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Correlation of serum prostatic surface antigen (PSA) values with various prostatic histopathological biopsy lesions

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Abstract

Introduction: Prostatic cancer among males is the most common neoplasm in most developed countries. Prostate Specific Antigen (PSA) has been widely used in screening, diagnosis and management of patients with prostate cancer. However, it may be elevated in other prostatic lesions and surgical procedures as well.

Objectives: The objective was to determine the relationship between serum PSA levels and histologic findings in corresponding biopsy specimens and also to determine the efficacy of serum PSA levels in screening of prostatic carcinoma.

Results: 30 prostatic biopsies were studied and their corresponding PSA values obtained. These were diagnosed on histopathology as Benign Prostatic Hyperplasia (BPH); BPH with inflammation; Prostatitis and Prostatic Adenocarcinoma. In these, 22(73.33%) were diagnosed as BPH with PSA levels ranging from 4ng-22ng/ml. 3 patients(10%) were diagnosed as BPH with inflammation with PSA level ranging from 1.17ng/ml-11.98ng/ml. 1 case(3.33%) diagnosed as Prostatitis had PSA level 110.22ng/ml. 4 patients(13.33%) diagnosed with adenocarcinoma, had PSA ranging from 8.9ng/ml-2584.42ng/ml. One patient (25%) however showed PSA value of 8.9ng/ml. Mean serum PSA value was 120ng/ml.

The positive predictive value for increasing PSA levels was 18.18% for PSA>4ng/ml; 27.2% for PSA>10ng/ml; 50% for PSA>20ng/ml and 75% for >100ng/ml.

Conclusion: Serum PSA level elevation usually implies Prostatic carcinoma. However it may be elevated in other benign lesions of prostate; or the levels may not always be elevated in carcinoma. Thus, given a significant number of false positives and false negatives, it cannot be regarded as a 100% accurate screening marker in assessing an individual's risk for prostatic ca.

Keywords: Serum PSA, screening, Prostatic Carcinoma

Introduction

Tumor markers are substances present in, or produced by, a tumor itself or produced by host in response to a tumor that can be used to differentiate a tumor from normal tissue or to determine the presence of a tumor based on measurements in blood or secretions [1, 2].

Prostate cancer is the second most common cause of cancer and the sixth leading cause of cancer death among men worldwide. It is the second leading site of cancer among males in large Indian cities like Delhi, Kolkata, Pune and Thi'puram, and third leading site of cancer in cities like Bangalore and Mumbai [3].

Looking at the rise in mortality associated with Ca Prostate, there's an undoubted need for an efficient, easy to perform, widely acceptable, cost effective screening tool for diagnosis of prostatic cancer at an opd based setting.

Prostate Specific Antigen (PSA) has emerged as the most applicable and important tumor marker for carcinoma prostate [4]. It is a serine protease produced by ductal and acinar epithelial cells of normal, hyperplastic, and malignant tissue of the prostate. First identified by Wang *et al* [5] in 1979, it has become a widely used serum marker for early detection and monitoring of patients with prostate cancer (PCa) [6-8]. It provides the clinicians with unique and important information about the diagnosing, staging and monitoring of patients with prostatic cancer [9].

However it is now evident that a raised PSA level can also occur in non-malignant conditions like Benign Prostatic Hyperplasia (BPH), inflammation, and as a result of various diagnostic and surgical procedures. These conditions may raise serum PSA level and cause unnecessary

paranoia amongst individuals and also a presumptive misleading of treatment plans in Prostatic Carcinoma detection programs that use PSA as a screening test [10]. Therefore, the objective of this study was to determine the relationship between serum PSA levels and histological findings in corresponding biopsy specimens; and also to determine the efficacy of serum PSA levels in screening of prostatic carcinoma.

Materials and Methods

A total of 30 TURP (Transurethral Resection of Prostate) specimens obtained from Department of Surgery. A detailed history of every patient with particular reference to age, presenting complaints of obstructive voiding such as hesitancy, poor flow, intermittent stream, dribbling, sensation of poor bladder emptying, episodes of retention and irritative symptoms like frequency, nocturia, urgency, urge incontinence and abnormality on DRE were recorded. All patients underwent thorough general physical examination, abdominal examination including genitourinary examination. Indications of biopsy were suspicion of malignancy on Digital Rectal Examination and increased serum PSA values. The serum PSA levels were determined in Biochemistry dept. There was no immediate manipulation on prostate (DRE, prostate massage, endoscopic examination) before taking a blood sample for PSA. The received TURP biopsy specimens were routinely processed in the dept of Pathology, KVG Medical College & Hospital. Samples were fixed in 10% formalin and embedded in paraffin. Thin-cut sections were stained with Hematoxylin and Eosin (H&E) and a histopathological diagnosis was established for each case. Results were computed using data percentage analysis and SPSS software analysis.

