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Raising cut-off value of prostate specific antigen (PSA) for biopsy in symptomatic men in India to reduce unnecessary biopsy

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***Background & objectives*: The characteristics of prostate specific antigen (PSA) for trans-rectal ultrasonography guided prostate biopsy in men with lower urinary tract symptoms (LUTS) are not well defined. This study was carried out to analyse the threshold of PSA for biopsy in symptomatic men in India.**

***Methods*: From January 2000 to June 2011, consecutive patients who had digital rectal examination (DRE) and PSA testing done for LUTS were included in this study. PSA was done with ELISA technique. Patients with acute or chronic prostatitis, prostatic abscess, history of surgery on prostate within the previous three months and patients on 5α-reductase inhibitors or on urethral catheter were excluded.**

***Results*: Of the 4702 patients evaluated, 70.9 per cent had PSA of less than 4 ng/ml and 29.1 per cent had PSA of more than 4 ng/ml. Of these, 875 men with a mean age of 65.72±7.4 (range 50-75 yr) had trans rectal ultrasonography (TRUS) guided biopsy. Twenty five men had biopsy at PSA level of <4 ng/ml due to positive DRE, 263 at 4.1-10ng/ml, 156 at 10.1-20 ng/ml and 431 at >20 ng/ml. Positive predictive value of PSA in ranges of 4.1-10, 10.1-20, >20 ng/ml was 15.2, 24 and 62.6 per cent, respectively with negative DRE. PSA cut-off to do biopsy was derived by ROC curve as 5.82 ng/ml for all the men. When the subjects were further stratified on the basis of DRE findings, a cut-off of 5.4 ng/ml was derived in men with normal DRE.**

***Interpretation & conclusions*: A cut-off for biopsy in symptomatic men with negative DRE could safely be raised to 5.4 ng/ml, which could avoid subjecting 10 per cent of men to undergo unnecessary biopsy.**

Key words Biopsy - digital rectal examination - positive predictive value - prostate specific antigen - ROC - sensitivity - specificity

Incidence of prostate cancer in western population has been known to be greater than in Indians[1]. Screening with serum prostate specific antigen (PSA) has resulted in stage and age migration thereby facilitating detection of prostate cancer at an earlier stage. It is still not clear whether this stage migration has resulted in a decrease in cancer related deaths or not. Randomized trials conducted have not resolved the debate over the utility of PSA screening and the issues of overdiagnosis and overtreatment are still overshadowing the benefits of PSA screening[2,3].

In countries where PSA screening is a routine, more than 90 per cent of prostate cancers are being detected as a localized disease and only 4 per cent

of prostate cancers present in metastatic stage[4]. In India, the majority of patients present in advance stages (unpublished observation). In countries where population based screening is not practiced, an appropriate strategy based on the disease profile, and PSA threshold level could still be used to reduce the number of patients being detected in advance stages[5-7].

Due to lack of data from India, it would not be correct to adopt the guidelines made for a different race living in different social and geographical environment. PSA screening in India is not a common practice and only patients coming to urology clinics with lower urinary tract symptoms (LUTS) are tested for their PSA levels. Despite lack of valid data from India, the PSA threshold for biopsy has widely been used as 4 ng/ml, which has a very low specificity[8]. Several studies have shown that men with LUTS have the same risk of having prostate cancer as asymptomatic men of the same age[9-11]. But men with LUTS have an increased risk of unnecessary biopsy if the threshold is taken as the same as in the asymptomatic men[9,10].

This study was aimed at defining the cut-off value of PSA for biopsy in symptomatic Indian men so that the risk of unnecessary biopsy could be reduced.

Material & Methods

From January 2000 to June 2011, consecutive patients who had undergone digital rectal examination (DRE) and PSA testing for lower urinary tract symptoms in the department of Urology, Sanjay Gandhi Post Graduate Institute of Medical Sciences (SGPGIMS), Lucknow, India, were included in the study. Patients > 75 yr of age and those with clinical evidence of prostatitis, positive urine culture, patients on urethral catheter, 5α blocker reductase inhibitors and those who had surgery or biopsy on prostate in the preceding three months were excluded. Serum PSA was measured by an immunoenzymetric assay with kits (Can Ag PSA EIA, Fujirebio Diagnostics, Sweden) with minimum detectable value <0.1 ng/ml. The normal range of PSA used was 0 to 4.0 ng/ml. The study protocol was approved by the institute's ethics committee and written informed consent was obtained from all patients.

