# Correlation between Prostate Specific Antigen and Acid Phosphatase with Histopathological Findings in Various Prostatic Pathologies

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***Abstract***

***Background****: Prostatic enlargement can be due to tumor or other causes in old age which causes significant morbidity and mortality. Prostatic cancer and benign prostatic hyperplasia are two common entities which affects the prostate. Prostate cancer is increasing in its frequency day by day.*
***Aim****: To correlate the values of PSA (total and free) and free PSA/total PSA ratio, and acid phosphatase (total and tartrate labile) with histopathological findings.*
***Material and Methods****: The study was conducted in 100 patients in the age group 50-80 years. Serum acid phosphatase (total & tartrate labile) and serum PSA (total and free) estimations were done in all cases with appropriate controls (10 age matched controls were selected for serum studies). TURP chips from patients were sent to the department of Pathology for histopathological examination and correlated with serum acid phosphatase and PSA levels.*
***Results****: Serum acid phosphatase levels (total and tartrate labile) in patients with BPH and prostatic carcinoma were found to be 8.218±2.75U/L, 1.47±0.35U/L and 17.386±5.28U/L, 14.048±4.92U/L respectively. The total PSA, free PSA and free/total PSA ratio in patients with BPH and prostatic carcinoma were found to be 9.62±2.47ng/ml, 2.91±0.63ng/ml, 0.304±0.032 and 22.42±12.37ng/ml, 1.59±0.83ng/ml, 0.072±0.01 respectively. In histopathology, 75 cases were diagnosed as BPH and 25 as prostatic carcinoma.*
***Conclusion****: Free PSA/ total PSA ratio is a better marker of prostatic carcinoma than total PSA and acid phosphatase levels and thus this investigation can prevent unnecessary invasive prostatic biopsies to a great extent.*

**Keywords**: *Benign prostatic hyperplasia, prostatic carcinoma, prostate specific antigen, acid phosphatase*

## I. INTRODUCTION

Prostatic cancer is the most common tumor of males in developed countries. It has been estimated that over 200,000 men in United States are diagnosed annually with prostate cancer and 300,000 men still die from this disease each year. Prostate cancer incidence is increasing in India too. Currently, it ranks 5th in incidence and 4th in mortality for men in Mumbai [1]. It accounts for 33% of all malignant tumors in men and responsible for 9% of all deaths due to cancer [2]. Carcinoma of the prostate is the most common form of cancer in men in the United States and is responsible for 10% of cancer death in this population [3].

### *A. Anatomy [4]*

In the course of first 3 months of intrauterine life the prostate develops from endodermal buds from urogenital sinus and lining of primitive urethra. The surrounding mesenchyme condenses to form the stroma of the gland. Prostate utricle develops in the region of mullerian tubercle similar to uterus or vagina in females. The prostate is an accessory gland of the male reproductive system which is a fibromuscular gland. The prostate consists of stromal and glandular components. Smooth muscle cells, fibroblasts and endothelial cells are in the stroma. The glandular component is composed of acini and ducts which contain neuroendocrine cells, secretory cells and basal cells. The prostate has the greatest number of neuroendocrine cells of the genito-urinary organs. Most cells contain serotonin; others include somatostatin, calcitonin and katacalcin. The cells co-express PSA and prostatic acid phosphatase. The ducts and acini are recognized at low power magnification. With advancing age the ducts become complex and glands branched and arranged in lobules and surrounded by stroma.

### *B. Biochemical parameters*

In the 1940s and 50s prostatic acid phosphatase (PAP) emerged as the world's first clinically useful tumor marker. But in 1980s PAP fell in disapproval as PSA performed remarkably better than PAP in all aspects. In patients with high risk prostate cancer several studies have established PAP as an important predictive factor. In high-risk patients who need high levels of chemotherapy or radiotherapy, PAP is considered to be valuable to predict distant failure [5]. Due to its poor sensitivity, PAP fell in disapproval. Thus PSA emerged as a better screening and monitoring tool for prostate cancer and therefore PAP's strength was overlooked

[6]. But PAP may still turn out to be a clinically valuable tool.

