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Indian Journal of Pathology and Oncology

Journal homepage: www.ijpo.co.in

Original Research Article

Association of serum prolactin levels with benign and malignant breast conditions and its utility as a predictor of breast cancer

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Abstract

Background: The global burden of breast cancer is increasing, and it has become the most common malignancy in the female sex worldwide with increasing incidence of young onset breast cancer. Cheap and effective screening modalities are needed to reduce the mortality and morbidity associated with the disease and its treatment. Prolactin's role in breast oncogenesis and tumor progression has been established. Further studies are required to determine the association of prolactin levels with both benign and malignant breast conditions and if prolactin levels change on treating those conditions.
Materials and Methods: Recent literature was reviewed to formulate the method of the study. Serum prolactin levels were sent at the time of diagnosing benign and malignant breast diseases, and after one month of surgery or starting conservative treatment. Statistical tests were applied to determine the cut off value to discriminate benign and malignant breast diseases and whether the associations of serum prolactin levels with benign and malignant diseases were significant.
Results: The receiver operating characteristics curve analysis yielded a serum prolactin level cut-off value of 15.78 ng/mL at the time of diagnosis. Around 85.83% of the patients with benign breast diseases had serum prolactin levels lower than 15.78 ng/mL and around 85.77% of the patients with malignant breast diseases had serum prolactin levels greater than 15.78 ng/mL. The mean prolactin levels decreased significantly one month post treatment.
Conclusion: The rationale of using serum prolactin levels as a screening tool for breast cancer, discriminator between benign and malignant breast diseases and a monitoring tool to check the response of management have been discussed.

Keywords: Benign breast diseases, Breast cancer, Prolactin, Screening, Tumor marker, Young onset breast cancer.

Received: 20-08-2025; **Accepted:** 14-10-2025; **Available Online**: 17-10-2025

1. Introduction

The world is seeing a rise in breast diseases, both benign and malignant. Worldwide, breast cancer is the most common cancer affecting women, and its incidence and mortality rates are expected to increase significantly over the next years.[1,2] Survival has increased over the past few decades, with the introduction of improved screening mammography and treatments. However, progress has not been seen equally among all ethnicities/races or with all breast cancer subtypes (e.g. triple negative). In 2020, approximately 2.3 million new breast cancer cases were diagnosed and over 685,000 deaths due to breast cancer were recorded.[3] Even during and after the treatment of breast cancer there is significant morbidity in the form of lymphedema, seroma, stiffness, alopecia and other chemotherapy and radiotherapy related side effects. Even benign breast diseases which affect nearly half of biological females, adds to substantial anxiety and healthcare use among these patients due to the apprehension of having a malignant disease. Even after existing screening algorithms,

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https://doi.org/10.18231/j.ijpo.12959.1760415900

most individuals with breast cancer at the time of diagnosis present with symptoms of a palpable breast lump which eventually warrant a more invasive and aggressive treatment approach as compared to if it was diagnosed earlier. Young onset breast cancer (onset at less than 40 years of age) is increasing globally as screening protocols in non-high-risk individuals start at 40 years of age. Therefore, there is a dire need of a cheap and non-invasive screening modality which can be started at a younger age than the existing screening age group which labels individuals of a population of being at a greater risk of developing breast cancer so that they can be vigorously and thoroughly worked up for it and be diagnosed way before the patient has any palpable lump. This would enable clinicians to offer less invasive and less aggressive treatment modalities with minimal morbidity to the patients which would ultimately improve disease adjusted life years, quality adjusted life years and survival. Such a modality could also be a significant step towards cancer prevention.

Prolactin is a hormone produced by specialized cells called lactotrophs in the anterior part of the pituitary gland which is regulated by the hypothalamus. It plays various roles in the body including milk synthesis, mammary gland development and regulation of sex hormones. The production of prolactin in the anterior pituitary is affected by factors like dopamine, estrogen, thyrotropin releasing hormone and certain drugs which affect the pathways of these hormones and the hypothalamic pituitary axis. Apart from other functions of prolactin in the body, it's role in breast oncogenesis and tumor progression has been established.[4] The mammary epithelium that breast cancer arises from is a hormone regulated epithelium. Hyper estrogenic conditions are well known risk factors of breast cancer. Estrogen counteracts the inhibitory effect of dopamine on prolactin and therefore increases prolactin levels. It has also been noted that in breast cancer patients with increased prolactin levels, there is an increased risk of metastatic progression. In vivo studies have revealed that transgenic mice overexpressing prolactin develop estrogen receptor positive or estrogen receptor negative mammary carcinomas within the first 12 to 18 months of life.[4] The study aims at identifying a cut-off value of serum prolactin levels to differentiate between benign and malignant breast conditions and establishing the association of prolactin levels with both benign and malignant breast conditions and if prolactin levels change on treating those conditions.

