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Comparative Analysis of Clinical and Pathological Characteristics of Breast Cancer among Premenopausal and Postmenopausal Women

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ABSTRACT

Breast cancer shows distinct clinical and pathological characteristics between premenopausal and postmenopausal women, potentially affecting disease progression and treatment outcomes.Understanding these differences is essential for optimizing management strategies.**Objectives:** To compare the clinical and pathological characteristics of breast cancer among premenopausal and postmenopausal women.**Methods:** This retrospective study was conducted at the Department of Histopathology, Quaid-e-Azam Medical College, Bahawalpur, from January to December 2024. A total of 188 breast cancer patients (94 premenopausal, 94 postmenopausal) were included.Clinical variables such as age at diagnosis, family history, tumor laterality, clinical stage, lymph node involvement, and metastasis were analyzed, along with pathological features like histological type, tumor grade, molecular subtype, and hormone receptor status. Data were analyzed using a t-test and a chi-square test. **Results:** The mean age at diagnosis was significantly lower in premenopausal women (46.96 ± 5.29 years) compared to postmenopausal women (65.87 ± 10.82 years) ($p<0.001$). A positive family history was more common among premenopausal patients (37.2% vs. 23.4%, $p=0.039$). Lymph node involvement was higher in premenopausal women (73.4% vs. 59.6%, $p=0.045$). Tumor laterality, clinical stage, metastasis, histological type, tumor grade, molecular subtype, and hormone receptor status were similar between groups ($p>0.05$). **Conclusions:** It was concluded that premenopausal women presented at a younger age, with more frequent family history and lymph node involvement, suggesting a potentially aggressive disease course. However, pathological tumor characteristics were comparable. Early detection and genetic risk assessment are crucial, particularly in younger women.

INTRODUCTION

Breast cancer remains the most commonly diagnosed malignancy among women globally, with approximately 2.3 million new cases and 685,000 deaths reported annually [1]. It exhibits distinct clinical and pathological differences based on menopausal status, which carry important prognostic and therapeutic implications. While postmenopausal breast cancer accounts for nearly two-thirds of all cases worldwide, premenopausal breast cancer is more common in regions with younger population structures, such as parts of Africa and Asia [2]. Understanding these differences is critical to improving diagnostic strategies and patient outcomes. The incidence of breast cancer varies markedly across populations. In high-income countries, postmenopausal breast cancer predominates and is typically detected early through organized screening programs [3]. However, in low- and middle-income countries, younger women are disproportionately affected, often presenting with

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advanced disease due to limited access to screening, financial constraints, cultural barriers, and healthcare infrastructure deficiencies [4]. These socioeconomic and healthcare access challenges contribute to delayed diagnosis, greater lymph node involvement, and poorer survival outcomes among premenopausal women. Conversely, trends in high-income countries reveal stabilizing or declining rates of postmenopausal breast cancer, while premenopausal incidence is rising [5]. These observations emphasize the need to develop age- and menopause-specific screening and prevention strategies. Etiological differences further distinguish breast cancer in premenopausal and postmenopausal women. Genetic factors, notably BRCA1 and BRCA2 mutations, play a significant role in early-onset breast cancer, particularly triple-negative breast cancer (TNBC) [6]. In contrast, hormonal and lifestyle factors, such as prolonged estrogen exposure, obesity, and delayed menopause are more relevant to postmenopausal breast cancer development [7]. High body mass index (BMI) increases postmenopausal breast cancer risk by elevating endogenous estrogen levels, whereas it appears protective in premenopausal women [8]. Other factors, including nulliparity, late age at first pregnancy, and alcohol consumption, influence both groups differently [9]. Given the hereditary nature of many early-onset breast cancers, genetic counselling and screening offer critical opportunities for improving outcomes among high-risk premenopausal women. Early identification of BRCA mutations can facilitate enhanced surveillance, risk-reducing interventions, and tailored therapeutic strategies, particularly in regions where breast cancer presents aggressively at younger ages. Biologically, premenopausal breast cancers are typically more aggressive, with higher-grade tumors, increased Ki-67 proliferation indices, and a greater prevalence of HER2-positive and triple-negative subtypes [10]. Post-menopausal tumors are more often estrogen receptor (ER)-positive, making them more amenable to endocrine therapies [11]. Premenopausal patients also tend to present with larger tumors, more frequent lymph node involvement, and distant metastases, resulting in worse survival outcomes [12]. Lower ER and PR positivity among premenopausal tumors further complicates treatment [13]. Despite these known differences, additional comparative studies are warranted to further delineate how menopausal status affects breast cancer presentation and progression. Improved understanding of these distinctions is vital for refining screening approaches, personalizing treatment protocols, and enhancing survival rates.

