The Clinical Utility of Measuring Total PSA, PSA Density, γ-Seminoprotein and γ-Seminoprotein/Total PSA in Prostate Cancer Prediction

Ryusei Sasaki, Tomonori Habuchi, Kazunari Sato, Toshiya Akao, Hideaki Kakinuma, Zhang Li-Qing, Wang Lizhong, Shigeki Matsuo, Shuuhei Sasaki, Osamu Ogawa and Tetsuro Kato

1Department of Urology, Akita University School of Medicine, Akita, 2Akita Municipal Hospital, Akita and 3Kyoto University Graduate School of Medicine, Kyoto, Japan

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Background: To evaluate whether serum total prostate-specific antigen (PSA), PSA density (serum total PSA level divided by prostate volume), γ-seminoprotein and γ-seminoprotein/total PSA ratio could predict prostate cancer (PCa) prior to biopsy.

Methods: A total of 316 consecutive patients who had undergone transrectal prostate biopsy and/or transurethral resection were examined. The prostate volume was determined by transrectal ultrasonography (TRUS) and the ability of the above-mentioned four variables to distinguish PCa from benign prostatic hyperplasia (BPH) was evaluated.

Results: PCa was detected in 61 cases. Receiver-operating characteristic (ROC) analysis revealed that both the PSA density and serum total PSA were the most useful predictors of PCa among the four variables. For the patients with a serum total PSA level of 4.1–10.0 ng/ml, PSA density was significantly more accurate than total PSA (p < 0.005). An optimum PSA density value of 0.18 was chosen as a cutoff because it showed the highest sum of sensitivity and specificity, 92 and 54%, respectively. Using this PSA density cutoff, the number of biopsies could have been reduced to 57 from 63% when compared with a PSA density of 0.15.

Conclusions: PSA density was significantly more accurate than other variables in predicting PCa. To avoid unnecessary biopsies, the PSA density cutoff value of 0.18 would be recommendable for determining a prostate biopsy for Japanese males with a serum total PSA level of 4.1–10.0 ng/ml.

Key words: prostate cancer – prostate-specific antigen – PSA density – free/total PSA

INTRODUCTION

Prostate cancer (PCa) now constitutes a major and escalating international health problem, although the worldwide prevalence of clinical PCa varies considerably from one country to another. The lowest incidence has been reported in the Far East, especially in mainland China and Japan (1). In Japan, however, the number of new cases of PCa soared from 6482 in 1988 to 9000 in 1994, causing a 1.5-fold increase in the number of deaths due to PCa in the last 10 years (2). These figures have led epidemiologists to predict a dramatic increase in both the incidence and death rates from PCa by the year 2015 if effective improvements in prevention, early diagnosis and treatment are not made.

Prostate-specific antigen (PSA) is a useful tool in the diagnosis and monitoring of men being evaluated for or who have PCa (3). The yield of PCa by prostate biopsy is >50% in patients with a serum PSA level of >10.0 ng/ml (4), while the likelihood of PCa in patients with a serum PSA level of 4.1–10.0 ng/ml (intermediate serum total PSA level) is 22–27% (4). Management of subjects with a serum PSA level within this range seems to be controversial since a substantial number of patients with benign prostatic hyperplasia (BPH) are within the same range of serum PSA (5). In an effort to identify PCa and, at the same time, to reduce unnecessary biopsies, various indices, such as PSA density (6,7), free/total PSA (8–10), PSA velocity (PSAV) (11), PSA transition zone volume (PSATZ) (12,13) and age-specific PSA reference range (14), have been...
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In the present study, we assessed the accuracy of total PSA, γ-sp, PSA density and γ-sp/total PSA in predicting PCa in Japanese males. We also assessed the optimum cutoff value of PSA density for the subgroup of patients with a serum total PSA level of 4.1–10.0 ng/ml in order to avoid unnecessary prostate biopsies.

MATERIALS AND METHODS

Between April 1995 and April 1997, pretreatment serum samples from 316 Japanese patients with clinically localized PCa or BPH were subjected to the present analysis. All patients had lower urinary tract symptoms and were referred to our institutions for urological evaluation. All the patients underwent systematic (sextant) transrectal ultrasound (TRUS)-guided needle biopsy using 18-gauge biopsy needles (Biopryt, C. R. Bard, GA, USA) before initiation of treatments; a biopsy was performed even if there were no suspicious sites on digital rectal examination (DRE) and TRUS. Patients were assigned to either a PCa or a BPH group according to the pathological findings of specimens obtained by biopsy and/or transurethral resection. Thus the present subjects were selected from a community-based urological practice and do not represent a screened population. All patients with PCa were thoroughly examined for staging by DRE, serum total PSA, serum γ-sp, TRUS, intravenous urography, retrograde urethrosigmoidy, pelvic computed tomography (CT) and bone scanning. According to the TNM classification (16), all PCa patients were defined as having T1-3N0M0 tumors.

