.3
>70 years	2	1.7
Marital status		
Married	102	85
Unmarried	18	15
Parity		
Yes	92	76.7
No	28	23.3
Ethnicity		
Sindhi	32	26.7
Urdu	54	45
Punjabi	22	18.3
Pashto	5	4.2
Balochi	3	2.5
Other	4	3.3
Family history of cancer		
Yes	49	40.8
No	71	59.2
Family history of breast cancer		
Yes	42	35
No	78	65
Menopausal status		
Premenopausal	63	52.5
Postmenopausal	57	47.5
Body Mass Index		
<18	4	3.3
>18-23	4	3.3
23-25	62	51.7
25-30	45	37.5
>30	5	4.2
Lactation		
Yes	95	76.7
No	28	23.3

The clinical characteristics of the patients are presented in Table **2**. The cancer was located on the left side in 43 (35.8%), on the right side in 71 (59.2%), and was bilateral in 6 (5%) patients. The histological type was infiltrating ductal carcinoma in 101 (84.2%), lobular carcinoma in 17 (14.2%), and other types in 2 (1.7%).

Table 2: Clinical characteristics of patients.

Characteristics	Frequency	Percentage
Side		
Left	43	35.8
Right	71	59.2
Bilateral	6	5
Histological type		
Infiltrating duct	101	84.2
Lobular	17	14.2
Others	2	1.7
Histological grade		
I	6	5
II	78	65
III	36	30
Ki67		
<20%	32	26.7
>21%	88	73.3
Tumor size		
<2 cm	6	5
2-5 cm	58	48.3
>5 cm	55	45.8
5	1	0.8
Multifocal /Multicentric		
Yes	29	24.2
No	91	75.8
Axillary lymphnode		
Yes	90	75
No	30	25
TNM stage		
I	7	5.8
II	46	38.3
III	54	45
IV	13	10.8
Nuclear stage		
I	9	7.5
II	75	62.5
III	36	30
HER2 status		
Positive	45	37.5
Negative	67	55.8
Borderline	5	4.2
Unknown	3	2.5
Estrogen receptor		
Positive	75	62.5
Negative	45	37.5
Progesterone receptor		
Positive	57	47.5
Negative	63	52.5

Histological grading showed that 6 (5%) patients had grade I, 78 (65%) had grade II, and 36 (30%) had grade III cancer. The Ki67 index was <20% in 32 (26.7%) patients and >21% in 88 (73.3%) patients. Tumor size was <2 cm in 6 (5%), 2-5 cm in 58 (48.3%), and >5 cm in 55 (45.8%), with 1 (0.8%) having an unknown size.

Multifocal or multicentric tumors were present in 29 (24.2%) patients, while 91 (75.8%) did not have multifocal/multicentric tumors. Axillary lymph node involvement was present in 90 (75%) patients and absent in 30 (25%).

Regarding TNM staging, 7 (5.8%) patients were in stage I, 46 (38.3%) in stage II, 54 (45%) in stage III, and 13 (10.8%) in stage IV. Nuclear grading showed 9 (7.5%) in grade I, 75 (62.5%) in grade II, and 36 (30%) in grade III.

HER2 status was positive in 45 (37.5%), negative in 67 (55.8%), borderline in 5 (4.2%), and unknown in 3 (2.5%). Estrogen receptor status was positive in 75 (62.5%) patients and negative in 45 (37.5%). Progesterone receptor status was positive in 57 (47.5%) and negative in 63 (52.5%).

Table **3** represents the Association of Age groups with tumor characteristics. For histological grade, grade I was found only in the 30-50 age group, accounting for 6 (100%) of the cases (p=0.237). Grade II was observed in 4 (5.1%) patients under 30 years, 50 (64.1%) patients aged 30-50 years, 22 (28.2%) patients aged 51-70 years, and 2 (2.6%) patients over 70 years. Grade III was found in 5 (13.9%) patients under 30 years, 19 (52.8%) in the 30-50 age group, and 12 (33.3%) aged 51-70 years. However, the histological grade was not significantly associated with the age of the patient (p=0.237).

Significant associations (p<0.05) were found for axillary lymph node involvement (p=0.01) and TNM stage (p=0.03). This suggests that age groups were significantly associated with the likelihood of axillary lymph node involvement and TNM staging, indicating a potential impact of age on these specific clinical characteristics.