This study aims to compare the clinical and pathological features of breast cancer between premenopausal and postmenopausal women to support better risk stratification and inform the development of targeted therapeutic interventions.

METHODS

This retrospective study was conducted at the Department of Histopathology, Quaid-e-Azam Medical College, Bahawalpur, over six months from 5th August 2024 to 4th February 2025. Ethical approval was obtained from the Institutional Review Board (Letter No. 2499/DME/QAMC Bahawalpur). The study population comprised female patients diagnosed with breast cancer, categorized based on menopausal status. Premenopausal women were defined as those experiencing regular menstrual cycles or within 12 months of their last menstrual period, while postmenopausal women were defined as those with amenorrhea for at least 12 months or who had undergone bilateral oophorectomy. Inclusion criteria were histo-pathologically confirmed cases of breast cancer with complete medical records documenting both clinical and pathological features. Exclusion criteria included male breast cancer patients, patients with incomplete records, and patients with prior malignancies or previous cancer treatments before diagnosis. Patients with a history of other cancers or prior therapies were excluded to minimize confounding effects on tumor behavior, receptor status, and lymph node involvement, ensuring that the clinical and pathological characteristics analyzed reflected the natural course of primary breast cancer without modification by earlier oncological treatments. A written informed consent was taken. Patients with missing clinical or pathological data were excluded from the final analysis to maintain data integrity. A consecutive non-probability sampling technique was employed, whereby all eligible breast cancer patients meeting the inclusion criteria during the study period were included to minimize selection bias. The sample size of 188 patients (94 premenopausal and 94 postmenopausal) was calculated using lymph node involvement rates (76.60% in premenopausal vs. 57.51% in postmenopausal patients) reported by Kocaöz *et al.,* [14]. Lymph node status was selected as the primary outcome variable for sample size estimation due to its critical prognostic value in breast cancer, its well-documented differences between pre- and postmenopausal women, and its availability from routine pathology reporting in our setting. Calculations were based on achieving 80% statistical power with a 5% significance level, using two-tailed testing. The sample size was calculated using an online sample size calculator, applying the formula for comparison of two proportions. Data were extracted retrospectively from histopathology reports and clinical case files. Histopathology reports provided detailed information on tumor type (ILC, IDC, or other types), tumor grade (low, intermediate, or high), molecular subtypes (Luminal A, Luminal B, HER2-enriched, Triple-negative breast cancer), hormone receptor status (ER, PR, HER2), and Ki-67 proliferation index. Clinical case files were

