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# SERUM PROLACTINE LEVELS AND PROLACTINE RECEPTOR EXPRESSION IN PREMENOPAUSAL BREAST CANCER: A POTENTIAL PREDICTIVE BIOMARKER?

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**Abstract**

Premenopausal breast cancer (PBC) is often more aggressive than postmenopausal cases, with prolactin playing a key role in tumor development. This study examines the relationship between serum prolactin levels, prolactin receptor (PRLR) expression, and clinicopathological features in PBC patients. Methods this cross-sectional study was conducted from 2021 - 2022 at multiple hospitals in Pekanbaru, Indonesia. Thirty-five PBC patients and 35 healthy controls were included. Serum prolactin levels were measured using ELISA, and PRLR expression was assessed via IHC. Statistical analysis was performed using independent t-tests and correlation analysis ($p < 0.05$). Results PBC patients had higher prolactin levels (51.96±80.40 ng/mL) than controls (20.83±15.74 ng/mL, $p = 0.031$). PRLR expression was detected in over 90% of tumors, with a significant correlation between prolactin levels and cancer stage ($p = 0.035$). Discussion these findings suggest prolactin contributes to PBC progression, with higher levels linked to advanced stages, possibly through JAK2/STAT5 signaling. Conclusion serum prolactin levels and PRLR expression are associated with cancer stage, supporting their potential as biomarkers for early detection and disease progression. Further studies are needed for validation.

**Keywords**: *Biomarker; Breast Cancer; Hormone Receptor; Prolactin; Prolactin Receptor.*



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## INTRODUCTION

Breast cancer remain the most common malignancy among women worldwide, and premenopausal women account for a substantial proportion of affected individuals. The incidence of breast cancer increases progressively with age; however, tumors occurring before menopause frequently demonstrate higher histological grades, increased proliferative activity, and poorer clinical outcomes compared to postmenopausal disease (Bosompem et al., 2024). Hormonal regulation, particularly through estrogen and prolactin, exerts major influence on tumor initiation and progression in this population, identifying premenopausal breast cancer as a biologically distinct and clinically significant entity (Schuler & O'Leary, 2022; Zheng et al., 2018).

Prolactin functions as a peptide hormone primarily responsible for lactogenesis, yet it also contributes to breast tumorigenesis. Elevated circulating prolactin concentrations correlate with an increased likelihood of developing breast carcinoma, indicating its possible role as a tumor-promoting factor (Schuler & O'Leary, 2022; Hathaway et al., 2023). After binding to the prolactin receptor (PRLR), prolactin activates intracellular signaling cascades such as JAK2–STAT5, which enhance cellular proliferation, survival, and differentiation. The high expression of PRLR in malignant breast epithelium supports its oncogenic relevance and links prolactin activity to disease aggressiveness (Hathaway et al., 2023; Wang et al., 2016).

Experimental and clinical studies have clarified the molecular mechanisms underlying prolactin-mediated oncogenesis. Activation of the STAT5 transcription factor by PRLR signaling promotes tumor cell growth and resistance to apoptosis, contributing to the maintenance of malignant phenotypes (Hathaway et al., 2023). Characterizing the mechanism among circulating prolactin levels, PRLR expression, and downstream molecular pathways provides essential understanding of hormone-dependent oncogenic regulation in premenopausal breast cancer (Schuler & O'Leary, 2022).

Evaluating serum prolactin concentrations together with PRLR expression in breast tissue enables comprehensive assessment of prolactin's role in tumor biology and clinical behavior. Identifying these associations may refine prognostic evaluation and reveal potential therapeutic targets for hormone-modulated breast malignancies (Bosompem et al., 2024; Hathaway et al., 2023). This study investigates the correlation between serum prolactin levels, PRLR expression, and clinicopathological characteristics in premenopausal breast cancer, providing evidence for prolactin as a candidate predictive biomarker.