Findings on DRE, like asymmetry, induration or nodularity were considered as positive DRE. Men who had PSA of more than 4 ng/ml or positive DRE irrespective of PSA concentration were referred for trans-rectal ultrasonography (TRUS) guided biopsy. Ten to 12 core systematic biopsies were done in all cases except in those with hard nodular prostate with markedly elevated PSA and positive bone scan in whom sextant biopsy and biopsy from the nodule was done. In subjects with histopathologically diagnosed prostate cancer, clinical stage was evaluated according to tumour mode metastasis (TNM) classification established by the Union Internationale Contre le Cancer (UICC) and American Joint committee on Cancer (AJCC)[12]. Patients were stratified in four PSA concentration levels <4, 4.1-10, 10-20 and >20 ng/ml with positive or negative DRE.

Positive predictive value (PPV), PSA test sensitivity and specificity at various PSA cut-off values as well as receiver operating characteristic (ROC) curve analysis were performed with the help of SPSS 15 (Chicago, USA). The ROC curves were plotted as 1 minus specificity (*i.e.* the false positive rate) versus sensitivity for patients who had biopsy irrespective of DRE findings and in those who had PSA of more than 4 ng/ml and normal DRE to derive true sensitivity and specificity at various cut-off levels of PSA.

Results

A total of 4702 men between the ages of 50 and 75 yr were initially screened with DRE and PSA. Of these, 3335 (70.9) had PSA level <4 ng/ml, 556 (11.8%) had between 4.1-10 ng/ml, 254 (5.4%) men had PSA level between 10.1-20 ng/ml, and 557 (11.8%) had more than 20 ng/ml. PSA positivity rate was 29.1 per cent.

Five hundred and seventeen men, who did not have biopsy due to associated morbidity and discretion of the treating urologist (taking into account the age of the patient, DRE finding and PSA levels) were excluded from the final analysis. Total 875 biopsies were done in which 25 were done at PSA level <4 ng/ml due to positive DRE, 263 at 4.1-10 ng/ml, 156 at 10.1-20 ng/ml and 431 at >20 ng/ml (Table I). The mean age was 65.72 ±7.4 yr and the mean prostate volume was 45.25 ±17.

Considering all the patients who had biopsy based on PSA and DRE, ROC curve could derive a cut-off of 5.82 ng/ml with true sensitivity of 95 per cent but at a low specificity of 21 per cent (area under curve, AUC 0.83±0.012 95% CI (10.748-0.895 *P* <0.001). (Fig.1, Table II). When the subjects were further stratified on the basis of DRE findings, ROC curve in men with abnormal PSA and normal DRE could derive a cut-off of 5.40 ng/ml with 95

Table I. Positive predictive values (PPV) of prostate specific antigen (PSA) and digital rectal examination (DRE) in 876 patients who had biopsy done

PSA range (ng/ml)	DRE	Biopsy done	Cancer	PPV (%)
<4	- ve	0	-	-
	+ve	25	5	20
4.1-10	- ve	216	33	15.2
	+ve	47	28	59.57
10.1-20	- ve	96	23	24
	+ve	60	41	68.3
>20	- ve	115	72	62.60
	+ve	316	301	95.2
Total		875	503	

