Percent free prostate-specific antigen is effective to predict prostate biopsy outcome in Chinese men with prostate-specific antigen between 10.1 and 20.0 ng ml$^{-1}$

Rui Chen$^{1,6}$, Li-Qun Zhou$^{2,4}$, Xiao-Bing Cai$^{4}$, Li-Ping Xie$^{4}$, Yi-Ran Huang$^{2}$, Da-Lin He$^{6}$, Xu Gao$^{1}$, Chuan-Liang Xu$^{1}$, Qiang Ding$^{1}$, Qiang Wei$^{1}$, Chang-Jun Yin$^{2}$, Shan-Cheng Ren$^{1}$, Fu-Bo Wang$^{1}$, Ye Tian$^{10}$, Zhong-Quan Sun$^{1}$, Qian Fu$^{12}$, Lu-Lin Ma$^{13}$, Jun-Hua Zheng$^{14}$, Zhang-Qun Ye$^{15}$, Ding-Wei Ye$^{16}$, Dan-Feng Xu$^{17}$, Jian-Quan Hou$^{18}$, Ke-Xin Xu$^{19}$, Jian-Lin Yuan$^{20}$, Xin Gao$^{21}$, Chun-Xiao Liu$^{22}$, Tie-Jun Pan$^{23}$, Ying-Hao Sun$^{4}$; on behalf of Chinese Prostate Cancer Consortium

Percent free prostatic-specific antigen (%fPSA) has been introduced as a tool to avoid unnecessary biopsies in patients with a serum PSA level of 4.0–10.0 ng ml$^{-1}$, however, it remains controversial whether %fPSA is effective in PSA range of 10.1–20.0 ng ml$^{-1}$ in both Chinese and Western population. In this study, the diagnostic performance of %fPSA and serum PSA in predicting prostate cancer (PCa) and high-grade PCa (HGPCa) was analyzed in a multi-center biopsy cohort of 5915 consecutive Chinese patients who underwent prostate biopsy in 22 hospitals across China from January 1, 2010 to December 31, 2013. The indication for biopsy was PSA>4.0 ng ml$^{-1}$ or/and suspicious digital rectal examination. Total and free serum PSA determinations were performed by three types of electrochemiluminescence immunoassays with recalibration to the World Health Organization standards. The diagnostics accuracy of PSA, %fPSA and %fPSA in combination with PSA (%fPSA + PSA) was determined by the area under the receivers operating characteristic curve (AUC). %fPSA was more effective than PSA in men aged ≥60 years old. The AUC was 0.584 and 0.635 in men aged ≥60 years old with a PSA of 4.0–10.0 ng ml$^{-1}$ and 10.1–20.0 ng ml$^{-1}$, respectively. The AUC of %fPSA was superior to that of PSA in predicting HGPCa in patients ≥60 years old in these two PSA range. Our results indicated that %fPSA is both statistically effective and clinical applicable to predict prostate biopsy outcome in Chinese patients aged ≥60 years old with a PSA of 4.0–10.0 ng ml$^{-1}$ and 10.1–20.0 ng ml$^{-1}$.

Asian Journal of Andrology (2015) 17, 1017–1021; doi: 10.4103/1008-682X.150846; published online: 24 April 2015

Keywords: Chinese population; diagnosis; percent free prostate-specific antigen; prostate cancer; prostate carcinoma tumor antigen; prostate-specific antigen

INTRODUCTION

Prostate cancer (PCa) is the second-most frequently diagnosed malignancy in male globally. Although its incidence in China is much lower than in Western countries, it ranks the fastest growing malignancy in incidence in recent years due to changing lifestyle and raising health awareness. Despite the emerging biomarkers, prostatic-specific antigen (PSA) and its derivatives remain the most widely used and clinical practical test for PCa detection. Percent
free PSA (%fPSA) has been demonstrated to improve positive rate at prostate biopsy and reduce unnecessary biopsies for men with a serum PSA level of 4.0–10.0 ng ml\(^{-1}\) in population with patients from Caucasian and African origin.\(^{1,6}\)

