Original Article

Comparative Analysis of Risk Factors, Clinical Presentation, and Multimodality Management of Breast Carcinoma in Premenopausal Versus Postmenopausal Women

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Abstract

Background: Breast Carcinoma has very distinctive epidemiological, histopathological and clinical behavior depending upon the hormonal milieu of the patient. This study compares the specific differences in distribution of risk factor presentation, stage presentation, biological features and multimodal treatment response between pre- and post-menopausal women presenting with breast cancer in a tertiary care referral setup in Northern India. **Material and Methods:** Prospective, comparative clinical study of long duration was conducted with a well-defined cohort of women who were brought to the outpatient department of the hospital for biopsy of breast cancer. Patients were divided into two groups of comparison: Premenopausal (Group A) and Postmenopausal (Group B) patients with definitive menopausal status at diagnosis. Reproductive risk factors, clinical TNM staging, immunohistochemical profiling of receptor status (ER, PR, Her2/neu), surgical execution type, choice of adjuvant chemotherapy, and level of radiation treatment compliance were among the factors that were evaluated. **Results:** The findings showed that two cohorts had different clinical behaviours. High-risk genetic and reproductive indicators were significantly more associated with premenopausal women (Group A) such as positive family history of breast malignancy, a lower median parity, and shorter lifetime lactation periods. In addition, the premenopausal patients were mainly at advanced clinical stages (T3/T4 tumor stages and extensive involvement in the axillary lymph nodes) and high biological features (triple-negative or Her2/neu over-expressing phenotype). Conversely, postmenopausal women (Group B) had a greater percentage with hormone-receptor-positive (ER+/PR+) tumors and with lower grade histologies. As a result, Group A needed more aggressive multimodality therapy with the use of higher rate of modified radical mastectomy (MRM), neo-adjuvant chemotherapy regimens and intensive loco-regional radiation treatment cycles to achieve margin clearance. **Conclusion:** The conclusion is that the breast carcinoma presented in premenopausal women from Northern India were of aggressive nature with late presentation at advanced stages and presented with high-grade biological profile. Each is a separate variant highlighting the importance of early, specific screening schemes, increasing genetic risk counseling and tailored therapeutic strategies optimised for the high-risk disease variants found in younger premenopausal patients.

Keywords: Breast carcinoma; premenopausal; postmenopausal; risk factors; clinical presentation; hormone receptor status; management.

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Introduction

Breast carcinoma is the most common and the most deadly cancer among women in the world, and it is a significant public health issue. Over the past two decades there has been a huge epidemiological change in India where breast cancer has now become the leading form of malignant disease in urban and rural women.[1]

Clinical evidence has been rapidly accumulating that breast cancer is a very heterogeneous disease, in which a number of distinct genetic changes, histopathological features and clinical behaviours occur. Among the most basic clinical characteristics that differentiate these tumors is the age at which the patient is at the time of diagnosis. Ovarian senescence and the resulting change in peripheral aromatization of androgens (post-menopause) significantly alters the tissue microenvironment and the oncogenic mechanisms that underlie breast tumorigenesis compared to a pre-menopause state with cyclically produced ovarian estrogens.[2,3]

In Western countries, breast cancer is traditionally reported to primarily affect the sixth and seventh decades of life, with the

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majority of cases being postmenopausal, hormone-receptor-positive breast cancers. On the other hand, cases with the Indian demographic profile are more likely to be diagnosed in women younger than 50 years of age, with many cases diagnosed at least a decade earlier than the cases in western women. Breast cancer in premenopausal women is often hormone-receptor negative (ER and PR), has a high grade and biological aggression (high proliferation rate). Triple-negative breast cancer (TNBC) is a frequent manifestation of such aggressive biological features.[4,5]

The presentation is unique for the different clinical questions it raises on the interaction between lifestyle, reproductive risk factors and genetic risk factors in the etiology of cancer in various age groups. Reduced menopausal estrogen exposure by factors like early menarche, late menopause, nulliparity, delayed age at first full-term pregnancy, shorter duration of breastfeeding and metabolic obesity varies between pre- and postmenopausal women.[6,7]

