

Correlation of prostate specific antigen level with histopathological findings in patients with prostatic disease

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Abstract

Background: Carcinoma of prostate is one of the common tumors of old age in men. Although there is great apprehension in these patients when they are associated with even mild increase in the prostate specific antigen level (PSA) which can be seen in various benign lesions of prostate. With digital rectal examination (DRE), prostate specific antigen (PSA) remains a major screening tool for early detection of prostate cancer. **Materials and method:** The study includes 150 cases who presented clinically as prostatic lesions and in whom the PSA levels and tissue biopsy was available and was further correlated among spectrum of prostatic disease. **Results:** All cases with abnormal DRE were turn out to be malignant lesion on biopsy and was found that the cut off of PSA level for malignancy was 19.5ng/ml. The median PSA levels for benign prostatic hyperplasia (BPH), prostatitis, prostate intraepithelial neoplasia (PIN) and adenocarcinoma is 5ng/ml, 10 ng/ml, 14 ng/ml and 81ng/ml respectively. Statistically there was no significant difference of the PSA levels between low grade prostate intraepithelial neoplasm and high grade. **Conclusion:** In Benign prostatic lesion, PSA level ranges between 0 to 4.0ng/ml. The cut off value of 19.5ng/ml of PSA is most sensitive and specific for the detection of malignant lesion in the prostate. In addition to elevated level of more than 4.0ng/ml and abnormal DRE with TURP biopsy is most useful and accurate diagnostic method for prostatic lesions. All raised PSA levels cases were not malignant thus it is required to use this biochemical marker judiciously to minimize the apprehension among these patients.

Keywords: Prostate, Prostate intra-epithelial neoplasm, Prostate specific antigen, Digital rectal examination

Introduction

The incidence of prostate cancer is rising worldwide as a consequence of transition of world adult population into elderly population resulting in a great apprehension in patients as well as clinicians if they encounter increased prostate specific antigen (PSA) levels.

This is attributed to the improvement of health services, and more importantly understanding the sensitivity and specificity of PSA levels in diagnosing various prostate diseases with the help of prostate specific antigen (PSA) testing. The rationale for screening is the detection of early disease (organ confined) which is amenable to cure [1, 2].

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Material and Method

A total of 150 cases who presented with prostatic disease and in those tissue biopsies with serum PSA levels were assessed, were included in this study which were done in the Department of Pathology, Kasturba Hospital, Manipal from January 2014 to January 2016. Out of total 150 cases, 108 cases were from trans-urethral resection specimen, 39 cases of needle biopsies, two cases of trans-urethral resection with de-roofing and one case of total prostatectomy. Relevant clinical and radiological investigations were collected from case files with the intention to observe the usefulness of PSA levels in various prostatic diseases including prostatic adenocarcinoma. Cases with only tissue biopsy or with only PSA levels were excluded.

Results

Linear correlation of disease in prostate was seen in various age groups. With the advancement of the age the transition of the disease was seen from most benign lesion to more aggressive malignant disease (Table 1). The presenting complaints were very widely spread and duration of these complaints ranged from as less as one week to a long duration of two years. There was no significant difference found between the mode of presentation of benign and malignant disease. Majority (73%) of the patients presented with obstructive lower urinary tract symptoms which included difficulty in micturition, burning micturition, nocturia and increased frequency of micturition. Digital rectal examination (DRE) in combination with PSA can help in the detection of various prostatic lesions. All with abnormal findings on DRE were grouped under suspicious and were further confirmed on histology (Table 2). It was also noted that most of the cases with suspicious on DRE turned out to be adenocarcinoma on histo-morphological examination.

Table-1: Distribution of cases in different age groups (n= 150).