2. Materials and Methods

The study was a prospective observational study conducted in the Department of General Surgery, Department of Radiation Oncology and Department of Pathology, Lala Lajpat Rai & Associated Hospitals, Ganesh Shankar Vidyarthi Memorial Medical College, Kanpur, Uttar Pradesh, India from April 2024 to March 2025. The study was conducted after the approval of the Ethical Committee of Ganesh Shankar Vidyarthi Memorial Medical College, Kanpur, Uttar Pradesh, India on the first of April 2024 (Approval number- EC/152/April/2024). Patients from Kanpur and cities around Kanpur were recruited from the Outpatient Department (OPD) and Inpatient Department (IPD) of Department of General Surgery and Department of Radiation Oncology at Lala Lajpat Rai & Associated Hospitals, Ganesh Shankar Vidyarthi Memorial Medical College, Kanpur, Uttar Pradesh, India, from April 2024 to March 2025. Each patient who met the inclusion criteria was given a random number. Patients were listed in order based on these random numbers. Patients who met any exclusion criteria were excluded from the study. 550 patients were then randomly selected from this list. 43 patients who lost to follow up and dropouts were removed from this list along with 7 other random eligible patients to reach the desired sample size of 500. Written informed consent was obtained from each participant. The clinical details of the patients were recorded according to the working proforma of this study. In this study, 500 participants of biologically female sex were taken among which 247 had benign breast diseases and 253 had malignant breast diseases. At the time of diagnosis, serum prolactin levels were sent by pooling three fasting venous blood samples 20 minutes apart on the morning of the second day of the menstrual cycle of reproductive patients and any nonspecific day for postmenopausal patients. Serum prolactin levels were measured using the chemiluminescence immunoassay method at the Department of Pathology, Lala Lajpat Rai & Associated Hospitals, Ganesh Shankar Vidyarthi Memorial Medical College, Kanpur, Uttar Pradesh, India. After this, the specific management for each patient was started. For the diagnoses which warranted no surgical treatment, serum prolactin levels were again sent using the same method after one month of starting the conservative treatment. For the diagnoses which were eventually managed surgically, serum prolactin levels were sent using the same method after one month of the day of surgery.

2.1. Inclusion criteria

Patients of biologically female sex with confirmed benign and malignant breast diseases. Patients giving timed samples. Premenopausal patients (considered pre-menopausal if their menses had not ceased, or they have had a hysterectomy with at least 1 ovary remaining). Postmenopausal patients (considered postmenopausal if their natural menses had ceased permanently, or they have had a bilateral oophorectomy).

2.2. Exclusion criteria

Patients not willing to provide consent for the study. Pregnant or lactating patients. Patients with pituitary adenomas. Patients with polycystic ovarian syndrome, metabolic syndrome or any other chronic disease. Patients on antiepileptics, antidepressants like tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), antipsychotics, antihypertensives like methyldopa, reserpine,

verapamil and others like metoclopramide, opioids, H2-antihistamines, hormonal drugs and oral contraceptives.

Data was entered into Microsoft Excel and analyzed using SPSS Version 26.0. Categorical variables were expressed as proportions while continuous variables were expressed as means and standard deviation, if normal or as median and interquartile range if not normal. Chi-square test was used to assess statistically significant difference between two or more groups for variables which were categorical in nature. Comparison of normally distributed continuous variables between two groups was done using independent t-test while comparison of non-normally distributed continuous variables between two groups was done using Mann-Whitney test. Comparison of normally distributed continuous variables across single time interval was done using paired t-test. A receiver operating characteristics curve was used to assess the diagnostic validity of serum prolactin in identification of malignancy. *P*-value of less than 0.05 was considered statistically significant. The 'Standards for Reporting Diagnostic accuracy studies' guidelines were followed by the investigators. The primary outcome measure was the association of serum prolactin levels with breast cancer and the secondary outcome measure was the cut-off value obtained to differentiate between benign and malignant breast conditions,

3. Results

The mean age of the 500 patients taken in this study was 39.61 with a standard deviation of 10.81. The age range of the patients was 18 years to 75 years. Among these, 247 patients had benign breast diseases and 253 had malignant breast diseases. The normal value of serum prolactin was considered less than 25 nanograms per milliliter (ng/mL).