In addition, delayed presentation continues to be a big problem in developing countries because of the lack of awareness and routine screening. This is often the reason for the presentation of the disease in an advanced stage, necessitating intense multimodality treatment approaches including surgery, neo-adjuvant/adjuvant systemic chemotherapy, hormonal modulation and loco-regional radiotherapy. It was a prospective study to compare the risk factor profile, clinical presentation, histopathological features and multimodality management of pre- and postmenopausal breast carcinoma patients at tertiary care centre in northern region of India.[8-10]

Materials and Methods

Study Design and Ethical Framework: This prospective, comparative observational clinical study was conducted over a two-year period within the Department of General Surgery in coordination with the Department of Radiation Oncology at the Shri Ram Murti Smarak Institute of Medical Sciences (SRMS-IMS), Bareilly, Uttar Pradesh, India. The study protocol was reviewed and granted formal approval by the Institutional Ethics Committee. All participating individuals provided written informed consent prior to data collection and therapeutic evaluation.

Participant Selection and Stratification: The study cohort included female patients presenting with primary, histologically or cytologically confirmed breast carcinoma who met the following eligibility criteria:

Inclusion Criteria: Female patients across all adult age groups with newly diagnosed, biopsy-proven unilateral or bilateral primary breast carcinoma who were planned for or underwent multimodality treatment at our center.

Exclusion Criteria: Patients presenting with recurrent breast cancer after previous definitive treatments elsewhere; individuals with a history of primary synchronous or metachronous malignancies in other organ systems; patients presenting with advanced metabolic encephalopathy or critical multi-organ failure at baseline; and individuals who declined to participate or left the center prior to completing primary staging and treatment planning.

Eligible participants were stratified into two comparative study groups based on their menopausal status at the time of initial clinical presentation:

Group A (Premenopausal Cohort): Women with active, regular menstrual cycles or those experiencing temporary or lactational amenorrhea matching standard premenopausal clinical criteria.

Group B (Postmenopausal Cohort): Women who had experienced permanent cessation of menstruation for at least 12 consecutive months due to natural ovarian senescence or previous surgical/bilateral oophorectomy.

Clinical Presentation and Risk Factor Mapping: A comprehensive, structured clinical proforma was completed for each patient to collect data on relevant risk factors, reproductive history, and clinical presentations. Sociodemographic variables recorded included age, urban/rural residence, and socioeconomic index. Detailed reproductive profiling mapped age at menarche, parity status, age at first full-term pregnancy, total duration of lifetime breastfeeding per child, and any use of exogenous oral contraceptive pills (OCP) or hormone replacement therapy (HRT). A detailed family history was obtained to identify any maternal or paternal first- and second-degree relatives with a confirmed diagnosis of breast, ovarian, or endometrial malignancies.

Clinical evaluation included a detailed assessment of primary symptoms (e.g., self-detected painless lump, painful mass, nipple discharge, skin tethering, ulceration, or axillary fullness) and symptom duration before presentation. Physical examination included thorough bilateral breast and axillary evaluations to determine clinical tumor dimensions, mobility, skin involvement, and fixed or mobile axillary and supraclavicular lymphadenopathy.

Diagnostic Staging and Biological Profiling: Primary staging was established using a combination of high-resolution bilateral digital mammography, breast and axillary ultrasonography, and chest radiography, supplemented by abdominal ultrasonography or contrast-enhanced computed tomography (CECT) of the chest, abdomen, and pelvis when advanced or metastatic disease was suspected. Clinical and pathological staging followed the American Joint Committee on Cancer (AJCC) TNM staging manual.

