



ESTIMATION OF TOTAL AND FREE PROSTATE SPECIFIC ANTIGEN IN CARCINOMA BREAST

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ABSTRACT

Objectives- To estimate the value of total and free PSA and to evaluate the diagnostic role of PSA in carcinoma breast. **Material And Methods** - The study was conducted on 50 female patients with carcinoma breast and 50 normal females at RIMS, Ranchi Jharkhand. **Results** - We demonstrated that estimation of PSA in carcinoma breast can be regarded as a marker for diagnosis of breast cancer. Although, free PSA as the predominant molecular form is highly specific and statistically significant ($p < 0.005$) for breast cancer. **Conclusion-** Hence to conclude from my study is that there is definitely a role of PSA in carcinoma breast and can be recommended to all patients with carcinoma breast.

KEYWORDS : Total PSA, Free PSA, Carcinoma breast

INTRODUCTION

Tumour markers are used for detection of risk, population screening, diagnosis, staging and prognosis of cancers. It can also predict the response to the therapy, the presence of occult metastasis and monitor the course of disease. Various tumour markers have been studied singly or in combination in carcinoma breast. Most of these are high on running costs, in terms of laboratory infrastructure.

In India breast cancer is the second most common cancer in women next to cervical cancer. According to National Cancer Registry Programme in India the frequency of breast cancer prior to 25 years occurred above 50 years of age, but in present day women in the age group of 25-40 years of age has high frequency of breast cancer. Highest incidence of breast cancer is seen in the age 45-49 years. Multiple factors are associated with an increased risk of developing breast cancer; these can be genetic, environmental and histological factors.

Prostate specific antigen (PSA) is a valuable tumour marker for the diagnosis and management of prostate carcinoma. Currently, PSA is a highly valuable marker for prostate cancer screening, diagnosis and postsurgical monitoring of prostate cancer patients, as well as for the detection of micrometastasis [1]. It was believed that PSA was produced exclusively by the epithelial cells of the prostate gland. It is widely accepted that PSA is not prostate specific [2]. PSA has been shown to be expressed in many forms of female tissues. The breast is a major female organ able to produce PSA. It is detected in both normal and abnormal breast tissues, as well as in breast fluids including milk, nipple aspirate, and cyst fluid. Androgen and progesterone, via their receptors, regulate the production of PSA in breast tissues. Clinical studies demonstrate that PSA in breast cancer is associated with the expression of oestrogen receptor and progesterone receptor. PSA is produced by the majority of breast tumours and may be a favourable indicator of prognosis in breast cancer [3, 4].

PSA is a 33kDa glycoprotein containing 237 amino acids, 4 carbohydrate side chains and multiple disulphide bonds which is homologous with the proteases of the kallikrein family and hence called human glandular kallikrein-3 (hk-3). PSA is a serine protease discovered in 1970, has two molecular forms namely Free PSA (33kDa) and bound PSA (100kDa). PSA bound to proteinase inhibitors of α -1

antichymotrypsin [PSA-ACT] is known as bound PSA. Total PSA is free and bound PSA together [5, 6].

The gene encoding PSA has been sequenced and localized to chromosome 19. It is similar to the kallikrein -1 gene with 82 % homology. PSA exists in two forms in the blood circulation. Most PSA is complexed with the protease inhibitors α 1-antichymotrypsin (ACT) (molecular weight 1, 00,000 Da) and α 2-macroglobulin (AMG) and a minor component is free PSA (molecular weight 28,430 Da). Most immunoassays measure both free and ACT-complexed PSA but not PSA-AMG, which is sterically inhibited. The metabolic clearance rate of PSA follows a two-compartment model, with initial half-lives of 1.2 and 0.75 hours for free PSA and total PSA and subsequent half-lives of 22 and 33 hours.

In 1989, PSA expression was first discovered through immunohistochemical reactions in some apocrine foci of female fibrocystic breast tissue as well as in breast cancer (BC), casting doubt on the specificity of this kallikrein only for prostatic epithelium [7].