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reviewed to collect patient age at diagnosis, menopausal status, family history of breast cancer, tumor laterality (right or left breast), clinical stage at diagnosis (based on TNM classification), lymph node involvement (based on histopathological examination of resected nodes), and presence of distant metastasis. Tumor location and lymph node involvement were specifically confirmed from operative notes and pathology reports, ensuring data accuracy. All data were analyzed using SPSS version 25.0. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. The Shapiro-Wilk test was used to assess the normality of continuous variables. For normally distributed data, the independent t-test was applied to compare continuous variables between groups, while the Mann-Whitney U test was considered for non-normally distributed variables. The chi-square test was used to compare categorical variables. Effect sizes for categorical comparisons were calculated using odds ratios (OR) with 95% confidence intervals. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 188 female breast cancer patients were included in the study, with an equal distribution of 94 (50%) premenopausal and 94 (50%) postmenopausal women. All patients had complete clinical and pathological data; no missing data were encountered during analysis. The mean age at diagnosis was significantly lower among premenopausal women (46.96 ± 5.29 years) compared to postmenopausal women (65.87 ± 10.82 years) (p<0.001). A positive family history of breast cancer was more frequently observed in premenopausal women, with 35 patients (37.2%) compared to 22 patients (23.4%) in the postmenopausal group. This difference was statistically significant (p=0.039), with an odds ratio (OR) of 1.92 (95% Confidence Interval (CI): 1.01–3.63). Tumor laterality analysis revealed that left breast involvement was more common in both groups, affecting 58 (61.7%) of premenopausal women and 47 (50.0%) of postmenopausal women. However, this difference was not statistically significant (p=0.106, OR: 1.60; 95% CI: 0.91–2.81). The clinical stage at presentation (Stage I–IV) did not differ significantly between groups (p=0.635). Among premenopausal patients, 23 (24.5%) were diagnosed at Stage I, 36 (38.3%) at Stage II, 28 (29.8%) at Stage III, and 7 (7.4%) at Stage IV. In postmenopausal women, 17 (18.1%) were diagnosed at Stage I, 35 (37.2%) at Stage II, 32 (34.0%) at Stage III, and 10 (10.6%) at Stage IV. Lymph node involvement was significantly more frequent among premenopausal women, with 69 (73.4%) patients demonstrating positive lymph node metastasis compared to 56 (59.6%) postmenopausal women (p=0.045). The odds of lymph node positivity were significantly higher in premenopausal women (OR: 1.87; 95% CI: 1.01–3.47). The presence of distant metastasis at diagnosis was found in 15 (16.0%) of premenopausal and 21 (22.3%) of post-menopausal women.This difference was not statistically significant (p=0.266, OR: 0.66; 95% CI: 0.31–1.39), suggesting comparable rates of metastatic disease at initial presentation (Table 1).

Table 1: Comparison of Clinical Characteristics Between Premenopausal and Postmenopausal Breast Cancer Patients

Contributing Factors	Premenopausal (n=94)	Postmenopausal (n=94)	p-Value	Odds Ratio (95% CI)
Age at Diagnosis (Years, Mean ± SD)	46.96 ± 5.29	65.87 ± 10.82	<0.001	–
Family History of Breast Cancer (Yes)	35 (37.2%)	22 (23.4%)	0.039	1.92 (1.01–3.63)
Tumor Location (Left Breast)	58 (61.7%)	47 (50.0%)	0.106	1.60 (0.91–2.81)
Clinical Stage I at Diagnosis	23 (24.5%)	17 (18.1%)	0.635	–
Stage II at Diagnosis	36 (38.3%)	35 (37.2%)		
Stage III at Diagnosis	28 (29.8%)	32 (34.0%)		
Stage IV at Diagnosis	7 (7.4%)	10 (10.6%)		
Lymph Node Involvement (Positive)	69 (73.4%)	56 (59.6%)	0.045	1.87 (1.01–3.47)
Presence of Metastasis at Diagnosis	15 (16.0%)	21 (22.3%)	0.266	0.66 (0.31–1.39)

The Ki-67 proliferation index, a marker of tumor aggressiveness, was similar between the two groups, with a mean of 49.37 ± 22.77 in premenopausal patients and 50.95 ± 26.22 in postmenopausal patients (p=0.661). Regarding histological type, invasive ductal carcinoma (IDC) was the predominant histological subtype, occurring in 77 (81.9%) of premenopausal and 80 (85.1%) of postmenopausal patients. This distribution was not statistically different (p=0.839, OR: 0.77; 95% CI: 0.33–1.77). Invasive lobular carcinoma (ILC) was diagnosed in 12 (12.8%) premenopausal and 10 (10.6%) postmenopausal women, while other histological variants were rare (5.3% vs. 4.3%, respectively). Tumor grade distribution also did not differ significantly between groups (p=0.341). Among premenopausal women, 35 (37.2%) had low-grade tumors, 42 (44.7%) had intermediate-grade tumors, and 17 (18.1%) had high-grade tumors. In postmenopausal women, 26 (27.7%) had low-grade, 46 (48.9%) had intermediate-grade, and 22 (23.4%) had high-grade tumors. The distribution of molecular subtypes revealed that Luminal A was the most prevalent subtype in both groups, found in 35 (37.2%) of premenopausal and 32 (34.0%) of postmenopausal