Histopathological classification was confirmed via core needle biopsy or definitive surgical specimens. Slides were evaluated to determine histological type (e.g., Infiltrating Ductal Carcinoma [IDC], Infiltrating Lobular Carcinoma [ILC]) and Nottingham histological grade. Immunohistochemical (IHC) staining was systematically performed to quantify Estrogen Receptor (ER), Progesterone Receptor (PR), and Human Epidermal Growth Factor Receptor 2 (Her2/neu) expression. Her2/neu scoring followed standard guidelines, with equivocal 2+ cases referred for fluorescent in situ hybridization (FISH) analysis when clinically indicated.

Multimodality Treatment Protocols and Statistical Analysis: Therapeutic strategies were determined by a multidisciplinary tumor board based on disease stage, age, and biological subtype. Surgical interventions included Breast Conservation Surgery (BCS) or Modified Radical Mastectomy (MRM) with concurrent axillary lymph node dissection. Systemic chemotherapy was administered in either a neo-adjuvant (preoperative) or adjuvant

setting, utilizing standard anthracycline- or taxane-based regimens. Radiotherapy was delivered using linear accelerators to the chest wall or preserved breast tissue and regional nodal basins. Endocrine therapy (e.g., Tamoxifen or Aromatase Inhibitors) was prescribed for hormone-receptor-positive disease.

Data were entered into Microsoft Excel and analyzed using SPSS version 25.0. Continuous variables are expressed as means ± standard deviations (SD) and compared using the independent Student's t-test. Categorical variables are presented as absolute frequencies and percentages, with statistical differences evaluated using Pearson's Chi-Square test or Fisher's Exact test as appropriate. All tests were two-tailed, and a P-value <0.05 was considered statistically significant.

Results

Sociodemographic and Reproductive Risk Factor Profiling

The final study cohort comprised 100 women with primary breast carcinoma, with 46 patients stratified into Group A (Premenopausal) and 54 patients into Group B (Postmenopausal). The mean age at diagnosis was 41.2 ± 5.3 years for Group A and 58.7 ± 6.8 years for Group B. Analysis of reproductive profiles revealed significant structural variations between the two cohorts. A positive family history of breast or ovarian malignancy in first- or second-degree relatives was significantly more common in premenopausal patients compared to the postmenopausal cohort (17.4% vs 5.6%; P = 0.042).

Premenopausal women also demonstrated a significantly lower median parity status (2.1 ± 0.8 vs 3.6 ± 1.2; P = 0.003) and a shorter mean cumulative lifetime duration of breastfeeding (18.4 ± 6.2 months vs 34.2 ± 10.5 months; P < 0.001) than postmenopausal patients. Differences in the age at menarche (P = 0.241) and past history of OCP use (P = 0.612) did not cross the threshold for statistical significance.

Table 1: Comparison of Risk Factors and Reproductive Variables

Risk Factor / Reproductive Variable	Premenopausal (n=46)	Postmenopausal (n=54)	P-value
Mean Age at Diagnosis (Years)	41.2 ± 5.3	58.7 ± 6.8	< 0.001*
Positive Family History of Breast Ca	8 (17.4%)	3 (5.6%)	0.042*
Mean Parity (Number of Children)	2.1 ± 0.8	3.6 ± 1.2	0.003*
Cumulative Breastfeeding (Months)	18.4 ± 6.2	34.2 ± 10.5	< 0.001*
Early Menarche (<12 Years of Age)	11 (23.9%)	9 (16.7%)	0.241

Clinical Staging and Tumor Characteristics at Presentation

The primary clinical presentation for the majority of patients in both groups was a self-detected painless lump. However, premenopausal women reported a significantly shorter mean duration of symptoms before seeking care (3.4 ± 1.8 months vs 5.9 ± 2.4 months; P = 0.002), despite presenting with more advanced disease stages. This suggests a faster biological growth rate in younger patients.

Clinical tumor staging revealed that premenopausal women had a significantly higher prevalence of T3 and T4 locally advanced lesions at presentation compared to postmenopausal patients (54.3% vs 33.3%; P = 0.021). Axillary lymph node involvement was also significantly more frequent in Group A, with 67.4% presenting with clinically positive, matted, or mobile axillary lymphadenopathy (N1/N2 disease) compared to 44.4% in Group B (P = 0.016). Consequently, a larger proportion of premenopausal women presented with Stage III locally advanced breast cancer (47.8% vs 27.8%; P = 0.012).

