Accurate Cut-off Point for Free to Total Prostate-Specific Antigen Ratio Used to Improve Differentiation of Prostate Cancer from Benign Prostate Hyperplasia in Iranian Population

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Purpose: Our aim was to determine a more predictive cut-off value for free to total prostate-specific antigen ratio (f/tPSA) to better differentiate prostate cancer (PCa) from benign prostate hyperplasia (BPH) in Iranian patients with serum PSA levels between 4 and 20 ng/mL.

Materials and Methods: This study was performed on 332 men with serum tPSA level of 4 to 20 ng/mL. All patients underwent transrectal ultrasound guided biopsies. Serum levels of tPSA and fPSA were measured by Roche immunoassay Elecsys 2010. Relationship between f/tPSA and cases of PCa was determined.

Results: Prostate cancer detected in 49 (15%) patients. Incidence of PCa for serum tPSA level < 10ng/mL and serum tPSA level of 10.1 to 20 ng/mL was 17 (6.7%) and 32 (39.5%), respectively. Mean f/tPSA value was significantly lower in PCa patients (0.12 ± 0.01) than in benign histology group (0.16 ± 0.03). Among patients with serum PSA level of 4 to 10 ng/mL (n = 251), mean f/tPSA in benign histology group (n = 234) was 0.16 ± 0.08 and in PCa group (n = 17) was 0.13 ± 0.06 ($P < .05$). For serum PSA level of 10.1 to 20 ng/mL (n = 81), mean f/tPSA in benign histology group (n = 49) was 0.16 ± 0.08 and in PCa group (n = 32) was 0.12 ± 0.05 ($P < .05$). The cut-off value of 0.12 produced 76% sensitivity and 71 % specificity, whereas the cut-off value of 0.14 yielded 83.5 % sensitivity and 61% specificity.

Conclusion: Determination of f/tPSA ratio improves differentiation of Pca from BPH. We recommend a cut-off value of 0.14 to be applied to Iranian patients.

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Keywords: prostatic neoplasm, prostate-specific antigen, benign prostate hyperplasia, early detection of cancer, biopsy

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INTRODUCTION

Measurement of serum level of prostate specific antigen (PSA) is widely used for early detection of prostate cancer (PCA) and to monitor the clinical manifestation of patients with PCa.[1] It must be stressed that PSA is not PCa specific, but tissue specific, and non-malignant disorders such as benign prostate hyperplasia (BPH) or prostatitis can affect serum PSA concentration.[2] Moreover, a number of studies demonstrated that not every case of PCa increases the PSA level.[3,4] In practice, the use of PSA for clinical staging is restricted.[5] Various adjustments,

such as PSA density (PSA divided by prostate volume) or blood based molecular diagnostics, PSA discriminating by age, and PSA velocity have therefore been attempted to improve the diagnostic value of PSA associated parameters,[6,7] but the procedures are rather complicated.[7]

In plasma, PSA exists predominantly as a complex with serine protease inhibitors such as α_1-antichymotrypsin, α_1-protease inhibitor, and α_2-macroglobulin. Approximately, 10% to 30% of total PSA (tPSA) is not bound to serum proteins and is called free PSA (fPSA). Numerous studies have demonstrated a lower ratio of fPSA to tPSA (fPSA/tPSA) in patients with PCa, calculated as a percentage of fPSA.[8,9] This implies that the accurate measurement of serum fPSA level is critical for patients whose serum levels of total PSA falls between 4 and 10 ng/mL and who do not exhibit abnormal findings upon digital rectal examination (DRE). Free to total PSA ratio (f/ tPSA) is used to enhance the specificity of cancer detection. Partin and colleagues[10] reported that f/tPSA in serum more accurately distinguishes PCa from a nonmalignant disease; thereby, avoiding unnecessary biopsies with negative results for cancer. In particular, f/tPSA has been shown to be more precise as an indicator for prostate biopsies in men with serum tPSA levels less than 10 ng/mL.[11,12]

In some western countries a cut-off value between 0.20 and 0.25 for f/t PSA has been recommended.[13,14] This study was carried out in order to determine the cut-off value of the f/tPSA in Iranian population.

