



## Prevalence of Prostate Carcinoma in the Indian Population: The Need to Revise Serum Prostate Specific Antigen (PSA)

*Nandan R. Pujari*

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### ABSTRACT

**Introduction:** This prospective study is an attempt to revise the serum prostate specific antigen (PSA) cutoff level to suit the Asian population.

**Materials and Methods:** A prospective study was carried out on 172 male patients who underwent transrectal ultrasound (TRUS) prostate biopsies. Only those patients with a serum PSA level within the range of 4 to 10 mg/mL were included in this study. The decision to perform the biopsy was undertaken only after further evaluation using free:total PSA ratio.

**Results:** Of the 172 patients, 9 (5.23%) patients had adenocarcinoma prostate with a Gleason's score ranging from 4 to 7. In total, 163 (94.7%) patients had benign pathology. Serum PSA ranged from 4.2 to 9.8 ng/mL.

**Conclusion:** The cutoff level of serum PSA beyond which investigations are warranted in Asians is controversial at present, and further multicentric trials involving a larger number of patients must be carried out to arrive at a consensus.

### INTRODUCTION

Serum prostate specific antigen (PSA) is an invaluable tool for the detection, staging, and monitoring of men diagnosed with prostate cancer. After the clinical application of serum PSA, identification of cancers confined to the prostate has improved curability. Prostate cancer is the fourth most common male malignant neoplasm worldwide; however, the incidence and prevalence of carcinoma prostate in Asia is the lowest in the world, but the serum PSA cutoff value is treated within the same range as their Western counterpart. This leads to unnecessary investigations in this patient populace. Our prospective study is an attempt to revise the serum PSA cutoff level to suit the Asian population.

### MATERIALS AND METHODS

A prospective study was carried out on 172 male patients with serum PSA level within the range of 4 to 10 mg/mL and who underwent transrectal ultrasound-(TRUS) guided prostate

biopsies. Their age ranged from 57 to 72 years (mean age: 65.2 years). They had initially presented with lower urinary tract symptoms in the urology clinic. All patients underwent detailed clinical examination, including a digital rectal examination (DRE). All patients underwent serum PSA examination and an ultrasound examination of the abdomen and pelvis. Only those patients with serum PSA levels within the range of 4 to 10 mg/mL were included in this study. Patients on anticoagulants were not included in the study. Patients with an active urinary tract infection were included in the study only after the infection was treated and the urine culture showed no growth of organisms. The decision to perform the biopsy was undertaken only after further evaluation using free:total PSA ratio. A free:total PSA ratio cutoff of 0.18 was considered the selection criteria for biopsy. An extended core biopsy technique (12 or 13 cores) was used for performing the transrectal prostate biopsies. All patients received antibiotics prior to the biopsy. A single team performed biopsies, a single pathologist saw histological slides, and PSA was determined in the same laboratory using a single method. All these conditions were maintained to minimize

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**CORRESPONDENCE:** Nandan R. Pujari, MS, DNB (Urology), MGM Medical College, Mumbai, Maharashtra, India (pnandan20@gmail.com)

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statistical fluctuation due to interobserver variability.

All patients were asked to follow up 1 week after the biopsy. During the follow-up visit, clinical examination was performed and histopathology reports were reviewed. The most common complication was hematuria, which subsided spontaneously in all patients. None of the patients developed clot retention. Three patients developed urinary infection, which subsided with oral antibiotics. Seven patients reported hematospermia, which subsided by 2 to 3 weeks. Four patients developed urinary retention, which required catheterization. All 4 patients responded to tamsulosin and passed urine on a trial void after 1 week. Patients with adenocarcinoma of the prostate were then further investigated (computed tomography scan and bone scan) and were staged accordingly.

## RESULTS

Of the 172 patients, 9 (5.23%) patients had adenocarcinoma of the prostate with a Gleason's score ranging from 4 to 7 (mean: 5.3). Six patients had organ-confined disease of which 4 patients underwent radical prostatectomy and 2 patients opted for watchful waiting. Three patients had metastatic disease and underwent bilateral orchidectomy. One hundred and sixty-three (94.7%) patients had benign pathology (Figure 1). Serum PSA ranged from 4.2 to 9.8 ng/mL. One patient had high-grade prostatic intraepithelial neoplasia (HGPIN) and has undergone repeat prostate biopsy twice with similar histopathology reports. This patient is on close follow-up. None of the patients had atypical small acinar proliferation (ASAP).