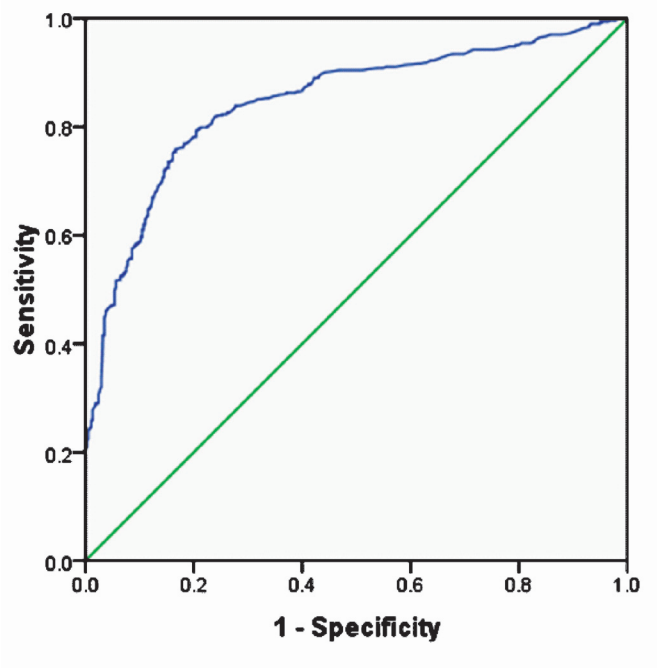

Fig. 1. Receiver operating characteristic (ROC) for serum PSA to detect cancer in patients with PSA of more than 4 (blue line) and normal DRE patients (427) (green line). Diagonal segments are produced by ties.

per cent sensitivity and with 12 per cent specificity (AUC 0.74 ± 0.33 95% CI 0.683-0.813 $P<0.001$) (Fig. 2; Table II).

The detection of prostate cancer varied according to the PSA level, with a greater percentage of cancers detected in direct association with rising PSA levels (Table I). Positive predictive value for detection of prostate cancer at PSA level 4.1-10 ng/ml with normal DRE was 15.2 per cent and in PSA range of 10.1-20 ng/ml it was 24 per cent.

Discussion

Routine PSA screening has resulted in a stage and age migration, thereby detecting cancer at younger age and at early stages[13]. Two randomized trials on prostate cancer screening have not thrown much light on the benefit of screening in general population[2,3]. A recent US Preventive Task Force has substantiated the fact that PSA screening leads to overdiagnosis and overtreatment and does not reduce mortality to justify the adverse outcome resulting from the treatment, and has given grade D recommendation[14].

In countries like India, where incidence of the prostate cancer is lower than the western population, doing PSA for all men after one particular age as recommended in the West, would not be useful[15]. Though one may argue that picking cancer at an early stage may not change the biological course of the disease, yet with available treatment options, it has been demonstrated that cancer specific survival is much better in lower stages of the disease than in advance stages[15].

Ideal screening test should have high sensitivity and specificity. PSA was adopted as an initial screening tool and a cut-off level of 4 ng/ml was suggested, without a useful balance between sensitivity and specificity, PSA level as a screening test was started being used clinically based on two clinical trial in early 1990s[8,16]. This cut-off with a sensitivity of 79 per cent, and specificity of 59 per cent became the most commonly used cut-off for TRUS biopsy all over the world[8,17]. In the present study with 59 per cent of specificity we could derive a cut-off of 8.7 ng/ml with the sensitivity of 82 per cent. In the Prostate Cancer Prevention Trial, the specificity of PSA at 4 ng/ml in healthy and asymptomatic men (placebo arm) has been shown to be 92.7 per cent resulting in further lowing of PSA cut-off for biopsy[18].

As is known, PSA is not a diagnostic test and it is only a first step towards taking a decision for biopsy. With a very low specificity, there is an inherent risk of doing unnecessary biopsy at the threshold of 4 ng/ml[19]. There are other derivatives in the measurement of PSA to reduce the number of unnecessary biopsy like free PSA, PSA density and PSA velocity but according to European Association of Urology guidelines the use of such alternative measurements is of limited value

Table II. Area under curve, sensitivity and specificity at various cut-off levels of PSA

Variables	Area under ROC global accuracy				Cut-off points (ng/ml)	Sensitivity (%)	Specificity (%)
	Area	SE	95% CI	*P* value			
All patients who had biopsy (irrespective of DRE) N=875	0.83	0.012	0.74 -0.89	<0.001	5	97	14.2
					5.82	95	21
PSA >4 ng/ml with normal DRE (N=427)	0.74	0.33	0.68 -0.81	<0.001	5	96	9
					5.4	95	12