MATERIALS AND METHODS

This study was performed in Mehrad General Hospital between October 2005 and October 2006. The subjects were chosen from patients who referred to the hospital mostly for routine checkup, although number of them had complaints such as frequency and dysuria. Prior to DRE, fPSA and tPSA were measured for all these patients using the Roche immunoassay Elecsys 2010. Three hundred and forty-one patients with the mean age of 62 years and serum PSA levels between 4 and 20 ng/mL were recruited in this study. None of them had urinary tract infection such as prostatitis. All of the participants gave their written informed consent and agreed to proceed with study protocol. Thereafter, serum fPSA and tPSA were measured again. Free to total PSA ratio was calculated from dividing fPSA by tPSA. All patients were referred for 10-core prostate biopsies using transrectal ultrasound. A sextant biopsy was performed from the apex and base of the right and left parasagittal planes of the prostate with 10 core biopsies, including an additional 3 cores from the peripheral zone positioned more laterally on each side. Nine patients refused to undergo biopsy leaving a final study population of 332. Each core was histologically examined for pathological grading and mapping. Two experienced pathologists independently performed histopathological examinations. Pathologists did not know free and total PSA values. Demographic and clinical characteristics of patients with and without prostate PCa were compared using student *t*-test. Receiver Operating Characteristics (ROC) curves were generated for fPSA, tPSA, and f/tPSA. *P* value less than .05 was considered statistically significant.

RESULTS

Of 332 participants, 283 (85%) had benign histology, while 49 (15%) had PCa. Incidence of PCa for serum tPSA level < 10ng/mL and serum tPSA level of 10.1 to 20 ng/mL was 17 (6.7%) and 32 (39.5%), respectively. Age, fPSA, and tPSA were similar for the cancer and benign histology groups (Table 1).

Table 1. Characteristics of Benign Histology Group and Prostate Cancer Group*

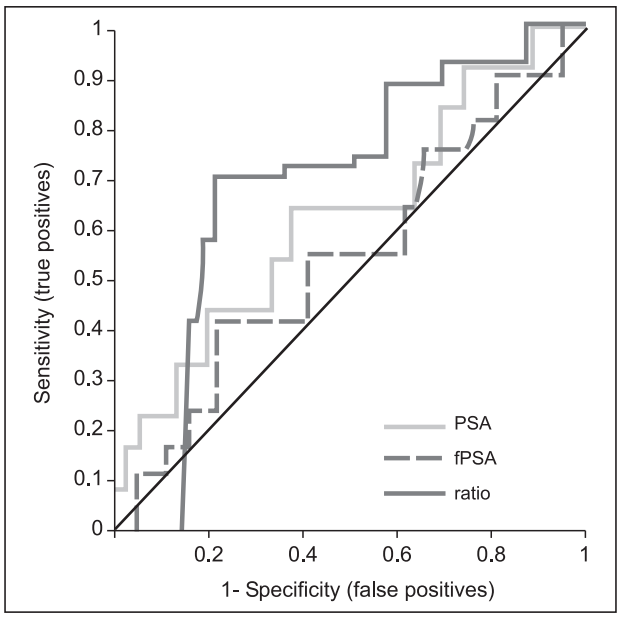
	Benign Histology Group (n = 283)	Prostate Cancer Group (n = 49)	*P*
Age (yrs)	62.66 ± 7.8 (48 to 63)	64.17 ± 8.1 (51 to 76)	.59
PSA (ng/mL)	8.52 ± 2.08 (4.2 to 14.2)	10.25 ± 3.76 (6.08 to 19.2)	.132
fPSA (ng/mL)	1.1 ± 0.7 (0.08 to 2.4)	0.98 ± 0.6 (0.05 to 1.9)	.124
f/tPSA	0.16 ± 0.03 (0.05 to 0.36)	0.12 ± 0.01 (0.08 to 0.21)	.015

*PSA indicates prostate-specific antigen; fPSA, free PSA and f/tPSA, free to total PSA ratio.

