Proper Cut-off Value of Free to Total PSA Ratio for Detection of Prostate Cancer in Korean Men

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To assess whether the free-to-total prostate specific antigen (PSA) ratio (F/T PSA ratio) would enhance prostate cancer detection in Korean men with serum total PSA levels between 4 and 20 ng/ml. Methods: A total of 240 consecutive patients whose serum PSA levels were between 4 and 20 ng/ml were enrolled in this two-year study. All patients underwent ultrasound-guided transrectal biopsies of the prostate gland. The F/T PSA ratio was measured using the Roche immunoassay. Results: Of the 240 patients, 202 (84%) had benign histologies, while 38 (16%) had prostate cancer. The two patient groups were well matched for age. The mean F/T PSA ratio showed a statistically significant difference between the two groups: in the benign histology group it was 0.14 (0.04 - 0.37), and 0.10 (0.08 - 0.20) in the prostate cancer group ($p<0.05$). Out of the 183 patients with a PSA level between 4-10ng/ml, the mean F/T PSA ratios were 0.14 and 0.11 in the benign histology (n=158) and prostate cancer groups (n=25), respectively ($p<0.05$). From the 57 patients with a PSA level between 10 - 20 ng/ml, the mean F/T PSA ratios were 0.14 and 0.10 in the benign histology (n=44) and prostate cancer groups (n=13), respectively ($p<0.05$). Overall, when the cut-off value of the F/T PSA ratio was 0.10, the sensitivity and specificity were 75.0% and 76.5%, while for the cut-off value of 0.15 they were 83.3% and 39.7% respectively. Conclusion: Our data demonstrated the usefulness of the free to total PSA ratio in distinguishing benign prostate disease and cancer disease, hence eliminating unnecessary biopsies. It is recommended that a cut-off value for the F/T PSA ratio of 0.10 be applied to Korean men which this is lower than the value used in Western countries.

Key Words: Prostate cancer, biopsy, free PSA, Korea

INTRODUCTION

Detecting prostate cancer is an extremely important task for urologists. In order to provide a definitive diagnosis for prostate cancer, a prostate biopsy is required. The most basic and important proxy for determining the need for a biopsy is the serum prostatic specific antigen (PSA) level.[1] If a patient's PSA level is above 10 ng/ml, then there is a high probability of prostate cancer, with little dispute among urologists[2]: most would agree that a biopsy is in order. By contrast, of those patients whose PSA level is between 4 and 10 ng/ml, only 25% are diagnosed with prostate cancer[3]; as such, in these instances, the specificity of PSA is reduced, resulting in many unnecessary biopsies. Consequently, urologists have proposed several different methods to enhance the sensitivity and specificity of PSA: these methods frequently use parameters, such as the PSA velocity, PSA density, PSA density adjusted by transitional zone volume (PSATZ density), age specific PSA, free to total (F/T) PSA ratio and molecular forms of PSA.[4-9]

Recent reports on PSA claim that the F/T PSA ratio is lower among prostate cancer patients than among benign prostate disease patients.[10,11] This implies that correctly measuring the serum free PSA level is critical for patients whose serum total PSA level falls between 4 and 10 ng/ml and who do not exhibit abnormal findings upon DRE.

Based on numerous research findings, a number of Western countries now use a cut-off value for the F/T PSA ratio of between 0.20 and 0.25.[11,12] Nevertheless, prostate cancers exhibit lower incidence in Korea than in Western countries,[13] with different age specific PSA and PSA density

between those countries.[14,15] In light of this, a modified cut-off value for the F/T PSA ratio, which is more pertinent to Korean men, is required. In this study, a standard for determining the cut-off value for the F/T PSA ratio in Korea was sought.

MATERIALS AND METHODS

Our observations at the Yonsei Medical Center, between March 2001 and March 2003, included a total of 240 patients whose serum PSA levels fell between 4 and 20 ng/ml. Patients who might show an increase in their serum PSA level due to conditions other than BPH or prostate cancer, such as prostatitis or urinary retention, were excluded from this study.

