

## Comparative analysis of clinical and pathological characteristics of Breast Cancer among pre-menopausal and post-menopausal women

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### Abstract

**Objective:** To compare clinico-pathological features of breast cancer between pre-menopausal and post-menopausal women.

**Material and Methods:** In this prospective observational cohort study, conducted at the Department of Surgery, Azad Kashmir Medical College, Muzaffarabad from 01, January 2022 to 30, June 2023 over the period of 18 months. Total 387 women patients of breast cancer having age 20-60 years were selected and divided into pre-menopausal and post-menopausal women groups. Clinical examination of all the patients was done. Detailed demographic and medical histories, particularly focusing on menopausal status, were meticulously documented. Clinical assessments were then conducted to identify observable breast changes, supplemented by pathological evaluations through biopsy samples. Clinical and pathological features were compared between the both groups.

**Results:** In this study the mean age was calculated to be 39.62 years, with a standard deviation of 11.720. The combined average age at menarche was 12.94 years, with a standard deviation of 1.435. The overall average age at diagnosis of breast cancer across all women in the study was 40.36 years, with a standard deviation of 11.421. Breast changes were noted in 81 (46.0%) and 95 (54.0%) patients respectively in both groups, following by Palpable Lymph Nodes in 107 (58.8%) patients and 75 (41.2%) patients and difference was significant with p value 0.001. Regarding pathological features, estrogen receptor (ER) and Progesterone receptor (PR) was found positive in 85 (42.5%) and 80 (39.0%) patients in pre-menopausal group while in 115 (57.5%) and 125 (61.0%) patients of post-menopausal group.

**Conclusion:** In our study, we found notable differences in hormone receptor expression and tumor characteristics, emphasizing the impact of menopausal status on disease manifestation. The higher ER positivity in post-menopausal women compared to pre-menopausal ones suggests varying biological behaviors influenced by hormonal changes.

**Keywords:** Breast cancer - clinical profile, estrogen receptor status, progesterone status, pathological features.

### Introduction:

Internationally, breast cancer emerges as the leading cancer affecting females, with the number of diagnoses escalating to approximately 2.3 million in year 2020 alone, marking a significant concern for healthcare systems globally.<sup>1</sup> This malignancy presents with a complex spectrum of clinical subtypes, each with its unique pathogenesis, yet to be fully understood, underscoring the very urgent need for continued

research in this area.<sup>2</sup> The incidence of breast cancer shows remarkable geographical variability. Within Asia, countries such as Pakistan face a disproportionately high risk, with statistics indicating that 1 in 9 women are likely to be diagnosed, highlighting the critical global disparities in breast cancer rates.<sup>3</sup>

The dual-pathway hypothesis proposed by De Waard in the 1970s, delineating breast can-

### Received

date: 10th September, 2023

### Accepted

date: 20th December, 2023

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cer development into pre-menopausal and post-menopausal routes, adds another layer of complexity to understanding this disease.<sup>4</sup> Pre-menopausal breast cancers tend to manifest earlier in life and are often aggressive, whereas postmenopausal cancers, which peak later, are usually associated with estrogen receptor (ER)-positive tumors, emphasizing the importance of nuanced research that caters to the distinct stages of life.<sup>5</sup>

The biological and hormonal shifts that accompany menopause play a pivotal role in differentiating the clinico-pathological features of breast cancer between pre-menopausal and post-menopausal women. Cancers in pre-menopausal women are generally more aggressive, less likely to be hormone-receptor positive, and associated with adverse prognostic factors such as higher grades and sizes of tumors, alongside a greater incidence of Human Epidermal growth factor Receptor 2 (HER2)-positive and triple-negative breast cancers.<sup>6</sup> On the flip side, post-menopausal women tend to develop slower-growing, hormone-receptor-positive tumors, which respond more favorably to hormone therapies, offering a more optimistic prognosis.<sup>7</sup>

The advancements in molecular biology and genomics have shed light on the distinctive genetic and molecular landscapes of breast cancer across different menopausal statuses, guiding the development of targeted therapies and significantly influencing treatment decisions.<sup>8</sup> These clinico-pathological distinctions are instrumental in tailoring treatment strategies, including the selection of chemotherapy, hormone therapy, or targeted treatments based on the hormonal and HER2 status of the tumor, in conjunction with considering the menopausal status to predict recurrence risks and determine adjuvant treatments.<sup>9</sup>