Yu H, Berkel H. studied Prostate-specific antigen (PSA) in women and stated that breast is a major female organ able to produce PSA. PSA is detected in both normal and abnormal breast tissues as well as in various breast fluids including milk, nipple aspirate, and cyst fluid. They also stated that high concentration of PSA is found in amniotic fluid and the levels change with gestational age [8].

Thus, the present study is designed to estimate the levels of serum total and free PSA in carcinoma breast and to evaluate their role and significance. PSA can also be used as a diagnostic and prognostic marker of breast cancer in women but we need further studies and in a much larger population.

AIMS AND OBJECTIVES

- To estimate the value of total and free PSA.
- To evaluate the diagnostic role of PSA in carcinoma breast.

MATERIAL AND METHODS

The study was an observational study conducted on female patients with carcinoma breast admitted in surgical ward at Rajendra Institute of Medical Sciences, Ranchi during the period of January 2018-October 2019

Sample Size: A total of 100 subjects were taken.

Group A- Includes 50 patients which were diagnosed with carcinoma breast.

Group B- Includes 50 females as control who were of the same age group.

Inclusion Criteria

All female patients who were diagnosed with carcinoma breast of any age group before the treatment and surgery.

Exclusion Criteria

Female patients suffering from:

Tuberculosis, Rheumatic fever, Haemolytic anaemia, Hypertension, Diabetes mellitus, Hepatitis, Jaundice, Pancreatic diseases, Pregnancy or breast feeding, Bone diseases, Cardiac failure, Myocardial infarction, Ulcerative colitis and other malignancies.

Reference Values

Normal Females - < 0.01 ng/ml [9].

Methodology

Blood sample was obtained with informed consent from each cases and controls and a proper questionnaire was provided. Proper physical examination and history was taken.

Biochemical Examination

1. Total PSA 2. Free PSA

Method Of Sample Collection

Patients were instructed about the procedure of sample collection and to remain calm and compose.

Following safety measures were followed while collecting the blood samples:

Wearing gloves before and after handling blood.

Changing gloves after handling of each patient or when contaminated.

Washing hands frequently.

Disposal of items in appropriate containers.

Disposal of needles immediately upon removal from patients. Cleaning up any blood spills with a freshly made 10% bleach disinfectant.

Needles of 20 or 22 G Size were used for blood samples. Needles were put in disposable unit immediately after their use. 70% isopropyl alcohol was used in cotton swab to wipe and sterilize the skin.

PROCEDURE

Antecubital vein of the arm was preferred and used most frequently for collection of blood. First the surface was palpated and the path of vein was traced with index finger. Arteries were identified and avoided as they pulsate and are more elastic and have a thick wall. Once the preferred site was selected, gloves were put on. Venepuncture site was cleaned with alcohol preparation, cleansing in a circular fashion. The site was allowed to dry.

The tourniquet was applied 3-4 inches above the selected puncture site. Precaution was taken not to apply tourniquet too tightly to avoid injury. Venepuncture performed with patient's arm rested in a comfortable position. Tourniquet was removed as soon as the blood appeared in the syringe. About 5-6 ml of blood was withdrawn. When blood has been collected, a cotton ball or gauze piece was placed over the site and the

needle withdrawn in a smooth and cautious manner so as not to bruise the vein or skin. After withdrawing the needle, gentle pressure was applied to the cotton ball over the puncture site. The patient was asked to apply pressure for 2-3 minutes to prevent oozing of blood from puncture site. Then blood samples were put in an appropriate vial.

The serum sample blood was allowed to clot by placing it in the rack at room temperature for at least 30 minutes. Then it was centrifuged at 3000 rpm for 10 minutes and then the serum was separated. The serum samples were stored at 80°C. The clear serum was then analysed for the estimation of serum Total PSA and Free PSA.

