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INVESTIGATING THE IMPACT OF AGE AND PARITY ON BREAST CANCER RISK: A STUDY AT KTH PESHAWAR

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ABSTRACT

Background: *Breast cancer is the most prevalent cancer in women all over the world, and one of the major causes of cancer deaths. Although age and parity are the most known risk factors that have been well studied in the Western population, its use in low and middle-income countries such as Pakistan is unclear. It is worth mentioning that regional clinical observation indicates that breast cancer is very prevalent in grand multiparous women and this observation contradicts the perceived protective effect of multiparity.*

Purpose: *The study was aimed at evaluating the parity and age relations with breast cancer risk and stage at diagnosis among women in northwestern Pakistan.*

Methods: *The study was a prospective descriptive study that was performed in Khyber Teaching Hospital, Peshawar, on a population of 163 women with primary breast cancer. Demographic, reproductive, and tumor data determined such as age, parity, age at which a child was born, and Ki-67 proliferation index were obtained through a semi-structured proforma. Categorical variables were analyzed relating to AJCC stage descriptively and by post-stratification chi-square test with the use of significance levels of $p \leq 0.05$.*

Findings: *Mean age at diagnosis was 48.29 years (SD=10.24), with the most frequent at the end of the forties and the beginning of the fifties. The mean parity was 2.6 (SD = 1.7), the mean number of pregnancies was 3.9 (SD = 2.1), which means that reproductive exposure was more moderate than in the previous studies. The age of first birth was 18.8 years (SD = 8.63), indicating that there was a high degree of variability in age of first birth which was very early. The levels of Ki-67 indicated intermediate-to-high proliferation (mean = 37.96, SD = 22.17). The Chi-square test demonstrated that there were significant relationships among AJCC stage and both age group (2 = 18.456, 9 -1, p = 0.0302) and age at first birth group (2 = 17.717, 9 -1, p = 0.0386), but not between parity group (p = 0.1872).*

Conclusion: *This cohort of breast cancer is more common among midlife women who are moderately parity and very young at the time of first birth (~ 18.8 years). Although total parity is not a significant predictor of the disease stage, older age and earlier age at first childbirth are still found to be significantly correlated with higher AJCC stages.*

Keywords: *Age; parity; age at 1st birth, TNM stage; ER/PR/HER2; Ki-67; prospective study, Pakistan*

INTRODUCTION

Breast cancer is most diagnosed and identified type of cancer in women all over the world, and its incidence is varied in all populations.[1] It is the most common type of cancer, as well, the leading cause of cancer-related deaths in women. The risk factors of breast cancer such as age, gender, race, genetic factors, hormonal factors, family history, ionizing radiation, and lifestyle characteristics are all necessary to have an effective prevention and early detection strategy [2-5]. Although such an increase in the rate of breast cancer has become a universal problem, nonetheless, it is quite interesting to note that most of these established risk factors of the western world are not equal in the people of our world [6].

As an example, there is a reported relationship between the null parity/ low parity and breast cancer and multi-parity has also shown to lower the risk as it is presently available in the literature but in our own practice most of our patients with breast cancer are multi-parous despite their low parity. Furthermore, another confirmed risk factor is age where risk of breast cancer grows with the growing age.[7]

The risk of breast cancer is always related to its advancement and age. The incidences rates are progressive varying with age, with the highest incidences recorded in between postmenopausal women due to the changes in hormonal levels such as the decreased levels of estrogen and progesterone during menopause leading to changes in the breast tissue that can predispose an individual to carcinogenesis [8,9]. Moreover, the genetic mutations and the exposure to environmental carcinogens with age are also critical factors contributing to breast cancer, thus the importance of age-specific intervention and screening measures.[10]

In regard to parity, the mean / median age of our population who has cancer is 43.3 years in comparison to a very high age at which diagnosis is made in the available literature across the globe [11]. This thus must be researched to indicate whether age is a factor in predisposition of the patient against breast cancer and moreover to determine whether age is a factor in relation to tumor biology in our group of patients. The information available in Pakistan is minimal and no huge volumes of studies have been conducted on our population. By undertaking this research at our institution where the turnover of patients is quite high, we would come up with results that would not only help us develop a deeper understanding of the etiological factors of breast cancer within our population but would also give us the initial substrate on which to start on the guidelines of developing a screening program and primary prevention in the future.

Purpose: The aim of the study is to evaluate the relationship between parity, age and breast cancer risk among the women in north western Pakistan.