## METHODS

Cross-sectional comparative study conducted from 2021 to 2022 across multiple hospitals in Pekanbaru, Indonesia. Investigators enrolled premenopausal women aged 40–50 years with histopathologically confirmed breast cancer who had undergone immunohistochemical analysis for estrogen receptor (ER), progesterone receptor (PR), HER2, Ki-67, and prolactin receptor (PRLR). Participants with a history of ovarian malignancy were excluded. After confirming eligibility, venous blood and breast tissue samples were collected for biochemical and histopathological evaluation. The control group consisted of healthy women matched by age, ethnicity, and socioeconomic background, excluding individuals with first-degree relatives diagnosed with breast or ovarian cancer. Clinicopathological parameters analyzed in the premenopausal breast cancer cohort included tumor size, nodal status, histological grade, ER and PR status, HER2 expression, Ki-67 index, and PRLR expression. Serum prolactin levels were quantified using enzyme-linked immunosorbent assay (ELISA), and PRLR expression was assessed semiquantitatively using fibroadenoma tissue as reference. Statistical analysis included descriptive evaluation and independent t-tests for group comparisons, and correlations between prolactin-related variables and breast cancer incidence were examined using appropriate inferential methods with a significance threshold of $p < 0.05$.

## RESULTS AND DISCUSSION

This research analyzes 35 premenopausal breast cancer (PBC) patients aged 40–50 years and 35 healthy controls matched by age, ethnicity, and socioeconomic background. Patients show a mean age of 43.66 ± 3.52 years and a mean body mass index of 26.83 ± 2.31 kg/m². Most participants maintain regular menstrual cycles and report a breastfeeding duration of one to two years. Ductal carcinoma dominates all cases, and 74.3% exhibit grade III histology. Estrogen and progesterone receptor negativity appear in 57.1%

of tumors, HER2 positivity reaches 40.0%, Ki-67 elevation (≥14%) occurs in 97.1%, and triple-negative subtype accounts for 17.2%. Tables 1 and 2 summarize reproductive and clinicopathological characteristics.

Table 1. Reproductive Characteristics of Premenopausal Breast Cancer Patients (n = 35)

| Variable | Result |
|---|---|
| Age (years) | 43.66 ± 3.52 |
| Education | |
| - High school or below | 31 (88.6%) |
| - College | 4 (11.4%) |
| Menstrual cycle | |
| - Regular | 34 (97.1%) |
| - Irregular | 1 (2.9%) |
| Cycle length (days) | |
| - < 20 | 17 (48.6%) |
| - 21–30 | 18 (51.4%) |
| Body Mass Index (kg/m²) | 26.83 ± 2.31 |
| Age at first childbirth (years) | |
| - < 20 | 7 (20.0%) |
| - 20–25 | 17 (48.6%) |
| - 26–30 | 2 (5.7%) |
| - > 30 | 4 (11.4%) |
| Breastfeeding history | |
| - Yes | 32 (91.4%) |
| - No | 3 (8.6%) |
| Duration of breastfeeding (years) | |
| - < 1 | 5 (14.3%) |
| - 1–2 | 24 (68.6%) |
| - > 2 | 3 (8.6%) |
| Number of children | |
| - None | 5 (14.3%) |
| - 1–2 | 10 (28.6%) |
| - 3–4 | 14 (40.0%) |
| - > 4 | 6 (17.1%) |