Age	BPH	PROSTATITIS	PIN	ADENOCARCINOMA	TOTAL
40 – 50	2(28.6%)	3(42.9%)	2(28.6%)	0	7
51 – 60	18(48.6%)	10(27%)	3(8.1%)	6(16.2%)	37
61 – 70	15(30.6%)	16(32.7%)	8(16.3%)	10(20.4%)	49
71 – 80	17(38.6%)	14(31.8%)	7(5.9%)	6(13.6%)	44
> 80	3(23.1%)	2(15.4%)	3(23.1%)	5(38.5%)	13
Total	55	45	23	27	150

After evaluating various prostatic lesions and comparing them with the PSA levels we found that 100% of the cases with PSA levels of more than 100ng/ml has shown various grades of adenocarcinoma. Maximum variability of PSA levels was seen in cases of benign prostatic hyperplasia (BPH) as compared to inflammation and in-situ neoplasm. (Table 3) Also we found median and interquartile range of various lesions in the prostate when we correlated histological diagnosis with PSA levels. (Table 4)

In case of prostatitis, majority of the cases had a PSA value in the range of 4 – 10ng/ml. The PSA levels were higher in acute prostatitis when compared to chronic prostatitis but statistically there was no significant difference between the two (Table 5). Among prostate intraepithelial neoplasm (PIN) majority of the cases were associated with benign prostatic hyperplasia and also prostatic inflammation. There was only one case which showed exclusively high grade PIN. Also two cases of adenocarcinoma had high grade PIN as an associated lesion. Among the two types of PIN, maximum level of PSA was seen in low grade PIN which had associated BPH and acute prostatitis. Statistically there was no significant difference between the PSA values in low grade and high grade PIN.

Adenocarcinoma was graded according to Gleason's scoring system. Tumors with a Gleason's score of 5 to 7 were considered as moderately differentiated and with a score of 8 to 10 were considered as poorly differentiated. There were no cases with a score of 2 to 4 which are well differentiated tumors. Moderately differentiated tumors had PSA levels above 10ng/ml but less than 100ng/ml. In case of poorly differentiated tumors 9 of total 22 cases had PSA levels above 100ng/ml. Hence the values were higher in poorly differentiated tumors (Table 6).

Table-2: Cases with suspicious DRE having adenocarcinoma.

Age range	DRE Suspicious	Adenocarcinoma
40 - 50	0	0
51 – 60	9	6
61 – 70	10	10
71 – 80	9	6
>80	6	5
TOTAL	34	27

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We also calculated the sensitivity and specificity of PSA to detect malignancy at different cut off points. The serum PSA has a good sensitivity and specificity at a cut off value of 19.5ng/ml, with a sensitivity of 96.3 and specificity of 86.2 seen in this study. It was found that cases with a PSA level above 19.5ng/ml were more of malignant lesions compared to benign (Table 7). The sensitivity, specificity, positive predictive value and negative predictive value at a cut off of 19.5ng/ml were 96.3, 86.18, 60.47 and 99.07 respectively.

Table-3: Distribution of different PSA range in various prostatic lesions.

PSA range (ng /ml)	Histopathology Diagnosis of prostatic lesions				TOTAL
	BPH	PROSTATITIS	PIN	ADENOCARCINOMA	
0 - 4	22	4	4	0	30
4.01 - 10	25	19	4	0	48
10.01 - 20	4	16	8	2	30
20.01 - 100	4	6	7	16	33
>100	0	0	0	9	9

Table-4: Histopathological diagnosis with PSA level.

Cases		PSA (ng/ml)			
		Minimum	Maximum	Median	IQR(interquartile range)
	N				
BPH	55	0.4	46	5	7
ADENOCARCINOMA	27	10	1525	81	97
PIN	23	0.03	58	14	20
PROSTATITIS	45	3	90	10	9

Table-5: Correlation of PSA with prostatitis and PIN.

	n	PSA (ng/ml)			p value
		Minimum	Maximum	Median	
Acute prostatitis	13	3	90	11	0.079
Chronic prostatitis	32	4	27	8	
Low grade PIN	15	0.03	58.3	14.6	0.245
High grade PIN	08	2.8	23.8	15.9	

Table- 6: PSA values in adenocarcinoma of different grade.

