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ESTIMATION OF FREE PROSTATE SPECIFIC ANTIGEN (fPSA) AS A TUMOUR MARKER IN FEMALE BREAST CANCER

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ABSTRACT Breast cancer remains the most frequently diagnosed malignancy among women worldwide and a leading cause of cancer-related mortality. PSA (Prostate specific antigen) is a 33 kDa serine protease expressed at a high level in the epithelium of the human prostate gland. 'free PSA' is that form of PSA that is not bound to an inhibitor. Serum fPSA level is measured in Histologically and clinically proved female breast cancer patients by immunoassay both pre surgically and post surgically and in control group. Free PSA decreased more dramatically after surgery, strongly indicating that this fraction is produced by breast cancer. PSA can be used as a prognostic indicator of breast cancer and as an indicator of completion of surgery.

KEYWORDS : Breast cancer, tPSA , fPSA, VITROS 5600.

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer among women globally and continues to be a leading cause of cancer-related mortality. According to the World Health Organization (WHO), approximately 2.3 million women were diagnosed with breast cancer in 2022, resulting in an estimated 670,000 deaths worldwide. India ranks among the highest in breast cancer-related mortality, accounting for approximately 98,337 deaths in that year alone[1]. In response to this growing global health crisis, the WHO launched the Global Breast Cancer Initiative, which aims to reduce global breast cancer mortality by 2.5% annually through improved strategies for early detection, diagnosis, and treatment.

PSA circulates in two principal forms: total PSA (tPSA), which includes both free and protein-bound fractions, and free PSA (fPSA), the unbound form. Under normal physiological conditions in women, PSA predominantly exists in a bound state. However, studies have demonstrated that free PSA concentrations are higher in malignant breast tumors, whereas benign breast conditions exhibit a predominance of bound PSA [3]. This distinction has led researchers to propose that the free-to-total PSA ratio could serve as a useful indicator in differentiating between benign and malignant breast diseases. Furthermore, elevated PSA levels in breast cancer patients have been associated with increased tumor aggressiveness and disease progression [2,3], suggesting its potential utility as both a diagnostic and prognostic marker.

Urbanization, later age at marriage, age at first birth, reduced breastfeeding, westernization of diet, physical activity patterns, ageing, early menarche and late menopause, family history increases the risk of breast cancer. A history of atypical hyperplasia, lobular carcinoma in situ or ductal carcinoma in situ (as determined by a breast biopsy) increases the risk of developing invasive breast cancer.

Having mutations in BRCA1, a gene on chromosome 17 that controls cell growth or BRCA2, a gene on chromosome 13 that suppresses cell growth, are associated with increased risk of breast cancer.

PSA (Prostate specific antigen) is a 33kDa serine protease [4] expressed at high levels in the epithelium of the human prostate gland. However, studies have demonstrated that PSA can also be secreted in females, especially from prostate equivalent Skene's peri- urethral gland and tissue like breast and ovary (Papotti et al., 1989). PSA is found in normal and hyperplasic breast tissue and majority of breast tumors and breast cysts. Jungchan Nam, Minyoung yoo et al. in 2015 suggested that PSA is a biomarker for breast carcinoma [5]. 'free PSA' is that form of PSA that is not bound to an inhibitor which could comprise both enzymatically active PSA and the inactive 'nicked' form. Using immunoassay techniques, it is found that the predominant form of PSA in the sera of women without breast cancer is PSA bound to ACT (serine protease inhibitor alpha 1 anti-chymotrypsin), whereas free PSA constitutes the predominant molecular form in breast carcinoma. Free PSA decreases more dramatically after surgery, strongly indicating that this fraction is produced by breast tumors. It can be used as a prognostic indicator of breast cancer and as an indicator of completion of surgery and recurrence.

MATERIALS AND METHODS

Study Area: Gauhati Medical College & Hospital, Guwahati, India in the Departments of Biochemistry and State Cancer Institute GMCH.