## DISCUSSION

Among urologic malignancies, prostate cancer has greatly benefited from the discovery and application of tumor markers. Since its discovery in 1979 to clinical application in the late 1980s, PSA has evolved into an invaluable tool for the detection, staging, and monitoring of men diagnosed with prostate cancer [1,2]. Whereas the majority of prostate cancers in the 1980s and early 1990s commonly arose with an abnormal digital rectal examination (DRE) or elevated PSA, or both, today most prostate cancers arise as clinically non-palpable (stage T1c) disease with a PSA between 4 and 10 ng/mL. The evolving demographics and natural history of prostate cancer have resulted in a stage migration to non-palpable, clinically localized (stage T1c) disease and a parallel reduction in mortality [3,4]. Although PSA screening has improved survival, outcomes are not the same for all T1c detected disease as some of these cancers may not pose a threat to survival [5]. Despite routine application of PSA assays, limitations of specificity for this marker remain. Although PSA is widely accepted as a prostate cancer tumor marker, it is organ specific and not disease specific. Unfortunately, there is an overlap in the serum PSA levels among men with cancer and those with benign disease. Thus, elevated serum PSA

Figure 1. A graph depicting the number of patients with benign and malignant histopathology.

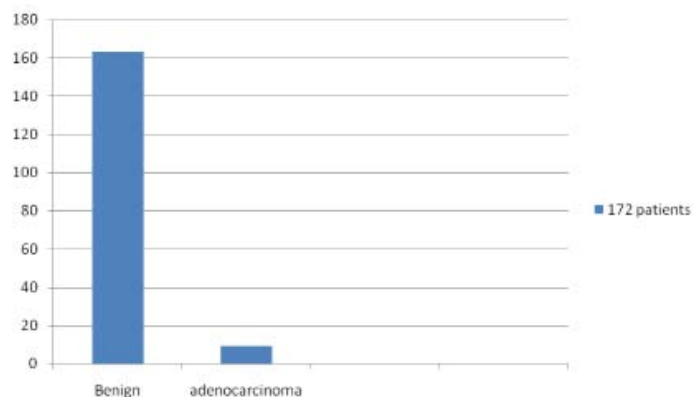
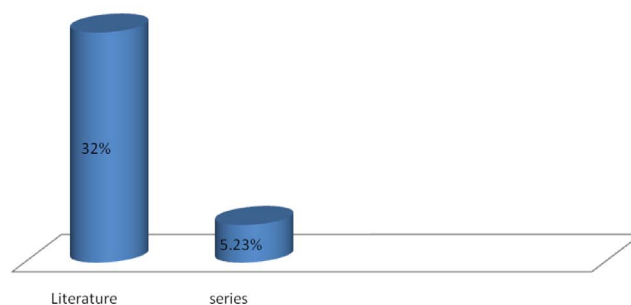


Figure 2. A graph depicting the percentage of malignancy in the range of serum PSA of 4 to 10 ng/mL.



levels may reflect alterations within the prostate secondary to tissue architectural changes such as cancer, inflammation, or benign prostatic hyperplasia (BPH). Currently, serum PSA levels as low as 2.6 ng/mL are used as a threshold to perform transrectal ultrasound-guided biopsy in Western literature. Although up to 30% of men presenting with an elevated PSA may be diagnosed following this invasive procedure, as many as 75 to 80% are not found to have cancer. To this end, the application of PSA derivatives such as PSA density, PSA velocity, age-adjusted values, and, more recently, molecular derivatives have attempted to improve the performance of PSA [6,7]. The majority of men with PSA elevations have serum levels in the range of 4 to 10 ng/mL [8]. In these men, the most likely reason for PSA elevation is prostate enlargement, not prostate cancer, because of the high prevalence of BPH in this population.

Table 1. Distribution of studied cases by age, other variables, and biopsy outcome.