Biochemical Estimation

Estimation of Prostate-specific Antigen (PSA) by ABOTT (Architect Plus I 1000SR)

The biochemical parameters undertaken for the estimation of serum total PSA and free PSA was determined in a fully automated ABOTT (Architect Plus I 1000SR)

The Access Hybritech PSA assay is a two-site immunoenzymatic "sandwich" assay.

PRINCIPLE

A sample is added to a reaction vessel with mouse monoclonal anti-PSA alkaline phosphatase conjugate and paramagnetic particles coated with a second mouse monoclonal anti-PSA antibody. The PSA in the sample binds to the immobilized monoclonal anti-PSA on the solid phase while, at the same time, the monoclonal anti-PSA conjugate reacts with a different antigenic site on the sample PSA. Separation in a magnetic field and washing removes material not bound to the solid phase. A chemiluminescent substrate, Lumi-Phos 530 is added to the reaction vessel and light generated by the reaction is measured with a luminometer. The light production is proportional to the concentration of PSA in the sample. The amount of analyte in the sample is determined by means of a stored, multi-point calibration curve.

Detection limit: 0.008 ng/ml

The ARCHITECT Free PSA assay is a two-step immunoassay to determine the presence of free PSA in human serum, using Chemiluminescent Microparticle Immunoassay (CMIA) technology with flexible assay protocols, referred to as Chemiflex. In the first step, sample and anti-free PSA coated paramagnetic microparticles are combined. Free PSA present in the sample binds to the anti-free PSA coated microparticles. After washing, anti-PSA acridinium-labeled conjugate is added in the second step. Pre-Trigger and Trigger Solutions are then added to the reaction mixture; the resulting chemiluminescent reaction is measured as relative light units (RLUs). A direct relationship exists between the amount of free PSA in the sample and the RLUs detected by the ARCHITECT i optical system.

Statistical Method And Data Analysis

Statistical analysis was done using SPSS software. The data was represented by counts, percentage and mean \pm standard deviation. Statistical analysis of the biochemical tests of Total PSA and Free PSA was done by unpaired t-test to compare the parameters in carcinoma breast cases and control.

A P value of <0.05 was considered statistically significant.

OBSERVATION AND RESULTS

The present study is an observational study comprising of 100 patients including 50 cases of carcinoma breast (Group A) and 50 cases of control (Group B) in Rajendra Institute of

Medical Sciences, Ranchi during the period January 2018-October 2019. The general characteristics of the study populations are stated below:

Table 1 – Distribution Of Cases (Group A) According To Age

Age Distribution of Cases (Group A)		
Age	Cases (n=50)	Percentage %
20-45 Years	24	48
46-65 Years	25	50
>65 Years	1	2
Total	50	100

Table 1 shows the distribution of cases (Group A) according to age in carcinoma breast.

Minimum age was 23 years and maximum was 73 years. Mean age was found to be 45.70 ± 10.929 years.

Maximum (25) number of cases were found in the age group 46-65 years and minimum (01) number of cases were found in the age group >65 years.

Table 2 Distribution Of Control (Group B) According To Age

Age Distribution of Control (Group B)		
Age	Cases (n=50)	Percentage %
20-45 Years	32	64
46-65 Years	17	34
>65 Years	1	2
Total	50	100

Table 2 shows the distribution of control (Group B) according to age.

Minimum age was 30 years and maximum was 73 years. Mean was found to be 45.50 ± 10.053 years.

Maximum (32) number of cases were found in the age group 20-45 years and minimum (01) number of cases were found in the age group >65 years.

Table 3 - Distribution Of Total PSA Value According To Age In Cases (Group A)

Variables	Total PSA Level (ng/ml)					
Age	0.08	0.158	0.026	0.093	0.022	Total
20-45 Years	22	0	1	1	0	24
46-65 Years	23	1	0	0	1	25
>65 Years	01	0	0	0	0	1
Total	46	1	1	1	1	50

Table 3 shows the distribution of Total PSA according to age in cases (Group A).

The value of Total PSA in cases (Group A) was found in the range of 0.008- 0.158 ng/ml.