Table 1: Serum prolactin levels at the time of diagnosis and one-month post-treatment of benign and malignant breast diseases

Mean Prolactin ± SD	At diagnosis (ng/mL)	One-month post-treatment (ng/mL)	*p*-value
Benign (*N*=247)	11.72 ± 6.78	11.28 ± 4.95	<0.001
Malignant *(N*=253*)*	20.86 ± 5.94	17.52 ± 4.69	<0.001

SD: Standard deviation; ng/mL: Nanograms per milliliter; *N:* Number of patients; *p*-value: Probability value Independent t-test used, test values: -16.037 and -12.678 respectively

Table 2: Comparison of mean prolactin levels at the time of diagnosis to after one month of treatment according to the age of the patient

	Age group (years)	Mean Prolactin ± SD (ng/mL)		Test value; p-value
		At diagnosis	One month post-treatment	
Benign lesion (*N*=247)	<20	29.6 ± 25.06	18 ± 8.27	1.743; 0.142
	21 – 30	11.28 ± 4.46	11.08 ± 5.17	2.665; 0.009
	31 – 40	10.85 ± 3.81	11.14 ± 3.98	3.221; 0.002
	41 – 50	9.18 ± 4.43	7.87 ± 0.76	1.033; 0.378
	51 – 60	15.26 ± 4.33	8.79 ± 0	-
Malignant lesion (*N*=253)	21 – 30	22.17 ± 2.46	18.45 ± 2.58	3.851; 0.018
	31 – 40	21.87 ± 4.45	18.55 ± 3.84	6.859; <0.001
	41 – 50	20.39 ± 5.03	17.85 ± 4.84	7.295; <0.001
	51 – 60	20.2 ± 6.55	16.46 ± 4.94	8.009; <0.001
	>60	25.15 ± 12.77	15.92 ± 4.1	2.883; 0.016

SD: Standard deviation; ng/mL: Nanograms per milliliter; *N:* Number of patients; *p*-value: Probability value; no malignant cases in <20 years age group; no benign cases in >60 years age group Paired t-test used.

Table 3: Characteristics of receiver operating curve at the time of diagnosis

Characteristic of ROC curve	Value at the time of diagnosis
Area under the curve	87.7%
Ideal cut-off value	15.78 ng/mL
Sensitivity	85.7%
Specificity	83.6%

ROC (Receiver Operating Characteristics): To assess the validity of serum prolactin in the identification of benign and malignant breast diseases; ng/mL: Nanograms per milliliter

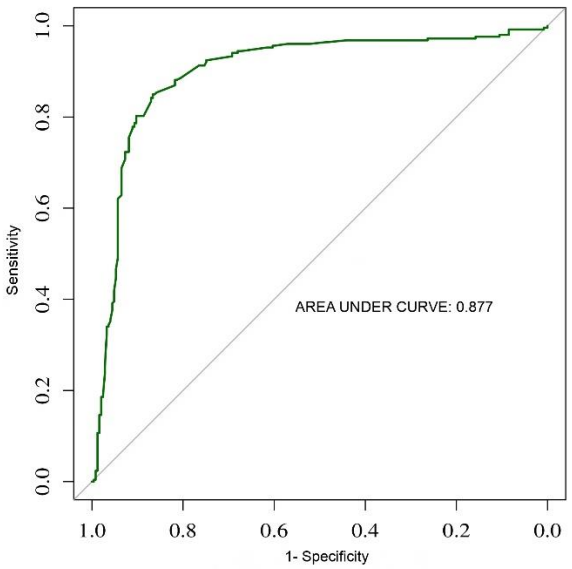

Figure 1: Receiver operating curve at the time of diagnosis

Table 4: Number of patients with benign breast diseases below the cut-off value and patients with malignant breast diseases above the cut-off value at the time of diagnosis

	Prolactin level	**Benign (*N*=247)**	**Malignant *(N=253)***	***Test value; p*-value**
At the time of diagnosis	< 15.78 ng/mL	212 (85.83%)	37 (14.62%)	256.35; <0.001
	> 15.78 ng/mL	34 (13.76%)	217 (85.77%)	

ng/mL: Nanograms per milliliter; *N:* Number of patients; *p*-value: Probability value
Chi-square test used.

Prolactin levels above 15.78 ng/mL were positively associated with breast cancer with an odds ratio of around 36 and negatively associated with benign breast diseases.

