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Original Article

Determination of a Cut-off Point for Prostatic Specific Antigen to Avoid Unjustified Biopsy Among Asymptomatic Elderly Men

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Abstract

Background: To our knowledge, there is no national screening program for prostate cancer in Egypt. The Uro-surgery department in Alexandria University established a screening program for prostate cancer among men aged 55 years or more in January 2012.
Objective: To determine a valid Prostatic Specific Antigen (PSA) cut-off point for performing Transrectal Ultrasonography (TRUS) guided biopsy among asymptomatic elderly men.
Methods: A screening cross sectional study was conducted on a convenient sample of 1207 men aged ≥55 years who were attending urology department, Alexandria University for non-prostatic symptoms during years 2013 and 2014. Digital Rectal Examination (DRE) and PSA level measurement were performed for all included subjects. TRUS guided biopsy was done for those who found to have PSA > 4ng/ ml and or suspicious DRE.
Results: Among subjects who had PSA level of 4.1-10, the Positive Predictive Value (PPV) for cancer prostate was 54% among those with suspicious DRE findings as compared to 0 among those with non-suspicious DRE. For PSA level of 10.1-20 and >20 with suspicious DRE, PPV was (77% and100% respectively). The mean serum total PSA was 77 and 0.6 ng/ ml for patients with and without prostatic cancer respectively (p= 0.0001). The yield of cancer prostate among all screened men was 103/1207= 8% and 103/157= 66% among those with PSA> 4 ng/ ml and or having suspicious DRE and were biopsied. Considering all men who had biopsy, ROC curve could derive a cut-off value of 10.05 ng/ml with a sensitivity of 92% and a specificity of 92.6%. Inability to perform biopsy for men with PSA ≤4 ng/ml was the main limitation.
Conclusion: In a country of relatively low prevalence of prostate cancer like Egypt, a cut-off point of PSA in combination with DRE for doing TRUS biopsy could be 10.05 ng/ ml among asymptomatic men ≥55 years of age with a likelihood ratio of 12.43.

Keywords: Prostate cancer, screening, Transrectal Ultrasonography guided biopsy, Prostatic Specific Antigen level, Egypt

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INTRODUCTION

Prostate cancer is a common health problem. A marked variation in its incidence and prevalence exists between Western, Asian and Arabic populations. It was reported that about 68 per cent of prostate cancer cases occurred in more developed countries. The lowest incidence was in Asia and Africa.(1) The incidence of prostate cancer was reported to be about 74–127/100,000 men in the United States of America (USA)(2), as compared to only 3, 10.2 and 14.5/100,000 men in Saudi Arabia(3), Oman(4) and Kuwait(5). In Egypt, cancer prostate is much less frequent than that of liver. Age standardized incidence rate (ASR per 100,000 population) of prostate cancer varies from 2.66 to 5.92 in various regions of Egypt as reported by national population-based cancer registry program in Egypt in 2014.(5) For men with an elevated prostate specific antigen (PSA) level or a suspected lesion detected by digital rectal examination (DRE), trans-rectal ultrasound-guided (TRUS) prostate biopsy is the standard procedure for prostate cancer diagnoses.(5) In western countries, a prostate specific antigen cut-off point of 4 ng/ ml is used for recommending a biopsy with a positive predictive value (PPV) of approximately 30%. This

means that slightly less than one in three men with an elevated PSA will have prostate cancer detected on biopsy.[5]

However, in view of low incidence of prostate cancer and limited resources, it is required to identify the cut-off point of PSA for doing TRUS biopsy among asymptomatic Egyptian men.

This study was conducted to determine a valid PSA cut-off point for performing Trans-rectal ultrasonography (TRUS) guided biopsy among asymptomatic men.

METHODS

A screening cross sectional study was carried out. The target population included men 55 years old or above with non-prostatic symptoms, admitted to the Uro-surgery department, Alexandria main University hospital (AMUH) from January 2013 till December 2014 and accepting enrolment in the screening program. Exclusion criteria were diabetes, infertility and patients presented with lower urinary tract pathology. A total of 1207 men were enrolled for doing digital rectal examination (DRE) and PSA testing.

