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Evaluation of Serum Prostate Specific Antigen as a Biomarker for Breast Carcinoma

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ABSTRACT

Objective: Prostate-specific antigen (PSA) is a very important tumor marker for prostate cancer. The PSA was thought to be produced exclusively by the epithelial cells of the prostate gland, but a large body of evidence suggests that PSA is not a prostate-specific molecule and has been shown to be present in many forms of female tissues. The aim of the study is to evaluate serum PSA levels as a biomarker for breast carcinoma.
Methods: This was a prospective study where patients presenting with breast lump with a trucut/FNAC report suggestive of benign or malignant lesion were taken as the case group and all patients undergoing an ultrasound to rule out any ovarian/endometrial pathology were taken as the control group at Justice K S Hegde Charitable Hospital, Mangalore. A total of 150 patients, were taken for this study. Blood sample was taken from the subject and PSA testing was performed using immunoassay methods.
Results: The average PSA value from each group was calculated and an increase in the average serum PSA was noted among the malignant subjects. The Kruskal value analysis was performed and a p-value of 0.046 was obtained, showing that there is a difference in median PSA levels among the groups. Multiple comparison of PSA by using Mann Whitney U test showed that there was a difference in median prostate specific antigen level between the groups ($p < 0.05$). The group 3 (malignant subjects) showed increased serum PSA levels as compared to the normal and benign subjects.
Conclusion: The current study demonstrated increased serum PSA levels among the malignant cases as compared to the benign cases and control group. Therefore, serum PSA level may serve in differentiating benign and malignant breast carcinoma.
Key words: Tumor, prostate specific antigen, breast, benign lesion, malignant

INTRODUCTION

Breast cancer accounts for about one-third of cancer cases in women and more than 10% of all cancers worldwide (1). Breast cancer remains one of the most important causes of mortality among women worldwide, and in recent years, its prevalence among the younger population has also started to escalate. In the year 2018, over 2 million new cases were recorded (1). Furthermore, the identification of risk factors and comorbidities affecting breast cancer incidence or progression has become an area of intense research. In the present scenario,

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it has led us to an intense search for many new methods for diagnosis of breast malignancy at an early stage and provide them with the necessary treatment at the earliest. Studies have also identified potential biomarkers in human serum for early cancer detection and evaluation of drug efficacy (1). In cancer screening, blood-based markers play a major role in general population risk assessment to treatment response evaluation and recurrence monitoring (1).

Human blood components referred to as the window for the homeostasis of individual's health with their rich content of diverse cellular and molecular elements in blood, However, despite a large number of studies related to biomarkers for common cancers, blood based diagnostic tests that inform about the presence of cancer at an early stage and predict treatment response have been difficult to develop (2).

Serum PSA has also been used to monitor the progression of the disease during the course of the treatment. Prostate-specific antigen (PSA) which is also known as the gamma- seminoprotein (3).

In women, PSA is found in the female ejaculate at concentrations roughly equal to the male semen (4). Other than semen in men and female ejaculate, the highest concentrations of PSA in biological fluids are found to be detected in breast milk and amniotic fluid (5-7). Low concentrations of PSA are found to have been identified in the urethral glands, endometrium, normal breast tissue and salivary gland tissue as well (5-7). PSA can also be found in the serum of women with breast, lung, or uterine cancer and in some patients with renal cancer (6). Our study comes along on these lines where the estimation of serum PSA among the females was to be undertaken and if the serum PSA shows an elevation this could be considered as one of the early indicators of breast carcinoma and such women would be subjected to further workup for breast malignancy. Therefore, the present study mainly aims to assess serum PSA as a prognostic indicator for early detection of breast carcinoma.

METHODS

A total of 150 female patients were recruited for the study after signing the informed consent. Among them 50 served as control group, 50 as benign group and 50 as malignant group as per the inclusion and exclusion criteria. Women above the age of 18 years diagnosed with a benign or malignant breast disease on FNAC or Tru-cut biopsy were included in the control group. Women above the age of 18 years without any breast disease and women who have undergone an ultrasound to rule out any ovarian or endometrial pathology were included in the control group. Any women less than the age of 18 years, any women diagnosed with benign or malignant breast disase who have undergone treatment for the breast disease, all women currently on or has a h/o taking OCP in the last 3 months, women with any ovarian or endometrial pathology, antiandrogen treatments with spironolactone, flutamide, or finasteride. and all women in the lactating period. Data was tabulated and analyzed with SPSS 15.0 for Windows (SPSS Inc. Chicago. IL, USA). Kruskal wallis test was applied for the study followed by Mann Whiteney U test. P-value <0.05 was considered statistically significant.

