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ORIGINAL ARTICLE

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# Limited usefulness of the free-to-total prostate-specific antigen ratio for the diagnosis and staging of prostate cancer in Japanese men

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**Abstract**
***Background.*** The objective of this study was to evaluate the clinical significance of measuring the free-to-total (f/t) prostate-specific antigen (PSA) ratio for the differentiation of prostate cancer from benign prostatic hypertrophy (BPH) and for the staging of prostate cancer in Japanese men.
***Methods.*** Before treatment, tPSA and fPSA were measured in 147 patients with prostate cancer and in 253 with BPH, using immunofluorometric techniques. Furthermore, the f/t PSA ratio and the tPSA density of the whole prostate (PSAD) were calculated.
***Results.*** The tPSA and PSAD levels in patients with prostate cancer paralleled the clinical stage, and were significantly higher than the levels in patients with BPH, while the f/t PSA ratio was not associated with clinical stage, despite the significantly lower values in prostate cancer patients than in BPH patients. Furthermore, the tPSA and PSAD values, but not the f/t PSA ratio, were significantly different between patients with pathologically extraprostatic disease and those with organ-confined disease. Calculation of the specificity of each assay within the range of 80%–95% sensitivity showed that tPSA and PSAD provided better specificities than the f/t PSA ratio. However, there was no significant difference in specificities among these three assays. In prostate cancer and BPH patients with PSA values of 4.1–10 ng/ml, the specificities of tPSA and PSAD were also superior to that of the f/t PSA ratio.
***Conclusion.*** These findings suggest that measurement of the f/t PSA ratio does not provide any significant additional information for the diagnosis and staging of prostate cancer in Japanese men when tPSA and PSAD values are available.

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## Introduction

Serum prostate-specific antigen (PSA) has been demonstrated to be a useful marker for the diagnosis and staging of prostate cancer. However, it appears to have limited value, particularly in patients with intermediate PSA levels, because elevation of serum PSA can be observed in patients with nonmalignant diseases, such as benign prostatic hypertrophy (BPH) and prostatitis.[1] Hence, to enhance specificity and sensitivity for the diagnosis and staging of prostate cancer, the usefulness of several PSA-associated parameters has been evaluated, including PSA density (PSAD), PSA velocity, and age-specific reference ranges.[2–4] However, there is no method that has been sufficiently reliable to allow clinical decision-making in an individual patient for the differentiation of prostate cancer from benign disease or for the prediction of prostate cancer extension.

Recently, it has been demonstrated that PSA can be detected in several forms in serum. Most PSA is complexed with serum protease inhibitors; that is, approximately 70% to 90% is bound to $\alpha_1$-antichymotrypsin (PSA-ACT), with a smaller amount being complexed with $\alpha_1$-antitrypsin, $\alpha_2$-macroglobulin, intern-$\alpha$ trypsin inhibitor, and C protein, whereas 10% to 30% of total PSA (tPSA) is not bound to serum proteins, and is called free PSA (fPSA).[5] The predominant forms of measurable PSA were found to be PSA-ACT and fPSA, while other forms of PSA were observed in small fractions of tPSA. Several studies have shown that serum from patients with prostate cancer contains a lower proportion of fPSA than serum from patients with benign prostatic disease.[5,6] Thus, the free-to-total (f/t) PSA ratio appears to be more closely associated with the progression of prostate cancer than serum PSA. However, to our knowledge, results regarding the ability of the f/t PSA ratio to detect prostate cancer and to predict its histopathological features are controversial.[6–10] Therefore, in the present

study, we retrospectively analyzed the clinical usefulness of measuring the serum f/t PSA ratio for the differential diagnosis as well as the staging of prostate cancer.

## Patients and methods

A total of 147 patients with prostate cancer and 253 patients with BPH were enrolled in this study, and all data presented in this study were collected from the records of these patients in August 2003. Blood samples were collected before digital rectal examination (DRE) and transrectal ultrasound (TRUS) of the prostate from patients who had not received any treatment for prostate cancer.

All patients were confirmed pathologically as having BPH or prostate cancer, by systematic sextant transrectal biopsies of the prostate conducted under TRUS guidance. Indications for prostate biopsies were a serum tPSA level greater than 4.1 ng/ml and/or a suspicious DRE result, irrespective of TRUS findings. The clinical stage was classified according to the criteria advocated by the Japanese Urological Association and The Japanese Pathological Society, based on the findings of TRUS, DRE, pelvic computed tomography, magnetic resonance imaging, and bone scan. After collection of the blood samples, the blood was allowed to clot for 10 min at room temperature; then serum was separated by centrifugation at 2000 *g* for 10 min at 4°C, and the sample was assessed immediately.