Study Population: Histologically and clinically proved female breast carcinoma patients admitted for surgery. Study Period: one year

Study Design- Case control, non-interventional, hospital based observational study.

Sample Design: Samples were collected from the oncology and surgical ward after obtaining written consent.

Sample Size: Total of 168 participants are recruited which comprises as follows: 56 participants with benign breast lesion, 56 participants with malignant breast cancer and 56 normal healthy female participants.

Inclusion Criteria

1. Female breast cancer patients who have been newly diagnosed, both clinically and histologically proved by FNAC (Fine Needle Aspiration Cytology).
2. Female breast cancer patients in the age group of 18 years and above.
3. Patients who had not undergone any prior chemotherapy, radiotherapy, or surgical intervention for breast cancer.

Exclusion Criteria

1. Patients with a history of any malignancy other than breast cancer.
2. Patients undergoing hormone replacement therapy or taking hormonal medications that could influence PSA levels.
3. Pregnant or lactating women.
4. Patients with severe systemic illnesses, autoimmune disorders, or infectious diseases.
5. Patients who had received any prior cancer treatment, including surgery, chemotherapy or radiotherapy.

Selection Criteria For Controls:

1. Age-matched healthy female volunteers with no history of malignancy, benign breast disease, or chronic illness.
2. Normal findings in clinical breast examination and imaging.
3. No history of hormonal replacement therapy (HRT) or oral contraceptive use in the past six months.

SAMPLE COLLECTION AND TRANSPORTATION

Procedure

A tourniquet is applied just above the intended venipuncture site (preferably the ante-cubital vein). One clot vial is filled with 5 mL of venous blood that is drawn under stringent sterile and antimicrobial settings using a sterilized needle which can be disposed.

To avoid exposure to contaminants, every sample is gathered and

brought to the testing facility in sealed condition in one hour after being received. Cold boxes were utilized during transport to maintain a stable temperature, and the specimens were processed in accordance with established laboratory protocols.

After allowing the clot specimens to clot, they are spin in a centrifuge for three to five minutes at 3000 rpm. The serum is isolated and analyzed in the Central Clinical Laboratory's Biochemistry department. If the analysis has not been completed within 8 hours of blood collection, the serum vials are appropriately labeled and stored at –20°C.

However, in this study all estimations are completed within 24 hours of collection of blood samples.

ESTIMATION OF BIOCHEMICAL PARAMETERS:

Estimation of Serum fPSA and tPSA levels: The VITROS 5600 Integrated System is employed to quantitatively assess serum fPSA and tPSA levels.

STATISTICAL ANALYSIS

Data Processing and Analysis Tools

Data has been entered and analyzed using SPSS (Statistical Package for the Social Sciences) version 26.0. Continuous variables (e.g., PSA levels) are expressed as mean ± standard deviation (SD).

Statistical Tests Used

- Independent t-test or Mann-Whitney U test – Used to compare PSA levels between breast cancer patients and controls.
- Receiver Operating Characteristic (ROC) curve analysis – Used to assess PSA's diagnostic accuracy, sensitivity, and specificity. Association with p-value of < 0.001 were considered to be statistically significant.

RESULT ANALYSIS:

Table 1: fPSA In Presurgical And Postsurgical Patients Of Breast Cancer.

Group			N	Mean	Std. Deviation	P value
Benign	fPSA	Pre	56	0.660	0.121	**p < 0.001**
		Post	56	0.349	0.109	
Malignant	fPSA	Pre	56	0.768	0.092	**p < 0.001**
		Post	56	0.311	0.179	
Control	fPSA		56	0.062	0.073	

Table 1 shows that preoperative fPSA levels were highest in malignant cases (0.768 ng/ml) and compared to benign cases (0.660ng/ml) and mean fPSA in control group. Postoperative fPSA levels significantly decreased, indicating its potential as a prognostic marker. P- value is <0.001, shows highly statistical significance.

