

Prostate-specific antigen screening of men with lower urinary tract symptoms (opportunistic screening) and of asymptomatic men undergoing executive health check: an audit from two institutions

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ABSTRACT

Introduction: We evaluated incidence of prostate-specific antigen (PSA) positivity (>4ng/mL) and cancer detection rate on prostate biopsy in two populations of men, one undergoing opportunistic testing for lower urinary tract symptoms and another during routine health checks.

Methods: Data regarding PSA screening, rectal examination (RE), transrectal ultrasound-guided biopsy, clinical stage, and risk assessment grouping according to NCCN guidelines were studied. Group A included patients with lower urinary tract symptoms (LUTS) (opportunistic screening) at SGPGIMS, Lucknow and Group B included healthy men who had executive health check-up with PSA testing at Medanta the Medicity, Gurugram.

Results: PSA positivity rate in 9906 symptomatic men for LUTS (Group A) and 24919 healthy men (Group B) was 28.4% and 3% respectively. In group A, PSA positivity rate was 28.4% but only around half of all men with an indication underwent a biopsy. Among men with PSA of 4–10 ng/mL, cancer was detected in 93 of 241 who underwent a biopsy (38.5%). In Group B, only 69 men (9.3% of those with an elevated PSA) underwent a prostate biopsy, of which 38/57 (with PSA of 4–10 had cancer. In Group A, the cancers was metastatic in 61.5% men, while none in-Group B had metastatic disease.

Conclusion: Opportunistic screening and executive health check with PSA identifies a significant number of men with PSA positivity and may help decrease the proportion of men diagnosed in metastatic prostate cancer.

INTRODUCTION

Prostate cancer is not considered a major health problem in India. However, there has been an upsurge in the new cases of prostate cancer and the annual percentage change has been reported from 0.14% to 8.6%.^[1,2] According to the population-based national cancer registry in India, prostate cancer is the second most common male cancer in Kolkata, third in Delhi, Mumbai, Pune, Patiala, Bengaluru, and 5th in Chennai and Bhopal.^[3] Although this may not represent the true

incidence in population, it gives a better understanding of disease spectrum of prostate cancer in India.

Population-based screening with prostate-specific antigen (PSA) for detecting prostate cancer in early stages is a standard practice. This has resulted in stage migration from metastatic to localized disease at presentation. Despite this stage migration, the impact of screening on improving survival has been controversial. Due to the lack of population-based screening in India, most urologists resort

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to opportunistic screening, i.e., obtaining a PSA test in men with lower urinary tract symptoms (LUTS). Further, many asymptomatic men are also screened for prostate cancer within the purview of an executive health check-up.

We present a retrospective analysis of data from two cohorts of population with 2 different screening patterns to know whether PSA screening of men symptomatic for LUTS and asymptomatic, healthy men has made any impact on PSA positivity, cancer yield, and stage migration at presentation.

METHODS

Institutional Review Board approval from both the institutes (A-02PGI/EMPIEC/45/7.2.16 XXXXX and MICR 1058/2020 XXXXX) was taken for the study. The corresponding author confirms availability and access to all data. The medical database on the hospital information system (HIS) of patients in the age group of 45–75 years, presenting with LUTS in the department of urology (Group A) was reviewed from January 2006 to December 2016. Patients who had their initial PSA at the participating institutes were included. Patients with urethral catheter, positive urine culture, prostatitis, taking 5 α blocker reductase inhibitors and those who had prostate surgery or biopsy within the preceding 3 months were excluded from the study.

Similarly, data about serum PSA screening from HIS of healthy men without any voiding symptoms, in the age group of 45–75 years, who had an executive health check-up at the second institute between January 2010 and December 2019 (Group B) were recorded.

Serum PSA screening was performed in a single laboratory in each institute following standard guidelines. It was measured using an immunoenzymatic assay kit (Can Ag PSA EIA, Fujirebio Diagnostics, Sweden) in Group A and with immunometric assay in Group B. In Group A, rectal examination (RE) was performed and any asymmetry, induration or nodularity was considered as positive RE. Men who had PSA of more than 4 ng/mL or had positive RE had trans-rectal ultrasound (TRUS) guided biopsy. As there was no RE finding available from Group B, prostate biopsy was performed only when the PSA was more than 4 ng/ml. A twelve-core systematic biopsy was performed in all the cases except for some patients in Group A who had a hard nodular prostate on RE in whom only a sextant biopsy was carried out.

Clinical stage was assessed according to tumor node metastasis (TNM) classification by American Joint committee on Cancer (AJCC) 8th Edition.^[4] Clinical risk group classification (Low, intermediate, high, very high risk and metastatic disease) was based on NCCN guidelines 2017.^[5] Statistical analysis was done using the Statistical

Package for Social Sciences (SPSS) Version 24.0 IBM, Bangalore, India. Unpaired Student's *t*-test was applied to compare the groups.