Operational Definitions

Age: This is described as the number of years passed after a woman was born up to the diagnosis of breast cancer.[6]

Parity: The parity refers to the number of pregnancies that a woman has been carrying to viable gestational age classified as nulliparous (0), low parity (1-2) and multiparous (>=3). [7]

Age at first birth: AGE is the number of years that the patient has completed at the time of birth of the first live born child [8].

Breast Cancer: It describes breast cancer as a malignant tumor that begins in the breast tissue, and is diagnosed by a histopathological examination. [8]

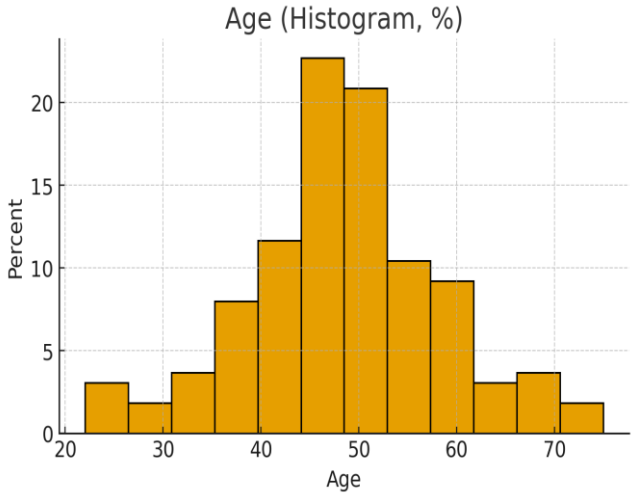
Methodology:

This was a prospective descriptive study done at the Department of Surgery, Khyber Teaching Hospital, Peshawar. Women diagnosed with primary breast cancer who reported to the breast clinic of the hospital were categorized as the target population and none of them had secondary breast cancer. The sample size was calculated according to the formula of every 8th woman based on the total Pakistani population of 30.18million, with a projected prevalence of breast cancer amongst the study population of 12.49, therefore, giving the minimum population required of 163 patients, which was found to be enough to provide meaningful subgroup analysis by age groups. Eligible participants were enrolled using a consecutive non-probability sampling technique. The collection of data was done through a semi-

structured pro forma which recorded demographic and personal data including age, nationality, marital status, menstrual status, parity and age at first child bearing, and tumor variables including histopathological type, receptor status (ER, PR, HER2), Ki-67 proliferation index and clinical stage after obtaining informed consent on the same. Categorical variables such as nationality, marital status, menstrual, any treatment taken on conception, family history of breast cancer, cancer type, Ki-67, and clinical Stage were computed to be in frequencies and percentages. To address effect modifiers, mean, median and S.D were finally gathered on age, parity and age at first childbirth. Test of significance were done using post-stratification chi-square test. There was a p-value of 0.05 or less which was taken as significant.