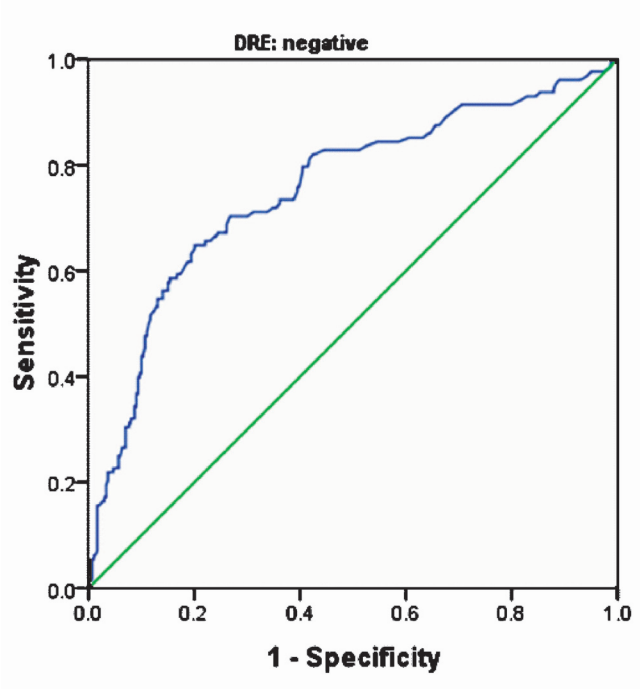

Fig. 2. Receiver operating characteristic (ROC) curve for serum PSA to detect cancer in patients with PSA of more than 4 ng/ml (blue line) and normal DRE (green line) in patients (N=427). Diagonal segments are produced by ties.

and not included in the routine practice[20]. Similarly, age specific PSA has not been found to safely avert the need for prostate biopsy in a population aged 60-69 yr[21].

PSA positivity rate (number of men screened who have PSA of more than 4 ng/ml) when PSA threshold was taken as 4 ng/ml has been reported as 12 per cent from one of the pooled analyses in screening for asymptomatic men in general population[22]. PSA positivity rate was found to be 29.1 per cent in the present study in the symptomatic men. This difference in positivity rate was consistent with the difference observed in symptomatic vs. healthy men (51 vs. 08%) by Catalona *et al*[8]. This difference in positivity rate could be attributed to the presence of benign prostate hyperplasia (BPH) component in symptomatic men and this has been seen in ProtecT trial of association of LUTS and PSA levels, where it was found that history of BPH was positively associated with a higher level of PSA with an OR of 1.43 (95% CI 1.18-0.74)[23].

It is a known fact that with increase in serum PSA levels, its positive predictive value to detect cancer also increases. The term cancer detection rate is often used incorrectly as the denominator is taken as number of patients who are screened for PSA and not the ones who are biopsied. There could be an impact of verification bias because to derive test characteristics, patients with PSA < 4 ng/ml are considered negative for malignancy in absence of biopsy[24].

In western population, the positive predictive value of PSA in the range of 4-10 ng/ml is around 32 per cent, which increases to more than 60 per cent at PSA level >10 ng/ml[16]. Our study demonstrated that PPV of PSA in the range of 4-10 ng/ml was 15.2, and 24 per cent in patients with PSA 4 to 20 ng/ml. Similar low PPV has been reported in Asian population by a study on symptomatic men from Korea, where PPV in PSA range of 4-10 ng/ml was found to be 15.95[25]. These findings indicate that the race, genetic difference and diet pattern are important factors causing significant difference in the positive predictive value of detecting cancer in PSA range of 4-20 ng/ml[4,26].

In the present study, despite a higher PSA test positivity, the PPV of PSA in symptomatic men was low. This means that a significant number of PSA positive men are unnecessarily subjected to biopsy. One of the ways to reduce the number of unnecessary biopsy is

to raise the cut-off level of total serum PSA. Without compromising its sensitivity a cut-off value of 5.4 ng/ml with a sensitivity of 95 per cent was derived.

There were several limitations to this study. Firstly, we did not biopsy men with PSA of less than 4 ng/ml, secondly symptoms using validated instrument like American Urological Association - International Prostate Symptom Score (AUA-IPSS) were not correlated with the PSA levels.

Owing to a relatively low positive predictive value of total serum PSA, the significant proportion of patients presenting with LUTS in PSA range of 4-10 ng/ml were subjected to an unnecessary biopsy. The results of this study suggest that the PSA threshold for TRUS guided biopsy in Indian men with LUTS and negative DRE, may be raised to 5.4 ng/ml. This would still detect 95 per cent of cancers and avoid unwarranted biopsy in 10 per cent of men. Further studies need to be done to verify these findings.

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