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Association of parity and age at menarche with molecular subtypes of invasive breast cancer

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Background: Breast cancer is the most frequently diagnosed malignancy among women worldwide and remains a major public health concern. Reproductive factors, including parity and age at menarche, influence cumulative lifetime estrogen exposure and may contribute to the biological characteristics of breast cancer. However, evidence regarding their association with molecular subtypes of invasive breast cancer remains limited, particularly in Indonesia.

Purpose: To determine the association between parity and age at menarche with the molecular subtypes of invasive breast cancer among patients treated.

Methods: This analytic observational study employed a cross-sectional design using secondary data from medical records of 125 patients diagnosed with invasive breast cancer in 2025. Participants were selected using random sampling based on predefined inclusion and exclusion criteria. The independent variables were parity and age at menarche, while the dependent variable was the molecular subtype of invasive breast cancer determined by immunohistochemistry. Univariate analysis was used to describe participant characteristics, and bivariate analysis was performed using the Chi-square test. The strength of the associations was measured using Odds Ratios (ORs) with 95% confidence intervals (CIs). Statistical significance was established at $p < 0.05$.

Results: Most participants had a normal-to-late age at menarche (60.0%) and were multiparous or grand multiparous (52.0%). Luminal B was the predominant molecular subtype (32.0%), followed by Luminal A (27.2%), HER2 (22.4%), and Triple-Negative (18.4%). A significant association was observed between parity and molecular subtype ($p = 0.003$; OR=0.282; 95% CI=0.119–0.672). Age at menarche was also significantly associated with molecular subtype ($p = 0.002$; OR=0.229; 95% CI=0.087–0.606). Women with early menarche and nulliparity or primiparity were more likely to present with non-Luminal A molecular subtypes.

Conclusion: Parity and age at menarche were significantly associated with the molecular subtypes of invasive breast cancer. Early menarche and low parity were more frequently associated with aggressive non-Luminal A molecular subtypes, highlighting the importance of reproductive history in breast cancer risk assessment and individualized management.

Keywords: Age at Menarche; Breast Cancer; Molecular Subtypes; Parity; Reproductive Factors.

INTRODUCTION

Breast cancer is the most common cancer among women worldwide and a leading cause of cancer-related mortality (Watkins, 2019; Sung et al., 2021). According to 2020 GLOBOCAN data, there were approximately 2.3 million new cases of breast cancer and 685,000 deaths globally (Sung et al., 2021). In Indonesia, breast cancer remains the most prevalent cancer among women and represents a growing

health issue (Ministry of Health of the Republic of Indonesia, 2023). In Lampung Province, Breast cancer remains one of the leading non-communicable diseases contributing substantially to the disease burden in Lampung Province (Lampung Province Health Office, 2024).

Breast cancer is a heterogeneous disease characterized by diverse biological, histopathological,

and molecular features (Herawati et al., 2021; Suparna & Sari, 2022). Based on immunohistochemical analysis, breast cancer is classified into several molecular subtypes: Luminal A, Luminal B, HER2, and Triple-Negative (Perou et al., 2000; Setiawan, 2023). Each subtype exhibits distinct clinical characteristics, therapeutic responses, and prognoses (Song, 2023).

Reproductive factors play a role in the incidence of breast cancer. Age at menarche and parity are closely linked to the duration of estrogen exposure throughout a woman's reproductive life (Collaborative Group on Hormonal Factors in Breast Cancer, 2012). Early menarche results in prolonged estrogen exposure, thereby increasing breast epithelial cell proliferation and the risk of malignant transformation (Colditz & Rosner, 2000). Conversely, pregnancy and breastfeeding can exert a protective effect through the terminal differentiation of breast epithelial cells into a more mature state (Lambertini et al., 2021). Several studies indicate that reproductive factors not only influence the risk of developing breast cancer but are also associated with variations in breast cancer molecular subtypes (Kurniawan et al., 2025; Bernadatte et al., 2022).

Although reproductive factors have been widely investigated as risk factors for breast cancer, evidence regarding their association with molecular subtypes remains inconsistent, particularly among Indonesian women. Previous studies have mainly focused on breast cancer incidence rather than subtype classification, while data from Lampung Province are still unavailable. Therefore, this study was conducted to evaluate the association between parity, age at menarche, and molecular subtypes of invasive breast cancer.

RESEARCH METHOD

This study employed an analytic observational design with a cross-sectional approach. The study was conducted at Dr. H. Abdul Moeloek Regional General Hospital, Lampung Province, Indonesia, using secondary data obtained from the medical records of patients diagnosed with invasive breast cancer between January and December 2025.

The study population comprised all female patients diagnosed with invasive breast cancer who underwent immunohistochemical examination during the study period. A total of 125 eligible patients were included using simple random sampling. Patients were eligible if they had complete medical records containing information on parity, age at menarche, and molecular subtype based on immunohistochemical examination. Patients with incomplete medical records or missing immunohistochemical results were excluded from the study.

The independent variables were parity and age at menarche. Parity was categorized into nulliparous–primiparous and multiparous–grand multiparous. Age at menarche was classified into early menarche and normal-to-late menarche according to the categories documented in the medical records. The dependent variable was the molecular subtype of invasive breast cancer, determined by immunohistochemical examination and classified as Luminal A, Luminal B, HER2-enriched, and Triple-Negative. For bivariate analysis, molecular subtypes were further grouped into Luminal A and Non-Luminal A.