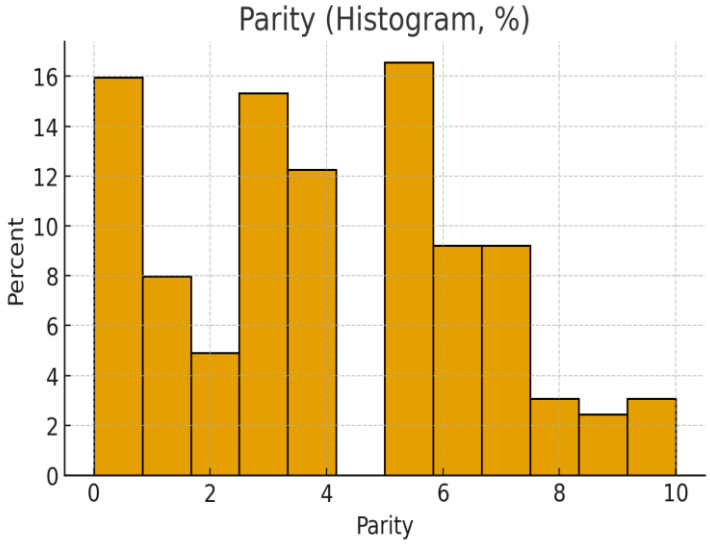
Results & Analysis

Age

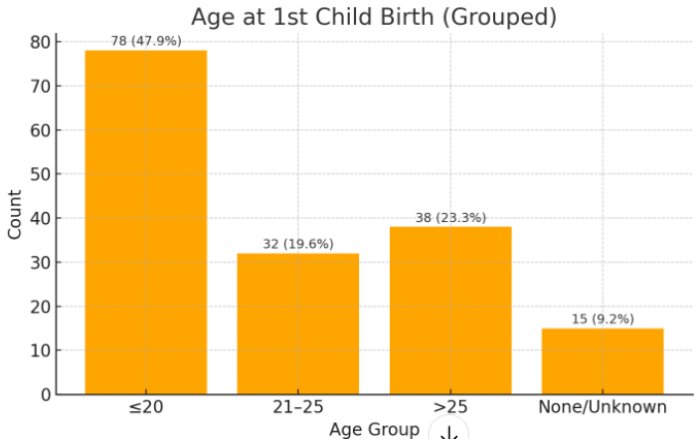


Most patients cluster in midlife; the tallest bins sit in the late-40s/early-50s with thinner tails below 30 and above 65, showing a mid-age concentration rather than very young/elderly extremes.

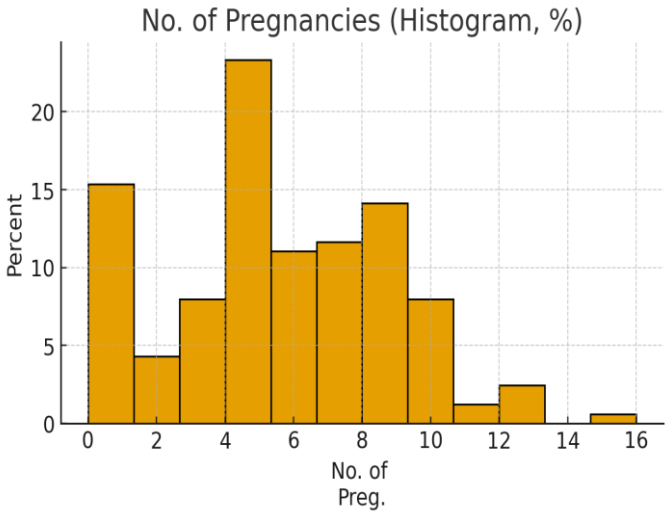
Parity



Age at first Birth

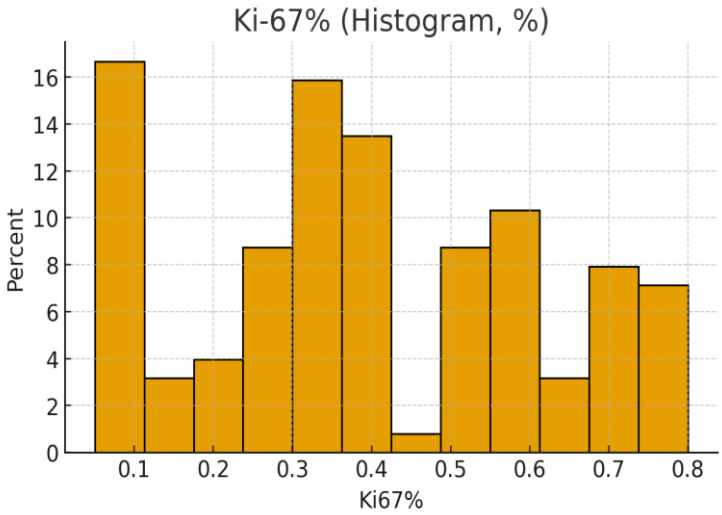


No. of Pregnancies



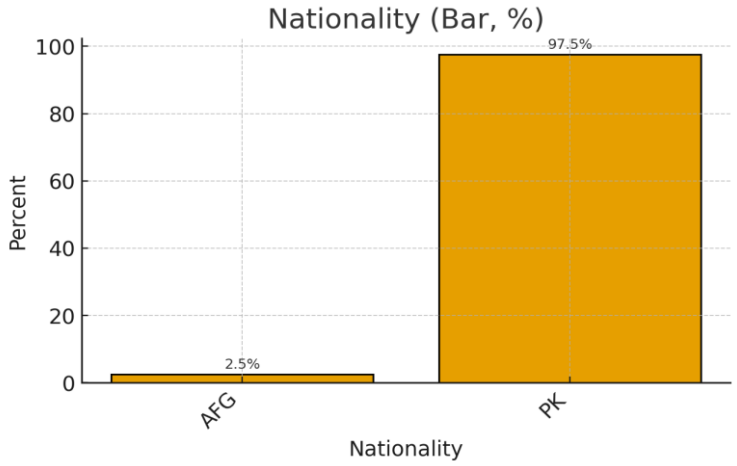
Centered around 5–7 with a notable tail into double digits, consistent with a wide spread of reproductive exposure across the cohort.