For axillary lymph node involvement, 8 (8.9%) under 30 years, 52 (57.8%) aged 30-50, 30 (33.3%) aged 51-70 had involvement, while 1 (3.3%) under 30 years, 23 (76.7%) aged 30-50, 4 (13.3%) aged 51-70, and 2 (6.7%) over 70 years had no involvement (p=0.01).

For the TNM stage, stage I occurred in 5 (71.4%) aged 30-50, 1 (14.3%) aged 51-70, and 1 (14.3%) over 70 years (p=0.03). Stage II was found in 1 (2.2%) under 30, 33 (71.7%) aged 30-50, 11 (23.9%) aged 51-70, and 1 (2.2%) over 70 years. Stage III occurred in 5 (9.3%) under 30, 32 (59.3%) aged 30-50, and 17 (31.5%) aged 51-70. Stage IV occurred in 3 (23.1%) under 30, 5 (38.5%) aged 30-50, and 5 (38.5%) aged 51-70.

Table 3: Association of age groups with tumor characteristics.

Variables	Age Group				p-value
Histological grade	**<30 years n(%)**	**30-50 years n(%)**	**51-70 n(%)**	**>70 years n(%)**	
Grade I	-	6 (100)	-	-	0.237
Grade II	4 (5.10)	50 (64.10)	22 (28.20)	2 (2.60)	
Grade III	5 (13.9)	19 (52.80)	12 (33.30)	-	
Histological Type					
Infiltrating duct	9 (8.9)	62 (61.4)	29 (28.7)	1 (1)	0.559
Lobular	-	11 (64.7)	5 (29.4)	1 (5.9)	
Others	-	2 (100)	-	-	
Tumor size					
<2 cm	-	5 (83.3)	1 (16.7)	-	0.857
2-5 cm	3 (5.2)	37 (63.8)	17 (29.3)	1 (1.7)	
>5cm	6 (10.9)	33 (60)	16 (28.6)	1 (1.8)	
Multifocal/ Multicentric lesion					
Yes	1 (3.4)	19 (65.5)	8 (27.6)	1 (3.4)	0.653
No	8 (8.8)	56 (61.5)	26 (28.6)	1 (1.1)	
Axillary lymph node					
Yes	8 (8.9)	52 (57.8)	30 (33.3)	-	0.010
No	1 (3.3)	23 (76.7)	4 (13.3)	2 (6.7)	
TNM Stage					
I	-	5 (71.4)	1 (14.3)	1 (14.3)	0.030
II	1 (2.2)	33 (71.7)	11 (23.9)	1 (2.2)	
III	5 (9.3)	32 (59.3)	17 (31.5)	-	
IV	3 (23.1)	5 (38.5)	5 (38.5)	-	
Nuclear Stage					
I	-	6 (66.7)	3 (33.3)	-	0.456
II	4 (5.3)	50 (66.7)	19 (25.3)	2 (2.7)	
III	5 (13.9)	19 (52.8)	12 (33.3)	-	
HER2 status					
Positive	3 (6.7)	31 (68.9)	9 (20)	2 (4.4)	0.356
Negative	6 (9)	39 (58.2)	22 (32.8)	-	
Borderline	-	2 (40)	3 (60)	-	
Unknown	-	3 (100)	-	-	

DISCUSSION

In our study, histologic grading revealed that the majority of patients had grade II tumors (65%), followed by grade III (30%) and grade I (5%). These findings are consistent with a study by Zeeshan *et al*. (2019) conducted in Pakistan, which reported a higher proportion of grade II tumors (61%) and fewer grade I (7%) and grade III (32%) tumors, reflecting a similar distribution in the South Asian population[12]. However, a Western study by Inwald *et al*. (2013) observed a lower frequency of grade II tumors (48%) and a higher prevalence of grade III tumors (41%), suggesting more aggressive tumor biology in younger patients from Western populations [15]. The variation in histologic grade distribution between regions highlights the influence of genetic, environmental, and lifestyle factors on breast cancer presentation.

