



Preventing Unnecessary Invasive Cancer-Diagnostic Tests: Changing the Cut-off Points

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Abstract

Background: To determine a cut-off point of tPSA and PSAD to prevent unnecessary invasive cancer-diagnosing tests in the community.

Methods: This study was performed on 688 consecutive patients referred to our center due to prostatism, suspicious lesions on digital rectal examination and/or elevated serum PSA levels. All patients underwent transrectal ultrasound guided biopsies and obtained PSAD. Serum levels of tPSA and f/tPSA were measured by chemiluminescence. Comparisons were done using tests of accuracy (AUC-ROC).

Results: Prostate cancer was detected in 334 patients, whereas the other 354 patients were suffering from benign prostate diseases. The mean tPSA in case and control groups were 28.32 ± 63.62 ng/ml and 7.14 ± 10.04 ng/ml; the mean f/tPSA ratios were 0.13 ± 0.21 and 0.26 ± 0.24 in PCa and benign prostate disease groups; the mean PSAD rates were 0.69 ± 2.24 , 0.12 ± 0.11 , respectively. Statistically significant differences were found ($P < 0.05$). Using ROC curve analysis, it was revealed that AUC was 0.78 for tPSA and 0.80 for f/tPSA. Sensitivity was 71% for the cut-off value of 7.85 ng/ml. For f/tPSA ratio, the optimal cut-off value was 0.13 which produced the sensitivity of 81.4% and for PSAD, it was 15%.

Conclusions: As this trial is different from the European and American values, we should be more cautious in dealing with the prostate cancer upon the obtained sensitivity and specificity for PCa diagnosis (7.85 ng/ml for tPSA, 15% for PSAD and 0.13 for f/tPSA ratio).

Keywords: Cut-off Point, Prostate cancer, PSAD, tPSA, PCa diagnosis.

Introduction

Prostate-Specific Antigen (PSA) is a uniquely valid tumor and tissue marker for prostate cancer screening and early detection. The widespread use of serum PSA testing for early prostate cancer detection has increased the proportion of early stage cancer and is at least partially responsible for the recent decrease in prostate cancer mortality rates (1).

It is very difficult to distinguish prostate cancer from benign prostate disease, particularly in patients with serum total PSA (tPSA) levels of less than 10 ng/ml. Therefore, it would be very useful if there were tools that could precisely predict the presence of cancer. This would significantly reduce the number of unnecessary prostate biopsies among males with intermediate serum PSA levels, in whom it is currently difficult to deter-

mine whether a prostate biopsy is indicated (2). Strategies to enhance the performance of PSA test include PSA density (PSAD), measurement of free to total ratio (f/t PSA), age-related and race-specific ranges of PSA (3).

The aim of this study was predicting prostate biopsy candidates through performing tPSA ratio and PSAD tests, comparing the results with the control group and avoiding unnecessary biopsies.

Materials and Methods

Study design

All patients referred for prostate biopsy because of abnormal digital rectal examination (DRE) or a serum tPSA level of greater than 4 ng/ml were enrolled in Urology Research Center, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran between September 2009 and November 2010. This study was performed in accordance with the declaration of Helsinki and subsequent revision and was approved by the Ethical Committee of Tehran University of Medical Sciences. All men had complete information on age, tPSA, f/tPSA ratio and PSAD level, PV, DRE, transrectal ultrasound (TRUS) abnormalities and family history of PCa. All men underwent a TRUS-guided biopsy by a radiologist after providing a written informed consent.

Specimen collection

Serum levels of tPSA, fPSA and f/tPSA ratio were measured by LIAISON-Diasorin (Italy) Chemiluminescence. Transaxial and sagittal ultrasound of the prostate was performed by a radiologist (Bistoon Ultrasound Clinic) experienced in this procedure using 5-8MHZ Multi Frequency transducers (these are End-Fire probes from KERTZ Co., Austria). PSA density was calculated by dividing PSA by the prostate volume as determined by transrectal ultrasonography.