In 1979 Wang et al first identified prostate specific antigen (PSA) [7]. PSA is produced and secreted into seminal fluid at high concentrations. It is the first designed serum marker for the detection and monitoring of prostate carcinoma [8]. Its use as a marker for prostate cancer is attributed to the fact that normal prostate with intact basal layer has very low serum levels while disruption causes elevated levels of PSA. Immunoreactive PSA (total PSA [tPSA]) exists in two forms, a major fraction is bound to serum proteins (cPSA) and about 10-30% is free (fPSA). Values of tPSA between 4.0 and 10.0 ng/ml can be used to improve the specificity of PSA for prostatic carcinoma [9].

Conventionally, PSA level below 4 ng/ml is considered to have less likelihood for detectable prostatic cancer while above 4 ng/ml is considered abnormal. Values higher than 10 ng/ml strongly supports prostatic cancer while values between 4-10 ng/ml is a diagnostic gray zone. Thus prostate–specific antigen (PSA) has been considered as a very important tumour marker for prostatic carcinoma. A drawback of PSA is that is has been found to be elevated in benign prostatic conditions. Hence, effort to improve specificity was made and concluded that percent free prostate specific antigen is a better diagnostic tool for prostatic cancers [10]. Percent free PSA is lower in prostatic carcinoma than other benign prostatic conditions [11]. Finally histopathological changes detected on biopsies or resected prostatic tissue is the hallmark for the diagnosis of prostatic carcinoma [12].

Systemic therapeutic options for prostate cancer are improving. Several studies suggest that PAP could determine the benefit of aggressive adjuvant therapy in early stage patients [13, 14].

### *C. Histopathological findings [15, 16]*

#### *1) Normal prostate*

Normal prostate is composed of glands lined by two layers of cells: a basal layer of low cuboidal epithelium covered by a layer of columnar secretory cells. In many areas there are small papillary infoldings of the epithelium. These glands are separated by abundant fibromuscular stroma.

#### *2) Benign Prostatic Hyperplasia (BPH) or Nodular Hyperplasia*

Microscopically, prostate appears nodular. The composition of the nodules ranges from purely stromal fibromuscular nodules to fibroepithelial nodules with a glandular predominance. The glands are cystically dilated and lined by inner columnar and outer flattened epithelium.

#### *3) Adenocarcinoma*

In approximately 70% of cases, carcinoma of the prostate arises in the peripheral zone of the gland. Characteristically, on cross-section of the prostate the neoplastic tissue is gritty and firm. Microscopically, well defined gland pattern is seen. The glands are small and lined by a single layer of cuboidal to low columnar epithelium. The glands are crowded and lined by a single layer of cells with absence of outer basal layer. There is absence of gland branching or papillary infoldings. The cytoplasm of the tumor cells are pale-clear to amphophilic. Nuclei are large with one or more large nucleoli.

## II. MATERIAL & METHODS

The study was carried out prospectively at PKDAS in the Department of Pathology from November 2014 to May 2015 in 100 patients in the age group 50 – 80 years. Permission was obtained from the institutional ethics committee for conducting the study. Patients underwent routine blood tests along with biochemical parameters. After taking informed consent, the patients underwent TURP from the Department of Urology and the specimen was sent to the Department of Pathology for histopathological examination

### *A. Estimation of Biochemical Parameters*

Blood samples were taken before transurethral resection of the prostate and a week after digital rectal examination. Ten age matched control subjects were selected for serum studies.

a) Estimation of Acid phosphatase (Total and tartrate labile)
   Kinetic colorimetric method was used and absorbance read at 405nm by using micro lab 200 semi-auto-analyser.
b) Estimation of PSA - ELISA method.
c) Estimation of free PSA - ELISA method.

### *B. Histopathological Analysis*

TURP chips were fixed in 10% fresh formalin. After fixation, the tissues were processed for routine paraffin study. Sections of 3-5µ thickness were cut and stained routinely by H & E stain. Histopathological diagnosis was given as benign prostatic hyperplasia or carcinoma. Gleason's grading was done in carcinoma patients. The results of histopathology and biochemical parameters (serum acid phosphatase and PSA) were correlated and analyzed.

#### *1) Gleason Score*

Prognosis of prostate carcinoma is assessed with the help of Gleason score. The score ranges from 2 to 10. Based on 2 patterns on microscopy i.e. primary pattern (comprises most of tumor) and secondary pattern (comprises less of tumor) the grades are set by adding together these patterns to create Gleason score. Based on scoring the lesions are

considered low grade (2-6), moderate grade (7) and high grade (8-10). Gleason score in this study was determined using figure 1 and table 1.