Variable	Values	Biopsy Outcome		Cancer %
		Cancer	Benign	
age	50-59	1	62	1.6
	60-69	5	92	5.43
	70-79	3	18	16.66
total PSA (ng/mL)	4-7	2	88	2.27
	7-10	7	84	8.33
DRE	suspicious	3	169	1.77

DRE: digital rectal examination

The lifetime risk (from age 0 to 90 years) of death from prostate cancer is 3% and the lifetime risk of a diagnosis of prostate cancer is 17% (Surveillance, Epidemiology, and End Results [SEER] Program). The incidence of carcinoma prostate varies widely between countries and ethnic populations, and disease rates differ by more than 100-fold between populations. The lowest yearly incidence rates occur in Asia (1.9 cases per 100,000 in Tianjin, China) and the highest in North America and Scandinavia, especially in African Americans (272 cases per 100,000) [9]. Mortality also varies widely among countries, the highest being in Sweden (23 per 100,000 per year) and the lowest in Asia (< 5 per 100,000 per year in Singapore, Japan, and China) [9].

There are multiple complex causes for the worldwide and ethnic variations in prostate cancer incidence. Environment plays an important role in modulating prostate cancer risk around the world. Japanese and Chinese men in the United States have a higher risk for the development of prostate cancer and dying of it than do their relatives in Japan and China [10]. Likewise, prostate cancer incidence and mortality have increased in Japan as the country has become more westernized [11]. However, Asian Americans have a lower prostate cancer incidence than white or African American men do, indicating that genetics still plays a role in determining prostate cancer predisposition.

Studies suggest that dietary factors may contribute to prostate cancer development [12]. The incidence of latent prostate cancers is similar around the world, but the incidence of clinically manifest cancers differs, with Asians having the lowest rates of clinical prostate cancer. The most convincing evidence for the role of the diet and other environmental factors in modulating prostate cancer risk comes from migration studies

showing an increased incidence of prostate cancer in first generation immigrants to the United States from Japan and China [10]. These observations suggest that diet may play a role in converting latent tumors into clinically manifest ones. A strong positive correlation exists between prostate cancer incidence and the corresponding rates of several other diet-related cancers, including breast and colon cancers [12].

The positive predictive value of PSA testing for cancer detection increased from 12 to 32% for PSA levels of 4 to 10 ng/mL and as high as 60 to 80% for levels above 10 and 20 ng/mL [13]. Thus, men with PSA levels greater than 10 ng/mL and benign DRE have up to a 60% likelihood of being diagnosed with cancer and are unlikely to benefit from further improvement of PSA sensitivity and specificity. Thus, men with PSA levels greater than 10 ng/mL are encouraged to undergo a biopsy regardless of PSA derivative values. For men with PSA levels between 4 and 10 ng/mL, the specificity of cancer detection has been more challenging. Cancers discovered within this range are often earlier in stage, and potentially curable, yet might represent "insignificant," potentially non-life-threatening tumors. However, due to the considerable overlap in serum PSA concentrations in men with and without prostate cancer, this range has been described as the diagnostic "gray zone." Efforts to improve the diagnostic accuracy of PSA within this diagnostic gray zone include PSA density, PSA velocity, and age-specific PSA.

The literature describes the prevalence of adenocarcinoma prostate in the range of 4 to 10 ng/mL, with a serum PSA of up to 32% (Figure 2). In our series the prevalence is far lower (5.23%) than that described in the literature ( $P$  value: < 0.0001). A  $P$  value < 0.05 is significant. The  $P$  value was calculated using the Z test for proportion. This corresponds to the low incidence and mortality rate for adenocarcinoma prostate described among Asians. This data supports our opinion regarding revising of the cutoff value for serum PSA among Asians beyond which further investigations and biopsy should be planned to avoid the diagnosis of clinically insignificant cancers in this gray zone.

## CONCLUSION

The cutoff level of serum PSA beyond which investigations are warranted in Asians is controversial at present, and further multicentric trials involving a larger number of patients must be carried out to arrive at a consensus, since blindly following the current Western literature results in unnecessary interventions in this patient population. Methods for improved detection of clinically significant prostate cancer are needed.

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