Random systematic biopsies were performed using an automatic biopsy gun and a single-use,

18-gauge (Max-Core) needle with TRUS guidance. Basically, the biopsies consisted of 8 peripheral ones, 2 transition zones and 2 biopsies were obtained if suspicious areas were recognized in ultrasound images or DRE. On the same day, after the biopsy, the specimens were sent for processing and evaluation by an experienced pathologist.

The patients were compared in two groups: the case group consisting of any patient diagnosed with positive biopsy for prostate cancer and the control group consisting of any patient with negative biopsies such as normal, benign prostatic hyperplasia (BPH) or prostatitis.

Statistical analysis

Mean \pm standard deviation and the range of age, serum tPSA level, f/t PSA ratio, PSAD and PV were calculated in both groups. Variables of PSA-associated markers for the two different groups were compared using t-test with $P < 0.05$ considered statistically significant. The significance of PSA-based parameters for predicting prostate cancer was assessed based on receiver operating characteristics (ROC) curves, which are plots of the true positive rate (sensitivity) versus the false-positive rate (1-specificity) using all possible different cut-off values. The analyses were carried out with SPSS 13 software (SPSS Inc., Chicago, IL).

Results

A total of 688 consecutive screening volunteers with tPSA of more than 4ng/ml or suspicious areas in ultrasound images or DRE were assessed. Table 1 lists the study population characteristics of different PSA subgroups. Among 688 men, 48.5% had PCa and 354, 51.5% had benign prostate disease. The mean age in patients with and without PCa was 68.24 ± 8.65 and 62.79 ± 8.33 years, the range of tPSA was 0.7 to 620 and 7.14 to 10.04 ng/ml, the mean f/t PSA was 13.0% and 26.0%; also the mean PSAD in these groups was 0.69 ± 2.24 and 0.12 ± 0.11 , respectively.

Comparing the accuracy of different diagnostic tests (PSAD, f/t PSA, tPSA, fPSA) in detecting patients' PCa using ROC curve analysis showed that PSAD has the highest accuracy (0.85; 95%CI:0.82-0.88) (Table 2, Fig. 1). Moreover, the findings of the study indicated that the appropriate cut-off point for PSAD was

0.15ng/ml/cc and its sensitivity for discovering PCa patients is 76%. Although the diagnostic value of other tests was lower than PSAD, it should be noted that the most appropriate cutoff point for tPSA and f/tPSA is computed at 7.85 and 0.15, respectively.

Table 1: Characteristics of the subjects at baseline

	Case n=334		Control n=354	
	Mean ±SD	Range	Mean ± SD	Range
Age *	68.24±8.65	46-90	62.79±8.33	39-95
Total PSA (ng/ml) *	28.34±63.62	0.70-620	7.1±10.04	0.04-160
f/t PSA (%) *	0.13±0.21	0.20 -3.47	0.26±0.24	0.02-2.50
PSAD *	0.69±2.24	0.01-36.86	0.12±0.11	0.0 -1.15

*Statistically significant differences were found ($P < 0.05$)

Table 2: Comparing the accuracy of parameters for predicting significant prostate cancer with ROC analysis

Variables	Accuracy	95% Confidence interval
PSAD	0.85	0.82-0.88
f/tPSA	0.80	0.76-0.84
t PSA	0.78	0.75-0.82
f PSA	0.59	0.54-0.63

*(AUC: Area Under Curve)