The study found significant associations between age and specific tumor characteristics, particularly axillary

lymph node involvement, and TNM staging, suggesting that younger patients may present with more advanced disease. Understanding the relationship between age and breast cancer features is crucial for guiding personalized treatment strategies and improving prognosis, especially in resource-limited settings where early detection can be challenging [16].

The findings from this study align with those of several previous investigations regarding age-related breast cancer characteristics. Fernandes *et al*. similarly found that younger women tend to present with more aggressive disease, showing a higher prevalence of advanced TNM stages and lymph node involvement [17]. Additionally, Xie *et al*. reported a U-shaped relationship between age and breast cancer outcomes, with both younger and older women exhibiting worse survival rates than middle-aged women, further supporting the age-related variation in breast cancer behavior [18]. Rosenberg *et al*. also confirmed that tumor size and grade significantly impact survival across age groups, particularly highlighting the negative effect of larger tumors in younger women [19].

The study's finding of significant associations between age, axillary lymph node involvement, and TNM staging is particularly noteworthy. Tadros *et al*. demonstrated that younger women undergoing surgery for breast cancer often experience more frequent lymph node involvement compared to older women [20]. This could be attributed to more aggressive tumor biology, as highlighted by Gajdos *et al*. who emphasized that younger patients are more likely to have HER2-positive and triple-negative subtypes, which are linked to higher proliferation rates and poorer prognosis [21]. Furthermore, Lodi *et al*. found that while elderly women tend to present with more advanced local stages, younger women are more likely to develop lymph node metastasis at earlier stages, indicating distinct biological behavior based on age [22]. Clinically, these findings suggest that younger and older women may benefit from age-specific screening and treatment strategies, particularly regarding early detection and the management of lymph node metastasis.

The lack of significant associations between age and histological grade, histological type, and tumor size in this study could be influenced by the sample size or the heterogeneity of breast cancer. While Chen *et al*. found that younger women are more likely to present with larger tumors and more aggressive histological types, this is not consistently observed across all age groups [23]. Additionally, the study by Di Saverio *et al*. suggested that despite some variation in tumor grade across age groups, other factors, such as hormone receptor status and Ki67 expression, may play a more dominant role in determining tumor behavior [24]. Future studies with larger cohorts are needed to explore these variables further and refine treatment personalization based on age.

This study has several limitations, including its relatively small sample size and single-center design, which may limit the generalizability of the findings. Additionally, potential confounding factors such as variations in treatment protocols and genetic predispositions were not controlled for. These limitations suggest that the results should be interpreted cautiously, and broader studies are needed to confirm the findings.

Future research should focus on larger, multi-center studies to validate these findings and explore the role of age in breast cancer prognosis across diverse populations. Age-specific management strategies should be developed to optimize treatment outcomes, particularly in younger and older women. Incorporating these insights into clinical practice is crucial, especially in resource-limited settings, where tailored screening and early detection programs could significantly improve survival rates.

CONCLUSION

This study highlights the significant association between age and breast cancer characteristics, particularly axillary lymph node involvement and TNM staging, indicating that younger and older patients may present with more aggressive forms of the disease. Although age was not significantly associated with other tumor characteristics such as histological grade, type, or tumor size, the findings underscore the need for age-specific management strategies in breast cancer care. Tailored screening and treatment approaches, especially for younger and older populations, could improve early detection and outcomes. Integrating age-specific insights into clinical practice is essential for improving the prognosis of breast cancer patients, particularly in resource-limited settings where early detection and personalized care can significantly impact survival and quality of life.

ETHICS APPROVAL

The ethical exemption was obtained from the Institutional Review Board of Jinnah Hospital (JPMC), Karachi (Ref. letter No. F.2-81/2024-GENL/31/JPMC). All procedures performed in studies involving human participants followed the ethical standards of the institutional and/ or national research committee.

CONSENT FOR PUBLICATION

Written informed consent was taken from the patients.

AVAILABILITY OF DATA

The dataset can be obtained from the corresponding author upon a reasonable request.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Declared none.

AUTHORS' CONTRIBUTION

SNK: study concept and designing, critical reviewing. GH: result interpretation, manuscript drafting, critical review and revision of initial draft, KF: result analysis and interpretation, manuscript drafting, SZ: critical review and revision of initial draft, AR: critical review and revision of initial draft, RS: critical review and revision of initial draft, MA: data collection, MJ: Data collection.

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