Adenocarcinoma	Range of PSA (ng/ml)			Total
	10.01 -20	20.01 - 100	> 100	
Moderately differentiated	1	4	0	5
Poorly differentiated	1	12	9	22
Total	2	16	9	27

Table-7: Cases of adenocarcinoma detected at a PSA cut off point of 19.5ng/ml.

PSA (ng/ml)	Benign lesions	Adenocarcinoma	Total
<19.5	106	1	107
≥ 19.5	17	26	43
Total	123	27	150

Discussion

Prostate specific antigen (PSA) is exclusively produced by the epithelial cells lining the prostatic acini and ducts of prostatic tissue. This high specificity of PSA for prostate tissue has made it a preferred serum marker for carcinoma prostate. However, PSA is specific for prostate tissue but not for prostate cancer. The clinically applicable reference values of PSA is 0 - 4.0ng/mL [3, 4, 5] but even within the normal range of PSA a minimal risk of cancer does exist [4]. Intermediate values that are from 4.0ng/ml to 10.0ng/mL could be seen in patients with BPH, prostatitis, PIN and Prostatic cancer.

Majority of the patients were in the age group of 61 to 70 years. This is comparable to studies done by Jasani et al, [5] Lakhey M et al, [4] and Goswami et al [6] who reported similar age of presentation. Around 73% of the patients in this study presented with obstructive urinary symptoms which was similar to the studies done by FC et al, [7] Cruz J et al [8].

Among all cases, we had 36.6% with BPH, 30% prostatitis, 15.3% of PIN and 18% were adenocarcinoma. DP Murthy et al [9] had the similar findings, in which majority of the cases were of nodular hyperplasia, few of which were associated with prostatitis. In another study by Jasani et al, [5] 56% cases were of BPH, but the second most common lesion was adenocarcinoma in contrast to our study in which it was prostatitis.

If we look at the age of presentation of various prostatic lesions we found that BPH usually has its peak between 51-60 years of age, whereas prostatitis, PIN and adenocarcinoma usually present in the age group of 61-70 years. Similar findings were seen by Jasani et al, [5] whereas Goswami et al [6] had proposed that benign lesions had a mean age of presentation of 68.1 ± 8.1 and malignant lesions had a mean age of presentation of 70.3 ± 5.6 .

In our study, 48% had PSA levels above 10ng/ml which was comparable to a study done by D P Murthy et al, [9] Cavit et al [10] and Goswami et al [6] reported PSA levels of 4.01 to 10ng/ml in majority of their cases. 6% of the cases had a PSA value above 100ng/ml, which was comparable to the study done by D P Murthy et al [9] in which 11% of the cases had a PSA value above this level.

While comparing the serum PSA levels and histo-pathological diagnosis in our study, majority of the cases of BPH had a PSA levels within 10ng/ml. All the malignant lesions had values above 20ng/ml, six of them had above 100ng/ml among which one case had a value of 1525ng/ml. All cases with PSA above 100ng/ml were malignant, none were benign on biopsy. In cases of PIN there was no particular range of PSA in which the cases were predominantly distributed

Most of the cases of BPH had serum PSA levels less than 10ng/ml with 45% cases having between 4 – 10ng/ml and the rest of the cases within the normal value of 4ng/ml. In studies done by Jasani et al [5], Lakhey M et al [4] and Kshitij et al [11] majority of the cases had PSA within the normal range. In studies done by Goswami et al [5] and Ishtiaq Ali et al [12] majority of the cases had PSA in the range of 4 – 10 ng/ml which were comparable to our study.

It was also observed that majority of the cases with acute prostatitis had PSA level above 10ng/ml in contrast to the study done by Yamamoto et al [13] in which PSA levels was equally distributed in different ranges. Most of the cases of chronic prostatitis had PSA in the range of 4.01 to 10ng/ml in contrast to Yamamoto in which PSA levels was within the normal range. Jasani et al [5] had 5 cases of chronic prostatitis with PSA value within 10ng/ml.