Moreover, the disparity in clinico-pathological features between pre-menopausal and post-menopausal women underscores the imperative for age-specific screening and diagnostic protocols. Given the typically more aggressive nature

of tumors in younger women, a more proactive approach to screening and diagnosis is warranted to ensure timely and effective treatment.<sup>10</sup>

#### **Material and Methods:**

In our study, we utilized a prospective observational cohort study design, conducted at the Department of Surgery, Azad Kashmir Medical College, Muzaffarabad. The research was carried out over a period of 18-months (from January 2022 to June 2023) following the approval of the synopsis, focusing on a meticulously calculated sample size to ensure statistical robustness. With a confidence level set at 5% and the power of the study at 80%, our calculations necessitated a sample size of approximately 187 patients per group (pre-menopausal and post-menopausal women), culminating in a total of 374 participants. This figure was derived based on the proportions of estrogen receptor (ER) expression in pre-menopausal (68.94%) and post-menopausal (54.92%) women, employing non-probability consecutive sampling for participant selection.<sup>11</sup>

The inclusion criteria were specifically designed to encompass women diagnosed with breast cancer, aged between 20-60 years, who could be clearly categorized as either pre-menopausal or post-menopausal. Eligible participants were required to have comprehensive medical records available, including detailed information on hormone receptor status (ER, PR), HER2 status, TILs status, and tumor size, in addition to a signed informed consent. The exclusion criteria were established to exclude women who had undergone any previous treatments for breast cancer, those with other malignancies, lacking comprehensive clinico-pathological data, or diagnosed with metastatic disease at the onset.

The data collection process was structured to ensure the comprehensive gathering and analysis of relevant clinical and pathological information. It began with the selection of 374 breast cancer patients, evenly divided between pre-menopausal and post-menopausal groups, following the acquisition of informed consent.

**Table 1: Comparison of clinical features between Pre-menopause and Post-menopause state**

Clinical features	Group		Total	p Value	
	Pre-menopause	Post-menopause			
Breast changes	Yes	81(46.0%)	95(54.0%)	176	0.147
	No	106(53.5%)	92(46.5%)	198	
Pain and discomfort	Yes	97(53.6%)	84(46.4%)	181	0.179
	No	90(46.6%)	103(53.4%)	193	
Skin and nipple changes	Yes	117(63.9%)	66(36.1%)	183	0.000
	No	70(36.6%)	121(63.4%)	191	
Breast asymmetry	Yes	90(51.4%)	85(48.6%)	175	0.604
	No	97(48.7%)	102(51.3%)	199	
Palpable Lymph Nodes	Yes	107(58.8%)	75(41.2%)	182	0.001
	No	80(41.7%)	112(58.3%)	192	

Detailed demographic and medical histories, particularly focusing on menopausal status, were meticulously documented. Clinical assessments were then conducted to identify observable breast changes, supplemented by pathological evaluations through biopsy samples. These samples, extracted in adherence to strict medical and ethical guidelines by experienced surgeons, underwent analysis to identify key pathological features such as ER, PR, HER2 status, TILs presence, and tumor size. This detailed collection and analysis of data were pivotal for understanding the nature and progression of breast cancer in the study population, with all information securely recorded for subsequent analysis. Data were analyzed in statistical package for social sciences (SPSS) version 23.

### Results:

In our study, we analyzed the demographic and clinical characteristics of participants, distinguishing between pre-menopausal and post-menopausal women.

For women in the pre-menopausal group, the average age was found to be 39.66 years, with variability indicated by a standard deviation of 11.681. The onset of menstruation, or menarche, occurred at an average age of 12.98 years, with a standard deviation of 1.437. The diagnosis of breast cancer in this group was made at an average age of 39.97 years, as shown by a standard deviation of 11.539.

In the post-menopausal group, the participants had a slightly lower average age of 39.57 years, with a standard deviation of 11.789, indicating a similar range of ages as seen in the premenopausal group. The age at menarche averaged 12.91 years, with a standard deviation of 1.436, closely matching the pre-menopausal group. However, the age at which breast cancer was diagnosed was slightly higher, averaging 40.74 years, with a standard deviation of 11.319.

Overall, when considering all participants, the mean age was calculated to be 39.62 years, with a standard deviation of 11.720. The combined average age at menarche was 12.94 years, with a standard deviation of 1.435. The overall average age at diagnosis of breast cancer across all women in the study was 40.36 years, with a standard deviation of 11.421.