Table 2. Clinicopathological Features of Premenopausal Breast Cancer Patients (n = 35)

| Variable | Category | Result (n, %) |
|---|---|---|
| Clinical stage | IIA | 10 (28.6%) |
| | IIB | 2 (5.7%) |
| | IIIA | 15 (42.9%) |
| | IIIB | 5 (14.3%) |
| | IV | 1 (2.9%) |
| Histological type | Invasive ductal carcinoma | 35 (100%) |
| Grade | I–II | 9 (25.7%) |
| | III | 26 (74.3%) |
| ER status | Positive | 15 (42.9%) |
| | Negative | 20 (57.1%) |
| PR status | Positive | 15 (42.9%) |
| | Negative | 20 (57.1%) |
| HER2 status | Positive | 14 (40.0%) |
| | Negative | 21 (60.0%) |
| Ki-67 index | ≥ 14% | 34 (97.1%) |
| | < 14% | 1 (2.9%) |
| TNBC | Present | 6 (17.1%) |
| | Absent | 29 (82.9%) |
| Molecular subtype | Luminal B | 19 (54.3%) |
| | HER2-enriched | 10 (28.6%) |
| | TNBC | 6 (17.1%) |

This research identifies a marked elevation in serum prolactin among PBC patients compared with controls. Mean prolactin concentration reaches 51.96 ± 80.40 ng/mL in the PBC group and 20.83 ± 15.74 ng/mL in controls, showing a statistically significant difference ($p = 0.031$). The data indicate endocrine activation associated with malignant transformation (Table 3).

Table 3. Comparison of Serum Prolactin Levels Between PBC Patients and Controls

| Group | Mean (ng/mL) | SD | p-value |
|---|---|---|---|
| PBC patients | 51.96 | 80.40 | 0.031* |
| Controls | 20.83 | 15.74 | |

This research demonstrates positive prolactin receptor (PRLR) expression in more than 90% of PBC samples. The semiquantitative scoring system categorizes expression as 0 (none), +1 (<10%), +2 (10–50%), and +3 (>50%). Scores of 0 and +1 classify as negative. Figure 1 presents representative staining showing strong positive and absent PRLR immunoreactivity.

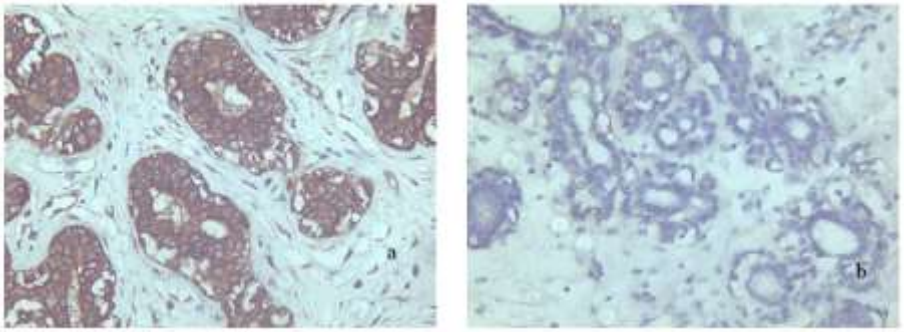


Figure 1. Representative immunohistochemical staining of PRLR in breast tissue: (a) strong positive expression (+3); (b) absent expression (0).

This research identifies a direct correlation between serum prolactin concentration and cancer progression. Higher prolactin levels associate with advanced disease stage ($p$ = 0.035), invasive histology ($p$ = 0.043), and elevated Ki-67 index ($p$ = 0.016). No significant correlation appears between prolactin concentration and ER, PR, or HER2 expression (Table 4).

Table 4. Correlation Between Serum Prolactin Levels and Clinicopathological Variables in PBC Patients

| Variable | Category | Mean Prolactin (ng/mL) | p-value |
|---|---|---|---|
| Pathology | Normal/benign | 20.83 | 0.043* |
| | Invasive | 51.96 | |
| Histological type | IDC | 23.23 | 0.003* |
| | ILC | 14.98 | |
| | Papillary | 29.73 | |
| Molecular subtype | Luminal B | 46.23 | 0.393 |
| | HER2+ | 21.92 | |
| | TNBC | 61.69 | |
| Grade | I–II | 29.68 | 0.126 |
| | III | 59.68 | |
| Stage | I–II | 100.57 | 0.035* |
| | III–IV | 23.24 | |
| ER status | Positive | 44.01 | 0.620 |
| | Negative | 57.93 | |
| PR status | Positive | 31.75 | 0.154 |
| | Negative | 67.12 | |
| HER2 status | Positive | 42.59 | 0.581 |
| | Negative | 58.21 | |
| Ki-67 index | < 14% | 239.60 | 0.016* |
| | ≥ 14% | 46.44 | |

