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Research Article

PSA as a Marker in Breast Cancer: A Clinico-Biochemical Analysis

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Abstract: Breast Cancer is one of the earliest detected neoplasm's in human beings. Present study comprises all those patients of cancer breast of all stages who attended the outdoor department and admitted in indoor wards of department of Biochemistry and Surgery of Hospital (Swami Vivekanand Subharti University) attached to Subharti Medical College, Meerut. All these patients were clinically evaluated completely by history, clinical examination and various invasive and noninvasive investigations to establish the diagnosis and find out the extent of disease in the body. 4.69% & 45.31% of the breast cancer patients were pre- & postmenopausal respectively. Maximum patients were found to be in stage III (37.5% & 26.56% of pre- & postmenopausal, respectively). 30.8% of premenopausal patients had an ER receptor positive tumour. The percentage of such patients in postmenopausal group was 61.1%. Most of the tumours in postmenopausal females were ER positive. 28.13% of premenopausal and 21.88% of postmenopausal patients had >3 lymph nodes affected. Peripheral PSA levels were observed at the time of diagnosis, in relation to stage, lymph node status, menopausal status, ER/PR status and flow cytometry. After treatment the PSA level were not different from pretreatment levels. During follow up the peripheral PSA levels showed no correlation with recurrence.
Keywords: Premenopausal, Postmenopausal, Prostate-specific antigen, Estrogen receptor.

INTRODUCTION

Breast Cancer is one of the earliest detected neoplasm's in human beings with references dating back to 525 BC. It is now the commonest malignancy in females in Delhi & Mumbai, while overall; it is second only to Cancer of Uterine Cervix in Indian ladies.

While increasing hygiene and improved healthcare facilities have helped control the viral infections that lead to cervical cancer, changing urban lifestyles are believed to be behind the increase in breast cancer [1].

Prostate specific Antigen (PSA) a well-established tumour marker for prostate cancer, is now believed to be not prostate specific, but present in other tissues as well. It is present in female tissues, predominantly the breast and its secretions and can be used as a predictive indicator for prognosis, diagnostic and treatment.

PSA is a 33kDa glycoprotein, and is a member of the human glandular kallikrein family, a locus of which is comprised to three genes and spans a 60-70kb region on chromosome 19q 13.3-q 13.4 [2, 3].

Low concentrations of PSA normally released in the blood. The clinical utility of PSA as a marker for prostate cancer emerged in 1980 with the initial report of elevated PSA levels in serum of prostate cancer patients [4, 5].

PSA immunoreactivity in breast cancer cystolic extract was first identified in 1994 [6-8]. Recent studies with ultrasensitive immunoassays demonstrated that approximately 70% of breast tumour cystolic extracts contained PSA [9]. Molecular analysis verified that the mRNA of breast tumour PSA was identified to prostatic PSA [10].

The fact that not all breast tumours produce PSA prompted studies of the utilization of PSA as a prognostic indicator in breast cancer. PSA positivity, low cellularity, diploid tumours, low S-phase fraction, less advanced disease stage, lower risk of relapse and longer overall survival [9, 11].

Steroid hormone receptors are favourable prognostic indicators in breast cancer, and receptor positive patients respond favourable to endocrine treatment. It has been found that among the steroid hormone receptor positive patients, the presence or

absence of PSA has no additional prognostic significance. However, in steroid hormone receptor negative patients, those with PSA positive tumours trend to have a reduced risk of relapse. This finding is supported by an observation in which two patients ovarian cancer metastatic from a breast primary were described. One of the patients, whose ovarian tumour was receptor positive and PSA negative, died soon after the administration of adjuvant therapy. The other, with a steroid hormone receptor negative but PSA positive tumour had a good response to adjuvant treatment and excellent disease free survival [11, 12].

The studies for PSA as biological marker in breast cancer are very few, and there is enough opportunity to explore this marker in relation to diagnosis and prognosis of breast carcinoma. The present study was, therefore, undertaken to assess if peripheral serum PSA levels can be correlated with diagnosis and prognosis of breast cancer.

MATERIALS & METHODS

Present study was held in the department of Biochemistry and Surgery of Hospital (Swami Vivekanand Subharti University) attached to Subharti Medical College, Meerut. It comprises all those patients of cancer breast of all stages who attended the outdoor department and admitted in indoor wards of this hospital.

All these patients were clinically evaluated completely by history, clinical examination and various invasive and noninvasive investigations to establish the diagnosis and find out the extent of disease in the body. All the findings were mentioned in the pretested perfoma.