Serum samples were obtained before performing DRE and TRUS and no patients received any hormonal therapy before blood sampling. Serum total PSA levels were measured with a Tandem-R PSA kit (Hybritech, San Diego, CA, USA). Serum γ-sp levels were measured with an enzyme immunoassay using a Chugai γ-sp kit (Chugai Pharmaceutical, Tokyo, Japan). The serum γ-sp measured with this kit has been shown to represent the serum free PSA (17). TRUS examination was performed using a TOSHIBA (Tokyo, Japan) SSA-260A CE with a 6.0 MHz multiplanar probe. With a patient in the lateral knee-to-chest position, multiple transverse and longitudinal views were recorded. Prostate volume was calculated with an equation for the prostate ellipsoid (maximum length × width × height × 0.52) (18). The PSA density was calculated by dividing the serum total PSA by the prostate volume measured by TRUS.

For statistical analyses, a subgroup of patients with a serum total PSA level of between 4.1 and 10.0 ng/ml was defined as an intermediate total PSA group. The values obtained were compared using the Mann–Whitney U-test for non-parametric analyses. The positive predictive value (PPV), sensitivity and specificity for the tests were calculated for total PSA, PSA density, γ-sp and γ-sp/total PSA. All statistical analyses were performed using SPSS software (SPSS, Chicago, IL, USA). The significance of total PSA, PSA density, γ-sp and γ-sp/total PSA for predicting PCa was assessed based on the receiver-operating characteristic (ROC) curve using the statistic analysis programs LABROC and CLABROC developed by Metz (19). The generalized Wilcoxon test was also used as described by Hanley and McNeil (20). Statistical differences were considered significant when p values were below 0.05.

RESULTS

OVERALL GROUP

Of 316 patients, PCa was found in 61 (19%) and BPH in 235 (81%). The mean age of patients with PCa was significantly higher than that of patients with BPH (p = 0.02). There was a significant difference in total PSA, PSA density, γ-sp and γ-sp/PSA between patients with PCa and BPH (p < 0.001) (Table 1).

The diagnostic utility of these four parameters for identifying patients with PCa was evaluated using ROC curve analysis. Figure 1 provides areas under the ROC curve (AUC) for a specified cutoff value of each parameter. An AUC assessed how well a parameter could correctly identify patients with PCa and its value indicates the likelihood of correct classification. The AUC was 0.8376 for total PSA, 0.6993 for γ-sp and 0.6837 for γ-sp/PSA between patients with PCa and BPH (p < 0.001) (Table 1). Significant differences in the AUCs were found between total PSA and γ-sp (p = 0.001) and between total PSA and γ-sp/PSA (p = 0.001), but not between total PSA and PSA density (p = 0.41) or between γ-sp and γ-sp/PSA (p = 0.25). Therefore, PSA density and total PSA were considered the most powerful predictors of PCa among the four variables.

| Table 1. Age, prostate volume, serum PSA, γ-sp, γ-sp/PSA and PSA density in patients with PCa and BPH |
|----------------------------------|------------------|-----------------|------------------|
| **PCa (n = 61)**                  | **BPH (n = 255)** | **p**            |
| Age (years)                       | 71.8 ± 1.1 (55.1–91.6) | 69.4 ± 0.4 (51.7–88.4) | 0.002            |
| Prostate volume (ml)              | 33.1 ± 2.5 (7.0–108.9) | 38.4 ± 1.4 (8.0–150.0) | N.S.             |
| Total PSA (ng/ml)                 | 29.2 ± 4.5 (4.4–180.0) | 7.1 ± 0.4 (0.4–57.1) | <0.001           |
| γ-sp (ng/ml)                      | 8.6 ± 1.3 (1.0–48.0)  | 3.7 ± 0.2 (0.2–26.0) | <0.001           |
| γ-sp/total PSA                    | 0.37 ± 0.04 (0.12–1.65) | 0.71 ± 0.04 (0.05–4.75) | <0.001           |
| PSA density (ng/ml/ml)            | 0.34 ± 0.04 (0.98–4.76) | 0.23 ± 0.01 (0.01–1.67) | <0.001           |

