The sensitivity and specificity of the total prostate specific antigen test in prostate cancer screening: A Short report

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Research note

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Abstract

Objective: The total prostate specific antigen (TPSA) test is still widely used in Ghana for PCa screening due to its simplicity and logistical challenges in the healthcare sector. This study aimed to determine the sensitivity and specificity of TPSA in PCa screening in Ghana.

Results: This was a **c**ross-sectional study that was conducted at the Department of Urology of the Komfo Anokye Teaching Hospital between January 2018 and December 2019. The study involved 69 male patients with histologically confirmed BPH or PCa. The study population was between 45 to 104 years. BPH patients constituted 74% (51/69) while 26% (18/69) were PCa patients. Venous blood samples were collected before the prostate examination and analysed for TPSA. The BPH group was statistically compared with the PCa group in terms of age and TPSA levels. The TPSA was significantly elevated in PCa (P=0.001). Univariate [OR: 8.684(1.757-42.927)] and multivariate [aOR:10.544(2.001-55.562)] analysis showed that TPSA was positively associated with PCa; but this association was only moderate (AUC:0.78, P<0.001) with a sensitivity of 83.3%, specificity 64.0% at a cut-off value of 20.0ng/ml. The TPSA test has only moderate performance in PCa screening and should always be complemented by a second screening test.

Introduction

The introduction of the TPSA test significantly improved the screening and early detection of PCa leading to a reduction in morbidity and mortality. The putative reference range for TPSA is < 4.0 ng/ml, and a value > 10.0 ng/ml is considered high and may necessitate a prostate biopsy for histological examination[1]. Although PSA is prostate specific, it is, however, not specific to PCa. TPSA is elevated in other conditions such as benign prostatic hyperplasia (BPH), prostatitis, and even prostate massage. There are significant overlaps in TPSA levels between PCa and BPH, and most especially in the 4.0–10.0 ng/ml range, which is usually referred to as the “diagnostic grey zone”[2]. The nonspecific elevation of TPSA may lead to poor performance characteristics in PCa detection, such as low sensitivity and specificity.

Modifications of the TPSA have been introduced in an attempt to improve the sensitivity and specificity in PCa detection with mixed outcomes. Examples of such medications include pro-PSA, free PSA (fPSA), and complexed PSA (cPSA). These newer methods are either used alone or in a combination of two or three [3, 4].

The TPSA might have been replaced with a newer and better PCa screening test in some parts of the globe, however, poor medical facilities and shortages of skilled health personnel in developing countries pose challenges to use these methods. The TPSA test is still widely used in low-income countries including Ghana [5]. In this study, we sought to determine the sensitivity and specificity of the TPSA test in PCa screening.

Methods

This was a cross-sectional study that was carried out between January 2018 and December 2019 at The Komfo Anokye Teaching Hospital (KATH). The study involved 69 men who reported to the Urology Department of KATH within the study period. The patients were referred to see a specialist Urologist following an initial visit to the general practitioner with prostate or urethral-related complaints. Venous blood samples were collected before the digital rectal examination (DRE) to avoid falsely elevated TPSA levels. Only those who underwent prostate biopsy following the outcome of the TPSA test and DRE, and were subsequently diagnosed histologically to have either BPH or PCa were included in the study. Patients who were diagnosed with other prostate-related conditions such as prostatitis, and those whose diagnosis was not histologically confirmed, were excluded. The study was not restricted by the age or ethnicity of the patients.

Blood TPSA was measured using the Enzyme-Linked Immuno-Assay (ELISA) method following the protocol described by Arthur, Yeboah [6]. The serum samples, together with a calibrator and control, were pipetted into wells in duplicates. Assay buffer was added and incubated at room temperature for 60 minutes to allow the immobilized primary rabbit antibody to bind to the PSA molecules. The wells were then washed 3 times with a wash buffer to remove all unbound sample antigens. The anti-PSA secondary antibodies conjugated with horseradish peroxidase (HRP) were then added to the wells and incubated for another 60 minutes to form a sandwich complex. Further washing was done to remove excess anti-PSA-HRP complexes. The substrate (HRP) was then added and incubated for 20 minutes for colour development before the reaction was stopped with the addition of 1N HCl. The absorbance of the reaction chromophore was measured at 450 nm and the corresponding TPSA value was read from a calibration graph after all controls had passed.

Prostate biopsies were immersed in 10% buffered formalin fixative. The tissues were subsequently passed through a series of methanol with increasing concentrations before been cleared in xylene and then embedded in paraffin wax. The tissue blocks were then sectioned using a microtome and then fixed on microscope slides. The process was reversed to remove the wax before they were then stained using Haematoxylin and Eosin (H&E) method as described by Feldman and Wolfe [7]. The stained tissues were then mounted on glass slides and then sent to a specialist pathologist for histological examination following standard diagnostic guidelines for BPH and PCa [8, 9].