We measured tPSA and fPSA using immunofluorometric assay systems (Roche Diagnostics, Mannheim, Germany). The f/t PSA ratio was calculated by dividing the fPSA value by the tPSA value. PSAD was calculated by dividing the tPSA value by the prostate volume. Prostate volume was determined by a single urologist (I.S.), based on the TRUS findings, as previously described.[12] Briefly, the antero-posterior (AP) and transverse (TR) dimensions were measured at their respective greatest dimensions, and the superior-inferior (SI) greatest dimension was measured at the maximum length from the base to the apex of the prostate in the middle sagittal plane. The prostate volume was calculated from the formula for a prolate ellipsoid:

$$\text{Volume} = 0.52 \times \text{TR} \times \text{AP} \times \text{SI}$$

Values from patients with and without prostate cancer were compared using the Mann-Whitney *U*-test. Probability values (*P* values) of less than 0.05 were considered statistically significant.

## Results

The clinical stage in the 147 patients with prostate cancer was stage B in 104 patients, C in 23, and D in 20. As shown in Table 1, there were significant differences between patients with prostate cancer and those with BPH, with respect to tPSA, PSAD, and the f/t PSA ratio. Significant differences in tPSA, PSAD, and the f/t PSA ratio were also observed even between patients with stage B disease and those with BPH. Furthermore, the tPSA and PSAD levels paralleled the clinical stage of prostate cancer, but the f/t PSA ratio did not.

Of the 147 patients with prostate cancer, 68 underwent radical retropubic prostatectomy and bilateral pelvic lymphadenectomy. Pathological examination demonstrated that the disease was organ-confined in 33 patients and nonorgan (extraprostatic extension)-confined in 35 patients. Table 2 shows the outcomes of analyses of PSA, PSAD, and the f/t PSA ratio in organ-confined versus

**Table 1.** PSA, PSAD, and the f/t PSA ratio according to clinical stage

| Variable | Prostate cancer | | | | |
|---|---|---|---|---|---|
| | Stage B ($n$ = 104) | Stage C ($n$ = 23) | Stage D ($n$ = 20) | Total ($n$ = 147) | BPH ($n$ = 253) |
| tPSA (ng/ml) | 15.2 ± 8.8 | 35.8 ± 19.8 | 214.5 ± 213.8 | 45.5 ± 39.3 | 8.5 ± 5.6 |
| PSAD[a] | 0.52 ± 0.36 | 1.9 ± 0.98 | 6.8 ± 9.1 | 1.6 ± 1.32 | 0.22 ± 0.17 |
| f/t PSA ratio[b] | 0.145 ± 0.063 | 0.127 ± 0.054 | 0.148 ± 0.068 | 0.142 ± 0.073 | 0.171 ± 0.073 |

PSA, prostate-specific antigen; PSAD, PSA density; f/t, free/total; BPH, benign prostate hypertrophy
[a] Calculated by dividing the tPSA value by the prostate volume
[b] Calculated by dividing the fPSA value by the tPSA value

**Table 2.** PSA, PSAD, and f/t PSA ratio in organ-confined and extraprostatic disease

| Variable | Overall ($n$ = 68) | Organ-confined ($n$ = 33) | Extraprostatic ($n$ = 35) | $P$ value |
|---|---|---|---|---|
| tPSA (ng/ml) | 14.9 ± 8.5 | 11.0 ± 7.9 | 18.6 ± 8.8 | <0.005 |
| PSAD[a] | 0.54 ± 0.27 | 0.40 ± 0.19 | 0.67 ± 0.29 | <0.001 |
| f/t PSA ratio[b] | 0.144 ± 0.067 | 0.150 ± 0.072 | 0.138 ± 0.057 | NS |

PSA, prostate-specific antigen; PSAD, PSA density; f/t, free/total; NS, not significant
[a] Calculated by dividing the tPSA value by the prostate volume
[b] Calculated by dividing the fPSA value by the tPSA value

**Table 3.** Specificity of the cutoff values of the different PSA assays at selected sensitivities

| ST (%) | Overall ($n$ = 400) | | | | | | PSA 4.1–10 ng/ml ($n$ = 184) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | tPSA | | PSAD[a] | | f/t PSA ratio[b] | | tPSA | | PSAD | | f/t PSA ratio | |
| | SP (%) | Cutoff (ng/ml) | SP (%) | Cutoff | SP (%) | Cutoff | SP (%) | Cutoff (ng/ml) | SP (%) | Cutoff | SP (%) | Cutoff |
| 95 | 46 | 4.9 | 45 | 0.12 | 38 | 0.29 | 15 | 4.6 | 17 | 0.11 | 13 | 0.30 |
| 90 | 46 | 5.3 | 51 | 0.16 | 39 | 0.25 | 29 | 4.9 | 40 | 0.14 | 20 | 0.27 |
| 85 | 47 | 5.8 | 56 | 0.20 | 41 | 0.20 | 37 | 5.3 | 42 | 0.15 | 23 | 0.26 |
| 80 | 53 | 7.1 | 63 | 0.24 | 44 | 0.18 | 44 | 5.5 | 47 | 0.17 | 39 | 0.20 |

PSA, prostate-specific antigen; PSAD, PSA density; f/t, tree/total; ST, sensitivity; SP, specificity
[a] Calculated by dividing the tPSA value by the prostate volume
[b] Calculated by dividing the fPSA value by the tPSA value

extraprostatic disease. In patients with organ-confined disease, the mean levels of PSA and PSAD were significantly lower than those in patients with extraprostatic disease. However, the difference in the f/t PSA ratio between organ-confined and extraprostatic disease was not significant.