Digital rectal examination (DRE): was done twice for each patient by two different senior staff members in left lateral position. Suspicious findings included irregular surface, asymmetry of prostatic lobes and hard nodule.

Serum total PSA:

Four ml of venous blood were withdrawn under standard aseptic technique. Serum was separated for determination of PSA. Serum samples were aliquot and stored at -20ºC until assayed. Quantitative determination of serum PSA was done using electro-chemiluminescence immunoassay in AMUH central laboratory. A value of ≤ 4 ng/ ml was considered normal. Values 4.1 – 10 ng/ ml represented a grey zone, in which patients were needed to be reassessed after 4 weeks courses of fluoroquinolones antibiotics, so in case of PSA drop down to ≤4 ng/ ml the TRUS biopsy was avoided and those with persistent PSA values 4.1-10 ng/ ml underwent trans-rectal ultrasound guided prostatic biopsy [9]. Patients presenting with values greater than 10 ng/ ml were strictly advised to the high need to perform TRUS biopsy.

Trans-rectal ultrasound (TRUS) guided extended prostatic biopsy:

TRUS guided extended prostatic biopsy, using 18gauge needle was done obtaining ≥10 prostatic cores in a systematic manner. This was done whenever there were any of suspicious DRE or serum total PSA >4 ng/ ml. The patients were divided into four subgroups by PSA level as follows: less than or equal 4, 4.1–10, 10.1–20, and more than 20 ng/ ml.

Statistical Analysis

The data were analyzed using the Statistical Package for Social Sciences SPSS, version 18 (PASW SPSS Inc. Chicago). Statistical analysis was performed considering $P<0.05$ statistically significant and with a 95% confidence interval (CI). Chi Square, Monte Carlo and Kruskal Wallis tests were used for comparing studied groups and 5% level of significance was used for interpreting results.

Positive predictive value (PPV) and sensitivity were calculated for each PSA level with and without DRE suspicious findings.

The receiver operating characteristic (ROC) curve was plotted as 1 minus specificity (*i.e*. the false positive rate) versus sensitivity for various PSA levels irrespective of the findings of DRE.

Ethical Considerations

The proposal of this study was reviewed and approved by the Institutional Review Board and the Ethics Committee of the Faculty of Medicine, Alexandria University. The study conformed to the International Guidelines for Research Ethics. Screening tests and types of information to be obtained were explained to the studied patients and their written consent was obtained. Privacy and confidentiality of the data were ensured all through the research work.

RESULTS

Distribution of the studied patients according to age, mean total serum PSA level, and family history: Table 1 shows that, the age of the studied men ranged from 55 to 84 years, with a mean of 64 ± 6 years and a median of 64 years. Concerning association with serum PSA, the table reveals that as the age increases the mean PSA also increases .The highest mean PSA level (75.2± 46.8ng/ ml) was among those who aged above 80 years as compared to 2.5± 7.3 ng/ ml among those who aged 55 to less than 60 years, 8.9± 65.4ng/ ml among those who aged 60 <70 and 9.4 ± 54.6ng/ ml among those who aged 70<80years.These differences were statistically significant as indicated by Kruskal Wallis test (P<.0001). As regard family history of cancer prostate, only 1% (n=12) of studied men had a positive family history of cancer prostate.