The patients underwent prostate biopsy, with either 6 or 12 cores, under the guidance of transrectal ultrasonography (TRUS). The biopsy was carried out under local or general anesthesia, and whether to administer 6 or 12 cores to a given patient was randomly decided-in particular, without regard to prostate volume. The patients were instructed to midnight NPO (no per oral) prior to the biopsy; and after the procedure were told to take fluoroquinolone for three to five days. All biopsies were carried out under the guidance of TRUS. A sextant biopsy was performed from the apex, mid and base of the right and left parasagittal planes of the prostate, with 12 core biopsies including an additional 3 cores from the peripheral zone positioned more laterally on each side.

After measuring the serum total PSA and free PSA levels, using the immunoassay (Roche®)

Diagnostics GmbH, Manheim, Germany), these values were used to calculate the F/T PSA ratio. Subsequently, several different characteristics of patients and prostate cancer patients were compared and analyzed, and the ROC (Receiver Operating Characteristics) curves of free PSA, total PSA and the F/T PSA ratio were also analyzed. All statistical analyses used the Student's t-test, which p values less than 0.05 considered significant.

RESULTS

According to the pathology of the prostate biopsy, 202 (84%) of the 240 patients were diagnosed with BPH, with the remaining 38 (16%) diagnosed with prostate cancer. These two groups showed no statistically significant differences in age, prostate volume, free PSA or total PSA. However, the mean F/T PSA ratios were 0.14 (0.04 - 0.37) and 0.10 (0.08 - 0.20) among the BPH and the prostate cancer patients, respectively, which showed a statistically significant difference (Table 1). When the total PSA was divided into two groups, according to the level (one with 4.1-10.0 ng/ml and the other with 10.1 - 18.65 ng/ml), the comparison of the F/T PSA ratios between the two groups again showed a statistically significant differences (Table 2).

Fig. 1 shows the ROC curves for the free PSA, total PSA, and the F/T PSA ratio. Table 3 shows comparative estimates for the area under each ROC curve. The area under the curve (AUC) for the F/T PSA ratio (0.691) was largest, followed by the total PSA (0.609) and then the free PSA (0.534).

Table 1. Characteristics between BPH and Prostate Cancer

	BPH	Prostate cancer	p-value
No. of patients (%)	202 (84)	38 (16)	
Age (year)	62.66	64.25	> 0.05
Prostate vol. (mL)	49.71	57.10	> 0.05
PSA (ng/mL)	7.71	9.40	> 0.05
Free PSA (ng/mL)	1.04	0.93	> 0.05
F/T PSA ratio	0.14	0.10	< 0.05

BPH, benign prostate hyperplasia; PSA, prostate specific antigen; F/T, free to total.

The AUC value for the F/T PSA ratio (0.691) deviated significantly from those for the total PSA and free PSA. Overall, when the cut-off value of the F/T PSA ratio was 0.10, the sensitivity and specificity were 75.0% and 76.5%, whereas those for the cut-off value of 0.15 were 83.3% and 39.7%, re-
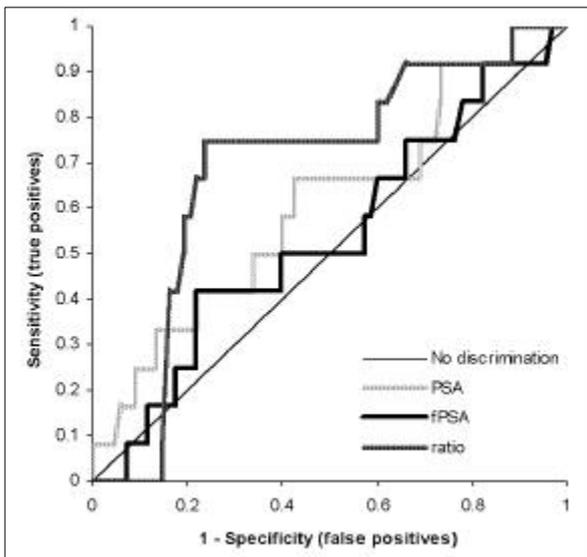

Fig. 1. ROC curve of PSA, free PSA and F/T PSA ratio. The AUC for the F/T PSA ratio (0.691) was largest, followed by the total PSA (0.609) and then the free PSA (0.534) (ROC: Receiver operating characteristics, PSA: prostate specific antigen, fPSA: free PSA, F/T: free to total, AUC: area under the curve).

spectively. The decreased percentages of unnecessary biopsies (efficiency) were 67.5% and 35.0% for the cut-off values of 0.10 and 0.15, respectively (Table 4).