RESULTS

A total of 9906 patients with mean age of 64.6 \pm 7.6 as Group A and 24919 healthy men with the mean age of 58.4 \pm 8.1 years as Group B were included for analysis [Tables 1 and 2]. In Group A, 2809 patients (28.4%) had PSA levels of more than 4 ng/mL which was higher than in Group B where 737 of the 24919 (3%) men had a PSA above 4ng/mL ($P < 0.0001$) [Tables 1 and 2].

In Group A, 1566 of 2831 (55%) men with an indication underwent a biopsy. This included 1544 men with a PSA >4ng/mL and 22 patients with PSA of <4 ng/mL who had an abnormal RE. The biopsy was positive in 5 (22.72%) of 22 men with PSA <4ng/mL. Among men with PSA of 4–10 ng/mL, cancer was detected in 93 of 241 who underwent a biopsy (38.58%) while in men with PSA >10ng/mL, it was detected in 863 of 1303 (66.23%) respectively [Table 1].

In Group B, among the 737 men who had raised PSA levels >4.0 ng/mL (mean PSA 8.59 \pm 9.01, range: 4.01–96.1), only 69 (9.3%) underwent a biopsy. Among them, cancer was detected in 38 of 57 (66.6%) men with PSA between 4 and 10 ng/ml and 9 of 12 (75%) with PSA >10ng/mL. Cancer detection rate for men with PSA between 4–10 ng/mL was significantly higher in Group B compared with Group A ($P = 0.0001$) [Table 2].

Opportunistic screening detected most of the cancers in metastatic (61.5%) and high and very high-risk stage (29.2%) but none of the men in executive health check had presented in metastatic stage [Table 3]. Nearly half of the cancer (47.34%) on presentation had Gleason grade group 4/5 in Group A vis-a-vis 14.8% (7/47) in Group B ($P = 0.001$). Interestingly 70% of men in Group A and 50% in Group B, who had raised PSA and no cancer on initial biopsy showed lymphoplasmacytic cell infiltration in the stroma indicating some form of chronic infection in the prostate.

Although biopsy yield was higher in men having executive health check, incidence of metastatic disease at the time of screening was significantly lower than that in symptomatic men.

DISCUSSION

As per the census of India, the average life expectancy of males in 2015 had increased to 68.35 years as compared to 66.51 years in 2010.^[6] With increasing awareness and growth of the robotic technology used for treating early prostate cancer, there has been a surge in the number of patients

Table 1: Prostate-specific antigen characteristics and biopsy yield rates in symptomatic men in Group A

Group based on PSA (ng/ml)	Number of patients (total=9906), n (%)	Mean±SD		RE positive (%)	Prostate biopsy done (%)	Cancer yield rate n (%)
		Age, years (range)	PSA (mg/dl)			
1 (<4)	7097 (71.6)	64.0±7.5 (45-75)	1.11±0.97	22 (0.32)	22 (0.3)	5 (22.72)
2 (4-10)	1106 (11.2)	65.6±6.6 (47-75)	6.32±1.69	74 (6.68)	241 (21.7)	93 (38.58)
3 (>10)	1703 (17.2)	65.9±7.5 (45-75)	232.10±2215.51	517 (30.09)	1303 (76.5)	863 (66.23)

PSA=Prostate-specific antigen, SD=Standard deviation, RE=Rectal examination

Table 2: Prostate-specific antigen characteristics and biopsy yield rates in men with executive health check (Group B)

Group based on PSA (ng/ml)	Number of patients (total=24919), n (%)	Mean±SD		Prostate biopsy done (%)	Cancer yield rate n (%)
		Age, years (range)	PSA (mg/dl)		
1 (<4)	24182 (97.0)	58.2±8.1 (45-75)	0.9±0.67 (0-4)	NA	NA
2 (4-10)	619 (2.5)	64.5±6.9 (45-75)	5.96±1.78 (4.01-10.9)	57 (9.2)	38 (66.6)
3 (>10)	118 (0.5)	66.15±6.95 (45-75)	25.3±10.8 (11-96.1)	12 (10.1)	09 (75)

PSA=Prostate-specific antigen, SD=Standard deviation, NA=not applicable as rectal exam was not done in men with executive health check.

Table 3: NCCN risk stratification based on serum prostate specific antigen levels across the study groups

NCCN risk group	PSA levels (ng/mL) in Group A				PSA levels (ng/mL) in Group B		
	<4, n (%)	4-10, n (%)	>10, n (%)	Total (968), n (%)	4-10, n (%)	>10, n (%)	Total (47), n (%)
Low	1 (0.1)	15 (1.5)	0	16 (1.6)	11 (23.4)	0	11 (23.4)
Intermediate	1 (0.1)	26 (2.6)	47 (4.8)	74 (7.7)	23 (48.9)	1 (2.1)	24 (51)
High and very high risk	1 (0.1)	37 (3.7)	243 (25.1)	281 (29.2)	6 (12.7)	6 (12.7)	12 (25.6)
Metastatic	2 (0.2)	15 (1.5)	573 (59.2)	590 (61.5)	0	0	0

PSA=Prostate specific antigen, NCCN=National Comprehensive Cancer Network

being detected with prostate cancer. Although it may not represent the change in the true incidence, it would be prudent to have a perspective in knowing burden of prostate cancer disease in India.