Results

The mean age of the patients in the study was 65.4 years. A histopathological correlation with serum PSA value was made in each case and documented. Out of 30 cases, the most common diagnosis made was Benign Prostatic Hyperplasia (BPH) in 22 cases (73.3 %) followed by Prostatic Adenocarcinoma (13.3%), BPH with inflammation (10%) and Prostatitis (3.3%). (Table 1)

Table 1: Histopathological Diagnosis

Histopathological diagnosis	n	%
Benign Prostatic Hyperplasia	22	73.3%
Adenocarcinoma	4	13.3%
BPH with inflammation	3	10.0%
Prostatitis	1	3.3%

In our study, 22 cases (73.33%) were diagnosed as BPH with PSA levels ranging from 0.22ng-22ng/ml. Another 3 patients (10%) in the study were diagnosed as BPH with inflammation with PSA level ranging from 1.17ng/ml-11.98ng/ml. 1 case (3.33%) diagnosed as Prostatitis had PSA level 110.22ng/ml. 4 patients (13.33%) that were diagnosed with adenocarcinoma, had PSA levels ranging from 8.9ng/ml-2584.42ng/ml. One patient (25%) however showed PSA value of 8.9ng/ml. Mean serum PSA value in the study was 120ng/ml. The above data has been tabulated below in Tables 2, 3 & 4.

Table 2: PSA in patients with Benign Prostatic Hyperplasia

PSA (ng/ml)	N	%
<4	8	36.3%
4-10	9	40.9%
10-20	4	18.18%
>20	1	4.54%

(Range of serum PSA: 0.22 to 22ng/ml)

Table 3: PSA in patients with Adenocarcinoma

PSA(ng/ml)	N	%
<4ng/ml	0	0
4-10ng/ml	1	25%
10-20ng/ml	0	0
>20ng/ml	3	75%

(Range of serum PSA: 8.9 to 2584.42 ng/ml)

Table 4: PSA in Patients with BPH with Prostatitis

PSA	N	%
<4ng/ml	0	0
4-10ng/ml	1	33%
10-20ng/ml	1	33%
>20ng/ml	1	33%

(Range of serum PSA: 4.17ng/ml to 21.98ng/ml)

The positive predictive value i.e. the ability of the screening tool to correctly detect carcinoma at various PSA cut-off levels was observed to be 18.18% for PSA>4ng/ml; 27.2% for PSA>10ng/ml; 50% for PSA>20ng/ml and 75% for >100ng/ml, depicted in the table below.

Table 5: PPV for increasing PSA cut off values

PSA	Positive Predictive Value
>4ng/ml	18.18%
>10ng/ml	27.27%
>20ng/ml	50%
>100ng/ml	75%

Discussion

PSA is produced exclusively by the epithelial cells lining the prostatic acini and ducts of prostatic tissue. Because of its high specificity for prostate tissue, PSA is the preferred serum marker for PCa. Unfortunately, PSA is specific for prostate tissue but not for prostate cancer. Moreover, it is also found in abnormal concentrations in normal and benign changes of the prostate such as BPH and other non-neoplastic prostatic lesions. Hence usefulness of PSA as an early detector of prostate cancer by itself is questionable, owing to the overlap in values in various conditions. The clinically applicable reference values of PSA is from 0 - 4.0 ng/mL. Values above 4ng/ml raises suspicion of malignancy warrants serial determination of the values. Majority of the cases with prostatic carcinoma have been observed to have a PSA value raised above 10ng/ml [10, 11]. Upon correlating the PSA values with corresponding histopathological diagnosis, we laid out a number of observations. The incidence of benign and malignant cases respectively in our studies was 86% and 13.3% respectively, which correlated with studies conducted by Chetal *et al* [12], and Akhter *et Al* [13] as illustrated below in the table 6.