Minimum (01) case was seen in the age group of >65 years while the maximum (24) cases were found in the age group of 20-45 years.

Minimum (0.008ng/ml) value of Total PSA was found in maximum (46) number of cases and maximum (0.158 ng/ml) value was found only in one case.

Table 4 - Distribution Of Total PSA Value According To Age In Control (Group B)

Variables	Total PSA Level (ng/ml)				
Age	0.008	0.021	0.018	0.031	Total
20-45 Years	28	02	01	01	32
46-65 Years	17	00	00	00	17
>65 Years	01	00	00	00	01
Total	46	02	01	01	50

Table 4 shows the distribution of Total PSA according to age in control (Group B).

The value of Total PSA in control (Group B) was found in the range of 0.008-0.31 ng/ml.

Minimum (01) case was seen in the age group of >65 years while the maximum (32) cases were found in the age group of 20-45 years.

Minimum (0.008 ng/ml) value of Total PSA was found in maximum (46) number of cases and maximum (0.31 ng/ml) value was found only in one case.

Table 5 shows the distribution of Free PSA according to age in cases (Group A).

The value of Free PSA in cases (Group A) was found in the range of 0.001-0.23 ng/ml.

Minimum (01) case was seen in the age group of >65 years while the maximum (25) cases were found in the age group of 46-65 years.

Minimum (0.001ng/ml) value of Free PSA was found in maximum (28) number of cases and maximum (0.23 ng/ml) value was found only in one case.

Table 6 shows the distribution of Free PSA according to age in control (Group B).

The value of Free PSA in control (Group B) was found in the range of 0.001-0.016 ng/ml.

Minimum (01) case was seen in the age group of >65 years while the maximum (32) cases were found in the age group of 20-45 years.

Minimum (0.001 ng/ml) value of Free PSA was found in maximum (21) number of cases and maximum (0.016 ng/ml) value was found only in one case.

Table 7- Comparison Of Total PSA Mean Value In Cases (Group A) And Control (Group B)

Comparison Of Total PSA Mean Value In Case (Group A) And Control (Group B)		
Variables	Cases	Control
Mean	0.0091	0.00382
Std. Deviation	0.004062	0.007782
P Value	<0.001	

Table 7 shows the comparison of Total PSA mean value in cases (Group A) and control (Group B). The mean was found to be 0.0091 and 0.00382 in cases (Group A) and control (Group B) respectively.

The standard deviation of Total PSA value in cases (Group A) and control (Group B) was 0.004062 and 0.007782 respectively. P value was < 0.001 and highly significant.

Table 8- Comparison Of Free PSA Mean Value In Cases (Group A) And Control (Group B)

Comparison Of Free PSA Mean Value In Case (Group A) And Control (Group B)		
Variables	Cases	Control
Mean	0.0382	0.322
Std. Deviation	0.07782	0.002859
P Value	<0.05	

Table 5 - Distribution Of Free PSA Value According To Age In Cases (Group A)

Variables	Free PSA Level (ng/ml)									
AGE	0.00	0.00	0.03	0.00	0.00	0.00	0.03	0.23	0.00	TOTAL
	1	2	9	6	3	5	7		4	AL
20-45 Years	16	05	0	02	0	0	01	0	0	24
46-65 Years	11	02	01	0	04	02	0	01	04	25
>65 Years	01	0	0	0	0	0	0	0	0	01
TOTAL	28	07	01	02	04	02	01	01	04	50
L										

Table 6 - Distribution Of Free PSA Value According To Age In Control (Group B)

Variables	Free PSA Level (ng/ml)									
AGE	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	TOTAL
	1	2	3	4	5	6	6	8	7	AL
20-45 Years	13	04	02	02	04	04	01	02	0	32
46-65 Years	07	02	02	02	01	02	0	0	01	17
>65 Years	01	0	0	0	0	0	0	0	0	01
TOTAL	21	06	04	04	05	06	01	02	01	50
L										

Table 8 shows the comparison of Free PSA mean value in cases (Group A) and control (Group B)

The mean was found to be 0.0382 and 0.322 in cases (Group A) and control (Group B) respectively.