Data are reported as mean ± S.E. (range). N.S., not significantly different.
INTERMEDIATE PSA GROUP

In total, 235 patients had a serum total PSA level between 4.1 and 10.0 ng/ml and 24 (10%) of them were histologically confirmed to have PCa. The mean age of patients with PCa was significantly higher than that of the patients with BPH ($p = 0.002$). There was no significant difference in total PSA, $\gamma$-sp and $\gamma$-sp/total PSA between patients with PCa and BPH (Table 2). The AUC was 0.6421 for PSA density, 0.5925 for $\gamma$-sp/total PSA, 0.5910 for total PSA and 0.4724 for $\gamma$-sp (Fig. 2). Significant differences were found in the AUC between PSA density and total PSA ($p = 0.001$), between PSA density and $\gamma$-sp ($p = 0.001$) and between PSA density and $\gamma$-sp/total PSA ($p = 0.001$). Consequently, for the intermediate total PSA group, PSA density was considered the most powerful predictor of PCa among the four variables.

DIAGNOSTIC PERFORMANCE OF PSA DENSITY AT VARIOUS CUTOFF VALUES

Since the ROC analysis indicated that the PSA density was the most useful variable in predicting PCa in the patients with the intermediate total PSA level, we next tried to define the optimum cutoff value for PSA density. The diagnostic performance of different thresholds for PSA density is shown in Table 3. Lowering the cutoff value to 0.11 (ng/ml/ml) resulted in a sensitivity of 100% and a specificity of 38%. Utilizing this, the number of biopsies could have been reduced to 156 (34%) from 235 and none of the PCa patients would have been missed. If the PSA density cutoff value was set at 0.15, which has been widely used for PCa detection (6,7), the sensitivity and specificity would be 92 and 47%, respectively; the number of patients requiring biopsies could have been reduced to 134 (43%) from 235 with a PCa detection rate of 92% (22/24). When the PSA density cutoff value was placed at 0.18, the sensitivity and specificity would be 92 and 54%, respectively; the number of biopsies could have been reduced to 120 (51%) with a PCa detection rate of 92% (22/24).

According to this analysis, a PSA density of 0.18 (ng/ml/ml) was considered optimum because it gave the highest sum of sensitivity and specificity and could have excluded a considerable number of patients from unnecessary prostate biopsies.
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DISCUSSION

Serum PSA is the most widely used tumor marker for PCa, but it is insufficient for differentiating PCa and BPH. Since the likelihood of patients with benign prostatic diseases having a serum total PSA level of 4.1–10.0 ng/ml is 83–88% (4), histological confirmation is an essential prerequisite for diagnosis of PCa. Consequently, TRUS-guided systematic prostate biopsy has been the current practice for urologists who encounter such patients. For early detection of PCa, Catalona et al. (21) recommended that all patients with a serum total PSA level of >4.0 ng/ml should undergo biopsies. However, its cost and overall inadequate performance hamper TRUS-guided prostate biopsy (22). Rietbergen et al. (23) reported that hematuria and hematospermia were encountered in 23.6% and 45.3% of the patients after biopsy. Fever, though it was low grade, was seen in 4.2% of the patients and 0.4% of the patients required hospitalization. Thus, although prostate biopsy is generally recognized as an essential test for PCa (22), screening methods with low morbidity have become an important issue in recent years.

Figure 2. Receiver-operating characteristic curves of total PSA (A), γ-sp (B), PSA density (C) and γ-sp/total PSA (D) between 4.1 and 10.0 ng/ml. The AUC value indicates the likelihood of correct identification of prostate cancer.

Table 2. Age, prostate volume, serum PSA, γ-sp, γ-sp/PSA and PSA density in patients with PCa and BPH with PSA level of 4.1–10.0 ng/ml