27 premenopausal and 16 postmenopausal women were studied as control patient on sex and age match to establish the standard value of PSA. These control patients include all those who were admitted in the department of surgery of this hospital for treatment of diseases other than any tumour.

Groups classified as-

A. The cases who did not receive any treatment in the past(Untreated or fresh case)
B. Cases who had received any type of treatment in past i.e., before attending outdoor of this hospital (previously treated patients) either by Surgery, Chemotherapy, Radiotherapy and combnation of above treatment modalities

Detailed information from these patients about the status of disease before any treatment, type and duration of these treatments and response were noted down. Base line value of PSA was estimated in both group A and B patients.

Patients admitted (Both of Group A and B) were treated according to treatment protocol for different stages. The serum PSA values of Breast cancer patients were estimated within less than 1 month prior to surgery or start of chemotherapy. They were then followed up with 3 month serum PSA estimation. The patients with inoperable carcinoma breast were subjected to random serum PSA estimation which was then followed up at 3 monthly intervals. The serum PSA of controls was also measured from a random sample of blood.

Various other parameters detecting the prognosis of disease were also noted in patients with carcinoma breast. The patients with carcinoma were staged according to the American Joint Committee on Cancer (AJCC) system 1992. This system is based on clinical examination of tumour(T), lymph nodes(N) and metastasis(M) i.e., TNM system.

The samples were collected in especially designed clot activator vials & the samples were taken immediately to the Department of Biochemistry, Subharti Medical College, Meerut for PSA analysis. PSA were assayed by two step enzyme immunoassay sandwich method with a final fluorescent detection (ELFA). Parameter was estimated by following the same standard protocol provided by the manufacturer (M/s Biomerieux).

RESULTS

The present study was carried out on 64 patients clinically diagnosed for Breast Cancer attending the Department of Surgery, OPD/admitted in the ward of Subharti Hospital, Meerut from December 2009 to 2010.

The samples were collected in especially designed clot activator vials & the samples were taken immediately to the Department of Biochemistry, Subharti Medical College, Meerut for PSA analysis.

The most common stage at presentation in premenopausal ladies was stage IIIB (21.87%). Same pattern was observed among the postmenopausal patients (14.06%).

Stage III alone constituted the commonest stage at presentation (37.5% in premenopausal females and 26.56 % in postmenopausal patients) reflecting that still the patients tend to ignore the presence of disease and present late.

The least common stage in both premenopausal and postmenopausal patients is stage I (3.1% and 1.56% respectively) (Table 1).

The control group (consisting of patients of diseases other than Breast or any other Cancer) was

found to be having same serum PSA value (<0.04ng/ml) irrespective of their menopausal status (Table 2).

Mean PSA value in serum was found to be same in all patients belonging to different tumour stages at presentation. No difference was observed in the serum PSA level in patients with tumours of different stages at presentation (Table 3).

The mean serum PSA level did not have any correlation with the number of lymph nodes either pre or postmenopausal breast cancer patients (Table 4).

The post-surgery values in this table depict the first value measured 3 months after the surgery. The healthy women have serum PSA value <0.04ng/ml irrespective of their age. The serum PSA levels of breast cancer patients was equal to controls (i.e., <0.04ng/ml) and this value remained unchanged after surgery as well (Table 5).

Administration of Anterior chemotherapy did not have any effect on serum PSA values. The values remained the same and were similar to the values in controls (Table 6).

The serum PSA level failed to show any correlation with any of the variables listed in table 7.

Table 1: Distribution of patients according to stages and menopausal status

Menstrual cycle	**No. of Patients (%)**	**Stage**					
		I(%)	IIA(%)	IIB(%)	IIIA(%)	IIIB(%)	IV(%)
Pre menopausal	35(54.69)	2(3.1)	3(4.69)	2(3.1)	10(15.62)	14(21.87)	4(6.25)
Post menopausal	29(45.31)	1(1.56)	2(3.1)	4(6.25)	8(12.5)	9(14.06)	5(7.81)
Total(%)	64(100)	3(4.68)	5(7.81)	6(9.37)	18(28.12)	23(35.93)	9(14.06)

Table 2: PSA levels in Control Groups

Menopausal Status	No. of Patients (%)	Mean PSA value (ng/ml)
Premenopausal	27	0.034
Postmenopausal	16	0.035

Table 3: PSA values according to stages in Pre- & Postmenopausal patients

Stage	**No. of Patients (Pre-menopause) (%)**	**No. of Patients (Post-menopause) (%)**	**Mean PSA value(ng/ml)**
I	2(3.1)	1 (1.56)	0.02
IIA	3(4.69)	2 (3.1)	0.023
IIB	2(3.1)	4 (6.25)	0.011
IIIA	10(15.62)	8 (12.5)	0.012
IIIB	14(21.87)	9 (14.06)	0.022
IV	4(6.25)	5 (7.81)	0.03
Total (%)	35(54.69)	29 (45.31)	