Distribution of the studied patients according to total serum PSA level and DRE findings: Figure 1 reveals the results of DRE carried out to screened patients. The percentage of patients with suspicious findings was directly related to the level of total serum PSA; as it was 0.1%, 24%, 83% and 97% for patients with PSA ≥4, 4.1- 10, 10.1- 20 and more than 20 ng/ ml respectively, (Monte-Carlo test, P<0.001). Based on screening tools, TRUS guided prostatic biopsy was done for 157 men; including 156 with serum PSA level >4 ng/ml in presence or absence of suspicious DRE findings and a single man with normal serum PSA (≤4 ng/ml) and a palpable hard nodule during DRE. Prostatic cancer was detected in 103 patients (65.6%). The rest (54 men; 34.4%) were found free of cancer by

prostatic biopsy (either suffered from benign prostatic hyperplasia (40) or prostatitis (14) as identified by pathological examination). Table 2 illustrates the results of prostatic biopsy in relation to PSA levels and DRE findings. For men who had PSA level ≤4ng/ml, only one patient had suspicious DRE where prostate cancer was diagnosed with biopsy. For biopsied men, Table 2 shows the PPV of the screening program. Among those who have PSA level of 4.1-10 with suspicious DRE, PPV is 54% as compared to 0 among those with non-suspicious DRE. A higher PPV is observed for those who had PSA level of 10.1-20 and >20 with suspicious DRE findings (77% and 100% respectively).

Distribution of biopsied men (TRUS) according to age, PSA level, DRE and prostatic biopsy results: More than half (59.23%) of prostate cancer cases had PSA level greater than 20ng/ml, 33% had PSA level of 10.1-20 ng/ml and 6.8% had PSA of 4.1-10ng/ml while only one case had PSA level ≤4ng/ml. DRE was suspicious in 94% of prostate cancer cases (Table 3).

Screening program Case Yield of prostate cancer: Among 1207 screened men, 103 prostate cancer cases were diagnosed using TRUS guided biopsy, which was performed on 157 patients in whom PSA was > 4 ng/ml and or suspicious DRE finding. Calculating the prevalence of prostate cancer among the different studied age groups revealed that all studied men 80 years and above had prostate cancer compared to 6.2%, 8.7%, and 13.7% among men aged 50 to less than 60, 60 to less than 70 and 70 to less than 80 years respectively and this difference was statistically significant ($p< 0.001$). Prostatic cancer detection rate among all screened men was (103/1207= 8%). Prostatic cancer detection rate among men who were biopsied using TRUS guided biopsy was (103/157= 65%). Considering all the patients who had biopsy based on PSA and or DRE, ROC curve could derive a cut-off of 10.05 ng/ml with a sensitivity of 92% and a specificity of 92.6% (area under curve, AUC 0.973 ± 0.012, 95% CI (.950-0.997 $P<0.001$). The likelihood ratio is (sensitivity/1-specificity) was equal to 12.4 (Figure 2).

Table 1: Distribution of the studied patients according to age and total serum PSA

Age (years) n=1207	No.	%	Serum total PSA (ng/ml)		Kruskal Wallis test
			Mean ±SD	Median (IQ range)	
50 –	291	24.0	2.5 ± 7.3	0.6 (0.3-3.3)	P < 0.0001
60 –	687	57.0	8.9 ± 65.4	0.8 (0.4-0.8)	
70 –	223	18.5	9.4 ± 54.6	1 (0.4-1)	
80 – 90	6	0.5	75.2 ± 46.8	77.5 (32.9-111)	
Age (years)					
Range			55-84		
Mean ± SD			64 ± 6 years		
Median			64 years		
Median PSA			0.8 ng/ ml 1st Quartile PSA=0.4 3rd Quartile PSA =1		

* significant ($p<0.05$)