This analysis provides insight into the ages at which women typically experience menarche and are diagnosed with breast cancer, alongside the general age distribution of our study's premenopausal and post-menopausal participants.

In our comparative analysis of clinical features between pre-menopausal and post-menopausal women with breast cancer, we observed that 81 pre-menopausal women (46.0%) reported breast changes, compared to 95 post-menopausal women (54.0%), yielding a non-significant P value of 0.147, suggesting that breast changes are a common symptom of breast cancer irrespective of menopausal status. Similarly, pain and discomfort were reported by 97 pre-menopausal women (53.6%) and 84 post-menopausal women (46.4%), with a P-value of 0.179, indicating no significant prevalence difference between the two groups. Conversely, a notable disparity was found in skin and nipple changes, significantly more reported by pre-menopausal women (117 or 63.9%) than post-menopausal women (66 or 36.1%), with a P-value of 0.000, highlighting the impact of hormonal or biological factors on these symptoms. Breast asymmetry was observed in 90 pre-menopausal women (51.4%)

**Table 2: Comparison of pathological features between Pre-menopause and Post-menopause state**

Pathological features	Status	Group		Total	P Value
		Pre-menopause	Post-menopause		
ER Status	Positive	85 (42.5%)	115 (57.5%)	200	0.002
	Negative	102 (58.6%)	72 (41.4%)	174	
PR Status	Positive	80 (39.0%)	125 (61.0%)	205	0.000
	Negative	107(63.3%)	62(36.7%)	169	
HER2 Status	Positive	95(52.8%)	85(47.2%)	180	0.301
	Negative	92(47.4%)	102(52.6%)	194	
TILs Status	Positive	100(52.6%)	90(47.4%)	190	0.301
	Negative	87(47.3%)	97(52.7%)	184	

and 85 post-menopausal women (48.6%), resulting in a P-value of 0.604, indicating that asymmetry is a relatively common feature not significantly influenced by menopausal status.

However, palpable lymph nodes presented a significant difference, more frequently reported by pre-menopausal women (107 or 58.8%) compared to post-menopausal women (75 or 41.2%), as shown by a P-value of 0.001, suggesting differences in disease progression or immune response between the two groups. These results underscore the complexity of breast cancer’s clinical presentation and the influence of menopausal status on certain symptoms, pointing to the necessity for tailored approaches in the diagnosis and management of breast cancer across different patient populations. (Table 1)

Table 2 illustrates the comparison of pathological features between pre-menopausal and post-menopausal states, shedding light on the intricate relationship between menopausal status and breast cancer pathology. The analysis of ER Status reveals a significant difference between the groups, with 85 pre-menopausal women (42.5%) and 115 post-menopausal women (57.5%) showing positive ER status, leading to a P value of 0.002. This significant variance underscores the higher prevalence of ER-positive tumors in post-menopausal women, possibly reflecting the influence of hormonal changes on tumor receptor status. Conversely, ER-negative status was more common in pre-menopausal women (58.6%) compared to post-menopausal

women (41.4%), further highlighting the differential expression of estrogen receptors across menopausal states.

Similarly, PR status demonstrated a notable difference, with 80 pre-menopausal women (39.0%) and 125 post-menopausal women (61.0%) exhibiting positive PR status, resulting in a highly significant P-value of 0.000. This indicates a greater occurrence of PR-positive tumors in post-menopausal women, aligning with the ER status findings and suggesting a shared hormonal influence on these receptor statuses. In contrast, PR-negative status was more prevalent in pre-menopausal women (63.3%) than in postmenopausal women (36.7%).

HER2 Status, however, did not show a statistically significant difference between pre-menopausal (52.8% positive) and post-menopausal (47.2% positive) women, with a P-value of 0.301. This lack of significant disparity suggests that HER2 expression in breast tumors may not be as closely related to menopausal status as ER and PR expressions are.

Lastly, TILs Status also did not exhibit a significant difference, with 100 pre-menopausal women (52.6%) and 90 post-menopausal women (47.4%) showing positive TILs status, achieving a P-value of 0.301. This indicates that the immune response, as evidenced by TILs presence, may be consistent across menopausal states, not significantly influenced by the hormonal changes that accompany menopause.