DISCUSSION

Measurement of the serum PSA level can play a pivotal role in the early diagnosis of prostate cancer.[1] However, the serum PSA level could also be high for some patients with benign prostate diseases,[2] with some prostate cancer patients showing low serum PSA levels.[16] Therefore, a form of screening tool with high specificity and sensitivity, is required. The PSATZ density, PSA velocity, age specific PSA and molecular forms of PSA are among these screening tools that can enhance the accuracy of diagnoses.[4-9] Nonetheless, these parameters have several limitations. For instance, measuring the PSA density is not possible without knowing the prostate volume of each patient. However, since measuring of the prostate volume requires TRUS, which may not be accessible to all patients, it is not a practical screening tool for the general public. Furthermore, several recent research findings have reported that the PSA density by itself is not an accurate measure for detecting prostate cancer.[17] Additionally, since

Table 2. Comparison of the Free to Total PSA Ratio between BPH and Prostate Cancer, Stratified by PSA

| Total PSA (ng/ml) | Free to total PSA ratio | | *p*-value |
	BPH	Prostate cancer	
4.1 - 10.0	0.14	0.11	< 0.05
10.1 - 20.0	0.14	0.10	< 0.05

PSA, prostate specific antigen; BPH, benign prostate hyperplasia.

Table 3. Area Under the Curve for the Differentiation of Prostate Cancer from BPH

	A.U.C.	95% C.I.	*p*-value
PSA	0.609	0.431 - 0.787	> 0.05
fPSA	0.534	0.354 - 0.713	> 0.05
F/T PSA	0.691	0.534 - 0.847	< 0.05

BPH, benign prostate hyperplasia; A.U.C., area under the curve; PSA, prostate specific. Antigen; F/T, free to total; C.I., confidence interval.

Table 4. Sensitivity and Specificity, Stratified by the F/T PSA Ratio

F/T PSA ratio	0.02	0.10	0.12	0.15	0.16	0.20
Sensitivity (%)	0	75.0	75.0	83.3	91.7	100
Specificity (%)	100	76.5	66.2	39.7	33.8	11.8
Efficiency (%)*		$67.5(3)^{\dagger}$	$56.4(3)^{\dagger}$	$35.0(1)^{\dagger}$	$28.8(0)^{\dagger}$	

F/T, free to total.
*Efficiency - decreased percentage of unnecessary biopsy.
†Number of missing prostate cancer.

the PSA velocity purports to measure the rate of change in the PSA level, continuous follow-up is necessary, with daily variations posing further problems. The age specific PSA shows differences across the races. Despite slightly enhancing the specificity, this parameter exhibits relatively low sensitivity compared to other parameters.[18] By contrast, the F/T PSA ratio, in relation to PSA alone, significantly increases the positive predictive value.[19] Several reports have already been devoted to studying the importance of the F/T PSA ratio, and it is widely accepted that the F/T PSA ratio is lower among prostate cancer than benign prostate disease patients.[10,11] Our study supports this finding, showing that only the F/T PSA ratio was significantly different between the two groups of patients: BPH and prostate cancer. Furthermore, even when the groups were further divided into those with PSA ranges greater than and less than 10 ng/ml, once again the F/T PSA ratio alone still showed statistically significant differences. Pursuant to this result, it was conclude that, regardless of the PSA range, the F/T PSA ratio was a critical parameter for detecting prostate cancer.