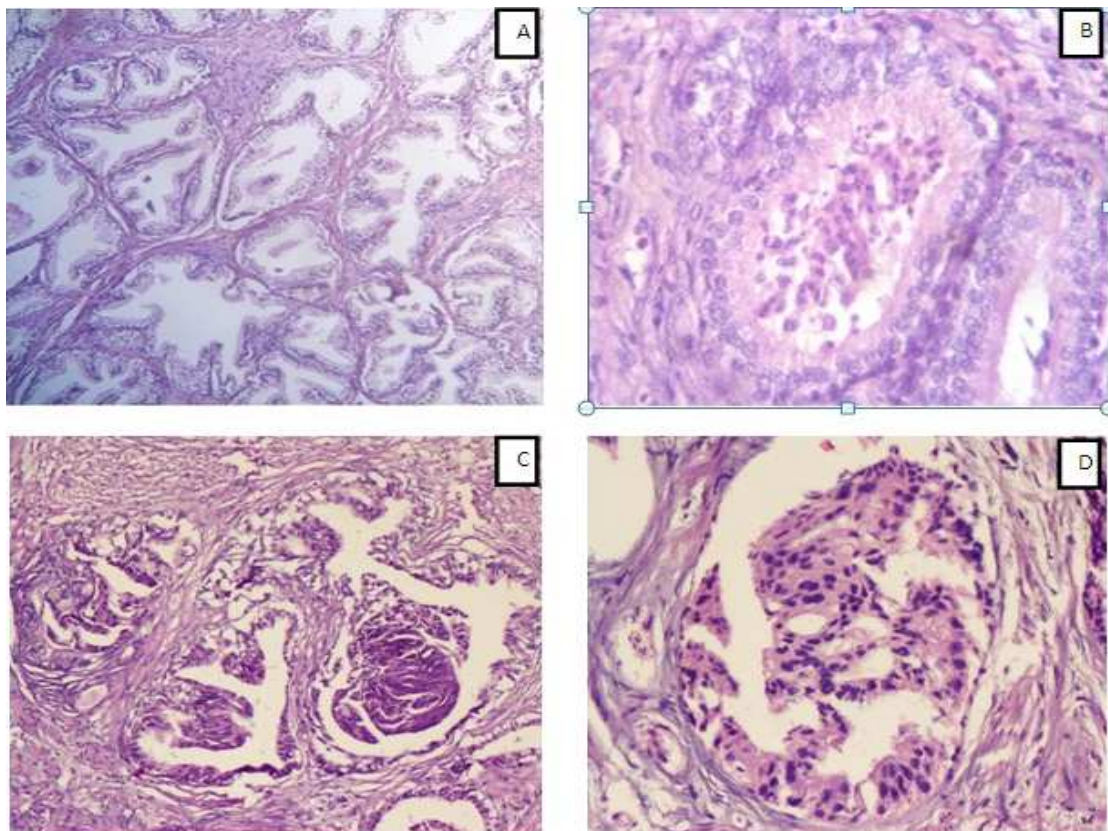
Prostate intraepithelial neoplasm (PIN) being a premalignant condition does not cause significant elevation in the serum PSA. In the present study, PSA levels in cases of PIN had a minimum of 0.03ng/ml and a maximum of 58.3ng/ml, median value being 14ng/ml. In a study done by Brawer et al [14] the minimum, maximum and median values of PSA in a study of 19 cases of PIN were 0.2ng/ml, 19.2ng/ml and 4ng/ml respectively. Porter J R and Brawer M K [15] reported 25 cases of PIN in whom PSA levels were in the range of 0.2 to 19.2ng/ml with a mean PSA value of 7.8ng/ml, they also compared the PSA levels in benign and malignant prostatic lesions to conclude that the levels in PIN were intermediate between these two groups.