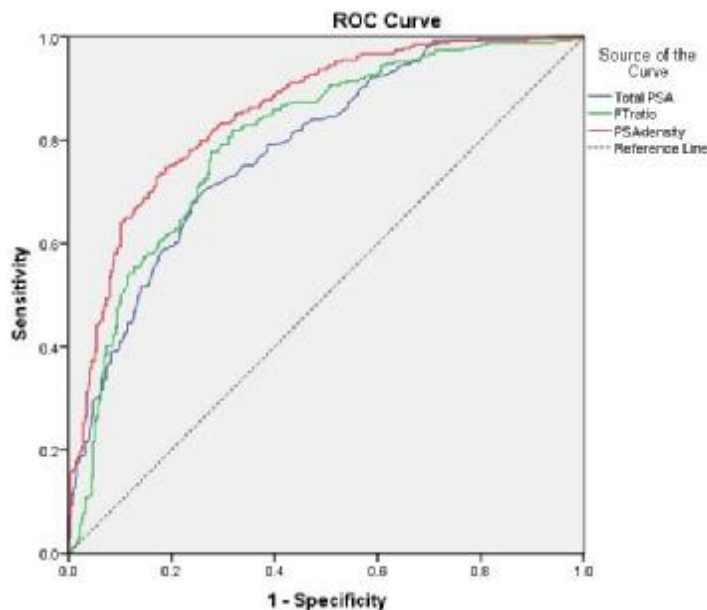


Fig. 1: ROC curve analysis in detecting patients' PCa

Discussion

There is a general agreement among clinicians on the point that tPSA screening can detect early stage PCa and most PCa cases detected by tPSA screening appear to be clinically important when pathological characteristics are used as a surrogate for biological potential (4,5). In our study, the statistical analysis showed that among Iranian men, there was a significant difference in serum PSA and PSAD levels of patients with and without prostate cancer. This finding was compatible with previous studies (6-8).

The present study suggests that the appropriate cut-off point for tPSA of Iranian men is 7.85 ng/ml, slightly different from those in other countries (9,10). In USA and Europe, men with a tPSA of <2.5 ng/ml have a low probability of having clinically detected prostate cancer (11,12). A recent study analyzing males with an initial tPSA of below 4.0 ng/ml who eventually had an increase to greater than 4.0 found that 57% of these tPSA increases were not prostate-cancer-related (13). Sheikh et al. reported benign prostate disease with tPSA levels up to 50ng/ml (8). Benign prostate disease is a common cause of tPSA elevation to levels greater than 10 ng/ml; that is contrary to the report from Western countries (14), where prostate cancer is the most common cause of t PSA levels >4ng/ml. This indicates that high or intermediate serum tPSA levels presented in our patients does not ensure that a man may or may not have PCa.

Our findings show that when f/tPSA cut-off point is 0.15, sensitivity is approximately 99% for PCa. Several studies reported that f/tPSA was one of the useful PSA-related markers to suggest prostate biopsy in subjects with intermediate tPSA levels (15). When an f/tPSA cutoff value of 15% was used as a criterion for biopsy, 54% of cancers would be detected, compared to 33% of non-PCas undergoing biopsy in normal American men with tPSA

levels of 2.51-4 ng/ml (16, 17). Eventually, a higher f/t PSA cutoff point could not be applicable in terms of selecting true cancer patients and leads to low specificity.

Several studies have examined the role of PSA density in predicting pathological parameters in prostate cancer outcomes. A PSA density of less than 0.15ng/ml/cc correctly identified 80% of clinically insignificant tumors (18). PSAD could serve as an additional parameter in predicting the negative outcome of prostate cancer with the cut-off value of 0.15ng/ml/cc within the PSA range of 4-10 ng/ml (sensitivity: 86.7% and negative predictive value: 91.5) (19). Our study shows that PSA density levels of less than 0.15 (AUC: 0.85) were highly predictive of insignificant cancer.

We had the following limitations in this study: it was not a population-based study and there were a small number of patients with serum tPSA levels of greater than 4ng/ml and suspicious DRE or TRUS. However, we showed that we can predict the probability of having significant laboratory parameters for prostate cancer. Ongoing studies are investigating the effects of screening and may overcome these problems. In conclusion, we believe that a cut-off value for PSAD is more valid than tPSA.

In conclusion, the incidence of cancer is very low in the Middle and Far East. Studies show that cut-off values >10 should be considered as prostatitis or BPH indicators. Our findings suggest the cut-off values of 7.85ng/mL for tPSA, 15% for PSAD and 0.13 for f/tPSA ratio and provide optimum sensitivity and specificity for PCa diagnosis. Therefore, it can be suggested that international cut-off points should not necessarily be applied to other regions.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc) have been completely observed by the authors.

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