According to European Association of Urology and American Urology Association guidelines, and United States Food and Drug Administration recommendations, the indication for %fPSA remains for men with a PSA of 4.0–10.0 ng ml\(^{-1}\). Although evidence exists that it may be useful in PSA range of 2.6–4.0 ng ml\(^{-1}\) and 10.1–20.0 ng ml\(^{-1}\) in Western population, studies identified %fPSA would have its greatest value in men with a serum PSA of 2.0–10.0 ng ml\(^{-1}\).\(^{7,8}\) Moreover, reports indicated the positive rate of total PSA above 10 to 20 ng ml\(^{-1}\) to be as high as 50% to 80% in Western population.\(^{9,10}\) Thus, the need for other diagnostic parameters in this PSA ranges is less urgent in men with a PSA level of 10.1–20.0 ng ml\(^{-1}\).

Interestingly, the detection rate of patients with the same PSA level is much lower in East Asian countries.\(^{11,12}\) %fPSA has the potential to be used as a diagnostic parameter in this PSA range. In this study, we attempt to examine the effectiveness of %fPSA in PSA range of 4.0–10.0 ng ml\(^{-1}\) and 10.1–20.0 ng ml\(^{-1}\) in a multi-center Chinese cohort and identify the statistical optimal PSA range for %fPSA.

**MATERIALS AND METHODS**

**Patients**

The study was approved by the Institutional Review Board of each participating hospital. This retrospective study consisted of consecutive patients who underwent initial transrectal ultrasound-guided (TRUS-guided) and transperineal prostate biopsies with serum PSA 4.0–20.0 ng ml\(^{-1}\). A search covering the time period from January 1, 2010 to December 31, 2013 was performed in the databases of 22 participating hospitals. Inclusion criteria were: patients visiting out-patient Department of Urology for health checkup and urinary symptoms; the indication for biopsy was abnormal digital rectal examination (DRE) result or/and PSA level >4.0 ng ml\(^{-1}\). Exclusion criteria were: urinary tract infections, urinary retention, recent instrumentation or catheterization of the urethra, and finasteride or hormonal treatment.

**Prostatic-specific antigen measurement and biopsy techniques**

Peripheral blood samples were obtained prior to DRE and prostate biopsies. Three types of PSA/PSA electro-chemiluminescence immunoassays were used in participating hospitals (Abbott AxSYM, Beckman Coulter Access and Roche Elecsys 2010) with recalibrated to the World Health Organization standards (PSA-WHO 96/670) using appropriate correction factors. The three dimensions of the prostate were measured by TRUS. Prostate volume (PV) was calculated with \(D1 \times D2 \times D3 \times (\pi/6)\).

**Statistical analysis**

Kruskal–Wallis test was used for accessing the detection rate of PCa in different %fPSA ranges. Mann–Whitney U-test was used for comparison of %fPSA and other clinical parameters. Univariate logistic regression analysis was used to access the correlation between clinical parameters and biopsy result. Variables with \(P < 0.1\) were included in multivariate analysis. Multivariate logistic regression models were used to predict PCa risk using stepwise strategy with 0.05 as inclusion criteria and 0.1 as exclusion criteria. We combined PSA and %fPSA using logistic regression to estimate the effectiveness of the combination of these two parameters (%fPSA + PSA). Receivers operating characteristic (ROC) curves were calculated for PSA and %fPSA, respectively, plotting sensitivity versus 1-specificity in predicting any PCa and high-grade PCa (HGPCa, Gleason score \(\geq 7\)). Areas under the ROC curves (AUC) were used to measure the diagnostic accuracy of PSA, %fPSA, and PSA + %fPSA. The statistical difference of AUC was calculated by Z test. The probability of biopsy-detected PCa at a given %fPSA level was predicted by performing locally weighted scatterplot smoothing.\(^{13}\)

All the analyses were conducted using Stata 13.0 (Stata Corp., College Station, TX, USA) and MedCalc v. 10.4.7.0 (MedCalc Software bvba, Mariakerke, Belgium).

**RESULT**

**Patients and clinical characteristic**

A total of 5915 cases from 22 hospitals across China were enrolled in this study. Detection rates of patients with a PSA of 4.0–10.0 ng ml\(^{-1}\) and 10.1–20.0 ng ml\(^{-1}\) were 25.3% and 36.5%. Basic information of these patients is illustrated in Table 1. The rate of positive DRE was 13.3% in the cohorts, but it ranges from 8.9% to 31.0% in different hospitals. Considered the subjective nature, we decided not to take the DRE result in the predicting model.