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women. Luminal B subtype was observed in 21 (22.3%) of premenopausal and 34 (36.2%) of postmenopausal patients. HER2-enriched subtype was diagnosed in 17 (18.1%) premenopausal and 9 (9.6%) postmenopausal patients, while triple-negative breast cancer (TNBC) was noted in 21 (22.3%) and 19 (20.2%) patients, respectively. These differences were not statistically significant (p=0.123). Estrogen receptor (ER) positivity was similar between groups, being present in 59 (62.8%) premenopausal and 58 (61.7%) postmenopausal women (p=0.880, OR: 1.05; 95% CI: 0.58–1.90). Progesterone receptor (PR) positivity was observed in 52 (55.3%) of premenopausal and 55 (58.5%) of postmenopausal patients (p=0.659, OR: 0.88; 95% CI: 0.49–1.58). HER2 positivity was detected in 21 (22.3%) of premenopausal and 18 (19.1%) of postmenopausal patients (p=0.589, OR: 1.22; 95% CI: 0.61–2.43)(Table 2).

Table 2: Comparison of Pathological Characteristics Between Premenopausal and Postmenopausal Breast Cancer Patients

Pathological Characteristics	Premenopausal (n=94)	Postmenopausal (n=94)	p-Value	Odds Ratio (95% CI)
Ki-67 Proliferation Index	49.37 ± 22.77	50.95 ± 26.22	0.661	–
Histological Type				
Invasive Ductal Carcinoma (IDC)	77 (81.9%)	80 (85.1%)	0.839	0.77 (0.33–1.77)
Invasive Lobular Carcinoma (ILC)	12 (12.8%)	10 (10.6%)		–
Other Types	5 (5.3%)	4 (4.3%)	–	–
Tumor Grade				
Low Grade	35 (37.2%)	26 (27.7%)	0.341	–
Intermediate Grade	42 (44.7%)	46 (48.9%)		
High Grade	17 (18.1%)	22 (23.4%)		
Molecular Subtype				
Luminal A	35 (37.2%)	32 (34.0%)	0.123	–
Luminal B	21 (22.3%)	34 (36.2%)		
HER2-Enriched	17 (18.1%)	9 (9.6%)		
Triple-Negative Breast Cancer	21 (22.3%)	19 (20.2%)		
Estrogen Receptor (ER) Positive	59 (62.8%)	58 (61.7%)	0.880	1.05 (0.58–1.90)
Progesterone Receptor (PR) Positive	52 (55.3%)	55 (58.5%)	0.659	0.88 (0.49–1.58)
HER2 Positive	21 (22.3%)	18 (19.1%)	0.589	1.22 (0.61–2.43)

DISCUSSION

Breast cancer exhibits unique clinical and pathological features in premenopausal and postmenopausal women, potentially impacting prognosis and treatment approaches. Our study found that premenopausal patients were diagnosed at a significantly younger age (46.96 ± 5.285 years) compared to postmenopausal patients (65.87 ± 10.824 years) ($p < 0.001$), aligning with previous research demonstrating earlier disease onset in younger women [14]. Kocaöz *et al.*, similarly, reported that the mean age of breast cancer diagnosis in premenopausal women was 46.84 years, while it was significantly higher at 66.02 years in postmenopausal women [14]. Additionally, studies from Nigeria and Ghana indicate that breast cancer peaks in the fourth and fifth decades of life among premenopausal women, reinforcing the necessity for early detection and targeted screening efforts in this population [15, 16].A family history of breast cancer was significantly more common among premenopausal women (37.2%) than postmenopausal women (23.4%) (p=0.039), suggesting a stronger hereditary component in younger patients. Ishaque and Asad also found that 27.1% of premenopausal breast cancer patients had a positive family history, highlighting the role of genetic predisposition in early-onset disease [17]. This underscores the importance of genetic counselling and risk assessment, particularly in younger patients with a familial history of malignancy [18]. A significant difference in lymph node involvement was observed, with premenopausal women more likely to have positive lymph nodes (73.4% vs. 59.6%, p=0.045). Kocaöz *et al.*, reported similar findings, demonstrating that 76.6% of premenopausal patients exhibited lymph node metastasis compared to 57.5% of postmenopausal patients (p<0.001) [14]. Studies from Nigeria and India have also confirmed that premenopausal breast cancer is associated with a higher frequency of nodal disease, further indicating a more aggressive clinical course [15, 19]. These findings suggest that premenopausal women are at a greater risk of regional spread at the time of diagnosis, which has implications for treatment planning and prognosis. Several biological and socio-environmental factors may contribute to the more aggressive presentation in premenopausal women. Biologically, younger patients tend to have higher Ki-67 proliferation indices, greater proportions of triple-negative and HER2-positive tumors, and lower hormone receptor expression, all contributing to rapid disease progression. Socioeconomic barriers and a lack of targeted screening programs for younger women in many regions further delay diagnosis. These findings highlight the importance of considering menopausal status during clinical management, advocating for earlier genetic