**Table 1: Gleason score description**

| Stage | Description |
|---|---|
| 1 | Single, separate, uniform glands in closely packed masses with a definite, usually rounded, edge limiting the area of tumor |
| 2 | Single, separate, slightly less uniform glands, loosely packed (separated by small amounts of stroma), with less sharp edge |
| 3a | Single, separate, much more variable glands, may be closely packed but usually irregularly separated, ragged, poorly defined edge |
| 3b | Like 3a, but very small glands or tiny cell clusters |
| 3c | Sharply and smoothly circumscribed rounded masses of papillary or loose cribriform tumor |
| 4a | Raggedly outlined, raggedly infiltrating, fused glandular tumor |
| 4b | Like 4a, with large pale cells |
| 5a | Sharply circumscribed, rounded masses of almost solid cribriform tumor, usually with central necrosis |
| 5b | Ragged masses of anaplastic carcinoma with only enough gland formation or vacuoles to identify it is adenocarcinoma |

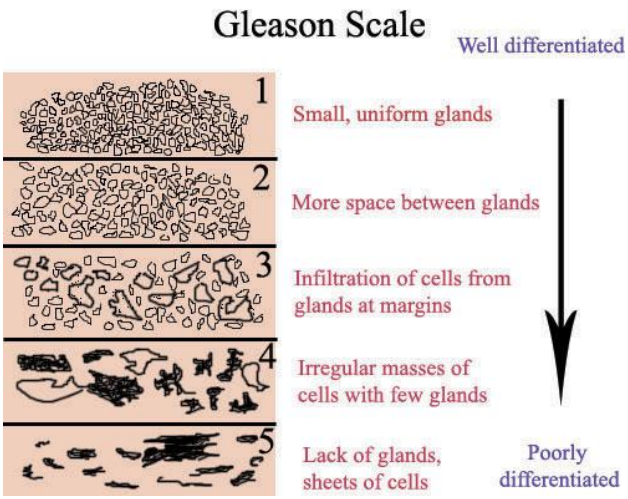


**Fig 1: Gleason score scale**

## III. RESULTS

**Table 2: Histopathological findings**

| Diagnosis | Cases | % |
|---|---|---|
| BPH | 75 | 75 |
| Prostate carcinoma | 25 | 25 |

**Table 3: Gleason score grading**

| Grade | Cases |
|---|---|
| Low | 12 |
| Moderate | 8 |
| High | 5 |

**Table 4: Serum acid phosphatase (total and tartrate labile) levels in controls, BPH and prostate carcinoma patients**

| Group | Cases | Acid phosphatase total (U/L) | Acid phosphatase tartrate labile (U/L) |
|---|---|---|---|
| Normal controls | 10 | 3.61±0.54 | 0.835±0.078 |
| BPH | 75 | 8.218±2.75 | 1.47±0.35 |
| Prostate carcinoma | 25 | 17.386±5.28 | 14.048±4.92 |
| P-value* | | <0.05 | <0.05 |
| Significance level | | Significant | Significant |

*The values obtained for BPH cases are compared with those obtained for carcinoma prostate.

**Table 5: Serum total PSA, free PSA and free/ total PSA levels in controls, BPH and prostate carcinoma patients**

| Groups | Cases | Total PSA (ng/ml) | Free PSA (ng/ml) | f/t PSA ratio |
|---|---|---|---|---|
| Normal | 10 | 1.92±0.78 | 1.07±0.40 | 0.568±0.078 |
| BPH | 75 | 9.62±2.47 | 2.91±0.63 | 0.304±0.032 |
| Prostate carcinoma | 25 | 22.42±12.37 | 1.59±0.83 | 0.072±0.01 |
| P-value* | | <0.05 | <0.05 | <0.05 |
| Significance | | Significant | Significant | Significant |

*The values obtained for BPH cases are compared with those obtained for carcinoma prostate.