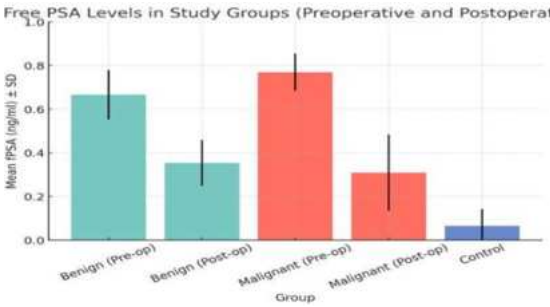

Fig 1: The mean values of fPSA in all cases in ng /mL

Table 2: Statistical Comparison Of fPSA Levels Between Study Groups

Comparison	t-value	p-value
Benign Pre vs Post	18.21	**P < 0.001**
Malignant Pre vs Post	23.94	**P < 0.001**
Benign vs Malignant (Pre-op)	5.99	**P < 0.001**
Benign vs Malignant (Post-op)	0.976	0.327
Benign Pre vs Control	36.91	**P < 0.001**
Benign Post vs Control	18.23	**P < 0.001**
Malignant Pre vs Control	47.77	**P < 0.001**
Malignant Post vs Control	11.62	**P < 0.001**

Table 2 presents the statistical comparison of free PSA (fPSA) levels. Highly significant differences (p < 0.001) were observed between preoperative benign and malignant cases, as well as between both groups and controls. Postoperative fPSA levels in benign and malignant cases showed no significant difference, suggesting a comparable reduction post-treatment.

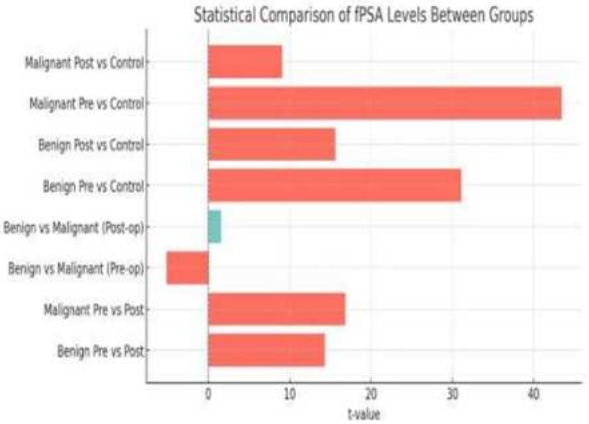

Fig 2 - Statistical Comparison Of Free PSA (fPSA) Levels Between Different Study Groups.

The horizontal bar graph represents t-values for each comparison, with highly significant differences (p < 0.001) highlighted in red. A dashed vertical line at t = 0 serves as a reference point. The green bars represent comparisons where the p- value is not statistically significant (p > 0.001), while the red bars indicate statistically high significant differences (p < 0.001).

Table 3: ROC Analysis For PSA As A Diagnostic Marker

Marker	AUC	Sensitivity (%)	Specificity (%)	Cutoff Value (ng/ml)
Total PSA	0.868	78.6%	75.9%	0.825
Free PSA	0.892	83.9%	75.9%	0.685
fPSA/tPSA Ratio	0.873	79.2%	76.7%	0.830

Table 3 shows that free PSA had the highest diagnostic accuracy (AUC = 0.892), followed by total PSA (AUC = 0.868). The fPSA/tPSA ratio also had high sensitivity (79.2%) and specificity (76.7%), making it a strong candidate for distinguishing between benign and malignant cases.

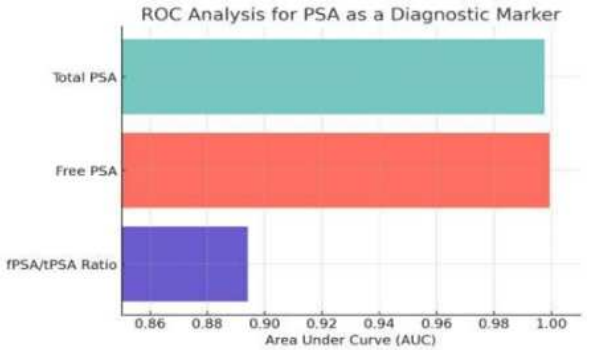

Fig 3 - ROC analysis for PSA as a diagnostic marker.