Table 2: Comparison of Clinical Presentation and Disease Stage

Clinical Stage Feature	Premenopausal (n=46)	Postmenopausal (n=54)	P-value
Mean Symptom Duration (Months)	3.4 ± 1.8	5.9 ± 2.4	0.002*
Advanced Tumor Size (T3 / T4)	25 (54.3%)	18 (33.3%)	0.021*
Positive Axillary Nodes (N+)	31 (67.4%)	24 (44.4%)	0.016*
Early Stage Disease (Stage I/II)	21 (45.7%)	36 (66.7%)	0.012*
Locally Advanced Disease (Stage III)	22 (47.8%)	15 (27.8%)	0.012*

Histopathological Grades and Immunohistochemical Molecular Subtypes

Histopathological evaluation showed that Infiltrating Ductal Carcinoma (IDC) was the predominant histological type in both cohorts, accounting for 91.3% of cases in Group A and 88.9% in Group B. However, premenopausal tumors presented with significantly less differentiated histologies, with 63.0% categorized as Nottingham Grade III high-grade lesions, compared to 37.0% in the postmenopausal cohort (P = 0.006).

Immunohistochemical molecular subtyping revealed highly significant biological variations between the groups. Postmenopausal women demonstrated a significantly higher prevalence of hormone-receptor-positive disease, with 64.8% of tumors expressing Estrogen Receptors (ER+) or Progesterone Receptors (PR+), compared to 39.1% in premenopausal women (P = 0.005). Conversely, premenopausal women showed a significantly higher incidence of aggressive biological subtypes, including Her2/neu over-expressing profiles (26.1% vs 11.1%; P = 0.043) and Triple-Negative Breast Cancer (TNBC; 34.8% vs 14.8%; P = 0.014).

Table 3: Comparison of Pathological and Biological Features

Pathological & Biological Feature	Premenopausal (n=46)	Postmenopausal (n=54)	P-value

High Histological Grade (Grade III)	29 (63.0%)	20 (37.0%)	0.006*
Hormone Receptor Positive (ER+/PR+)	18 (39.1%)	35 (64.8%)	0.005*
Her2/neu Over-expressing Subtype	12 (26.1%)	6 (11.1%)	0.043*
Triple-Negative Breast Cancer (TNBC)	16 (34.8%)	8 (14.8%)	0.014*
Infiltrating Ductal Carcinoma (IDC)	42 (91.3%)	48 (88.9%)	0.618

Multimodality Treatment Executions and Strategies

The advanced clinical stages and aggressive molecular subtypes observed in premenopausal women required more intensive multimodality treatment strategies. While Breast Conservation Surgery (BCS) was performed in a minority of patients in both cohorts, Modified Radical Mastectomy (MRM) was the primary surgical intervention, executed in 82.6% of premenopausal patients and 72.2% of postmenopausal patients (P = 0.174).

Regarding systemic interventions, premenopausal women required significantly higher rates of neo-adjuvant (preoperative) chemotherapy to downstage locally advanced tumors before surgical resection (39.1% vs 18.5%; P = 0.018). The administration of adjuvant systemic chemotherapy was also significantly more frequent in Group A compared to Group B (89.1% vs 59.3%; P = 0.001), reflecting the higher prevalence of hormone-receptor-negative and high-grade tumors. Adjuvant radiotherapy was delivered to 73.9% of premenopausal women and 51.9% of postmenopausal women (P = 0.017), driven by advanced T-stage and node-positive status. By contrast, the postmenopausal group had a significantly higher proportion of ER/PR positivity (64.8% vs 39.1%, p = 0.005) which led to an increased rate of compliance with adjuvant endocrine therapy.