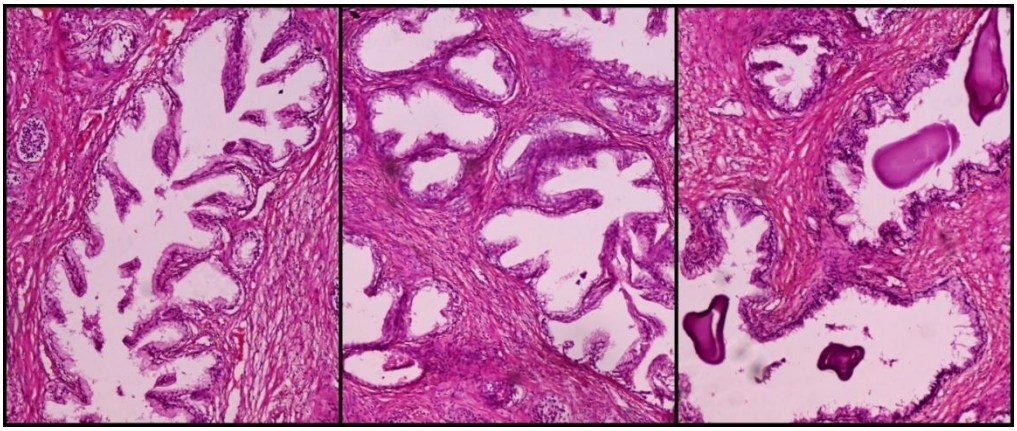

**Fig 2: Photomicrograph of BPH (10x) showing hyperplasia of glands having papillary-like infoldings, lined by myoepithelial cells and the stroma dividing the glands. Gland lumen shows pink corpora amylacea.**

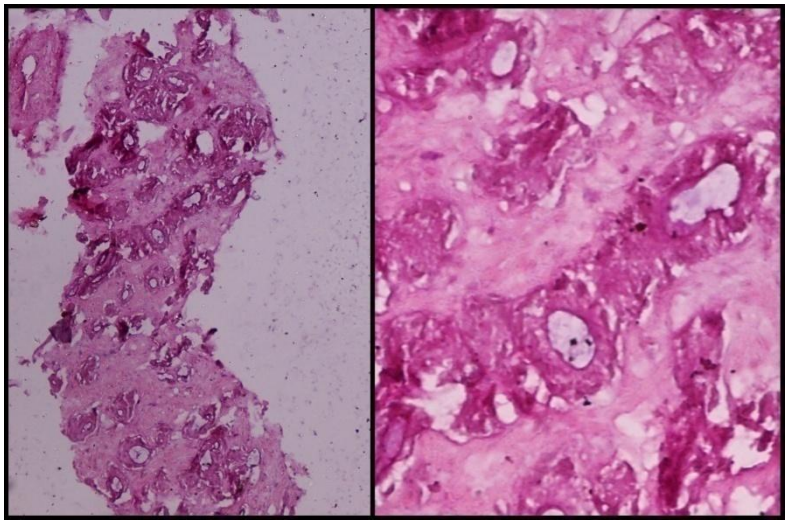

**Fig 3: Photomicrograph of carcinoma prostate (10x, 40x) showing multiple poorly formed glands with ill-defined lumina and/or incomplete nuclear complement. Gleason score 4+3=7**

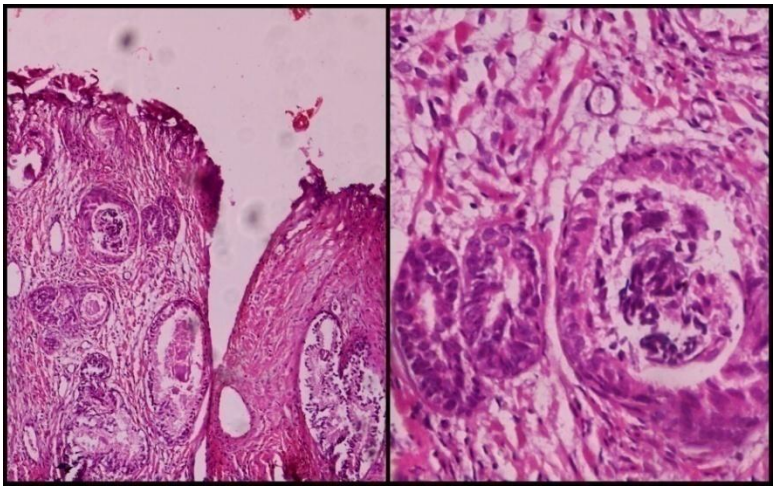

**Fig 4: Photomicrograph of carcinoma prostate (10x, 40x) showing neoplastic glands which are relatively uniform in size and shape (Gleason pattern 2) yet infiltrative around dilated atrophic benign glands (Gleason pattern 3). Gleason score 3+2=5**