Ki-67%



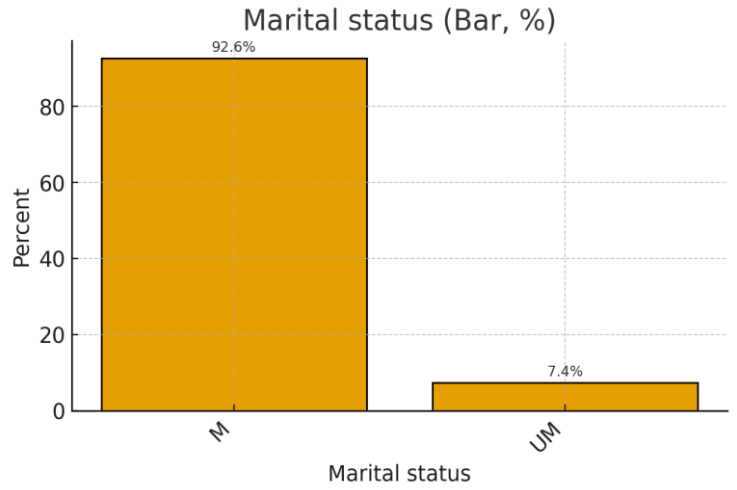
Proliferation indices are widely dispersed but center around intermediate–high values, implying substantial biological heterogeneity.

Nationality



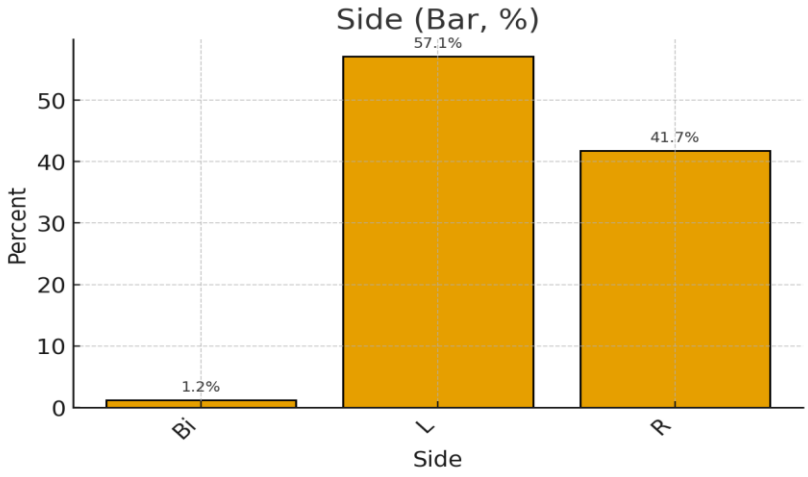
Nationality: overwhelmingly Pakistan with a small Afghanistan share.

Marital status

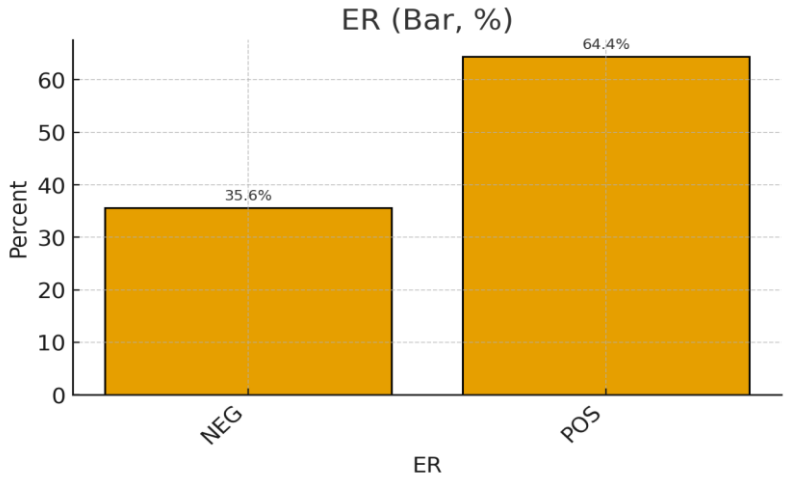


Marital status: mostly Married with a small Unmarried group.