Table 4: Value of PSA (ng/ml) with No. of lymph Nodes in different stages in Pre and post-menopausal women

Stage	**LN in premenopausal women**			**LN in postmenopausal women**		
	No LN	<3LN	>3LN	No LN	<3LN	>3LN
I	N=1 PSA value 0.023	1 0.024	- -	- -	- -	1 0.026
IIA	N=1 PSA value 0.025	2 0.022	1 0.031	- -	- -	2 0.036
IIB	N=1 PSA value-0.026	1 0.023	1 0.032	1 0.031	1 0.025	2 0.034
IIIA	N=2 PSA value0.023	1 0.024	7 0.029	- -	3 0.028	5 0.032
IIIB	N=1 PSA value 0.024	3 0.023	9 0.025	1 0.028	1 0.025	4 0.031

Table 5: PSA concentration in serum of healthy women, breast cancer patients, before and after surgery

Sample	No. of patients	Mean Serum PSA value (ng/ml)
Serum of Healthy women		
• All Subjects	43	0.023
• <50yrs	27	0.022
• ≥50yrs	16	0.024
Serum of breast cancer patients before surgery		
• All Subjects	35	0.025
• <50yrs	26	0.033
• ≥50yrs	9	0.028
Serum of breast cancer patients post-surgery		
• All Subjects	35	0.024
• <50yrs	26	0.026
• ≥50yrs	9	0.031

Table 6: Comparison of PSA and DNA index in Pre- & Postmenopausal women

Stage	No. of Patients	Ploidy		Mean PSA ng/ml
		<1	>1	
I				
IIA				
IIB	1(Both)		+(Both)	0.023
IIIA	1(Premenopause)	+(Premenopause)		0.025
IIIB	1(Both)		+(Both)	0.031
IV	1(Premenopause)		+(Premenopause)	0.022
Tx				

Table 7: Association between PSA and Clinico-pathological variables

Variable	No. of patients	Mean Serum PSA value (ng/ml)
Age(Years)		
<50	44	0.02
50+	20	0.021
StageI	3	0.03
II	11	0.033
III	41	0.011
IV	9	0.024
Nodal Status		
Negative	4	0.02
Positive	60	0.032
Tumour Size(cm)		
<1.5	3	0.023
>1.5	61	0.03
Estrogen Receptors		
Negative	9	0.029
Positive	35	0.034
Progesterone Receptors		
Negative	24	0.021
Positive	17	0.032
Relapse		
No	62	0.02
Yes	2	0.023
Death		
No	61	0.033
Yes	3	0.035

DISCUSSION

Study was performed in the Department of Biochemistry & Department of Surgery, Subharti Medical College, Meerut.

We included 64 carcinoma breast patients in our study. 27 patients of premenopausal state and 16 of postmenopausal state admitted to this hospital having disease other than cancer act as control groups. Values of Prostate Specific Antigen in the serum of patients and of control group was found to be <0.04ng/ml.

The patients of carcinoma breast were divided into two main groups i.e., premenopausal and postmenopausal. They were further classified according to UICC system.

According to Stages, the distribution of patients was as follows-

In Premenopausal state 3.1% were of stage I disease, 4.69% of stage IIA, 3.1% of stage IIB, 15.62% of stage IIIA, 21.87% in stage IIIB and 6.25% were of stage IV disease.

Among the postmenopausal state 1.56% were of stage I disease, 3.1% of stage IIA, 6.25% stage IIB, 12.5% of stage IIIA, 14.06% of stage IIIB and 7.81% were of stage IV.

In our study, most of the patients were found to be in stage III (Stage IIIA and IIIB) and in stage IV, both in premenopausal as well as postmenopausal groups.

We have estimated the level of serum PSA in patients of breast cancer and also in age matched controls in both pre and postmenopausal groups. The PSA levels in breast cancer patients as well as in controls were found to be identical (i.e., <0.04ng/ml) irrespective of their menopausal status. Thus the PSA level in serum failed to show any diagnostic value in cancer breast.

Lehrer S *et al*. [13] proposed that PSA is a secreted gene product which can accumulate within the tumour milleu, and may eventually enter the circulation. PSA thus released into serum may be easily measurable diagnostic and prognostic biochemical marker.