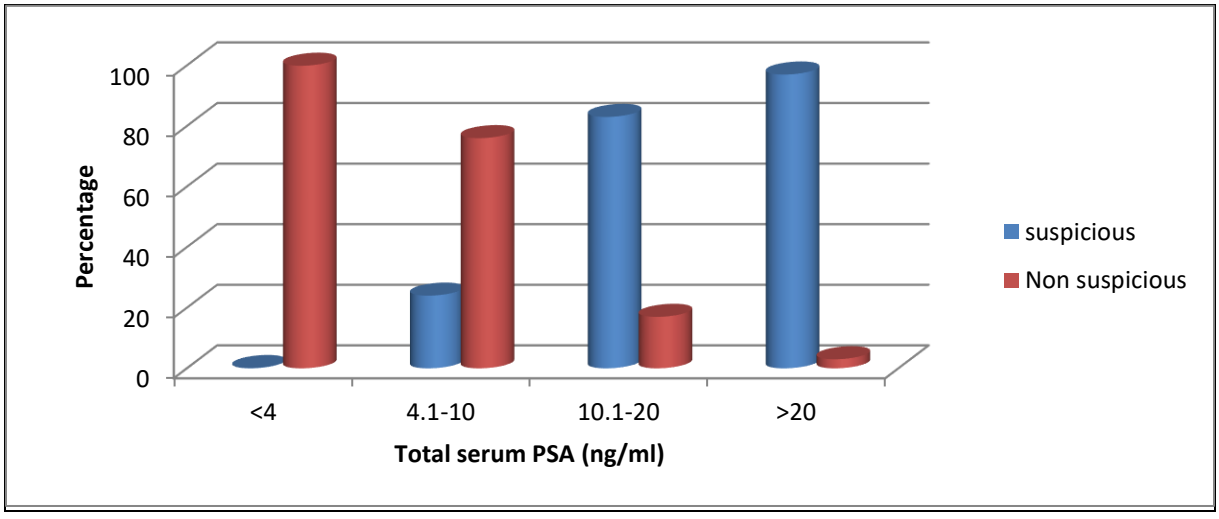

Figure 1: Distribution of the studied patients according to total serum PSA level and DRE findings

Table 2: Distribution of the studied patients according to their total serum PSA level in relation to DRE findings, and prostatic cancer detection

PSA (ng/ ml)	No. (%)	DRE	No. (%)	Prostate cancer	PPV
4.1 – 10	53 (4.4%)	Suspicious	13 (24%)	7	54
		Non-suspicious	40 (76%)	0	-
10.1 – 20	42 (3.5%)	Suspicious	35 (83%)	27	77
		Non-suspicious	7 (17%)	7	100
>20	61 (5.1%)	Suspicious	59 (97%)	59	100
		Non-suspicious	2 (3%)	2	100

Table 3: Distribution of biopsied men (TRUS) according to PSA level, DRE and prostatic biopsy results

		Prostatic cancer		Test of significance
		Yes (n=103) No. (%)	No (n=54) No. (%)	
PSA (ng/ ml)	≤4	1 (0.97%)	0	
	4.1- 10	7 (6.8%)	46 (85%)	Monte Carlo
	10.1- 20	34 (33%)	8 (15%)	p<0.001
	>20	61 (59.23%)	0	
DRE	Suspicious	94 (91%)	14 (26%)	Chi Square
	Non-suspicious	9 (9%)	40 (74%)	X^2=70.439 p<0.001