Mean f/tPSA in benign histology group was 0.16 ± 0.03 and in prostate cancer patients was 0.12 ± 0.01 ($P < .05$). Even after stratification of patients into 2 groups with serum PSA levels of 4.1 to 10 ng/mL (n = 251) and 10.1 to 20 ng/mL (n = 81), mean f/tPSA showed significant difference between two groups ($P < .05$) (Table 2). Among patients with serum PSA levels of 4.1 to 10 ng/mL, mean f/tPSA in benign histology group (n = 234) was 0.16 ± 0.08 and in PCa group (n = 17) was 0.13 ± 0.06 ($P < .05$). For serum PSA level of 10.1 to 20 ng/mL, mean f/tPSA in benign histology group (n = 49) was 0.16 ± 0.08 and in PCa group (n = 32) was 0.12 ± 0.05 ($P < .05$) (Table 3).

The ROC curves for tPSA range, fPSA, and f/ tPSA ratio are shown in Figure. Comparisons were made for the area under each ROC curve (AUC) (Table 4).

As shown in Table 4, AUC is significantly higher for f/tPSA (0.695) than for tPSA (0.602), and fPSA (0.554) indicating that f/tPSA is more predictive of PCa. Overall f/tPSA cut-off of 0.12 produced sensitivity of 76% and specificity of 71%, while for cut-off value of 0.14, sensitivity and specificity were 83% and 61%, respectively (Table 5).



ROC curve of PSA, fPSA, and f/tPSA ratio. The AUC for the f/tPSA ratio (0.695) was largest, followed by the tPSA (0.602), and then fPSA (0.554)

ROC: Receiver operating characteristics, PSA: Prostate specific antigen, fPSA: free PSA, f/t: free to total, AUC: area under the curve

Table 2. Comparison of the free to total PSA ratio between Benign Histology Group and Prostate Cancer Group

Total PSA ng/mL	Free to total PSA ratio		*P*
	Benign Histology Group	Prostate Cancer Group	
4.1 to 10.0	0.16	0.13	.017
10.1 to 20.0	0.16	0.12	.015

BHG: Benign histology group; PSA: Prostatic specific antigen

Table 3. Comparison of the free to total PSA ratio between Benign Histology Group and Prostate Cancer Group for PSA levels of 4.1 to 10 ng/mL and 10.1 to 20 ng/mL*

	4.1 to 10 ng/mL (n = 251)		10.1 to 20 ng/mL (n = 81)	
	Benign Histology Group	Prostate Cancer Group	Benign Histology Group	Prostate Cancer Group
No. of patients	234	17	49	32
f/tPSA	0.16 ± 0.08 (0.05 to 0.28)	0.13 ± 0.06 (0.06 to 0.21)	0.16 ± 0.08 (0.05 to 0.29)	0.12 ± 0.05 (0.07 to 0.19)

*f/tPSA, indicates free to total prostate-specific antigen ratio.

Table 4. Area under the Curve for the differentiation of prostate cancer from Benign Histology Group*

	AUC	95%CI	*P*
tPSA	0.602	(0.425 to 0.779)	.138
fPSA	0.554	(0.369 to 0.739)	.138
f/tPSA	0.695	(0.529 to 0.861)	.011

*AUC, indicates area under the curve; 95% CI, 95% confidence interval; tPSA, total prostate-specific antigen; fPSA, free PSA and f/t PSA, free to total PSA ratio.

Table 5. Sensitivity and Specificity of f/tPSA ratio*

f/tPSA	0.04	0.10	0.12	0.14	0.16	0.18	0.2	0.8
Sensitivity (%)	0	75	76	83	92	95	98	100
Specificity (%)	100	77	71	61	50	42	38	16

f/tPSA, indicates free to total prostate-specific antigen ratio.