<table>
<thead>
<tr>
<th></th>
<th>PCa (n = 24)</th>
<th>BPH (n = 211)</th>
<th>p</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>74.8 ± 1.1 (67.4–86.2)</td>
<td>70.6 ± 0.6 (51.7–88.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Prostate volume (ml)</td>
<td>25.8 ± 2.7 (7.0–54.6)</td>
<td>35.0 ± 1.9 (8.0–150.0)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Total PSA (ng/ml)</td>
<td>6.9 ± 0.3 (4.4–10.0)</td>
<td>6.9 ± 0.1 (4.1–10.0)</td>
<td>N.S.</td>
</tr>
<tr>
<td>γ-sp (ng/ml)</td>
<td>2.8 ± 0.6 (1.0–14.0)</td>
<td>3.1 ± 0.2 (0.4–17.0)</td>
<td>N.S.</td>
</tr>
<tr>
<td>γ-sp/total PSA</td>
<td>0.41 ± 0.08 (0.13–1.65)</td>
<td>0.47 ± 0.04 (0.05–3.17)</td>
<td>N.S.</td>
</tr>
<tr>
<td>PSA density (ng/ml/ml)</td>
<td>0.34 ± 0.04 (0.12–0.87)</td>
<td>0.26 ± 0.01 (0.05–0.94)</td>
<td>0.02</td>
</tr>
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Data are reported as mean ± S.E. (range). N.S., not significantly different.
In an attempt to predict PCa, various PSA indices have recently been proposed. Demura et al. (10) claimed that, by using the γ-sp antibody which recognizes free PSA exclusively, the γ-sp/total PSA ratio is useful in discriminating PCa from BPH. However, since their study population contained 34 (26.7%) stage D PCa patients and their PSA cutoff value was set at 3.0 ng/ml, the superiority of γ-sp/PSA ratio in detecting localized PCa might be limited. Kurita et al. (24) also reported that γ-sp/total PSA was most useful for detection of PCa with the prostate volume of <40 ml. Although the free/total PSA ratio has been reported as the most useful predictor of PCa, the clinical usefulness of free/total PSA for PCa in the Japanese male population has yet to be adequately demonstrated (25). Furthermore, the discrepancies of the levels of serum free PSA depending on the assay systems have been reported (26). Thus the efficacy of the free/total PSA for the early detection of the PCa must be interpreted carefully. On the other hand, Kanehara et al. (27) and Ohori et al. (28) indicated that PSA density was significantly more accurate than serum PSA levels for the early detection of PCa. Our study revealed that PSA density and total PSA were the most powerful predictors of PCa in the overall range. In the total PSA range between 4.1 and 10.0 ng/ml, which was described as a ‘gray zone,’ PSA density was significantly more accurate than serum PSA levels for the early detection of PCa. Our study revealed that PSA density and total PSA were the most powerful predictors of PCa in the overall range. In the total PSA range between 4.1 and 10.0 ng/ml, which was described as a ‘gray zone,’ PSA density was significantly more accurate than serum PSA levels.

Based on the data from Western patients (6,7), a PSA density of 0.15 has been widely used as a cutoff value. Only a few studies have evaluated the optimum PSA density level in predicting PCa for Japanese population. Gohji et al. (29) suggested that PSA density was superior to PSATZ in detecting PCa in Japanese PCa patients with a PSA level of 2.1–10.0 ng/ml and proposed an optimum cutoff value of PSA density of 0.18. Arai et al. (30) also claimed that PSA density improved the specificity of cancer detection in a Japanese population with a normal digital examination and an intermediate PSA level of 4.1–10.0 ng/ml. They proposed a PSA density of 0.19 in Japanese males as an optimum cutoff value. We found that the optimum PSA density was 0.18 because it gave the highest sum of sensitivity and specificity. Utilizing this, the number of unnecessary biopsies could be reduced to 57 from 63% when compared with a PSA density of 0.15.

The optimum PSA density values for Japanese proposed by us and others (29,30) seem considerably higher than those for Western people. This might come from the differences in physiological and genetic factors of the prostate. The mean size of the prostate gland is smaller and the mean serum PSA value is lower in Japanese males compared with those in white males (31). As PSA is secreted exclusively from the prostate epithelium and periurethral glands (32), the racial difference in the prostate volume may account for the racial difference in serum PSA levels. Meanwhile, Ross et al. (33) reported a significant difference in 5α-reductase activity between Japanese and Caucasians. Kantoff et al. (34) also claimed that a polymorphism of the 5α-reductase gene was associated with an increased risk of PCa. These findings suggest that the racial difference should be considered to standardize the PSA-related variables as predictors of PCa.

In conclusion, our results indicated that PSA density is the most useful variable among total PSA, PSA density, γ-sp and γ-sp/total PSA and that a PSA density cutoff value of 0.18 is optimum for differentiating PCa from BPH in the Japanese population with an intermediate serum PSA level.

### References