Discussion

This prospective comparative study outline certain differences in: reproductive risk factors, clinical profile, biological behavior of breast carcinoma in premenopausal and postmenopausal women in Northern part of India and multimodality management strategies. The results of our study align with many others that suggest that breast cancer in younger premenopausal women is a more aggressive disease than in the more indolent breast cancer profiles seen in older patients.

We found a high proportion of premenopausal breast cancer cases (46% of the study population), which is in accordance with the changing trends reported from Western countries, as in these areas breast cancer is mainly a disease of postmenopausal women, as opposed to South Asian countries. There is also a strong correlation between the disease in premenopausal women and a positive family history of breast malignancy (P = 0.042) indicating the involvement of genetic abnormalities, like the BRCA1 or BRCA2 mutations, in younger patient populations. This highlights a need for greater access to genetic counselling and early screening to patients in the region in a risk adapted setting.

The analysis of reproductive variables showed that shorter lifetime periods of lactation (P < 0.001) and lower median parity (P = 0.003) were related to premenopausal breast cancer. This result agrees with the previously established physiological model that breast tumorigenesis is protected by having more than one full-term pregnancy and prolonged lactation. The reproductive activities cause differentiation of the mammary glands, and also inhibit normal ovulatory activity, which limits exposure to endogenous cyclic estrogens over the life of the animal.

An important result in this study was that premenopausal women had significantly more advanced clinical features despite having a shorter duration of the symptoms before seeking care (P = 0.002), and of axillary lymph node involvement (P = 0.016), and larger tumor size (T3/T4, P = 0.021). This paradox suggests that breast tumors in younger (premenopausal) women have an aggressive phenotype with accelerated tumor doubling time and early metastatic dissemination. This growth mode accentuates problems with only symptom-awareness and the necessity of effective, risk-stratified screening programs in younger populations.

The high level of clinical aggressiveness is due to the underlying biological and immunohistochemical characteristics of the tumors. Premenopausal women had significantly higher prevalence of Nottingham Grade III histologies (P = 0.006), Her2/neu over expressing breast cancer (P = 0.043) and Triple Negative breast cancer (TNBC, P = 0.014). Postmenopausal women, however, had predominately hormone-receptor positive (ER+/PR+) tumours (P = 0.005), which are usually related to a better prognosis and sensitivity to endocrine modulation.

Immaturity and aggressive biological subtypes in premenopausal women required intensive, multimodality therapy strategies. This group had significantly increased use of neo-adjuvant chemotherapy (P = 0.018), adjuvant chemotherapy (P = 0.001) and loco-regional radiotherapy (P = 0.017) to downstage locally advanced lesions and to optimise margins and reduce the risk of recurrence, respectively. However, postmenopausal women were treated more often with adjuvant E.T. (P = 0.005), which is a targeted treatment and has a lower systemic side-effect profile.

The main constraints of the present study are its single center design and small sample size (n=100) that may not permit the generalizability of the present findings to other geographic and ethnic communities in India. Furthermore, this study included only initial clinical presentation and treatment selection, and assessment of long-term survival, loco-regional recurrence rates and toxicity of each treatment between the two groups would require prolonged longitudinal follow-up.

Conclusion

The current study clearly brings out the marked differences in breast carcinoma between pre and post menopausal women in Northern India at the clinical and biological levels. Breast cancer in premenopausal women has an aggressive clinical course, positive family history, high stage at presentation, high histological grade and an abundance of the triple-negative and Her2/neu over-expressing molecular subtypes. They require increased multimodality treatment methodology such as more of

the following: neo-adjuvant and adjuvant chemotherapy, loco-regional radiotherapy.

The results of this study highlight clinical need to define specific public health interventions. We believe that breast cancer awareness and targeted screening programs designed for younger women should be implemented, that genetic counselling in families with history of cancer should be made more widely available and that multimodality treatment for premenopausal breast cancer, with its more aggressive biological characteristics, should be optimized.

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Conflicts of interest

There are no conflicts of interest.

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