DISCUSSION

It is a common belief among many urologists that measurement of serum level of total PSA plays an important role in the early diagnosis of PCa.[1] However, serum level of total PSA may increase in some benign prostate diseases,[2] and on the other hand, in some patients with PCa, low serum PSA levels may be reported.[3,4] Therefore, there is an essential need for another modality with high specificity and sensitivity which can be used to differentiate benign disease from prostate carcinoma. The prostate-specific antigen adjusted for the transition zone volume, PSA velocity, age specific PSA, and molecular forms of PSA are among these screening tools that can enhance the accuracy of diagnosis;[6,7] however, they have their own limitations.[7]

Development of immunoassays specific for different forms of PSA helped in measuring free PSA in the presence of complex forms; hence, it is possible to calculate the percentage of free PSA or free to total PSA ratio.[15] Free to total PSA ratio, as first shown by Stenman and colleagues,[8] and Christensson and associates, [16] can more efficiently distinguish subjects with BPH from those with cancer than serum tPSA levels alone.[17] Different f/tPSA values in men with and without cancer can be used to determine cut-offs for doing prostate biopsy. Use of f/tPSA can reduce unnecessary biopsies in patients undergoing evaluation for PCa. In this way, yet some prostate cancers will not be detected.[13]

It is widely accepted that in patients with elevated serum PSA concentration, men with PCa tend to have lower f/tPSA values than men with benign prostate disease.[13,18] Our study also supports this, showing that f/tPSA was significantly lower in prostate cancer group than benign histology group. Even, when patients were subdivided into groups with serum PSA levels of lower and higher than 10ng/mL, mean f/tPSA showed statistically significant differences. Our results showed that regardless of PSA, mean f/tPSA is a useful diagnostic modality for detecting PCa.

In our study, of 332 patients with serum PSA levels between 4 and 20 ng/mL, only 15% had histologically proven PCa, which is much lower than values used in western countries. This can be explained by wide different geographical prevalence of PCa. The incidence of PCa in Asian countries is much lower than those observed in North American and North and Western European countries, with Southern European and South American countries displaying an intermediate incidence rate.[19] In addition, different nutritional status, prostate biopsy techniques, and perhaps different pathological examination methods are among confounding factors.[20]

Defining a proper cut-off value for f/tPSA is crucial, since it could offer better PCa detection. In this study, in order to determine the proper cut-off value, ROC curves were generated. Our results disagree with finding of Safarinejad in Iranian men.[20] In this population-based study, 3 670 Iranian men older than 40 years were mass checked by PSA-based screening. The author concluded that a f/tPSA threshold at ≤ 0.18 rather than ≤ 0.15 increased the sensitivity for detecting cancer from 85.2% to 94.5% while false-positives decreased by 30.8%. In another study by Hosseini and colleagues,[21] 3758 volunteer Iranian men older than 40 were mass checked by PSA-based screening and DRE. In that study, conventional systematic sextant biopsies, which accounted for 6 of the 10 cores in their biopsy scheme, detected 71% of the cancers. Therefore, some PCa will be ignored even with prostate biopsy. Based on our results, f/tPSA (AUC, 0.695; 95% CI, 0.529 to 0.896) is more predictive of cancer than fPSA and tPSA for patients with tPSA values of 4 to 20 ng/mL. When f/tPSA cut-off value was set at 0.12, sensitivity and specificity were 76% and 71%, respectively and when it was raised to 0.14, sensitivity increased to 83%, but the specificity reduced to 61%. Since there is no single cut-off value that would simultaneously yield high sensitivity and high specificity, a definite decision for prostate biopsy based on f/ tPSA values would be challenging. Cut-off value of 0.12 will detect 76% of cancers, but would subject 39% of men without cancer to prostate biopsy. On the other hand, cut-off value of 0.14 will improve cancer detection, detecting 83.5% of cancer patients with 49% false-positive rate.

In order to achieve the same sensitivity and specificity in the western countries, a lower cut-off value should be considered. Hence, cut-off value of 0.14 is suggested as a more appropriate cut-off value for Iranian patients. Lower cut-off value for our patients compared to western countries is due to racial differences in f/tPSA value and cancer prevalence.[22] Therefore, clinical application of commonly used f/tPSA values of 0.2 to 0.25 to justify prostate biopsy is not applicable for all ethnic groups.

CONCLUSION

Measurement of f/tPSA improves differentiation of PCa from BPH. With serum PSA level of 4 to 20 ng/mL, a cut-off value of 0.14 is recommended. Further population-based studies are required to elaborate more accurate f/tPSA ratio.

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CONFLICT OF INTEREST

None declared.

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