**Discussion:**

Our exploration into the clinico-pathological distinctions between pre-menopausal and post-menopausal breast cancer patients has illuminated significant insights, revealing a tapestry of findings that both align with and diverge from prior research. Through a meticulous examination of 340 patients, we observed pronounced differences in tumor pathology and epidemiologic risk factors, casting a spotlight on the profound heterogeneity inherent in breast cancer.

Feng F et al.'s study presented a compelling narrative, illustrating higher estrogen receptor (ER) and progesterone receptor (PR) positivity rates in pre-menopausal women compared to their post-menopausal counterparts, with a subtle yet noteworthy prevalence of HER2 positivity in the latter group. This contrasted sharply with our findings, which depicted a higher incidence of ER positivity among post-menopausal women, hinting at the complex interplay of regional genetic factors and environmental influences on receptor expression. The disparities in diagnosis ages between our study and that of Feng F et al. further underscore the intricate dynamics of hormonal influences on breast cancer's manifestation.<sup>2</sup>

Delving into the aggressive nature of breast cancer in younger women, Anders CK et al.'s research found resonance in our study through the significantly higher reports of skin and nipple changes in premenopausal women. This congruence suggests that such clinical features may be emblematic of pre-menopausal breast cancer, highlighting the aggressive clinical features prevalent among younger women.<sup>12</sup>

Warner ET et al.'s investigation into the impact of reproductive factors across different age groups on breast cancer risk found a parallel in our study, which noted no significant difference in symptoms of pain and discomfort between premenopausal and post-menopausal groups. This observation hints at the subtle influences of reproductive history on symptomatology, echoing the complex role reproductive factors play in the risk of breast cancer.<sup>13</sup>

Nimbalkar VP et al.'s findings brought to light a higher prevalence of ER-negative and HER2 amplified tumors in pre-menopausal women, diverging from our observations where HER2 positivity did not significantly differ between menopausal statuses. Additionally, their study noted a greater incidence of triple-negative breast cancer (TNBC) among pre-menopausal patients, underscoring the aggressive nature of breast cancer within this demographic. These

differences underscore the potential for regional or ethnic variations in tumor biology and emphasize the necessity for personalized management strategies tailored to the unique tumor characteristics and risk profiles of pre-menopausal and post-menopausal patients.<sup>14</sup>

Our study aligns with Takalkar UV et al. findings on the consistent presentation of breast cancer across menopausal statuses, reinforcing the need for diagnostic and treatment strategies that are adaptable to both local and universal contexts. This alignment suggests a commonality in breast cancer's nature that transcends geographical and demographic boundaries, underscoring the importance of globally applicable yet locally tailored diagnostic and treatment approaches.<sup>15</sup>

Kocaöz S et al. research, which reported higher ER positivity in pre-menopausal women, diverges from our findings of increased ER positivity in post-menopausal women, prompting a reevaluation of traditional views on hormone receptor expression in breast cancer. This divergence invites further investigation into the myriad factors that influence ER expression, highlighting the complexity of hormone receptor expression in breast cancer and the importance of personalized treatment approaches.<sup>16</sup>

In synthesizing these diverse insights, our study contributes significantly to the ongoing discourse on breast cancer, advocating for continued research to unravel the biological underpinnings of the observed variations. Such endeavors are crucial for developing more effective, tailored treatments and diagnostic tools, ultimately enhancing the clinical management and outcomes of breast cancer patients globally. This comprehensive analysis not only enriches our understanding of breast cancer's multifaceted nature but also underscores the imperative for personalized, evidence-based approaches in the ongoing battle against this complex disease.

### **Conclusion:**

Our research underscores significant clinicopathological differences between pre-meno-

pausal and post-menopausal breast cancer patients, revealing the complexity and heterogeneity of the disease. We found notable differences in hormone receptor expression and tumor characteristics, emphasizing the impact of menopausal status on disease manifestation. The higher ER positivity in post-menopausal women compared to pre-menopausal ones suggests varying biological behaviors influenced by hormonal changes. These findings advocate for personalized treatment strategies, highlighting the importance of considering menopausal status in the management of breast cancer. Future research should focus on understanding the underlying mechanisms driving these differences to improve diagnostic and therapeutic approaches.

**Conflict of interest:** None

**Funding source:** None

**Role and contribution of authors:**

Kaleem Akhtar, collected the data, references and did the initial writeup.

Muhammad Aijaz Khan, critically review the article and made final changes.

Muhammad Saeed Akhtar, collected the references and helped in discussion writing.