The utility of serum PSA as a diagnostic marker was, however, questioned by other status. M. Giai *et al*. [15] after a study on two hundred primary breast cancer patients status that serum PSA in women does not have potential for diagnosis or monitoring. Similarly Romppanen *et al*. [14], on the basis of a prospective case control study involving 2500 women which was included 90 histologically confirmed breast cancer patients have concluded that serum total PSA levels in benign disease and in breast cancer patients are not statistically different from those of healthy controls.

The stage of disease failed to show any correlation with PSA value in our study. This is consistent with the observations of Romppanen *et al*. [15] who observed the values to be having no significant difference among controls, breast cancer patients and those with benign breast disease. They observed that serum total PSA cannot be used to distinguish between healthy women and/or women with breast cancer or benign breast disease.

Giai M *et al*. [15] concluded after an extensive study that serum PSA levels are not useful for breast cancer patient diagnosis or monitoring. However, tumour levels of PSA appear to be valuable for breast cancer patient prognosis since patients with PSA positive tumours have much longer disease free and overall survival. This tumour cystolic PSA concentration, however, does not seem to influence the PSA concentration in the serum of breast cancer patients.

Our observations, however, do not support those of Diamendis EP *et al*. [16]. These authors have suggested that serum PSA is a potential prognostic indicator in breast cancer patients.

No correlation was found to be present between the values of PSA in serum of patients in different age groups. The values were similar (i.e., <0.04ng/ml) in patients and controls of different age groups.

The mean serum PSA value was same in patients of all tumour grades. This was also the same inpatients in both pre as well as postmenopausal groups. The grade of tumour, therefore, does not have any bearing on the serum total PSA level.

The patients in our study were divided into three subgroups according to the number of lymph nodes-

- Patients without lymph nodes involvement
- Patients with <3 lymph nodes involved
- Patients with >3 lymph nodes involved

These subgroups were further divided according to menopausal status. The value of serum was found to be similar in all these subgroups and the serum PSA thus failed to correlate with the number of lymph nodes in pre as well as postmenopausal patients.

Serum PSA levels were measured in breast cancer patients before the starting of definitive therapy, and was followed up at 3 monthly intervals. The levels

did not show any fall after surgery or chemotherapy, nor was any rise in serum PSA level observed as two of our patients had relapse. The administration of anterior chemotherapy also did not affect the serum PSA values and they remained the same before CTx, after CTx and after completion of treatment and also in follow up. So the serum PSA failed to demonstrate any prognostic implication in monitoring of breast cancer patients.

The findings of our study correlate very well with study of Giai M *et al*. in 1995[16]. They observed that high levels of tumour PSA were not correlate with high PSA levels in the presurgical sera. Serum PSA concentration in this study was not higher in patients with PSA positive breast cancers than in PSA negative cancers. When matched presurgical and postsurgical sera were examined, the PSA status in serum did not change significantly when the cancer was removed.

Yu H *et al*. [11] observed in 1995 that after adjusting for most of the variables studied, i.e., age, clinical stage, tumour size, histological grade, nodal status, ER and PR, PSA positive tumours still have a significantly decreased risk for relapse when compared to PSA negative patients. In contrast, our data did not show any correlation with risk of relapse and total serum PSA levels. They have further observed that in ER positive group, the risk of relapse was almost identical between PSA positive and PSA negative tumours. However, in the ER negative group, the risk for relapse was substantially reduced when the tumours were PSA positive. It may therefore, be helpful in detecting a subset of ER negative patients who are likely to behave favourable to adjuvant therapy and are going to have better survival and prognosis.

Our study also did not find any correlation of total peripheral PSA and DNA index, or S-phase fraction, ER/PR receptor status of the tumour. All these indicators are established tumour markers but total PSA was not affected by any of these variations.

A few studies have suggested that the serum PSA originates from tumours itself. The peripheral PSA levels, should therefore, have risen linearly with increased in tumour burdon and should have decreased with removal of tumour. Our observations do not support this hypothesis. Our data are consistent with other studies which suggest that serum PSA levels do not have any relation with prognosis in breast cancer patients, and tumour PSA positivity or negativity does not have any bearing on serum PSA levels.

CONCLUSION

- 54.69% of the breast cancer patients were premenopausal and 45.31% were postmenopausal.
- Maximum patients were found to be in stage III (37.5% of premenopausal and 26.56% of postmenopausal).
- 30.8% of premenopausal patients had an ER receptor positive tumour. The percentage of such patients in postmenopausal group was 61.1%.
- Most of the tumours in postmenopausal females were ER positive.
- 28.13% of premenopausal and 21.88% of postmenopausal patients had >3 lymph nodes affected.
- Peripheral PSA is not an acceptable biochemical parameter for the diagnosis, reponse to treatment and detection of early recurrence during follow up in breast cancer patients

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