Data were collected using a structured data extraction form from eligible medical records. Data quality was ensured through verification of record completeness and consistency before analysis. Univariate analysis was performed to describe the frequency and percentage distribution of each variable. The association between parity, age at menarche, and molecular subtype was analyzed using the Chi-square test. Odds Ratios (ORs) with 95% Confidence Intervals (95% CIs) were calculated to estimate the strength of the associations. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), and a p-value of less than 0.05 was considered statistically significant.

This study received ethical approval from the Health Research Ethics Committee of Dr. H. Abdul Moeloek Regional General Hospital, Lampung Province with number: No. 022/KEPK-RSUDAM/II/2026). Patient confidentiality was maintained by anonymizing all personal identifiers throughout the research process.

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RESEARCH RESULTS

Table 1. Characteristics of Respondents (N=125)

Table	Results	p-value	OR (95% CI)
Age at Menarche		0.002	0.229 (0.087-0.606)
Early	50/40.0		
Normal-Late	75/60.0		
Parity (n/%)		0.003	0.282 (0.119-672)
Nulliparous-Primiparous	60/48.0		
Multiparous-Grand Multiparous	65/52.0		
Molecular Type (n/%)			
Luminal A	34/27.2		
Luminal B	40/32.0		
HER2	28/22.4		
Triple Negative	23/18.4		

Based on the table above, the majority of respondents (75 patients; 60.0%) had a normal-to-late age of menarche, while 50 patients (40.0%) had an early age of menarche. Table 2 shows that the majority of respondents fell into the multipara-grand multipara group (65 patients; 52.0%), whereas 60 patients (48.0%) were nulliparous or primiparous. The most frequently identified molecular type among breast cancer patients was Luminal B (40 patients; 32.0%), followed by Luminal A (34 patients; 27.2%), HER2 (28 patients; 22.4%), and Triple Negative (23 patients; 18.4%). Thus, Luminal B was the dominant molecular subtype in the study population, while Triple Negative was the least frequent subtype.

Statistical analysis using the Chi-Square test yielded a p-value of 0.003 ($p < 0.05$), indicating a significant association between parity and the molecular type of invasive breast cancer in the patients. Similarly, the Chi-Square test yielded a p-value of 0.002 ($p < 0.05$), indicating a significant association between age of menarche and the molecular type of invasive breast cancer. Therefore, age of menarche is a reproductive factor associated with the molecular type of invasive breast cancer.

DISCUSSION

The study results indicate a significant association between parity and the molecular

subtype of invasive breast cancer ($p=0.003$). In the nulliparous-primiparous group, the majority of patients ($n=51$; 85.0%) presented with the Non-Luminal A molecular subtype, whereas the multiparous-grand multiparous group showed a higher proportion of the Luminal A subtype ($n=25$; 38.5%). These findings suggest that patients with low parity tend to have more aggressive molecular subtypes compared to those with higher parity.

Biologically, pregnancy induces terminal differentiation of breast epithelial cells, rendering breast tissue more mature and resistant to malignant transformation. Furthermore, pregnancy and breastfeeding contribute to reducing cumulative estrogen exposure throughout a woman's reproductive life. These factors are thought to play a role in lowering the risk of developing more aggressive breast cancer subtypes (Lambertini et al., 2021; Anderson et al., 2015).

These results align with another study which reported an association between reproductive factors and variations in breast cancer molecular subtypes. Women with fewer births or those who have never given birth tend to be at higher risk of developing breast cancer with more aggressive biological characteristics (Kurniawan et al., 2025).

Nevertheless, the development of breast cancer is a multifactorial process influenced by various other factors, such as genetic predisposition, age,

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lifestyle, obesity, hormonal therapy use, and environmental factors. Therefore, parity cannot be considered the sole determinant of breast cancer molecular subtypes; rather, it is one of the reproductive factors contributing to the biological characteristics of the tumor.

The study results indicate a significant association between age at menarche and the molecular subtype of invasive breast cancer ($p=0.002$). In the early menarche group, the majority of patients ($n=44$; 88.0%) presented with the Non-Luminal A molecular subtype, whereas in the normal-to-late menarche group, 28 patients (37.3%) presented with the Luminal A subtype. These findings suggest that early menarche tends to be associated with more aggressive breast cancer molecular subtypes.

Age at menarche serves as an indicator of the duration of estrogen exposure throughout a woman's reproductive life. Early menarche results in prolonged estrogen exposure, thereby increasing breast epithelial cell proliferation and heightening the likelihood of genetic alterations involved in the process of carcinogenesis. Prolonged hormonal exposure can also influence hormone receptor expression and the biological characteristics of the developing tumor (Collaborative Group on Hormonal Factors in Breast Cancer, 2012; Colditz & Rosner, 2002).

These findings align with the 2012 study by the Collaborative Group on Hormonal Factors in Breast Cancer, which demonstrated that women with an earlier age at menarche face a higher risk of developing breast cancer compared to those who experience menarche at an older age. Furthermore, other studies have indicated that early menarche is linked to increased lifetime estrogen exposure, which contributes to breast cancer development (Colditz & Rosner, 2002).

Nevertheless, age at menarche is not the sole factor influencing breast cancer development. Other reproductive factors such as age at menopause, age at first childbirth, and breastfeeding history as well as genetic and environmental factors, also play a role in determining the biological characteristics of the tumor. Therefore, the association observed in this study should be understood within the context of the interplay among various risk factors that influence

the development of breast cancer.

CONCLUSION

Parity and age at menarche were significantly associated with molecular subtypes of invasive breast cancer. Women with early menarche and nulliparity/primiparity were more likely to present with aggressive non-Luminal A subtypes. These findings support the importance of reproductive history in breast cancer risk stratification.

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