As mentioned above, although the F/T PSA ratio can help distinguish between benign prostate disease and prostate cancer, an exact cut-off value still remains to be established. Catalona et al. reported a cut-off value of the F/T PSA ratio of between 0.20 and 0.25.[11,12] If the cut-off value is set too high, there is a high probability of detecting prostate cancer, but numerous patients must undergo potentially unnecessary prostate biopsies. Conversely, if the cut-off value is set too low, this may reduce many unnecessary prostate biopsies, but only at the expense of letting several prostate cancers go undetected. As a consequence, most of

the current literature focuses on determining the proper cut-off value that will determine whether or not a prostate biopsy is needed.

An important motivation for our study was the fact that prostate cancers exhibit lower incidence in Korea than in Western countries, and the age specific PSA and PSA density are different in each country.[13-15] As a result, it is unclear whether the same cut-off value used in Western countries can be applied to Korean men. Our study attempted to answer this question, and sought to find a standard for determining the cut-off value of the F/T PSA ratio in Korean men.

In our study, among the 240 patients whose PSA level fell between 4 and 20 ng/ml, only 38 were diagnosed with prostate cancer, according to the prostate biopsies; this corresponded to a 16% incidence. Even if the possibility of missing a few instances of cancer was taken into account, this incidence, 16%, is substantially lower than the 25% or higher incidence, among patients with comparable PSA ranges in Western countries.

In order to determine the cut-off value of the F/T PSA ratio, an analysis using the ROC was conducted. When the cut-off value was set at 0.10, the sensitivity and specificity were 75.0% and 76.5%, respectively. Conversely, when it was raised to 0.15, the sensitivity increased to 83.3%, but the specificity was significantly reduced to 39.7%. The decreased rate of unnecessary biopsies (efficiency) also fell from 67.5% to 35.0% (Table 4). These values should be contrasted with other studies. The study by Pearson and colleagues showed the cancer detection sensitivity and specificity to be 76% and 94%, respectively, when the cut-off value of the F/T PSA ratio was set at 0.12.[20] In another study where the cut off value was set at 0.17, the same ratios were 92% and 57%,

respectively.[21] One of the reasons for the relatively low sensitivity, but yet similar specificity, of our results compared to those of Western countries was presumably the problem related to prostate biopsy. Sextant and 12 cores biopsies were randomly performed in our study, without a specific standard in our study. However, 6 or 12 cores biopsy based on the findings of TRUS and DRE might have yielded a higher sensitivity. In other words, a more meticulously targeted biopsy should have been performed in a larger prostate volume or in the presence of a nodular lesion on DRE. In addition the relatively low incidence (16%) of prostate cancer in our patient groups compared to those of Western countries could also account for the lower sensitivity. Therefore, increases in the incidence of prostate cancer and precise techniques for detecting the disease are expected to result in an increase in sensitivity.

In order to maintain a comparable sensitivity, specificity and efficacy to the data of Western countries, it is recommended that the cut-off value applied to Korean men should be lower than that in Western countries. Based on our study, and notwithstanding the cut-off value of 0.15 used commonly in Western countries, it is suggested that a more appropriate cut-off value when dealing with Korean patients would be 0.10. The exact reason for the discrepancy in the pattern of the F/T PSA ratio between Korean men and Western population is not certain, but it is our thinking this may be attributed to the lower detection rate of prostate cancer in Korea than in Western countries, and also to certain genetic and environmental differences between the different races. To address this question, a more extensive study focusing on this subject is needed. Furthermore, there is a need to establish an accurate cut-off value for the F/T PSA ratio that can be generally accepted by urologists in Korea, which would require a larger randomized prospective multicenter study.

In conclusion, our data has demonstrated the usefulness of the free to total PSA ratio in distinguishing benign prostate disease and cancer disease, hence eliminating unnecessary biopsies. It is recommended that a cut-off value for the F/T PSA ratio (0.10) be applied to Korean men which are lower than the value used in Western coun-

tries. While this lower cut-off value may yield lower sensitivity, It is believed this has more to do with the lower overall prostate cancer detection rate by prostate biopsy in Korea than in Western countries.

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