**Diagnostic performance of percent free prostatic-specific antigen in men in all age ranges with a prostatic-specific antigen of 4.0–10.0 ng ml\(^{-1}\) and 10.1–20.0 ng ml\(^{-1}\)**

Prostate cancer detection rates were significant lower in patients with lower %fPSA in both PSA range of 4.0–10.0 ng ml\(^{-1}\) and 10.1–20.0 ng ml\(^{-1}\) (Supplementary Table 1 and Supplementary Figure 1). Scatter plot depicting serum PSA levels, %fPSA and corresponding biopsy result is provided in Supplementary Figure 2. Locally weighted scatterplot scatter plots illustrating %fPSA level and the predicted probability of PCa at each %fPSA level is illustrated in Supplementary Figure 1. The discriminative power of %fPSA was stronger in men with a PSA level of 10.1–20.0 ng ml\(^{-1}\) than 4–10.0 ng ml\(^{-1}\). ROC curve analysis indicated that %fPSA outperform total PSA in predicting any PCa in PSA range of 10.1–20.0 ng ml\(^{-1}\) (0.614 vs 0.586, \(P < 0.0001\)) but not in 4.0–10.0 ng ml\(^{-1}\) (0.554 vs 0.534, \(P = 0.205\)) (Figure 1). The AUC of %fPSA was higher than PSA in predicting HGPCa in patients with PSA of 10.1–20.0 ng ml\(^{-1}\) (0.561 vs 0.529, \(P = 0.10\)) but not in 4.0–10.0 ng ml\(^{-1}\) (0.623 vs 0.555, \(P = 0.0001\)) (Figure 2).

**Influence of clinical parameters on the diagnostic performance of percent free prostatic-specific antigen**

Univariate logistic regression analyses indicated that older age, higher PSA, lower %fPSA, and larger PV were correlated with positive biopsy. Multivariate logistic regression analyses indicated that lower %fPSA, older age, higher PSA and smaller PV were independent predictors of PCa in all patients with a PSA of 4.0–10.0 ng ml\(^{-1}\) and 10.1–20.0 ng ml\(^{-1}\) (\(P < 0.0001\)).

In our previous study, it has been shown that %fPSA is not better than PSA in 2310 Chinese patients below 60 years who underwent TRUS-guided biopsy with a PSA of 4.0–10.0 ng ml\(^{-1}\). In the PSA range of 10.1–20.0 ng ml\(^{-1}\) in this data set, %fPSA was also not better than PSA in men aged <60 years old (Figure 1 and Supplementary Table 2). After stratification by PV, AUC of %fPSA was not superior to PSA in patients in all ages ranges with a PSA of 4.0–10.0 ng ml\(^{-1}\). The AUC of %fPSA was higher than PSA in TRUS-guided group (\(P = 0.002\)), the 10-core group (\(P = 0.002\)) and 8-core group (\(P = 0.038\)) in patients with PSA of 10.1–20.0 ng ml\(^{-1}\). Thus, we tested the performance of %fPSA and PSA in both the overall patients and patients aged over 60 years (Figures 1 and 2).
Table 1: Clinical variable in PCa and non-PCa subjects in two PSA ranges