RESULTS

The study included 150 female patients under the age group of 25-70 years. The subjects where further divided into different age groups as shown in *table 1*. The blood samples were assessed for serum PSA levels, the average serum PSA in benign, malignant and control were 0.0031, 0.0040 and 0.0037 ng/mL respectively. An increase in the serum PSA of malignant cases as compared to the benign was seen. The malignant cases were further divided based on the histopathology and compared with serum PSA, which showed an increase in the PSA levels among the invasive carcinoma histopathological type as shown in *table 2*. Benign cases, were further subdivided based of the histopathology and compared serum PSA levels, which showed a slight increase among the fibrocystic subtype (*table 3*).

Table 1 - Percentage frequency of study population as per age

Age Group	Frequency	Percentage
<30	28	18.60%
31-40	30	20%
41-50	49	32.60%
51-60	20	13.33%
61-70	15	10%
>70	8	5.30%

Table 2 - Sub-classification of the malignant cases, with the comparison of serum PSA

Histopathological Type	Number	Percentage	Average serum PSA ng/mL
Invasive carcinoma	43/50	86%	0.036
Medullary	3/50	6%	0.002
Mucinous	1/50	2%	0.004
Undifferentiated	3/50	6%	0.002

Table 3 - Sub-classification of the benign group, with the comparison of serum PSA levels

Benign Proliferative Breast Disease	Number	Percentage	Average serum PSA
Fibroadenoma	13/50	26%	0.005
Fibrocystic disease	18/50	36%	0.005
Other inflammatory disease			
• Suppurative granulomatous mastitis\	16/50	32%	0.002
• Leukocytoclastic vasculitis	14/50		
• Fat necrosis	1/50		
Phyllodes tumour	3/50	6%	0.002

Table 4 - Comparison of prostate specific antigen levels by using Kruskal-Wallis test

	Median	IQR	P value
Normal cases	0.002	0.002-0.002	0.046
Benign cases	0.002	0.002-0.0022	
Malignant cases	0.002	0.002-0.02	

*p<0.05 was considered statistically significant

Comparison of Prostate specific antigen levels by using Kruskal-Wallis test

The Kruskal value analysis was performed and a p-value of 0.046 was obtained and showing that there is a difference in median prostate specific antigen levels among the groups (*table 4*).

Multiple comparison of prostate specific antigen by using Mann-Whitney U test

Multiple comparison of Prostate specific antigen by using Mann Whitney U test was performed between the groups. On comparing group 1 and 3 and group 2 and 3, there was a difference in median prostate specific antigen level between those groups ($p< 0.05$). This indicates that group 3 (malignant subjects) showed a statistical rise in serum PSA as compared to the normal and benign subjects.

DISCUSSION

Breast cancer has emerged as the most common malignancy among females during the last few years with an incidence rate more than twice that of colorectal cancer and cervical cancer and about three times that of lung cancer (1,5). Some of the major risk factors include high body mass index, advanced age, family history of breast cancer, a long menstrual history, use of oral contraceptives, exposure to radiation, no childbearing, giving birth to the first child after age 30 (1,6). Death due to breast cancer has been reduced with screening approaches like mammography and other diagnostic approaches. To differentiate between benign and malignant lesions, lesion biopsies, ultrasound assessment, mammography evaluation has been undertaken, in view for diagnosing the same. According to previous studies that have been undertaken, on comparing PSA-negative breast cancer subjects with PSA-positive cancer subjects. The group with PSA negative breast cancer has relapse-free survival regardless of other clinical and pathological features suggesting that PSA is a new favorable prognostic indicator in breast cancer (7). PSA is one of the most important serum tumor markers, that has been used successfully for diagnosis and for the postsurgical management of prostate cancer (8). The hormonal receptors that are present in the breast are the estrogen, progesterone and androgen receptors. The expression of PSA is inhibited by estrogens but stimulated by the androgens. Estrogen plays an important role in the development as well as the progression of breast cancer. Therefore, depletion, antagonism or suppression of the estrogenic stimuli may prove effective in breast cancer management. It has been demonstrated that androgens exert an anti-estrogenic effect and hence can inhibit the proliferation of breast cancer cells. In fact, many previous studies have shown that androgens have been used as an effective treatment modality in many breast cancer patients (9,10).