Fig 3 The horizontal bar graph illustrates the Area Under Curve (AUC) values for total PSA, free PSA, and the fPSA/tPSA ratio. Free PSA exhibited the highest diagnostic accuracy (AUC = 0.892), followed by total PSA (AUC = 0.868). The fPSA/tPSA ratio also demonstrated high sensitivity and specificity, indicating its potential as a strong diagnostic marker for distinguishing between benign and malignant case.

DISCUSSION

The purpose of this study was to measure the serum free PSA (fPSA) level in 168 breast cancer patients presurgically and postsurgical. In the present study age of the subjects were between 18- 65 years in both study and control group.

The measurement of PSA levels in our study revealed significant differences between malignant, benign, and control groups, supporting its potential as a diagnostic and prognostic biomarker in breast cancer. Preoperatively, free PSA (fPSA) levels were highest in malignant

cases (0.768 ng/mL) and lowest in controls (0.062 ng/mL, respectively). This significant elevation in PSA levels in breast cancer patients compared to controls suggests that PSA expression is linked to tumor presence and hormonal influences.

Our findings align with previous studies, including Black et al. (2000)[3] and Romppanen et al. (2000)[6], who reported that breast cancer patients exhibit significantly higher PSA levels than healthy individuals. The presence of PSA in female breast tissue, originally thought to be exclusive to prostate tissue, has been attributed to hormonal regulation by estrogen and progesterone (Yu et al., 1997).[7]. Studies have shown that PSA levels tend to be higher in estrogen receptor-positive (ER+) breast cancers, suggesting that hormone-responsive tumors may have increased PSA expression (Diamandis et al., 1997).[8]

A particularly significant finding in our study was the postoperative decline in PSA levels across both malignant and benign cases. After surgical intervention, fPSA levels in malignant cases decreased from 0.768 ng/mL to 0.311 ng/mL. This dramatic reduction in PSA levels post-surgery reinforces the hypothesis that PSA levels correlate with tumor burden. A similar trend was observed in benign cases, fPSA levels also declined significantly following surgery. This decline is in agreement with findings from Yu et al. (1997)[9], who suggested that serum PSA levels decrease after tumor resection, confirming its potential role in monitoring treatment response. The fact that both benign and malignant cases showed a significant postoperative reduction of fPSA level further suggests that PSA may be a marker of breast tissue proliferation and hormonal activity, rather than being exclusive to malignant transformation.

CONCLUSION

This study offers significant insights into the potential of PSA, specifically free PSA (fPSA) and the fPSA/tPSA ratio, as a non-invasive biomarker for both the detection and prognosis of breast cancer. The marked differences in PSA levels between malignant, benign, and control groups, alongside the observed decrease in PSA levels following treatment, point to its potential clinical applications. The ROC curve analysis further validates PSA as a reliable diagnostic and prognostic marker, demonstrating strong sensitivity and specificity. Moreover, its relationship with tumor burden and menstrual status highlights the importance of PSA in tailoring personalized cancer care.

One limitation of this research is the relatively small sample size, which limits the ability to draw definitive conclusions. Therefore, additional studies with larger cohorts and more advanced detection technologies—capable of identifying even trace amounts of PSA—are necessary. It would also be valuable to examine PSA alongside other well-established tumor markers and hormonal factors. Such advancements could pave the way for the development of straightforward biochemical assays for the diagnosis and monitoring of breast diseases, including breast cancer.

Future research should focus on large-scale validation studies, exploring the integration of PSA with existing biomarkers, as well as conducting longitudinal assessments to determine PSA's ability to predict disease progression and recurrence. If proven effective, PSA could offer a cost-efficient alternative to more invasive diagnostic procedures, becoming a key tool in breast cancer screening and management.

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