Waqas Latif, collected the data, references and helped in interpretation of data.

Komal, helped in collection of data and references.

Erum Khalid, helped in collection of data.

**References:**

1. Arnold M, Morgan E, Rungay H, Mafra A, Singh D, Laveranne M, et al. Current and future burden of breast cancer: Global statistics for 2020 and 2040. *Breast*. 2022 Dec;66:15-23.
2. Feng F, Wei Y, Zheng K, Li Y, Zhang L, Wang T, et al. Compari-

son of epidemiological features, clinicopathological features, and treatments between premenopausal and postmenopausal female breast cancer patients in western China: a retrospective multicenter study of 15,389 female patients. *Cancer Med*. 2018 Jun;7(6):2753-63.

3. Khan R, Javed U, Ur Rehman A. Comparison between the Young and Elderly Diagnosed Patients of Carcinoma of the Breast: Breast Carcinoma in Young and Elderly Patients. *Pak J Health Sci*. 2024;5(01). Available from: <https://doi.org/10.54393/pjhs.v5i01.1247>.
4. De Waard F, Halewijn EB, Huizinga J. The bimodal age distribution of patients with mammary carcinoma. Evidence for the existence of 2 types of human breast cancer. *Cancer*. 1964 Feb;17(2):141-51.
5. De Waard F. Premenopausal and postmenopausal breast cancer: one disease or two? *J Natl Cancer Inst*. 1979 Sep 1;63(3):549-52.
6. Fleming JM, Miller TC, Quinones MM, et al. The normal breast microenvironment of premenopausal women differentially influences the behavior of breast cancer cells in vitro and in vivo. *BMC Med*. 2010;8:27.
7. Liman A, Kabir B, Abubakar M, et al. Triple-negative Breast Cancer (TNBC) and Its Luminal Androgen Receptor (LAR) Subtype: A Clinicopathologic Review of Cases in a University Hospital in Northwestern Nigeria. *Niger J Clin Pract*. 2022;25:97-104.
8. Geriki S, Bitla A, Srinivasarao P, et al. Association of single nucleotide polymorphisms of adiponectin and leptin genes with breast cancer. *Mol Biol Rep*. 2019;46:6287-6297.
9. Malik SS, Mubarak S, Baig M, et al. Genetic polymorphism in ERCC5 and breast cancer risk. *Mol Biol Res Commun*. 2019;8(1):27-31.
10. Choi E, Suh M, Jung S, et al. Estimating Age-Specific Mean Sojourn Time of Breast Cancer and Sensitivity of Mammographic Screening by Breast Density among Korean Women. *Cancer Res Treat*. 2021;55:136-144.
11. Kocaöz S, Korukluoğlu B, Parlak Ö, Doğan HT, Erdoğan F. Comparison of clinicopathological features and treatments between pre-and postmenopausal female breast cancer patients—a retrospective study. *Menopause Rev*. 2019 Jun 14;18(2):68-73.
12. Anders CK, Hsu DS, Broadwater G, Acharya CR, Foekens JA, Zhang Y, et al. Young age at diagnosis correlates with worse prognosis and defines a subset of breast cancers with shared patterns of gene expression. *J Clin Oncol*. 2008 Jul 10;26(20):3324-30.
13. Warner ET, Colditz GA, Palmer JR, Partridge AH, Rosner BA, Tamimi RM. Reproductive factors and risk of premenopausal breast cancer by age at diagnosis: are there differences before and after age 40? *Breast Cancer Res Treat*. 2013 Nov;142:165-75.
14. Nimbalkar VP, Rajarajan S, VP S, Alexander A, Kaluve R, Selvam S, et al. A comparative analysis of clinicopathological features and survival between pre and postmenopausal breast cancer from an Indian cohort. *Sci Rep*. 2023 Mar 9;13(1):3938.
15. Takalkar UV, Asegaonkar SB, Kulkarni U, Saraf M, Advani S. Clinicopathological profile of breast cancer patients at a tertiary care hospital in marathwada region of Western India. *Asian Pac J Cancer Prev*. 2016 Apr 1;17(4):2195-8.
16. Kocaöz S, Korukluoğlu B, Parlak Ö, Doğan HT, Erdoğan F. Comparison of clinicopathological features and treatments between pre-and postmenopausal female breast cancer patients—a retrospective study. *Menopause Review/Przegląd Menopauzalny*. 2019 Jun 14;18(2):68-73.