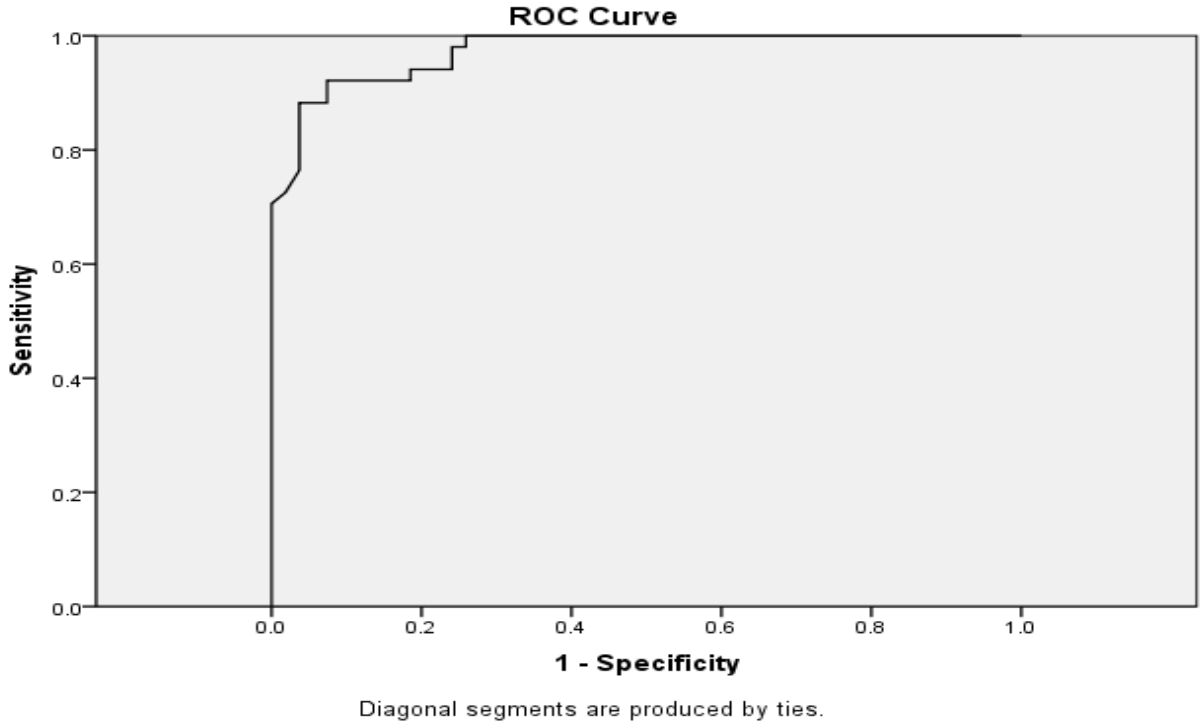

Figure 2: ROC curve for PSA levels and detection of cancer prostate

DISCUSSION

In Egypt; a recent population-based study conducted by Ibrahim et al in 2014 reported a proportion of prostate cancer as 4.27% of total cancers among men. [6] According to the present study, prostatic cancer cases were suspected in 8% (1 in 12) of asymptomatic screened men, presenting for non-prostatic problem to Alexandria University Uro-surgery department. Clinically localized prostate cancer generally causes no symptoms. Slowing of the urinary stream, arising at night to void, and increased urinary frequency are

common symptoms associated with aging but often are unrelated to the presence of prostate cancer. It is for this reason that early detection tests have been developed to identify prostate cancer while it remains confined to the prostate. Prostate-specific antigen testing and, to a lesser extent, DRE can detect prostate cancer at an earlier stage than it could be detected clinically. [10]

These two screening tools were utilized in the present study, for screening attending men aging ≥55 years of urology department for non-prostatic symptoms who totaled 1207 to evaluate their performance against TRUS guided biopsy as a gold standard among Egyptians with low prevalence of prostate cancer. Currently; improving the technique of TRUS guided biopsy by doing the extended technique, obtaining biopsies from ≥ 10 prostatic zones, lateral prostatic biopsies and the inclusion of prostatic apical biopsies allowed a significantly higher detection of prostatic cancer (at least 25% higher detection rate).[10] Another factors improving the yield of TRUS guided prostatic biopsies is the current use of local infusion anesthesia at the prostatic apex, beside the local anesthetic cream that decreased pain associated with biopsy and allowed better prostatic mapping and more prostatic cores to be sampled.[12,13]

