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·*Original Article*·

Total and free prostate-specific antigen indexes in prostate cancer screening: value and limitation for Japanese populations

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Abstract

Aim: To assess the efficacy and limitation of free/total prostate-specific antigen ratio (f/tPSA) at a single institution in Japan, focusing on the avoidance of pointless prostate biopsies. **Methods:** In total, 631 men between 44 and 93 years old (mean 69.8 years) with elevated PSA underwent power-Doppler ultrasoundgraphy-guided transrectal 10-core prostate biopsies at Niigata Cancer Center Hospital, and their histological features were investigated with total PSA (tPSA) and f/tPSA. **Results:** PCa was detected in 126 of 134 patients (94.3%) with tPSA of 26 ng/mL or higher. The detection rate was 59.4% for tPSA of 21–25 ng/mL, followed by 39.2% for 16–20 ng/mL, 30.0% for 11–15 ng/mL, 20.0% for 4.1–10 ng/mL and 7.6% for ≤ 4.0 ng/mL. f/tPSA of the PCa group was significantly lower than that of non-malignamt disorders in any tPSA ranges (mean 0.122 *vs.* 0.160, $P < 0.001$). Receiver-operating characteristics analyses showed that f/tPSA (AUC : 0.664) performed more valuably than tPSA (AUC : 0.559) in patients with tPSA between 3.0–10 ng/mL ($P < 0.01$). Although f/tPSA of 0.250 for the cut-off value might miss 1.8% PCa patients, it potentially spares 9.2% of unnecessary biopsies. **Conclusion:** f/tPSA is more valuable compared with tPSA alone for the prediction of the occurrence of PCa. We recommend 0.250 as the cut-off value for f/tPSA in PCa screening for Asian men having so-called grey-zone tPSA. (*Asian J Androl 2006 Jul; 8: 429–434*)

Keywords: prostate cancer screening; free/total prostate-specific antigen ratio; multi-site biopsy; single-institutional trial

1 Introduction

The prostate-specific antigen (PSA) test is a widespread tool used as an initial criterion for the early detection of prostate cancer (PCa), and is also used to monitor the clinical course of PCa patients [1]. Yet, the elevation of PSA does not necessarily indicate the presence of PCa, because PSA levels frequently rise in non-malignant disorders (NMD), such as benign prostatic hyperplasia (BPH) or prostatitis [2]. In practice, the use of PSA in clinical staging is restricted [3]. Various adjustments, such as PSA density (PSAD: PSA divided by prostate volume) or blood-based molecular diagnostics, have, therefore, been attempted to improve the diagnostic value of PSA-associated parameters [4, 5], but the procedures are somewhat complicated. Partin *et al.*[6] reported the ratio between free and total PSA (f/tPSA) in serum to more accurately distinguish PCa from NMD, thereby enabling the avoidance of unnecessary biopsies

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resulting in a negative finding for cancer [6]. In particular, for men with tPSA levels less than 10 ng/mL, f/tPSA is shown to be more precise for the indication of prostate biopsies [7, 8]. f/tPSA is reported to enhance the specificity in cancer detection as follows: fPSA, which is not complexed to the serum alpha-fraction protein, is mainly released from the adenomatous tissue of the prostate [9]. Correspondingly, f/tPSA in PCa cases is lower compared with those having NMD, such as BPH [5–8]. This relationship has been emphasized among patients with an elevated PSA between 4.0–10.0 ng/mL, where the outcome of biopsies is most equivocal and unpredictable [6, 8]. However, the use of f/tPSA is controversial [7, 10], because a largely overlapping fraction between PCa and NMD using varying cut-off levels for f/tPSA provides conflicting data in the correlation between the f/tPSA value and pathological outcome [6–8, 10]. Therefore, whether serological assays potentially improve the prediction of histological diagnosis and contribute to avoiding redundant tissue sampling is of general interest.

To date, there has been no study that consistently enrolled participants and examined the practical use of f/tPSA using well-designed prostate biopsies for Asian populations. In the current study, we assess the efficacy of tPSA and f/tPSA with 10 or more core biopsies using power-Doppler ultrasoundgraphy for the early detection of PCa at a single institution in Japan.