**Discussion**

This research shows a significant increase in serum prolactin levels among premenopausal breast cancer (PBC) patients compared with healthy controls. Elevated circulating prolactin reflects enhanced endocrine activity associated with tumor aggressiveness. Similar findings reported by Hathaway et al. (2023) demonstrate that higher plasma prolactin levels correlate with increased breast cancer risk and unfavorable prognostic features. Prolactin receptor (PRLR) expression further strengthens this relationship, with evidence indicating that tumors expressing PRLR exhibit more aggressive biological behavior (Hathaway et al., 2023; Schuler & O'Leary, 2022).

This research shows PRLR expression in more than 90% of PBC tissues, supporting an autocrine–paracrine model of prolactin signaling in breast carcinogenesis. Autocrine prolactin activates the JAK2–STAT5 signaling cascade, which enhances tumor cell proliferation, invasion, and survival (Schuler & O'Leary, 2022). Studies by Harvey et al. (2015), Gorvin (2015), and Perks et al. (2004) confirm that prolactin–PRLR interaction promotes oncogenic signaling that contributes to tumor progression. This mechanistic association aligns with the current findings, where serum prolactin levels increase proportionally with cancer stage, indicating that prolactin activity intensifies alongside disease advancement.

This research also highlights the evolving concept of prolactin as an oncogenic factor beyond its physiological role in lactation. Multiple investigations support its mitogenic and antiapoptotic effects on breast cancer cells (Altriche et al., 2024; Clevenger & Rui, 2022; Grible et al., 2021; Bermejo-Haro et al., 2023). Meta-analysis by Wang et al. (2016) further demonstrates that prolactin synergizes with estrogen-related pathways, enhancing tumor proliferation and survival. These findings underscore the complexity of prolactin-driven oncogenesis and emphasize its relevance as a potential molecular target for therapy (Schuler & O'Leary, 2022).

This research suggests that prolactin may serve as a clinically valuable biomarker for risk prediction and disease monitoring in breast cancer. The strong association between serum prolactin and tumor stage supports its potential integration into prognostic models. Combining prolactin measurements with molecular markers such as HER2, Ki-67, and hormone receptor profiles could refine early detection and improve risk stratification in PBC patients (Hathaway et al., 2023; Perks et al., 2004).

This research acknowledges several limitations. The cross-sectional design restricts causal interpretation between prolactin elevation and tumor progression. Future longitudinal studies should clarify whether hyperprolactinemia precedes malignant transformation or results from tumor progression. Further molecular analysis is required to identify downstream targets of prolactin signaling that mediate tumor heterogeneity and therapeutic resistance. Experimental data suggest that inhibiting PRLR signaling suppresses tumor growth in hormone receptor–positive subtypes, offering potential for prolactin-targeted therapy (Schuler & O'Leary, 2022). Validation of the prolactin–PRLR axis through clinical trials could establish a novel therapeutic framework for premenopausal breast cancer patients with high PRLR expression and elevated serum prolactin levels.

## Conclusion

This research demonstrates a significant association between serum prolactin concentration, prolactin receptor (PRLR) expression, and tumor stage in premenopausal breast cancer. The findings indicate that prolactin functions as both a biomarker of disease progression and a potential therapeutic target in this population. Validation through longitudinal, molecular, and interventional studies remains necessary to establish the prognostic and therapeutic relevance of the prolactin–PRLR axis. Further investigation should elucidate the interactions between prolactin signaling, estrogen activity, and other oncogenic pathways to advance the understanding of prolactin-driven breast carcinogenesis and guide future precision-based therapeutic strategies.

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