|                             | PSA 4–10 ng ml⁻¹ |   | PSA 10.1–20 ng ml⁻¹ |   |
|-----------------------------|------------------|---|---------------------|---|
| Number of subject (n)       | 796              |   | 1003                |   |
| Negative biopsy             | 2365             |   | 1751                |   |
| P                           | <0.0001*         |   | <0.0001*            |   |
| **Age**                     |                  |   |                     |   |
| Mean (s.d.)                 | 66.9 (7.7)       |   | 70.0 (7.7)          |   |
| Median (IQR)                | 71 (65–76)       |   | 71 (65–76)          |   |
| PSA                         |                  |   |                     |   |
| Mean (s.d.)                 | 7.3 (1.6)        |   | 7.3 (1.6)           |   |
| Median (IQR)                | 7.4 (6.0–8.7)    |   | 7.4 (6.0–8.6)       |   |
| %free PSA, (%)              |                  |   |                     |   |
| Mean (s.d.)                 | 15.0 (8.0)       |   | 15.4 (8.1)          |   |
| Median (IQR)                | 14.0 (10.0–19.0) |   | 14.0 (10.0–19.0)    |   |
| Prostate volume             |                  |   |                     |   |
| Mean (s.d.)                 | 42.9 (22.8)      |   | 43.0 (22.8)         |   |
| Median (IQR)                | 37.0 (27.6–52)   |   | 37.0 (27.7–52.0)    |   |
| Number of biopsy cores      |                  |   |                     |   |
| Mean (s.d.)                 | 10.7 (2.4)       |   | 10.7 (2.4)          |   |
| Median (IQR)                | 12 (9–12)        |   | 12 (9–12)           |   |

*Mann–Whitney U-test, comparing between the two PSA ranges. s.d.: standard deviation; IQR: interquartile range; PSA: prostate-specific antigen; PCa: prostate cancer; %fPSA: percent free prostatic-specific antigen

Diagnostic performance of percent free prostatic-specific antigen in men aged ≥60 years old with a prostatic-specific antigen of 4.0–10.0 ng ml⁻¹ and 10.1–20.0 ng ml⁻¹

The AUC was higher in men aged ≥60 years old with a PSA of 4.0–10.0 ng ml⁻¹ than with a PSA of 10.1–20.0 ng ml⁻¹ (0.584 vs 0.635) (Supplementary Table 3). Higher overall efficacy was yielded in PSA range of 10.1–20.0 ng ml⁻¹ than 4.0–10.0 ng ml⁻¹ in patients ≥60 years old when applying the reported cutoff value of 25% (44.1% vs 36.4%) (Table 2). Furthermore, for patients aged ≥60 years old with a PSA of 10.1–20.0 ng ml⁻¹ and all patients with a PSA of 10.1–20.0 ng ml⁻¹, 16.9% and 14.3% unnecessary biopsies would be avoided while maintaining a sensitivity of the 90% at the cutoff value of 23.4% (Table 2).

The AUC of %fPSA + PSA was also higher in PSA range of 10.1–20.0 ng ml⁻¹ than 4.0–10.0 ng ml⁻¹ in the whole cohort and patients ≥60 years. However, ROC analysis indicated adding PSA to %fPSA (%fPSA + PSA) had a limited impact on the AUC of %fPSA in both patients with PSA of 4.0–10.0 ng ml⁻¹ and 10.1–20.0 ng ml⁻¹ in the whole cohort (P = 0.205 and 0.494, respectively) and in patients ≥60 years (P = 0.675 and 0.704, respectively).

Proper reflex prostatic-specific antigen range for percent free prostatic-specific antigen

We further validated the effectiveness of %fPSA in patients ≥60 years in different PSA ranges from 4.0 to 20.0 ng ml⁻¹ (Supplementary Table 3 and Figure 3). The AUC of %fPSA was 0.584, 95% confidence interval (CI) (0.559–0.609) and 0.635, 95% CI (0.611–0.658) for PSA range of 4.0–10.0 ng ml⁻¹ and 10.1–20.0 ng ml⁻¹ for patients ≥60 years old (Figure 1). The highest AUC of %fPSA was observed in PSA range of 10.1–16.0 ng ml⁻¹ (0.647, 95% CI [0.620–0.674]) and the maximal improvement of AUC was observed in PSA 12.1–16.0 ng ml⁻¹ (0.137, 95% CI [0.099–0.176]).

DISCUSSION

Percent free prostatic-specific antigen is effective in Chinese men aged ≥60 years old with a prostatic-specific antigen of 10.1–20.0 ng ml⁻¹

Results of Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial suggested that race and ethnicity had little effect on %fPSA. But it included few East Asians living in their origin country. Although studies indicated a similar effectiveness of %fPSA in Chinese and other East Asian populations compared with the Western population, recent reports illustrated a limited improvement of %fPSA in younger Koreans with a PSA of 4.0–10.0 ng ml⁻¹ and in Chinese men with PSA 2.5–10 ng ml⁻¹ and 10.1–20.0 ng ml⁻¹. In our data set, the AUC of %fPSA was also close to that of PSA in the whole cohort but significantly higher than PSA in the older subgroup. However, there were only 274 patients with a PSA of 2.5–10.0 ng ml⁻¹ and 284 patients with a PSA of 10.1–20.0 ng ml⁻¹ in that study. Due to the lack of stratification, their findings were not in contrary to ours.