4. Discussion

The study showed that while only few patients with benign and malignant breast diseases had serum prolactin levels higher than the upper limit of the normal prolactin levels in non-pregnant and non-lactating adult patients of biologically female sex (25 ng/mL), a majority of patients with malignant breast diseases had serum prolactin levels of more than the cut-off value in the normal prolactin range (**Table 4**), which is zero to 25 ng/mL. While measuring prolactin, to avoid false high or low values serum prolactin levels were measured in pooled samples and not just a single sample which could give a false value owing to the pulsatile nature of pituitary hormones and various physiological or psychological factors. Two to three samples collected at an interval of 15 to 20 minutes minimizes the effect of its pulsatile nature.[5,6] On calculating the cut-off value of serum prolactin to differentiate between benign and malignant breast conditions analyzing the receiver operating characteristics curve, a value of 15.78 ng/mL was found (**Table 3**, **Figure 1**). Using this rationale of the study, serum prolactin levels which are quick, cheap, safe and readily available can be considered a predictor of breast cancer and added in the screening protocol of breast cancer even in individuals less than 40 years of age. Studies show that even after existing screening strategies, around 83% of breast cancer patients present with a palpable lump,[7] which calls for more aggressive treatment protocols as compared to when a palpable lump has not yet developed. The population in which serum prolactin level is found to be more than 15.78 ng/mL should be vigorously worked up towards breast cancer which can lead to early diagnosis even before there is a clinically palpable lump or any other symptom, which will ultimately lead to less morbid management and less complications related to various lines of management. This cut off value of 15.78 ng/mL can also be used to support other diagnostic modalities as an additional discriminator between benign and malignant breast conditions where there is diagnostic dilemma even after imaging and histopathological examination. The study also showed that after one month of surgery in malignant cases, the mean serum prolactin level significantly reduced. In benign breast conditions, the mean serum prolactin level showed a decrease after one month of starting conservative treatment or after one month of surgery, but the decrease was not as remarkable as in malignant cases (**Table 1**). This suggests that serum prolactin levels can be an easy and cheap indicator of response to therapy in malignant breast conditions. In the age group of 31 to 40 years for benign breast conditions, there was a slight increase in prolactin values from the time of diagnosis to one-month post-treatment (**Table 2**). The findings of this study are in congruence with previous studies showing prolactin as a risk predictor of breast cancer[8,9] with some studies also establishing it as a prognostic marker.[10,11] Hypoestrogenic

conditions are well known risk factor of breast cancer as estrogen induces the progesterone receptor and augments progesterone signaling.[12] Estrogen, in turn, stimulates pituitary prolactin production and secretion through its inhibition of hypothalamic dopaminergic suppression,[13] which further strengthens the association of prolactin levels with breast cancer. Moreover, a previous study demonstrated that prolactin protects human breast cancer cell lines against apoptosis, and this may have important implications for cancer treatment.[14] Although the current study excludes patients on antipsychotics, in the largest study of antipsychotics taken by women of the United States, a higher risk between antipsychotic drug use and increased risk for breast cancer was observed, with a differential higher association with antipsychotic categories that elevate prolactin.[15] Contrastingly, some studies suggest a dual role prolactin, proposing that prolactin may participate in breast tumor initiation, whereas in established breast cancer, it may contribute to reduce aggressiveness and dissemination.[16]

5. Conclusion

The integration of serum prolactin testing into routine breast cancer screening protocols presents promising clinical advantages, particularly for the early detection of young-onset breast cancer. Compared to conventional imaging, prolactin testing is safer, more affordable, and thus well-suited for resource-limited settings. It can serve as a valuable adjunct to mammography and ultrasound, especially when imaging results are inconclusive. Elevated prolactin levels in high-risk individuals could prompt closer surveillance and timely intervention, potentially improving clinical outcomes. Furthermore, understanding prolactin's role in tumor biology may open avenues for developing targeted therapies that inhibit the prolactin signaling pathway.

Despite these findings, certain limitations of the study must be acknowledged. The study was confined to a single institution, potentially limiting its generalizability. Additionally, the short one-month follow-up period may not reflect long-term trends in prolactin levels post-treatment. Future research should involve larger, multi-center cohorts and diverse populations to validate prolactin's diagnostic and prognostic utility. Longitudinal studies are also necessary to assess its role in disease progression and recurrence. Investigating prolactin's interaction with other hormonal and genetic markers could further elucidate its role in breast cancer pathogenesis.

In conclusion, breast diseases continue to impose a significant global health burden, with early detection remaining pivotal to improving outcomes. While imaging modalities remain effective, there is a pressing need for accessible and cost-effective biomarkers. This study underscores the potential of serum prolactin as a reliable screening marker, given its high sensitivity and specificity in distinguishing benign from malignant lesions. To translate these findings into clinical practice, standardized cut-off values must be established, and awareness regarding its utility should be raised. Incorporating prolactin testing into routine screening could enhance early diagnosis, particularly in underserved areas, thereby contributing to reduced morbidity and mortality from breast cancer.

6. Source of Funding

None.

7. Conflict of Interest

None.

8. Acknowledgement

The participants who gave consent for this study along with their families are acknowledged.

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Cite this article: Vatsal P, Chaudhary AK, Katiar V, Khan L, Verma JK, Verma YN, Shukla P. Association of serum prolactin levels with benign and malignant breast conditions and its utility as a predictor of breast cancer. *Indian J Pathol Oncol*. 2025;12(3):247–252.