The analysis of differences between variables in BPH and PCa was performed using unpaired *t*-test. Odds and adjusted odds ratios were determined using logistic regression analysis in IBM SPSS 23 (SPSS Inc., Chicago, IL, USA). Receiver operator characteristics (ROC) graph was constructed for TPSA by plotting the sensitivity against 100-specificity and the area under the curve (AUC) was determined using the Hanley and McNeil method in MedCalc v. 14.8.1.0 (MedCalc Software LTD, Belgium). The positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), and negative likelihood ratio (NLR) were also determined. A probability value of less than 0.05 was considered statistically significant.

Results

The general characteristics of the study population are summarized in Table 1. The total study population was between the ages of 45–104 years with a mean age of 69.3 (9.85) years. The ages of men diagnosed with BPH and PCa were between 45–104 years and 59–80 years and their mean ages were 69.0 (10.89) years and 70.2 (6.19) years respectively. The TPSA in the total study population ranged from 1.00 to 140 ng/ml with a mean TPSA of 32.68 (31.02) ng/ml. BPH patients had a mean TPSA of 24.16 (23.08) ng/ml while that of PCa was 56.84 (38.03) ng/ml. The difference in TPSA between BPH and PCa was statistically significant ($P < 0.001$).

The odds and adjusted odds ratios of TPSA in the prediction of PCa are summarized in Table 2. In the univariate analysis using quantitative independent predictor variables, the odds of PCa increased by 1.036 (95%CI: 1.015–1.058, $P < 0.01$) for every 1 ng/ml increase in TPSA. The odds were unaffected by age in the multivariate analysis. In the univariate analysis using categorical independent predictor variables, the odds that a patient in the study population would have PCa was 8.684 greater using a cut value of 20.0 ng/ml than using 10 ng/ml [OR: 8.684 (95%CI: 1.757–42.927, $P < 0.01$). After adjusting for age in the multivariate analysis, the odds of PCa increased to 10.544[(95%CI: 2.001–55.562), $P < 0.01$].

The PCa detection ability of TPSA was assessed by ROC analysis. The best cuff-off value was 20 ng/ml with an AUC of 0.78 ($P < 0.001$). The sensitivity was 83.3% and the specificity, 64.0% (Table 3).

Discussion

The common reference range for TPSA is < 4ngml and levels greater than 10 ng/ml are usually considered high. The objective of this study was to evaluate the value of TPSA in PCa screening. We observed in this study that the TPSA was significantly increased in PCa patients compared to BPH. However, the performance of TPSA in predicting PCa was only moderate.

The TPSA was significantly increased in PCa compared to BPH. This was consistent with other studies [10–13]. Both BPH and PCa are characterized by inflammation, which stimulates the production of PSA. High TPSA has been suggested to be a risk factor in the pathogenesis of PCa. PSA has a protease-like activity that affects the integrity of the extracellular matrix of cells and thus facilitates the metastasis of PCa [14]. Although TPSA is usually elevated in PCa than BPH on average, there is a substantial overlap in TPSA levels between BPH and PCa, especially within the diagnostic grey zone [2, 4, 15]. Evidence shows that BPH and PCa share common anatomic, pathologic, genetic, and epidemiological characteristics [16]. Further evidence of the association between PSA and PCa was shown by a significant increase in age-adjusted odds ratios with increasing TPSA levels, similar to the findings by Nakamura, Scorilas [17] and Lyu, Zhao [18].

The performance characteristics of TPSA were assessed by ROC analysis. The value of the AUC demonstrated that the association between TPSA and PCa was only fairly strong [19, 20]. This observation was also reported by other studies [10, 17]. The threshold or best cut-off value was higher

than what other authors reported [11, 18]. This could be explained by the observation that men of Black African ancestry have been shown to have higher levels of PSA than Asian or Caucasian due to differences in androgenic and genetic influences [21]

Using a cut of the value of 5.0 ng/ml, TPSA showed a false positive rate as high as 88% and specificity as low as 12.0%, although the sensitivity was 100%. Similarly, at the 10.8 ng/ml threshold, the false positive rate was 54.0% and the specificity 36.0%, although the sensitivity was at 88.0%. The sensitivity of TPSA was 83.3% at the best cut-off value, which is similar to findings from another study [10]. This was only a fairly good performance but less useful for a screening test which should preferably have a high sensitivity [22]. The specificity of TPSA was 64.0%, which will be considered as fairly good as was observed by other authors [10, 23]. The PPV and NPV were 45.5% and 91.4%, respectively. This implies that the TPSA test can detect only about 46 true PCa patients out of 100 but can correctly indicate as negative about 91 BPH patients as not having PCa [22]. From the performance characteristics considered in this study, the TPSA test showed a moderate performance in differentiating PCa from BPH and should always be complemented by a second screening test for effective detection of PCa.