To the best of our knowledge, this is the first study that demonstrated %fPSA is effective in Chinese men aged ≥60 years old with a PSA level of 4.0–10.0 ng ml⁻¹ or 10.1–20.0 ng ml⁻¹. It was considered that %fPSA was not effective in men with a PSA level >10.0 ng ml⁻¹ according to the EAU and AUA guidelines. However, our data illustrated %fPSA is both statistically and clinically in men with a PSA level of 10.1–20.0 ng ml⁻¹. Based on this data set, we suggested %fPSA could be used to delay or avoid biopsies in men with PSA 10.1–20.0 ng ml⁻¹ and %fPSA over 23.4%. However, the ideas of this article are to remind urologists to consider that the higher %fPSA level in this PSA range indicated a lower chance of PCa. The use of %fPSA in PSA 10–20 ng ml⁻¹ in Chinese population is just like to delay biopsies in Caucasians with a PSA 4–10 ng ml⁻¹ and a high %fPSA (for example 25%).

These phenomena may because of the lower PCa detection rate at the same PSA level in Chinese compared with the Western population. For instance, the PCa detection rate of patients with a PSA of 4.0–10.0 ng ml⁻¹ was 40.3% and 43.4% in consecutive clinical patients in Cleveland Clinic and Durham Veteran Affairs Hospital, and 34.8% and 41.4% in the European Randomized Study of Screening for Prostate Cancer Tarn and San Antonio Center of Biomarkers of Risk for Prostate Cancer program according to the result of Prostate Biopsy Cooperative Group. Although it has been reported that %fPSA was applicable in a Spanish cohort with a PSA level of...
10.1–20.0 ng ml\(^{-1}\), the detection rate of that cohort was very similar to that of this Chinese cohort but much lower than the reports of the Prostate Biopsy Collaborative Group. Thus, the effectiveness of %fPSA in patients with a PSA level of 10.1–20.0 ng ml\(^{-1}\) in Chinese may be similar to that in Western men with a PSA level of 4.0–10.0 ng ml\(^{-1}\). We suggest the result of the Spanish study was applicable only to cohorts with similar detection rate but not in other Western cohorts.

Proper reflex percent free prostatic-specific antigen range for percent free prostatic-specific antigen

The proper PSA range for %fPSA has been reported to be 2–20 ng ml\(^{-1}\), 3–15 ng ml\(^{-1}\) or 3–10 ng ml\(^{-1}\) in Western population\(^{20,21}\) and 7.0–10.0 ng ml\(^{-1}\) or 5.1–10.0 ng ml\(^{-1}\) in Japanese.\(^{16,22}\) PCa detection rate of these ranges are 20.4%–25.3% and 34.1%, respectively. But all of these studies included limited cases with PSA of 10.1–20.0 ng ml\(^{-1}\). In our data set, the optimal range was 10.1–16.0 ng ml\(^{-1}\) or 12.1–16.0 ng ml\(^{-1}\) which was higher than that of the Western population and Japanese. Compared with the Western population, prevalence of PCa in the same PSA range is lower in Chinese population.\(^{17,18}\) Although there is no a systematic analysis of this phenomenal and the underlying reasons of this phenomenal were not revealed, we suggested racial differences may play an important role. Recently, with the joint efforts of a group of Asian urologists, the PCa detection rates in several Asian countries have been summarized and the detection rates ranges from