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counselling, risk-adapted surveillance, and more aggressive multimodal therapeutic strategies in premenopausal patients to improve outcomes. Concerning pathological characteristics, no significant differences were observed between premenopausal and postmenopausal patients. Invasive ductal carcinoma (IDC) remained the predominant histological type, affecting 81.9% of premenopausal and 85.1% of postmenopausal patients (p=0.839), which is consistent with findings from various global studies [14, 20]. Tumor grade distribution was also comparable, with low, intermediate, and high-grade tumors occurring at similar frequencies in both groups (p = 0.341). Research from Ghana and Pakistan further supports these findings, showing that IDC remains the most common histological subtype regardless of menopausal status [16, 21]. The distribution of molecular breast cancer subtypes was similar between the groups, with Luminal A being the most prevalent, followed by Luminal B, HER2-enriched, and triple-negative breast cancer (TNBC). Although TNBC was slightly more frequent in premenopausal women (22.3%) than in postmenopausal women (20.2%), this difference did not reach statistical significance (p=0.123). However, the lack of statistical significance does not diminish the clinical relevance of TNBC in premenopausal patients. TNBC is inherently associated with a poorer prognosis due to its aggressive biological behaviour, lack of targeted hormonal therapies, and higher risk of early recurrence. Even without statistical significance in distribution between groups, its presence in younger women warrants heightened clinical vigilance and consideration of intensified chemotherapy regimens and closer follow-up in this subgroup. Hormone receptor status was also largely comparable between the two groups. Estrogen receptor (ER) positivity was observed in 62.8% of premenopausal and 61.7% of postmenopausal patients (p=0.880), while progesterone receptor (PR) positivity was noted in 55.3% and 58.5%, respectively (p=0.659). HER2 positivity was detected in 22.3% of premenopausal and 19.1% of postmenopausal patients (p=0.589). These findings align with Kocaöz *et al.*, who similarly found no significant variation in hormone receptor expression between the two groups [14]. However, research from Japan suggested that lean postmenopausal women had significantly higher Ki-67 expression and HER2 positivity, indicating that BMI and ethnic differences may influence tumor biology [21]. Despite similarities in tumor histology and receptor status, premenopausal patients in our study were more likely to present at advanced clinical stages. Previous research from Pakistan and Ghana has demonstrated that premenopausal women are more likely to be diagnosed at Stage III or IV, contributing to poorer prognostic outcomes [17, 20]. Bosompem *et al.*, similarly, reported that 80.7% of premenopausal and 87.0% of postmenopausal patients in Ghana were diagnosed at advanced disease stages, emphasizing the global challenge of late-stage breast cancer detection [16]. Additionally, Houda et al. found that the lack of routine screening before age 40 contributes to more aggressive disease presentations in younger women, highlighting the need for early detection programs tailored to high-risk populations [22].

CONCLUSIONS

This study highlights important clinical differences between premenopausal and postmenopausal breast cancer patients, while pathological characteristics remained largely comparable. Premenopausal women were diagnosed at a younger age and exhibited higher rates of family history and lymph node involvement, suggesting a potential genetic predisposition and a more aggressive clinical course. In contrast, no significant differences were observed between the two groups regarding tumor laterality, clinical stage at diagnosis, distant metastasis, histological type, tumor grade, or molecular subtypes. These findings emphasize that menopausal status predominantly influences the clinical presentation rather than tumor biology.

Authors Contribution

Conceptualization: SSG
Methodology: MA[1], MA[2]
Formal analysis: MSU
Writing review and editing: MS, MSU, BN

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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