2 Materials and methods

2.1 Patients and their characteristics and measurement of serum prostate-specific antigen (PSA)

Peripheral blood samples were obtained prior to digital rectal examination and prostate biopsies, and biochemical parameters including Tandem-R total and free PSA in the serum were measured [2, 11]. f/tPSA was acquired from dividing fPSA by tPSA. Although the cut-off level of serum tPSA for PCa is generally 2.5–10 ng/mL, it is affected by age and is correlated with an increased prostate volume frequently found in elder males as BPH [2, 6]. In the present study, all patients with total PSA 10 ng/mL or higher underwent prostate biopsies. We undertook prostate biopsies for 74.15% of patients with serum PSA levels less than 10 ng/mL, who provided informed consent. We did not apply any exclusion criteria, and, in total, 631 patients between 44 and 93 years old (mean 69.8 years), who presented at the Department of Urology, Niigata Cancer Center Hospital for PCa screening, were randomly enrolled in the present study. Clinical stages of the PCa cases were determined according to International Union Against Cancer (1997) guidelines using transrectal ultrasoundgraphy (TRUS) and computed tomography and/or magnetic resonance imaging in addition to isotoped-bone-scanning [11].

2.2 Transrectal prostate biopsy with transrectal ultrasoundgraphy and histological evaluation

All patients underwent transrectal 10-core prostate biopsies using transrectal power-Doppler ultrasoundgraphy (2102 Hawk, B-K medical, Glostrup, Denmark) with a 5.0–10.0 MHz biplanar probe, between August 1999 and February 2003. The procedures followed the method of standard sextant biopsy in addition to those for bilateral laterally directed biopsy and transition zone biopsy [11, 12]. Hypoechoic lesions seen by TRUS were additionally sampled, when they were not included in 10-cores sampling. Each core was histologically examined for pathological grading and mapping. Two experienced pathologists independently conducted histopathological examinations.

2.3 Statistical Analysis

Statistical comparisons were made using the Welch-corrected *t*-test, χ^2 tests, regression analysis and receiver-operating characteristics (ROC) analysis with StatView 5.0 software (Abacus Concepts, Berkeley, CA, USA) and Prism Version 3.02 (GraphPad software, San Diego, CA) for Windows-based computers.

3 Results

3.1 total prostate-specific antigen (tPSA) level and the ratio between free and total prostate-specific antigen (f/tPSA) value, stratified according to the histological outcome

First, we presented primary data for the relationship among tPSA, f/tPSA ratio and histological outcomes on a scatter diagram for patients with tPSA of 25 ng/mL or less (Figure 1). In Table 1, the number of patients and average f/tPSA were shown stratified according to the tPSA range and histological diagnosis obtained from biopsies. PCa was detected in 126 of 134 patients (94.3%) with tPSA of 26 ng/mL or higher. The detection rate was 59.4% for tPSA of 21–25 ng/mL, followed by 39.2% for 16–20 ng/mL, 30.0% for 11–15 ng/mL, 20.0% for 4.1–10 ng/mL and 7.6% for 4.0 ng/mL or less. Overall, f/tPSA of the PCa group (0.122) was significantly lower than

Table 1. Patient's background and average f/tPSA according to the tPSA range. tPSA, total prostate-specific antigen (PSA); f/tPSA, free/total PSA ratio; *n*; number of patients; NMD, non-malignant disorders; PIN, prostatic intraepithelial neoplasm; AAH, atypical adenomatous hyperplasia; PCa, prostate cancer. Since February 2000, PSA having accuracy below a decimal point has become available in any PSA range. The present study was prospectively undertaken without changing the initial criteria, and the measurement of PSA levels without figures below a decimal point has been used for those over 10 ng/mL.