The standard deviation of Free PSA value in cases (Group A) and control (Group B) were 0.07782 and 0.002859 respectively. P value was < 0.05 and was significant.

DISCUSSION

The present study was an observational study comprising of 100 patients including 50 cases of carcinoma breast (Group A) and 50 cases as controls (Group B) in Rajendra Institute of Medical Sciences, Ranchi.

Breast cancer is a leading cause of morbidity and mortality in females of developed countries and is the most common malignancy among North American women [10]. It is estimated that by the year 2000, 500,000 women worldwide will die from breast cancer. Currently, the most effective way to minimize morbidity and mortality from breast cancer is by early diagnosis and administration of therapy [11]. It is thus highly desirable to devise new methods of early diagnosis. Mammography is the most sensitive and specific screening modality for breast cancer; however, data presently available do not warrant a universal recommendation for mammography for all women [12].

AGE

In the present study of 50 cases (Group A) of carcinoma breast it was found that the minimum age of carcinoma breast was seen in 23 years of age and maximum in 73 years. Mean age was found to be 45.70 ± 10.929 years.

Maximum (25) number of cases were found in the age group 46-65 years and minimum (01) number of cases were found in the age group >65 years.

In the control study of 50 cases (Group B) the minimum age was 30 years and maximum was 73 years. Mean was found to be 45.50 ± 10.053 years.

Maximum (32) number of cases were found in the age group 20-45 years and minimum (01) number of cases were found in the age group >65 years.

Similar studies done by Soumen et al (2011) [13] also showed that the minimum age of carcinoma breast was 25 years and maximum age was 66 years. The mean age of carcinoma breast was 46.6 ± 9.55 years.

Fawzi et al (2013) [14] in their study also showed that the mean age for carcinoma breast patients was 49.1 ± 11.1 years and 48.1 ± 10.7 years in cases and control respectively which was very much similar to my study.

Syed et al (2015) [15] in their study also found that carcinoma breast was seen in the age group of 36 years to 85 years and 28 years to 63 years in cases and control respectively which was also similar to my study. The mean age was found to be 61 ± 3 years and 38 ± 4 years for cases and control which was also more or less similar to my study.

Elteza et al (2017) [16] also showed in their study that the mean for cases and control were 42.74 ± 10.37 years and 43.34 ± 10.95 years which was almost similar to my study.

TOTAL PSA

The value of Total PSA in cases (Group A) was found to be in the range of 0.008-0.158 ng/ml and the value of Total PSA in control (Group B) was found in the range of 0.008-0.31ng/ml. The mean was found to be 0.009 ng/ml and 0.00382 ng/ml in cases (Group A) and control (Group B) respectively. The standard deviation of Total PSA value in cases (Group A) and control (Group B) was 0.004062 and 0.007782 respectively. The relationship of Total PSA between cases (Group A) and control (Group B) was statistically significant (<0.001).

Yu H et al (1998) [17] in their study defined the value of Total PSA in the range of 0-8.8 ng/ml in carcinoma breast and 0-0.84 ng/ml in controls. This was not similar to my study.

Margot H. Black et al (2000) [18] in their study also defined the value of Total PSA in the range of 0-0.8153 ng/ml in cases and 0-0.0055 ng/ml in control which was similar to my study.

Hayder M. Abdalnabi et al (2011) [19] in their study also defined the value of Total PSA in the range of 1.38-5.00 ng/ml in cases and 0.0-0.0893 ng/ml in control which was similar to my study.

Fawzi C. Mashkoor et al (2013) [14] found out the value of Total PSA in the range of 0.10-3.62 ng/ml in cases and 0-1.3 ng/ml in control respectively. The mean was 1.373 ng/ml and 0.517 ng/ml respectively. This finding was similar to my study. The standard deviation was found to be 0.855 and 0.381 in cases and control in their study which however was not similar to my study.