Table 2: Diagnostic performance of %fPSA at cutoff value of 25% or maintaining a sensitivity of 90%

| Clinical parameter | All age group (ng ml\(^{-1}\)) | ≥60 years old (ng ml\(^{-1}\)) |
|--------------------|-------------------------------|-------------------------------|
|                    | 4.0–10.0 | 10.1–20.0 | 4.0–10.0 | 10.1–20.0 |
| %fPSA cutoff (%)   | 25       | 25        | 25       | 25        |
| Sensitivity        | 88.4     | 92.4      | 87.7     | 92.2      |
| Specificity        | 13.7     | 12.2      | 16.7     | 13.5      |
| Positive predictive value | 25.7       | 37.6      | 28.8     | 40.5      |
| Negative predictive value | 77.9     | 73.7      | 77.9     | 73        |
| Overall efficacy   | 32.6     | 41.4      | 36.4     | 44.1      |
| Avoided unnecessary biopsies | 13.7    | 12.2      | 16.7     | 13.5      |
| %fPSA cutoff (%)   | 26.2     | 23.4      | 26.8     | 23.4      |
| Sensitivity        | 90       | 90        | 90       | 90        |
| Specificity        | 12.05    | 15.25     | 14.3     | 16.9      |
| Positive predictive value | 25.6   | 37.9      | 28.8     | 40.9      |
| Negative predictive value | 78.1   | 73.4      | 78.7     | 72.7      |
| Overall efficacy   | 31.7     | 42.5      | 35.3     | 45.4      |
| Avoided unnecessary biopsies | 12.1 | 15.3      | 14.3     | 16.9      |

%fPSA: percent free prostatic-specific antigen
20% to 25% in most publication and databases.12 We suggested that there are racial difference between the Asian and Western population in the relationship between PSA and PCa. It was recently confirmed in two genome-wide association studies in Chinese and Japanese that the single nucleotide polymorphisms that may influence PSA level in healthy men were different from the Western population.23,24

Although there is no direct relationship between a lower incidence of PSA and a poor diagnostic accuracy of %fPSA, evidence shows that %fPSA is of better diagnostic accuracy in patients with a PSA of 4.0–10.0 ng ml⁻¹ (detection rate 49.0%) than PSA 2.51–4.0 ng ml⁻¹ (detection rate 24%).2 Thus, there is the rationale behind this higher PSA range for %fPSA in Chinese population.

Another consideration of introducing %fPSA into the diagnostic scheme is that there are more patients diagnosed with PCa with a higher PSA level in China and many other developing Asian countries than in Western countries. There are about the same number of patients with a PSA of 10.1–20.0 and 4.0–10.0 ng ml⁻¹ (46.5% vs 53.5%) in this consecutive biopsy cohort.

Potential bias in this study
First, 22 different institutes and three different assays were involved in PSA testing. The variability of total and %fPSA results among commercial assays has been decreased by calibration, but some studies indicated that interchangeability still exists after calibration.27,28 Second, abnormal DRE was not used as exclusion criteria in this study considering its subjective nature. The diagnostic accuracy of %fPSA may be weakened to some extent. Third, there is no national PSA-based PCa screening program in China and the indication for prostate biopsy depends on clinical decision. However, as we strictly enrolled consecutive biopsies, this cohort represents a practical clinical scenario in China.

Our results indicated that %fPSA is both statistically effective and clinically applicable to predict prostate biopsy outcome in Chinese patients aged ≥60 years old in PSA range of 4.0–10.0 ng ml⁻¹ and 10.1–20.0 ng ml⁻¹. Nevertheless, these findings should be validated in following prospective multi-center studies.

AUTHORS CONTRIBUTIONS
YHS, RC, XBC, LPX, and YRH designed the experiments. RC, DLIH, XG, CLX, QD, CJJ, SCR, YT, ZQS, QF, LLM, JHZ, ZQY, DWY, DFX, JQH, FBW, and KXX collected clinical data. RC, JLY, XG, CXL, TJP, and FBW analyzed the data. YHS, RC, LQZ, XBC, LPX, YRH, DLIH, and XG., drafted and revised the manuscript. All authors read and approved the final version of the manuscript.

COMPETING INTERESTS
All authors declare no competing interests.

ACKNOWLEDGMENTS
This work was supported by the Chinese Prostate Cancer Consortium, Program for Changjiang Scholars and Innovative Research Team in University scheme of the Ministry of Education of China (NO. IRT1111, Yinghao Sun) and the National Basic Research Program of China (2012CB518300, 2012CB518306, Yinghao Sun).