	tPSA range (ng/mL)	1.0–4.0	4.1–6.0	6.0–8.0	8.1–10	11–15	16–20	21–25	26–30	31–	Total
Mean f/tPSA (*n*)	NMD	0.182	0.156	0.155	0.159	0.163	0.131	0.174	0.096	0.150	0.160
		(43)	(66)	(62)	(49)	(47)	(20)	(9)	(1)	(4)	(301)
	PIN/AAH	0.193	0.133	0.180	0.171	0.166	0.190	0.154	0.101	0.065	0.166
		(5)	(12)	(19)	(10)	(16)	(11)	(4)	(2)	(1)	(80)
	PCa	0.113	0.135	0.122	0.119	0.126	0.123	0.121	0.119	0.117	0.122
		(4)	(18)	(16)	(20)	(27)	(20)	(19)	(15)	(111)	(250)
	Total	(52)	(96)	(97)	(79)	(90)	(51)	(32)	(18)	(116)	(631)

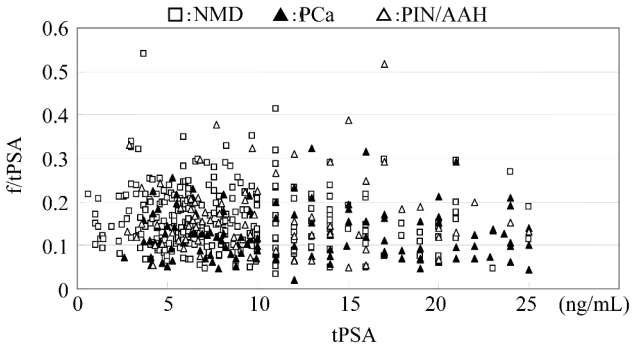

Figure 1. Primary data on a scatter diagram showing relationship among tPSA, f/tPSA ratio and histological results for patients with tPSA of 25 ng/mL or less. tPSA, total prostate-specific antigen; f/tPSA, free/total PSA ratio; NMD; non-malignant disorder; PCa, prostate cancer; PIN, prostatic intraepithelial neoplasm; AAH, atypical adenomatous hyperplasia.

Table 2. Most appropriate cut-off value for f/tPSA and values calculated on ROC curve according to respective tPSA ranges. tPSA, total PSA (prostate-specific antigen); f/tPSA, free/total PSA ratio; ROC, receiver-operating characteristics; AUC, area under curve.

tPSA range (ng/mL)	AUC of f/tPSA	cut-off value for f/tPSA	sensitivity	specificity
3.0–10	0.664	0.129	0.667	0.640
3.0–20	0.653	0.129	0.628	0.624
3.0–5.0	0.649	0.147	0.714	0.524
5.0–7.0	0.573	0.129	0.529	0.700
7.0–10	0.721	0.132	0.821	0.615
10–15	0.657	0.104	0.536	0.768

that of the prostatic intraepithelial neoplasm (PIN)/atypical adenomatous hyperplasia (AAH) (0.166) and the NMD group (0.160) ($P < 0.005$ and $P < 0.001$, respectively). Yet, f/tPSA varied among PCa patients with tPSA of 10 ng/mL or higher, NMD with tPSA of > 16 ng/mL or higher, and PIN/AAH cases (Figure 1).

3.2 Diagnostic accuracy using various cut-off values of the ratio between f/tPSA value obtained with receiver-operating characteristics curve (ROC)

The appropriate cut-off value for f/tPSA was calculated on the ROC curve for respective tPSA ranges. Comparisons were made between the PCa and the non-PCa group involving patients with NMD and PIN/AAH, and the area under curve (AUC) for f/tPSA, sensitivity and specificity with most valuable f/tPSA cut-off are shown in Table 2. AUC of the f/tPSA value varied among tPSA ranges, and it was smallest (0.573) for tPSA between 5.0 and 7.0, whereas it was greatest (0.721) for tPSA between 7.0 and 10.0 (Table 2). Between tPSA of 4.0–10 ng/mL (so-called grey-zone PSA), the AUC of f/tPSA was 0.644, and between tPSA of 3.0–10 ng/mL, f/tPSA (AUC: 0.664) was more valuable than tPSA (AUC: 0.559) for the indication of prostate biopsies (Figure 2). Simulated outcomes using various cut-off values for f/tPSA are shown in Table 3. For further analyses of men with tPSA of 3.0–10 ng/mL, we present data of 23 patients (2 PCa cases and 21 non-PCa cases) with tPSA levels of 3.0–4.0 ng/mL in addition to 272 patients with tPSA levels between 4.1 and 10 ng/mL (Table 3). Table 3 includes results from 56 cancer-positive biopsies and 239 negative biopsies in men with PSA between 3.0–