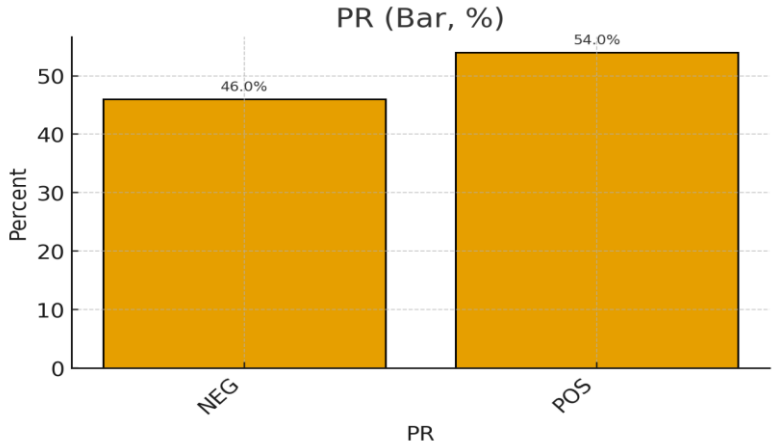
Side



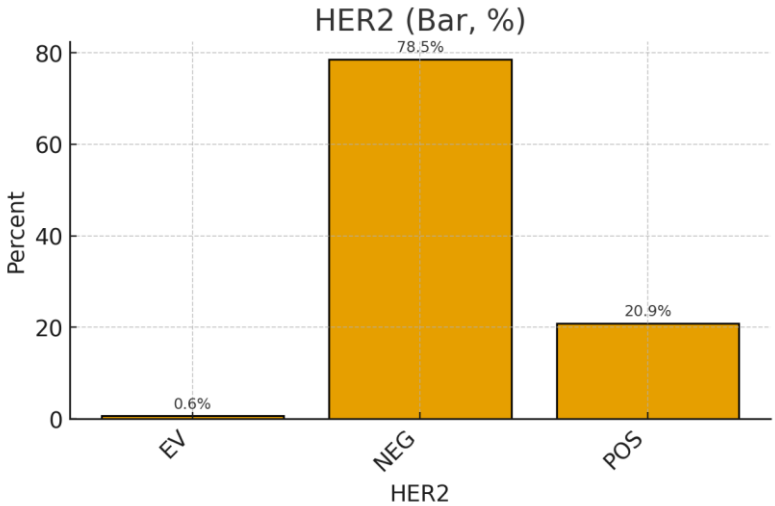
ER



PR

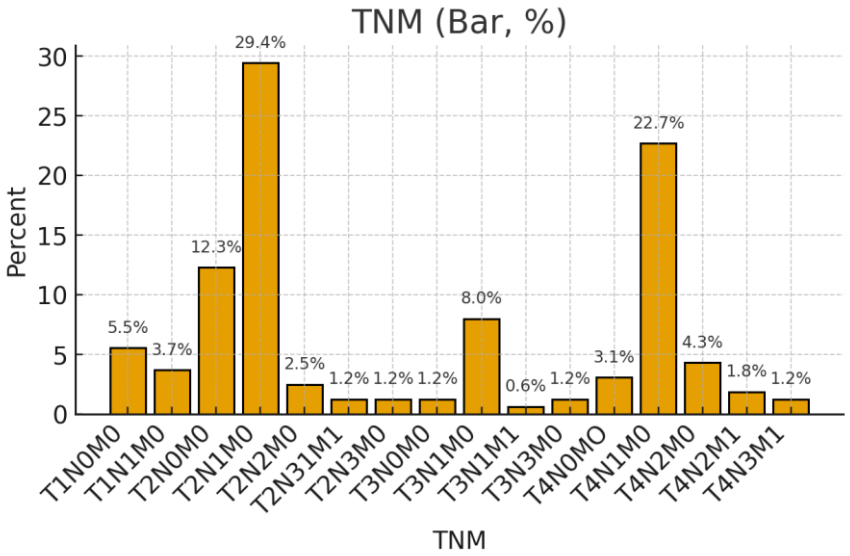


HER2



HER2 categories: positive/negative mix.

TNM



TNM spans early to advanced; later used to derive AJCC stage.

Table 1: & Table 2: The reproductive exposure in this cohort was moderate (mean parity 2.6; mean gravidity 3.9), although quite young at the time of first birth (mean age 18.8 years). The proliferative activity of tumors was intermediate-high (mean Ki-67 ≈ 38%). The results of chi-square testing showed that the age of the patient and the time of first birth contributed to AJCC stage significantly, but total parity did not. These trends imply that as the disease stage increases; temporal effects of the reproductive history (in particular, the earlier the first birth), and chronological age might be stronger than the number of births.