As the expression of serum PSA is steroid mediated, the presence of PSA immunoreactivity found in breast cancer cells may be considered to be an indicator of endogenous hormone balance between the estrogen and androgen or progestin. Hence detection of serum PSA in breast tumor may be valuable in predicting the prognosis of breast cancer patients. Detection of PSA in the serum of females requires highly sensitive assays as the concentration is very low. There is evidence that the serum PSA level in females is 106-fold lower as compared to prostatic or breast secretion (11). And with the routine use of PSA immunoassays for the management of prostatic carcinoma there has been a marked rise in the number of prostate cancers that have been detected (8).PSA which is a serine protease can act as a growth regulator by cleaving insulin like growth factor binding protein-3 (IGFBP-3) to release insulin-like growth factor-I (mitogen) or it can enzymatically activate latent human transforming growth factor-alpha (12,13). Detection of serum PSA may play a role in tumor progression and metastasis as it may degrade the extra cellular matrix proteins which are the fibronectin and laminin (14,15). Based on

previous studies, Narita et al. has shown that HER2 neu expression is associated with PSA negativity hence substantiating the role of PSA as a favorable prognostic marker in breast lesions (16). The purpose of this study was to establish serum PSA as a diagnostic marker for breast lesions. In this study sera from women with breast cancer, benign breast disease, and from women free of malignancies were analyzed for serum PSA using a PSA immunoassay (17). This study has shown an elevation of serum PSA among the breast malignancy as compared with benign breast lesions and women without breast lesions. Breast cancer is one of the leading causes of morbidity and mortality in females of the developed countries and is one of the most common malignancy among the North American women. At present, the most effective way to minimize morbidity and mortality from breast cancer is by early diagnosis along with the administration of the required therapy (9). Hence based on the above study it is desirable to devise new methods for early diagnosis as to provide early and appropriate treatment. At present mammography is the most sensitive and specific screening modality that is being used for breast cancer, however based on the data available at present there is no universal recommendation for mammography for all women (10). Many attempts are presently being made to identify various serological markers of breast tumors (18-20). Prospective markers for breast malignancy include carcinoembryonic antigen (CEA), carbohydrate antigen 15.3, tissue polypeptide-specific antigen, and mammary serum antigen (11,18-20). Based on a previous study the diagnostic sensitivity of free PSA as the predominant molecular form for breast lesions is approximately 20% and it was also found that free PSA as the predominant form for breast lesion is highly specific for breast cancer in comparison with benign breast disease and normal tissue. This high degree of specificity suggests that free PSA may have potential of clinical applicability either alone or in combination with other markers (11).

It is clear from previous studies that PSA could have a number of potential roles in breast cancer. PSA was shown to stimulate cell detachment, suggesting a possible role for PSA in tumor progression or metastasis (12). The hypothesis for the role of PSA in breast carcinoma could be that PSA degrades the extracellular matrix proteins fibronectin and laminin and because of the destruction of the epithelial basement membrane there could be facilitation of local invasion.

Previous similar study such as Mashkoor et al. (8) concluded that PSA levels were significantly higher in women with breast cancer than in healthy women and serum PSA could be considered as a useful marker in monitoring the response to the treatment, Gupta et al. showed that there were no significant differences in the PSA levels between Normal controls, subjects with benign breast disease as well as subjects presenting with breast carcinoma (21). Dash et al. (22) concluded that serum PSA was found to possess high specificity for breast cancer. In our study we have tried to establish the probable role of serum PSA. Our study had some limitations, although it was able to show an increase in serum PSA levels among the malignant subjects, it did not give us a value of cut off for serum PSA levels among females, it did not take into account the age association with serum PSA , and it did not correlate the value with receptor status.

CONCLUSION

Although serum PSA as the predominant molecular form is highly sensitive for breast cancer, its clinical utility is limited. The current study demonstrated increased serum PSA levels among the malignant cases as compared to the benign cases and control group. Therefore, serum PSA level may serve in differentiating benign and malignant breast carcinoma. However future studies would be required for to establish cut off levels of serum PSA among females who are at risk of developing malignancies.

Conflict of interests

The authors declare that there is no conflict of interest to current study

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Nil.

Ethical approval

This prospective study study was conducted at Justice K S Hegde Charitable Hospital, Deralakatte after procuring institutional ethical clearance (INST.EC/EC/108/2015-16).

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