B Sharma et al (2014) [20] found the value of Total PSA as <0.04 ng/ml in cases and control which was not similar to my study.

Syed H Emami et al (2015) [15] in their study defined the value of Total PSA of 0.77 ± 0.01 ng/ml in cases and 0.17 ± 0.016 ng/ml in control. My study was very much similar to this study.

Elteza T Jahir et al (2017) [16] found the mean of Total PSA to be 1.037 ng/ml and 0.129 ng/ml in cases and control respectively which was similar to my study.

FREE PSA

The value of Free PSA in cases (Group A) was found in the range of 0.001-0.23 ng/ml and the value of Free PSA in control

(Group B) was found in the range of 0.001-0.016 ng/ml.

The mean was found to be 0.0382 ng/ml and 0.0322 ng/ml in cases (Group A) and control (Group B) respectively. The standard deviation of Free PSA value in cases (Group A) and control (Group B) was 0.07782 and 0.00859 respectively. The relationship of Free PSA between cases (Group A) and control (Group B) was statistically significant (<0.05).

Margot H. Black et al (2000) [18] in their study defined the value of Free PSA in the range of 0-0.02451 ng/ml and 0-0.0006 ng/ml in cases and control which was similar to my study.

Hayder M. Abdulnabi et al (2011) [19] defined in their study the mean of Free PSA to be 2.3493 ng/ml and 0.668 ng/ml in cases and control respectively which was not similar to cases but was similar to control in my study.

The standard deviation was 1.3800 and 0.36806 in cases and control respectively which was not similar to my study.

Fawzi C. Mashkoor et al (2013) [14] defined the range of Free PSA to be 0-2.71 ng/ml and 0-0.55 ng/ml in cases and control respectively which was not similar to my study. The mean of Free PSA was found to be 0.828 ng/ml and 0.148 ng/ml in cases and control respectively which was also not similar to my study. Standard deviation was found to be 0.61 and 0.128 respectively.

Pavithra V et al (2014) [21] found the mean of Free PSA to be 0.2178 ng/ml and 0.0039 ng/ml in cases and control respectively and standard deviation to be 0.133394 and 0.01761 respectively which was not similar to cases but was similar to control in my study.

Syed H Emami et al (2015) [15] in their study defined the value of Free PSA to be 0.39 ± 0.12 ng/ml in cases and 0.009 ± 0.03 ng/ml in control. My study was very much similar to this study.

Elteza T Jahir et al (2017) [16] found the mean of Free PSA to be 0.864 ng/ml and 0.088 ng/ml in cases and control respectively which was not similar to my study.

CONCLUSION

Hence to conclude from my study is that there is definitely a role of Total and Free PSA in carcinoma breast and must be recommended to all patients. Finally, to conclude that we have demonstrated that free PSA as the predominant molecular form is highly specific for breast cancer, its clinical utility is limited at this time due to low sensitivity. Given the heterogeneity of the population of breast cancer patients, additional studies with larger cohorts of patients are required for the examination of molecular forms of PSA with regard to individual parameters such as risk of relapse or metastasis. Finally, the physiological mechanism behind the free PSA increase in breast cancer and its ramifications with respect to tumour progression should be further investigated.

RECOMMENDATION

There is association between serum level of Total PSA and Free PSA in carcinoma breast and regarded as a marker for diagnosis of breast cancer. We advise to send every patient with breast lump for Total and Free PSA estimation to detect cancer. My study shows that serum level of Total PSA and Free PSA is a diagnostic and useful tumour marker like in diagnosis of prostate carcinoma and also be used as a prognostic factor with carcinoma breast like progesterone and oestrogen receptor, but we need further studies and a much larger population size. A follow up study with monitoring of tumour marker levels post-treatment would have been better for establishing the prognostic value of PSA in breast carcinoma. PSA estimation in the breast tissue would also have been more specific.

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