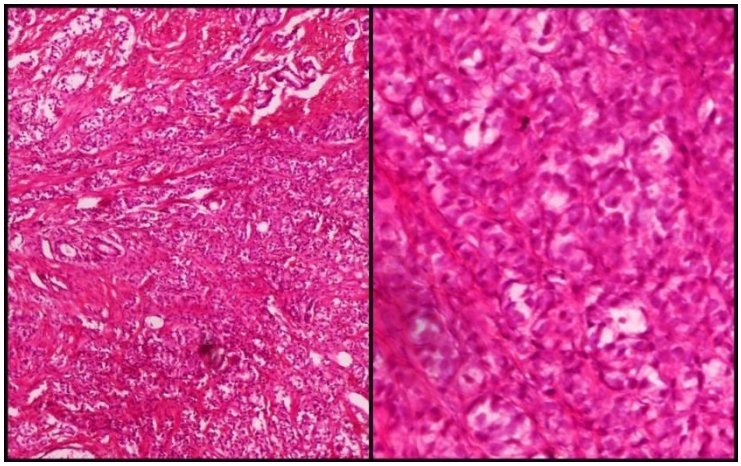

**Fig 5: Photomicrograph of carcinoma prostate (10x, 40x) showing solid sheets of tumor cells with only rudimentary gland formation. Gleason score 5+5=10.**

## IV. DISCUSSION

Although potentially curable, prostate cancer produces no symptoms for long time and majority of the patients seek medical attention only after the onset of symptoms related to advanced or metastatic disease. This accounts for high rate of mortality from prostate cancers. After 50, age-specific incidence rate of prostate cancer increases three or four folds for every 10 year increase in age [17]. Recently, the avenue for the diagnosis of carcinoma prostate has been enhanced by discovery of PSA as a screening tumor marker. PSA is the first organ-specific serum marker and clearly is the most important tumor marker for carcinoma prostate. PSA is produced exclusively by the epithelial cells lining the prostatic acini and ducts of prostatic tissue. PSA is favoured because of its specificity to prostatic tissue. Unfortunately, PSA is specific for prostate tissue but not for prostate cancer as abnormal levels are found in normal and benign changes of the prostate [18].

Serum PSA determination has certain limitations for the diagnosis of prostate cancer. Serum PSA levels are slightly elevated in cases of BPH because of prostate tissue specific protease property of PSA. As one of the tools for discriminating between prostate cancer and benign prostatic disease in patients showing a gray zone, the detection of free PSA and estimation of free PSA/ total PSA ratio have been widely used for improving the diagnostic accuracy especially for increasing specificity.

In the present study statistically significant increase in total PSA and free PSA values in BPH cases were observed. Prostatic carcinoma cases showed an increase in total PSA levels but the free PSA values were found to be < 10% of total PSA. When the total PSA and free PSA values in BPH and prostate carcinoma were compared, a significant difference was observed but also an overlapping of values in BPH and prostatic carcinomas cases were noticed. On the other hand, no such overlapping of

values or gray zone was observed in the cases of free PSA/ total PSA ratio. This clearly indicates that free PSA/ total PSA ratio is a dependable marker for the diagnosis of prostatic carcinoma.

## V. CONCLUSION

Serum acid phosphatase was found to be increased in BPH and prostate carcinoma cases as compared to normal controls, but higher values were observed in prostatic carcinoma cases. The serum level of total PSA and free PSA were found to be increased in BPH cases as compared to normal controls. The values of free PSA was found < 10% of total PSA in prostatic carcinoma cases. Free PSA/ total PSA ratio was > 25% in BPH cases and < 10% in prostate carcinoma cases. Thus free PSA/ total PSA ratio was regarded as a powerful tool to differentiate BPH from prostatic carcinoma cases. Furthermore, this method may prevent invasive prostate biopsies. Thus it may be concluded that free PSA/ total PSA ratio is a better marker of prostate cancer than total PSA and acid phosphatase levels. Finally a histopathological finding is confirmatory for diagnosis.

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