Discussion:

AJCC stage was related to age group significantly among this cohort (2 p=0.03) [12]. This has non-linear directional consistency with modern evidence that prognosis non-linearly depends upon age [13,14]: younger women and older women are both worse off when adjusted on the basis of biology and treatment [15,16,17:] this represents a difference in tumor behavior, comorbidity, and under-treatment at the age extremes (age 11)[18]. These resultant age-related gradients in outcome/stage underline the necessity to view such stage at presentation in both biologic and health-system terms[18].

Mean parity was small (2.6, SD 1.7) and did not have a significant relationship with stage (p 0.19). This matches those in the literature suggesting that parity is more effective in determining risk and subtype mix than stage at diagnosis[19]: an increased parity with breastfeeding has a tendency to reduce luminal A risk, and parity not with breastfeeding has a tendency to increase risk among particular groups; these are not homogeneous effects, and they are not always associated with earlier vs later stage at presentation [16,4]. Conversely, stage is effectively affected by screening history and access to care: elements not effectively described by parity alone[12,20.]

Mean age of first birth was 18.8 years (SD 8.6) and correlated with stage (2 p 0.039). Two potentially plausible routes through which reproductive timing influences cancer in the luminal, a subtype-specific risk difference, is that (i) long-term: early first-birth age elevates luminal cancer risk [19]; and (ii) the postpartum window, a period during which women have an excessively high risk of aggressive biology and distant metastasis up to ten years after delivery [3,15]. Recent data (in carriers of BRCA) prove poorer survival in case of diagnosis in 510 years after childbirth regardless of traditional factors [15,2]. These patterns provide a biological plausible ground of the stage observable on us[21].

The median age of the cohort at first birth was lower than the national median (22.8 years; 25-49 years) of the country (Pakistan) which is the median age at which women have their first birth, highlighting age-specific cohort reproduction [16]. Early bearing, social economic context: area-based deprivation and health

system factors are repeatedly associated with AD at diagnosis in multiple settings, which indicates that maybe social factors mediate some of the age at first birth in our study. Ki-67 was average-to-high (mean 2038, SD22), which indicated a high-proliferation case-mix. According to the present-day literature, Ki-67 is a helpful prognostic tool and constituent of risk stratification in HR-positive/HER2-negative disease measured in standardized situations [17,18]. Through this analytic variability, reproducibility and clinical interpretability is enhanced by International Ki67 Working Group (IKWG) training and cut-point frameworks (e.g., ≤5% "low", ≥30% "high") that put our cohort at the population level at a range of 17-18 that is within the range of high. The trend that age group and age at first birth but not parity group are related to stage thus is consistent with existing science: biologic tempo and postpartum effect (age/Age at first birth) and screening/access (often age-linked) are more proximate causes of stage than lifetime parity per se [11,3,15,12,16.]

Conclusion:
This cohort of breast cancer is more common among midlife women who are moderately parity and very young at the time of first birth (~18.8 years). Although total parity is not a significant predictor of the disease stage, older age and earlier age at first childbirth are still found to be significantly correlated with higher AJCC stages. These results indicate that timing factors of reproductive history can be of more importance than total parity in tumor progression and can be used to stratify risk and screening in specific regions particularly in women who started having children during adolescence or later in their teens.

Recommendations: Postpartum awareness, expedited referral pathways, and regular Ki-67 reporting should be prioritized in the context of the general prognostic staging. Being a single-center, retrospective study with non-random sampling, these findings should be validated in bigger multicenter prospective studies, which incorporate screening history, breastfeeding, social background, and molecular subtype.

AUTHOR'S CONTRIBUTION

The Following authors have made substantial contributions to the manuscript as under:

FS: Conception and study design, acquisition, analysis and interpretation of data, drafting the manuscript, approval of the final version to be published

ISA & MMK: Acquisition, analysis of data, drafting the manuscript, approval of the final version to be published

ZA & AW: Acquisition, analysis and interpretation of data, critical review, approval of the final version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Descriptive Stats with respect to Age, Parity & Age at First Birth

Table 1

Variable	Mean	SD
Parity (number of live births)	2.6	1.7
Number of pregnancies	3.9	2.1
Age at first birth (years)	18.8	8.63
Ki-67 (%)	37.96	22.17

Associations with AJCC Stage (Chi-Square)

Table 2

Predictor (Grouped)	χ^2	df	p-value	Significance
Age group	18.456	9	0.0302	Significant ($p<0.05$)
Age at first birth group	17.717	9	0.0386	Significant ($p<0.05$)
Parity group	—	—	0.1872	Not significant

Note: Significance evaluated at $\alpha = 0$.