The study revealed that the age of studied men ranged from 55 to 84 years, with a median age of 64 years. The majority (81%) of studied patients aged 55-70 years. This was in concordance with the American urological association (AUA) guidelines, recommending the highest benefit for screening within that age group (55- 70 years). [14] The median serum PSA level among asymptomatic men in the present study was 0.8 ng/ml. This finding is comparable to a Korean study[15] that examined 237 healthy men demonstrated that the median serum PSA level was 0.8 and 0.9'ng/mL for men younger and older than 50 years, respectively. 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 was found to be 13 per cent among screened asymptomatic men in this study. This finding is more or less comparable to that of the pooled analyses in screening for asymptomatic men in general population. [16] PSA positivity rate was found to be 29.1 per cent in a study of the symptomatic men[17]. This difference in positivity rate was consistent with the difference observed in symptomatic vs. healthy men (51 vs. 8%) by Catalona et al.[18] This difference in positivity rate could be explained by the presence of benign prostate hyperplasia (BPH) component in symptomatic men and this has been reported 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 1.18-1.74)[19]. Al-Abdin et al.,[20] recently published the outcome of screening in Saudi population. They could identify that; for patients with PSA 4.1- 10 ng/ ml, no single patient was diagnosed with cancer out of 52 patients and for patients with PSA > 10 ng/ ml, the prevalence of prostate cancer was 10/ 32 (31%). In this study; for patients with PSA 4.1- 10 ng/ ml, the prevalence of prostatic cancer was 7/ 53 (13%) and for patients with PSA > 10 ng/ ml, the prevalence of prostate cancer was 95/ 103 (92%). This shows that for PSA < 10 ng/ ml, the prevalence of prostatic cancer in Egyptian population is close to Saudi population of 13%, while for Egyptian men with PSA >10 ng/ ml, there is a higher probability to detect prostatic cancer (92%).

In this study, DRE revealed suspicious findings in 108/ 1207 (9%) of the screened men. That was slightly higher than the meta-analysis results, mentioning a rate of 5% to find suspicious DRE findings during screening for prostate cancer, regardless of PSA values.[21]

The current study shows that among men with PSA ≤4ng/ml, only one patient had suspicious DRE who revealed to have prostate cancer by biopsy. For patients with PSA values above 10 ng/ ml, there was no strong role for DRE, as all cancer cases could be identified solely based on only PSA screening. The interesting finding was for patients with PSA 4.1- 10 ng/ ml, as those constituted 53 patients; of whom none without suspicious DRE findings was diagnosed to have prostatic cancer following prostatic biopsy, while for patients in that PSA category, suspicious DRE findings were associated with a PPV to detect prostatic cancer using TRUS guided biopsy of 54% (7/ 13).

Inconsistent results concerning importance of DRE regarding its survival benefit were reported by European randomized study of screening for prostate cancer (ERSPC) and did not consistently require DRE.[22] However, some studies reported that PSA and DRE are somewhat complementary and their combined use can increase the overall rate of cancer detection[23]. A previous study of the pattern of prostate cancer presentation among the Egyptian population confirmed the pivotal role of DRE in the diagnosis of patients with prostate cancer as 77% of cases had a suspicious finding during examination. [24] In the present study, ROC derived a PSA cut-off of 10.05 ng/ml through combined use of DRE and PSA among asymptomatic men. This can avoid doing TRUS biopsy at the traditional cut off point (4 ng/ml) used in western countries and consequently the risk of complications, over diagnosis and risk of therapy.

CONCLUSION & RECOMMENDATIONS

In a country of relatively low prevalence of prostate cancer like Egypt, a cut-off point of PSA in combination with DRE for doing TRUS biopsy could be 10.05 ng/ ml among asymptomatic men ≥55 years of age with a likelihood ratio of 12.43.

Further research is recommended to assess the validity of the concluded PSA cut-off point combined with DRE

taking into consideration prostate cancer staging and clinically significant prostate cancer among detected cases.

Limitations of the study

Prostate biopsy is an invasive procedure and its indications are limited to only patients with high probability of having cancer prostate revealed by screening and symptomatic men. This made carrying out biopsy for asymptomatic men with a PSA level less than 4.1 ng/ ml unjustifiable and this is considered an important study limitation. Thus, ROC curve included only those who performed TRUS biopsy (157 men) in order to know the cancer status of every one to calculate sensitivity, specificity and consequently likelihood ratio. In addition, the sampling technique (convenient sample) is considered as a limitation to the study external validity.

Conflict of Interest: None to declare.

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