Limitations

The study was limited by the small sample size and the lack of other socio-demographic factors (aside from age) that could have been possible risk factors in PCa pathogenesis.

Declarations

Ethics approval and consent to participate

The study was approved by the institutional review board (IRB) of the hospital and written informed consent was obtained from all participants before the study

Availability of data and materials

Data available upon request

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Consent for publication

Consent for publication was granted

Competing interests

None

Authors' contributions

MB conceived the idea and performed the statistical analysis. **KEZ** collected the data and wrote the manuscript. All authors provided critical feedback, read and approved the final manuscript

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Tables

Table 1. General characteristics of the study population stratified by histological diagnosis

Variable	Age (years)				TPSA (ng/ml)			
	Total	BPH	PCa	PV	Total	BPH	PCa	PV
Number of values	69	51	18		69	51	18	
Minimum	45	45	59		1.00	1.00	7.00	
Maximum	104	104	80		140	100.00	140.00	
Mean	69.3	69.0	70.2	0.67	32.68	24.16	56.84	<0.001
STD	9.85	10.89	6.19		31.02	23.08	38.03	

Results presented as absolute numbers. STD; standard deviation, BPH; benign prostatic hyperplasia, PCa; prostate cancer, TPSA; total prostate specific antigen

Table 2. Univariate and multivariate logistic regression analysis

Variable	BPH	PCa	OR (95%CI)	aOR (95%CI)
Age (years)				
Total	69 (10.89)	70.17 (6.186)	1.012(0.958-1.069)	1
<65	17(81)	4(19)	1	1
65 - 74	20(69)	9(31)	1.912(0.499-7.33)	1
> 74	14(74)	5(26)	1.518(0.341-6.755)	1
TPSA (ng/ml)				
Total	24.16 (23.08)	56.84 (38.03)	1.036(1.015-1.058) *	1.036(1.015-1.058) *
≤ 10.00	22(92)	2(8)	1	1
10.01 - 20.00	10(91)	1(9)	1.100(0.089-13.592)	1.134(0.09-14.299)
>20.00	19(56)	15(44)	8.684(1.757-42.927) *	10.544(2.001-55.562) *

Result presented as number (percent) and mean (SD). BPH; benign prostatic hyperplasia. PCa; prostate cancer, PSA; prostate specific antigen, OR; odds ratio, aOR; adjusted odds ratios. *P<0.01

Table 3. The test performance characteristics of TPSA in the prediction of prostate cancer

Cut-off value	Sensitivity	Specificity	PLR	NLR	PPV	NPV	FPR	FNR
>5.0	100 (81.5-100)	12.0 (4.5-24.3)	1.14 (1.0-1.3)	0.0	29.0 (18.2-41.9)	100 (54.1-100)	88.0	0.0
>6.0	100 (81.5-100)	20.0 (10.0-33.7)	1.25 (1.1-1.4)	0.0	31.0 19.5-44.5)	100 (69.2-100)	80.0	0.0
>7.0	94.4 (72.7-99.9)	28.0 (16.2-42.5)	1.31 (1.1-1.6)	0.20 (0.02-1.4)	32.1 (19.9-46.3)	93.3 (68.1-99.8)	72.0	5.6
>8.0	94.4 (72.7-99.9)	34.0 (21.2-48.8)	1.43 (1.1-1.8)	0.16 0.02-1.1)	34.0 (21.2-48.8)	94.4 (72.7-99.9)	66.0	5.6
>9.0	88.9 (65.3-98.6)	36.0 (22.9-50.8)	1.39 (1.1-1.8)	0.31 (0.08-1.2)	33.3 (20.4-48.4)	90.0 (68.3-98.8)	64.0	11.1
>10.8	88.9 (65.3-98.6)	46.0 (31.8-60.7)	1.65 (1.2-2.2)	0.24 (0.06-0.9)	37.2 23.0-53.3)	92.0 (74.0-99.0)	54.0	11.1
>20.0	83.3 (58.6-96.4)	64.0 (49.2-77.1)	2.31 (1.5-3.5)	0.26 (0.09-0.7)	45.5 (28.1-63.6)	91.4 (76.9-98.2)	36.0	16.7

Results presented as percent (95%CI). PLR; positive likelihood ratio, NLR; negative likelihood ratio,

PPV; positive predictive value, NPV; negative predictive value, FPR; false positive rate, FNR; false negative rate