It has been an accepted trend to get PSA done in men, initially presenting to urologists with LUTS. Similarly healthy men are being offered PSA testing during their corporate or individual preventive health check-up. In the west, due to prevalent trend of population-based screening with PSA, almost 90% of the prostate cancers are detected in localized stage, where cure is possible. Unfortunately, early detection has generated a debate of over diagnosis and unnecessary treatment, which had prompted the United States preventive services task force (USPTF) to recommend against screening in men between 55 and 69 years.^[7,8] But lately, due recommendation has been changed from D to C, i.e., population-based screening can only be done after shared decision and informed consent.^[7,8]

Therefore, as of now it would not be wise to do population-based screening with PSA to detect early prostate cancer in India. So what is the best way out? The general perception among urologists is that most men present with prostate cancer in advanced stage, but there is no published data to support this notion. Prostate cancer screening with serum PSA became popular in 1991 based on the initial data reported by Catalona *et al.* In that series, PSA positivity in healthy volunteer and symptomatic men was 8.2% and 51%, respectively.^[9] Interestingly, rectal exam finding was not taken into consideration. Although the comparison is not

contemporary, PSA positivity in healthy and symptomatic men in the present study (3% and 29.35%, respectively) is twice as low as than that reported by Catalona *et al.*

Similarly, the yield of biopsy in present study has been found to be more in healthy men in comparison to symptomatic men. This could be due to spurious rise of PSA in symptomatic men due to BPH. In our earlier experience, we demonstrated that the low yield of biopsy in symptomatic men was due to presence of inflammation in the prostate, which falsely elevates the PSA.^[10,11] Yield of biopsy in symptomatic men with normal rectal examination has been lower than what is reported from the west and similar experience has been shared by 2 of the studies published from India.^[10-12]

Of men detected to have prostate cancer, stage and grades were much higher than their western counterparts.^[13] In the present dataset, only 19.5% patients presented with Gleason grade 3 + 3 and 47.34% patients had Gleason grade of 4 and 5. This is in contrast to the data on 383,039 men diagnosed with prostate cancer in the Surveillance, Epidemiology, and End Results database, wherein the percentage of Gleason score 8–10 disease among men aged 50–74 years was 25.1%.^[14]

In earlier review of cancer registries, 85% of prostate cancers were detected in metastatic stage in India as compared to the United States, where only 15% were diagnosed in the late stages.^[15] In the present study, opportunistic screening detected about 61.5% with metastatic disease. Though population-based screening may not be justified due to over diagnosis and over treatment, opportunistic screening has

definitely brought down the proportion of men detected in the metastatic stage.

Interestingly, none of the healthy men screened was found to have metastatic prostate cancer. Though number of biopsies is dismally low it appeared that the stage migration was better among men with symptoms. Only 9% men with an indication for biopsy in the healthy group got a biopsy compared to 55% in the symptomatic group. This would severely affect the comparability of data. It may be argued that screening all healthy men leads to over diagnosis and overtreatment but there is no denial of the fact that most of the men would be detected in nonmetastatic stage of the prostate cancer.

Though the debate on overtreatment for localized and for a very low risk prostate cancer is not settled, for countries like India, where population based screening is not done, reducing the number of men diagnosed in metastatic stage should be the goal. PSA screening, either opportunistic or in executive health checks, would significantly reduce the number of men diagnosed in metastatic stage. It is a well-accepted fact that the cancer specific survival is much better in lower stages of the disease than in advanced stages.^[16]

The limitations of our study were that, India being a diverse country with contrasting genetic, environmental, and dietary habits, natural history of prostate cancer may vary to some extent.^[17] There can be differences in urban (Group B) and rural or suburban population (Group A) too. The number of biopsies done for men with raised PSA was very few in both the groups probably due to non-protocol based approach, wherein urologists may decide against it looking at the associated co-morbidities or poor patient compliance. None of the patients in group A had bi or multi-parametric magnetic resonance imaging. Despite that, information from these two data sets with its sheer number and consistency of doing PSA from one laboratory would definitely add to the knowledge on PSA characteristics and disease profile in symptomatic and healthy men in India.

CONCLUSION

PSA positivity (>4ng/mL) in men symptomatic with LUTS and in healthy men undergoing a screening PSA test was lower than corresponding population in the west. Although population-based screening may not be a practice in our country, widespread use of opportunistic screening and PSA testing in executive health check would lower the percentage of men diagnosed in metastatic prostate cancer.

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