The median PSA level in case of low grade PIN was 14.6ng/ml. All the cases of low grade PIN were associated with BPH. The maximum value was 58.3ng/ml which can be attributed to the associated BPH and prostatitis. Osman Nuri et

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al [16] had reported the average PSA value in cases with low grade PIN was 11.32 ± 6.71 . In our study 10 of the total 15 cases of low grade PIN had PSA values above 10ng/ml. The higher levels of PSA in low grade PIN can be attributed to the associated BPH and prostatitis as is mentioned in other studies.

In cases of high grade PIN the minimum, maximum and median values of PSA were 2.8 ng/ml, 23.8ng/ml and 15.9ng/ml respectively. Out of the total eight cases, five cases had PSA levels between 10ng/ml to 20ng/ml. In his study, Benjamin Kulovac et al [17] concluded that the serum PSA level for high grade PIN was intermediate between BPH and carcinoma prostate. Also according to the study done by Yang J Y et al [18] the mean PSA level in 21 cases of isolated high grade PIN was 1.9ng/ml with a range of 0.7 ng/ml to 8ng/ml. The study concluded that high grade PIN does not cause significant elevation of serum PSA therefore, adenocarcinoma of prostate should be ruled out as a source of elevated PSA in patients with high PSA and isolated high grade PIN on needle biopsy.



A: X200, H&E Benign prostatic hyperplasia. B: X400, H&E Acute Prostatitis,
C: X200 H&E, Low grade PIN, D: X400, High grade PIN.

In our study, all the 27 cases of carcinoma prostate had PSA level above 10ng/ml. This is comparable to other studies in which majority of the cases of adenocarcinoma prostate had PSA above 10ng/ml, except for a study done by Goswami et al,[6] most of the studies in the literature had very few cases of carcinoma with PSA values within the normal reference range. Surprisingly in a study done by D P Murthy et al [9] 28.8% of the total 45 cases had PSA value within the normal range.

The minimum, maximum and median values of PSA in cases of carcinoma were 10ng/ml, 1525ng/ml and 81ng/ml respectively. Also in a study done by W Obara et al [3] the minimum, maximum and median values in carcinoma prostate were 24.53ng/ml, 333ng/ml and 58.3ng/ml respectively. In another study done by DP Murthy et al [9] the PSA levels in prostatic malignancy had a range of 3.9ng/ml to 629.5ng/ml.

We have also assessed the sensitivity and specificity of different cut off points of PSA in detecting malignancy. At a cut off value of 19.5ng/ml the sensitivity, specificity, positive predictive value and negative predictive value were 96.3,

86.18, 60.47 and 99.07 respectively. In a study done by W obara et al [3] the sensitivity of PSA for carcinoma prostate at cut off point of 4ng/ml and 10ng/ml were 89.8% and 83.7% respectively, specificity was 37% at 4ng/ml and 66% at 10ng/ml. In the same study the positive predictive value at 4ng/ml and 10ng/ml were 49% and 63% respectively. The cut-off point of 19.5ng/ml in our study is much higher compared to other studies.

While PSA level measurement is currently the best single test for early prostate cancer detection, digital rectal examination can also identify men with the disease. Studies done by Bretton et al [19] and Catalona et al [20] have suggested that combining both tests improves the overall rate of prostate cancer detection when compared to either test alone. In our study all the cases with abnormal digital rectal examination had abnormal PSA value and 79.4 % of the cases had malignant lesion on biopsy.

Conclusion

Prostate specific antigen (PSA) is specific for the organ prostate, this biochemical marker should be used in conjunction with digital rectal examination and biopsy (Needle or trans-urethral resection specimen) if required, to identify the benign or premalignant condition (PIN). We, in this study show that PSA >10ng/ml is seen in PIN and adenocarcinoma. The cut off value of 19.5ng/ml of PSA is most sensitive and specific for the detection of malignant lesion in the prostate. In Benign prostatic lesion, PSA level is in between 0 to 4.0ng/ml. Present study shows that DRE and PSA are the most useful front line methods for assessing and individual's risk of prostate cancer. In addition to elevated level of more than 4.0ng/ml and abnormal DRE with TURP biopsy is most useful and accurate diagnostic method for prostatic lesions.

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