We then calculated the specificity of each assay, within the range of 80% to 95% sensitivity, to evaluate the clinical usefulness of tPSA, PSAD, and the f/t PSA ratio for the differentiation of prostate cancer and BPH. As shown in Table 3, tPSA and PSAD provided better specificities than the f/t PSA ratio; however, there was no significant difference in the specificities among these three assays. In addition, the same analysis was performed in patients with serum PSA values of 4.1–10 ng/ml. In this subgroup, there were 47 patients with prostate cancer and 137 patients with BPH. In this patient group, despite there being no significant differences, the specificities of tPSA and PSAD were superior to that of the f/t PSA ratio.

## Discussion

Theoretically, the occurrence of the various PSA forms in serum allows for a better discrimination between prostate cancer and BPH;[1,6] that is, the proportion of PSA complexed with serum protease inhibitors increases in patients with prostate cancer, and there is an inverse association between tPSA and the f/t PSA ratio.[11] These findings suggest that the f/t PSA ratio may be more closely associated with the progression of prostate cancer than tPSA, and, accordingly, this ratio could be more useful for the staging and diagnosis of prostate cancer. However, it seems controversial whether the f/t PSA ratio is able to accurately detect prostate cancer and to predict histopathological findings,[6–10] and few studies concerning the significance of the f/t PSA ratio in Japanese men have been published.[12,13] Thus, the usefulness of the f/t PSA ratio in Japanese clinical practice has not been established. Therefore, in the present study, we evaluated the clinical usefulness of measurement of the f/t PSA ratio for the differentiation of prostate cancer from BPH and for the preoperative staging of prostate cancer.

We initially showed significant differences in tPSA, PSAD, and the f/t PSA ratio between patients with prostate cancer and those with BPH. Furthermore, tPSA and PSAD levels in patients with prostate cancer paralleled the clinical stage; however, the values for the f/t PSA ratio were scattered and not related to the clinical stage. We then evaluated the abilities of these three variables to differentiate extraprostatic disease from organ-confined disease in 68 patients who underwent radical prostatectomy. The tPSA and PSAD values provided significantly precise information as potential markers for biochemical staging, but the f/t PSA ratio did not. Moreover, despite there being no significant association between the f/tPSA ratio and other pathological factors, including the Gleason score, seminal vesicle invasion, and lymph node metastasis, tPSA and PSAD showed close relationships to these factors (data not shown). These findings suggest that the f/t PSA ratio may not be superior to tPSA and PSAD for predicting prostate cancer extension.

All three values assessed in this series differed significantly between patients with BPH and those with prostate cancer, suggesting that these values may be appropriate parameters to distinguish between these two patient groups. We therefore examined whether the f/t PSA ratio could diagnose prostate cancer more effectively than tPSA and PSAD. The specificities of these assays within the range of 80% to 95% sensitivity did not show any significant differences, despite the higher specificity of tPSA and PSAD than that of the f/t PSA ratio. We also performed the same analysis for patients with serum PSA values of 4.1–10 ng/ml, and similar results were observed in this patient group. Therefore, it may be difficult to avoid unnecessary prostate biopsies for the diagnosis of prostate cancer by the introduction of the f/t PSA ratio, even in patients with intermediate serum PSA levels.

As described above, there has been conflicting data regarding the value of the f/t PSA ratio in the detection and staging of prostate cancer.[6–10] These discrepancies may be explained by many factors, which may contribute to different conclusions. For example, the investigators employed different conditions for the preparation and storage of serum samples, as well as employing different immunofluorometric assay systems for the measurement of tPSA and fPSA. In addition, the study design (including whether it is in a retrospective or prospective setting) and study size, as well as patient age, range of tPSA values, and pathological definitions, may also influence the results.

Therefore, further studies involving a larger number of samples should be performed under identical conditions and with identical assay systems to draw definitive conclusions concerning the significance of the f/tPSA ratio. However, considering the results presented in this study, it seems to be more important to develop a novel marker system based on the molecular mechanism of prostate cancer progression rather than to investigate the usefulness of conventional PSA-associated parameters, including the f/tPSA ratio.

In conclusion, measurement of the f/t PSA ratio did not provide any significant additional information for the staging of prostate cancer or for the differentiation of BPH from prostate cancer when tPSA and PSAD were available in Japanese men. Therefore, it appears to be unnecessary to routinely measure the f/t PSA ratio for patients suspected of having prostate cancer.

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