Table 6: Comparison of incidences of benign and malignant lesions on histopathology

Lesion	Our study	Chital <i>et al</i>	Akhter <i>et al</i>
Benign	86%	89%	50%
Carcinoma	13.3%	11%	15%

BPH was the most commonly diagnosed entity on histopathology, showing a microscopic picture of dilated ducts and lumina, with proliferation of benign epithelial cells along with micropapillary projections into the glandular lumen. The serum PSA levels for these patients ranged from 0.22 to 22ng/ml; with 8 cases showing values <4ng/ml. One case however, showed an elevation of >20ng/ml. (Fig1)

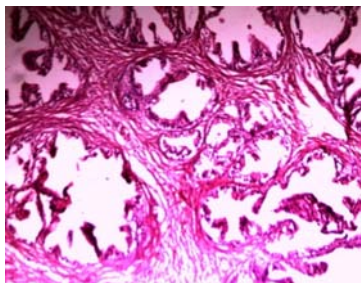


Fig 1: Microphotograph showing features of Benign Prostatic Hyperplasia (10x; Hematoxylin & Eosin)

BPH with inflammation was diagnosed based on histopathology features those of benign prostatic hyperplasia along with lymphocytic aggregates in and around the glandular lumen. (fig.2) All the three cases showed an elevation of >4ng/ml, raising a clinical suspicion of carcinoma. The highest level observed was 21.98ng/ml.

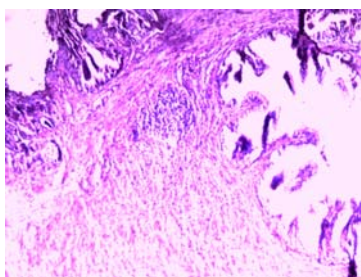


Fig 2: Microphotograph showing features of BPH with inflammation (Hematoxylin & Eosin; 10x)

Prostatitis was diagnosed in one case wherein dense infiltration of lymphocytes in glandular lumen as well as stroma was seen. (fig3)The PSA level for this case was raised to 88.6ng/ml. This finding was consistent with a study conducted by Seamond *et al* [14].

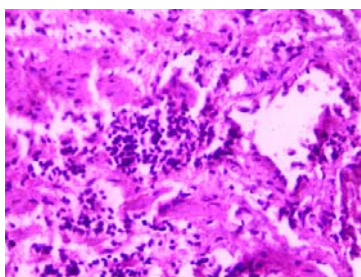


Fig 3: Microphotograph showing features of Prostatitis (Hematoxylin & Eosin; 40x)

According to these observations the presence of inflammatory component significantly raises PSA levels and can be a grave misleading factor in suspicion of carcinoma. Many reports indicate that the serum PSA level is elevated in patients with clinical acute prostatitis [15-17].

The mechanism through which histological inflammation within the prostate elevates serum PSA levels remains poorly understood. The epithelial cells surrounding the affected area may be stimulated to produce PSA through unknown substances released in association with the inflammatory processes [18]. On the other hand, Hasui *et al* suggested that the abnormal elevation of serum PSA levels is caused by leakage of PSA stored in the epithelial cells into the stromal tissue and blood circulating after epithelial cell death [19]. This was again supported by another study by Schattman *et al* [20] where they cited disruption of epithelial integrity by inflammatory infiltrate as the major causative factor for rise in PSA level.

Three cases of adenocarcinoma (Gleason grade 5a) were diagnosed in our study, showing a solid cribriform-like arrangement of tumor cells, lymphatic and perineural invasion of these tumor cells.(fig.4) Out of the three cases, 2 cases showed a value of >20ng/ml while one case showed a value as low as 8.9ng/ml.

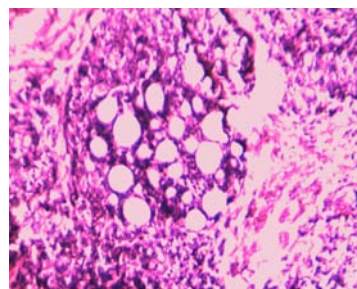


Fig 4: Microphotograph showing features of Prostatic Carcinoma (Hematoxylin & Eosin; 10x)

The positive predictive value of PSA in detecting prostatic Ca was 18.1% for PSA >4ng/ml; 27.2% for PSA >10ng/ml; 50% for >20ng/ml and 75% for >100ng/ml.

Hence the ability of the marker to correctly predict carcinoma showed an increase with increasing cut-off levels of serum PSA; and at no level it showed a ppv of 100%. This reinforces the fact that at any cut off level, PSA cannot accurately predict an individual as being inflicted with carcinoma. These findings were found consistent with Berman *et al* [21] and Akhter *et al*. (Table 5)

Table 7: Comparison of Positive Predictive Values by various authors

Cut off for Serum PSA	Present study	Akhter <i>et al</i>	Berman <i>et al</i>
>4ng/ml	18%	16.6%	50%
>10ng/ml	27.2%	24.2%	60%
>100ng/ml	75%	83.3%	95%

Conclusion

Elevation in serum PSA usually gives rise to suspicion of prostatic carcinoma. But according to the observations made in this study, it was revealed that it may be elevated in several other benign conditions of prostate, and also the levels may not always be significantly elevated in carcinoma. Hence it cannot be regarded as a 100% accurate screening tool in assessing an individual's risk for prostatic carcinoma.

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