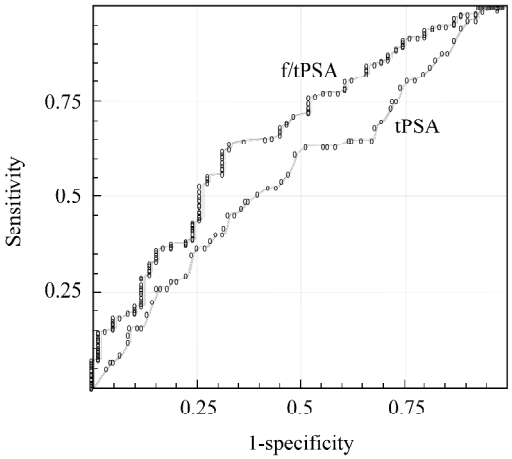

Figure 2. Receiver-operating characteristics (ROC) curve of f/t PSA (upper curve) and tPSA (lower curve) for patients with tPSA between 3.0 and 10 ng/mL. The area under curve (AUC) of f/t PSA was significantly greater than that of tPSA ($P < 0.01$). tPSA, total PSA (prostate-specific antigen); f/tPSA, free/total PSA ratio.

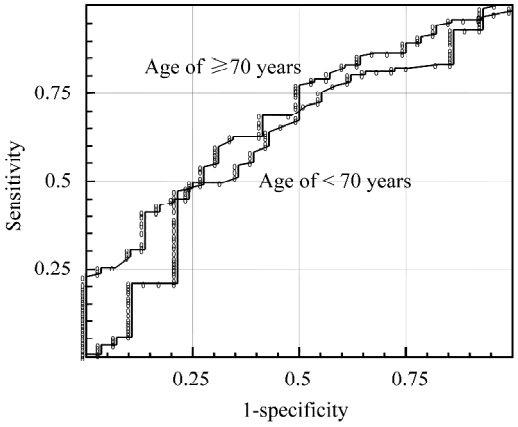

Figure 3. ROC curve of free/total PSA ratio (f/tPSA) for patients of 70 years or older (upper curve) and those under 70 years (lower curve) in total PSA (tPSA) between 3.0 and 10 ng/mL. The diagnostic value of f/tPSA was significantly higher for elderly men ($P < 0.05$).

Table 3. Various cut-off values for f/tPSA and simulated biopsy results in patients with tPSA levels between 3.0 and 10 ng/mL. Setting A: most appropriate cut-off value found on ROC. B: cut-off value that gives 90%-sensitivity. C: cut-off value having 100%-sensitivity. D: cut-off value recommended in our institution. tPSA, total PSA (prostate-specific antigen); f/tPSA, free/total PSA ratio.

Setting	f/tPSA value for cut-off	Missed cancer	Spared biopsies
A	0.129	19/56	153/239
B	0.215	6/56	47/239
C	0.260	0/56	17/239
D	0.250	1/56	22/239

10 ng/mL. An f/tPSA cut-off value of 0.215–0.260 can spare 47–17 of 239 biopsies, maintaining 90–100%-sensitivity, respectively. When a f/tPSA cut-off value of 0.250 is applied, 9.2% biopsies can be withheld, resulting in missed PCa cases of 1.8%.

3.3 Influence of age on the ratio between free and total prostate-specific antigen value

We further investigated the age-affected f/tPSA shift both for PCa and non-PCa cases. Among PCa cases with tPSA between 3.0 and 10, f/tPSA was not different between patients of < 70 and 70 years old or higher, whereas among NMD cases with tPSA between 3.0 and 10.0, f/tPSA was higher in patients of 70 years or higher (data not shown). Age-stratified analyses showed better performance of f/tPSA ratio in men of 70 years or older than in those under 70 years, with AUC of 0.642 *vs.* 0.603 ($P < 0.05$) (Figure 3).

4 Discussion

In the present study, the incidence of PCa in men with PSA levels between 4.1 and 10 (20.0%) and less than 4.0 ng/mL (7.6%) is low compared with those in a recent large study in the USA (approximately 35% and 15%, respectively) [13]. This discrepancy might be a result of racial difference and lifestyle [14]. However, in some previous studies in Japan, detection rates in men with such PSA ranges were almost equal to those in the USA or Western European countries [11]. We first discuss the significance of PCa screening for Asian men with PSA levels less than 10 ng/mL. The accepted cut-off level of PSA for PCa screening was 4.0 ng/mL, until Partin *et al.* [15] demonstrated that frequent extraprostatic extension even in cases with PSA levels ranged between 4.1 and 6.0 ng/mL. In the present study, relatively high cancer detection rates in Asian men with PSA levels between 4.0 and 10 ng/mL or even less than 4.0 ng/mL should also not be disregarded [16]. Moreover, recent evidence showed that 65% of cases with PSA less than 4.0 ng/mL were accompanied by multi-focal cancers, and

Table 4. Representative studies for assessment of f/tPSA in patients with so-called grey-zone PSA. tPSA, total PSA (prostate-specific antigen); f/tPSA, free/total PSA ratio.

tPSA (ng/mL) range	Applied f/tPSA cut-off	Sensitivity	Specificity	Missed cancer	Spared biopsies	Reference No.
4.1–10	0.299	0.907	0.240	8/85	47/196	[19]
4.1–10	0.377	0.923	0.072	10/131	33/457	[22]
4–10	0.263	0.90	0.26	2/16	17/64	[20]
2–10	0.25	0.90	0.38	9/90	77/205	[21]
3.0–10	0.215	0.90	0.196	6/56	47/239	Current study
	0.250	0.982	0.0920	1/56	22/239	

more than 35% of these were histologically revealed to have highly malignant potential [17]. Correspondingly, many PCa patients with tPSA less than 4.0 ng/mL in our present and previous studies were accompanied by clinically significant cancer (data not shown) [11]. In contrast, the fraction of men with PSA levels higher than 4.0 ng/mL represents approximately 21%, based on data from PCa screening for more than 9 000 men at our institution and associates (unpublished personal data from Niigata Cancer Certer), whereas the cause-specific mortality is approximately 1% in Japan [18]. This discrepancy might provide a reason for why many prostate biopsies are supposed to be insignificant for Asian men with PSA levels between 4.0–10 ng/mL. Therefore, the advent of more precise indexes/values is warranted to alleviate the aforementioned dilemma.

In the current study, f/tPSA appeared useful for the prediction of the occurrence of PCa in comparison with tPSA alone. Table 4 presents representative previous studies that examined performances of f/tPSA with 90%-sensitivity under grey-zone tPSA [19–22]. When given 90%-sensitivity, the cut-off value for f/tPSA ranged between 0.250 and 0.377 in these studies. Based on the present data, although the f/tPSA of 0.250 for the cut-off value might fail to notice 1 of 56 (1.8%) PCa patients, it potentially spares approximately 10% of pointless biopsies. Therefore, we propose a cut-off f/tPSA value of 0.250 for patients with grey-zone tPSA.

Various adjustments such as PSAD have been shown to improve the diagnostic value of PSA-associated parameters [4]. Also, the AUC of patients of 70 years or older is greater in the present study (Figure 3), suggesting that many elderly men have developed prostatic hyperplasia. We believe that f/tPSA is not only more precise but also concise for PCa screening, which does not require any special technique and equipment, but of course, patient's age, prostate volume, digital rectal examination and tPSA levels should be concurrently considered.

Approximately 40% of patients clinically diagnosed as having organ-confined disease already have extracapsular extension in the excised specimen [23]. Accordingly, 30–40% of patients with clinical T1c have locally advanced disease [3, 15]. Yet, outcomes of f/tPSA as a predictor of pathologic stage varied among previous trials [4, 24]. Therefore, accuracy in the screening step is also critical for subsequent therapeutic options, and further enhancement of the diagnostic modality is a challenging problem in the early check-up of prostate cancer for Asian populations. In addition, follow-up for men with negative biopsy results would be a critical issue in the next step. We are currently undertaking a study on the clinical course of such patient fractions in terms of increased velocity of PSA (PSA velocity) and transit of f/tPSA, evaluated by second or more biopsy sessions.

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