Supplementary information is linked to the online version of the paper on the Asian Journal of Andrology website.

REFERENCES
1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013; 63: 11–30.
2. Center MM, Jemal A, Lortet-Tieulent J, Ward E, Ferlay J, et al. International variation in prostate cancer incidence and mortality rates. Eur Urol 2012; 61: 1079–92.
3. Zhao P, Chen W. Chinese Cancer Registry Annual Report, 2004. Beijing: Peking Union Medical College Press; 2008.
4. He J, Chen W. Chinese Cancer Registry Annual Report 2012. Beijing: China Military Medical Science Press; 2013.
5. Catalona WJ, Partin AW, Slawin KM, Brawker MK, Flangan RC, et al. Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter trial. JAMA 1998; 279: 1542–7.
6. Catalona WJ, Partin AW, Slawin KM, Naughton CK, Brawker MK, et al. Percentage of free PSA in black versus white men for detection and staging of prostate cancer: a prospective multicenter clinical trial. Urology 2000; 55: 372–6.
7. Catalona WJ, Smith DS, Ornestein DK. Prostate cancer detection in men with serum PSA concentrations of 2.6 to 4.0 ng/ml and benign prostate examination. Enhancement of specificity with free PSA measurements. JAMA 1997; 277: 1452–9.
8. Marote J, Trilla E, Esquena S, Serralach F, Abascal JM, et al. The percentage of free prostatic-specific antigen is also useful in men with normal digital rectal examination and serum prostatic-specific antigen between 10.1 and 20 ng/ml. Eur Urol 2002; 42: 333–7.
9. Osterling JE, Jacobsen SJ, Klee GG, Pettersson K, Pironen T, et al. Free, complexed and total serum prostate specific antigen: the establishment of appropriate reference ranges for their concentrations and ratios. J Urol 1995; 154: 1090–5.
10. Catalona WJ, Richie JP, Ahmann FR, Hudson MA, Scardinio PT, et al. Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. J Urol 1994; 151: 1293–90.
11. Jeong IG, Lee KH. Korean Urological Oncologic Society Prostate Cancer Study Group. Percent free prostate specific antigen does not enhance the specificity of total prostate specific antigen for the detection of prostate cancer in Korean men 60-65 years old: a prospective multicenter study. J Urol 2008; 179: 111–6.
12. Rui C, Shançheng R, You M, Ng C, Christopher C, et al. Prostate cancer in Asia: a collaborative report. Asian J Urol 2014; 1: 15–27.
13. Cleveland WS. Robust locally weighted regression and smoothing scatterplots. J Am Stat Assoc 1979; 74: 829–36.
14. Gelman EP, Chia D, Prinsky PF, Andriole GL, Crawford ED, et al. Relationship of demographic and clinical factors to free and total prostate-specific antigen. Urology 2001; 58: 561–6.
15. Wang Y, Sun G, Pan JG, Guo JZ, Li T. Performance of PSA and %fPSA for prostate cancer in Chinese. A systematic review and meta-analysis. Prostate Cancer Prostatic Dis 2006; 9: 374–8.
16. Kuriyama M, Kawada Y, Ariai T, Maeda H, Egawa S, et al. Significance of free to total PSA ratio in men with slightly elevated serum PSA levels: a cooperative study. Urology Oncol 1998; 28: 661–5.
17. Huang M, Lin Y, Xu A, Ulhman M, Deng X, et al. Percent free prostate-specific antigen does not improve the effectiveness of prostate cancer detection in Chinese men with a prostate-specific antigen of 2.5-20.0 ng/ml: a multicenter study. Med Oncol 2014; 31: 925.
18. Xu J. The Xu’s chart for prostate biopsy: a visual presentation of the added value of biomarkers to prostate-specific antigen for estimating detection rates of prostate cancer. Asian J Androl 2014; 16: 536–40.
19. Vickers AJ, Cronin AM, Roobol MJ, Hugosson J, Jones JS, et al. The relationship between prostate-specific antigen and prostate cancer risk: the Prostate Biopsy Collaborative Group, Clin Cancer Res 2010; 16: 4374–81.
20. Woodrum DL, Brawker MK, Partin AW, Catalona WJ, Southwick PC. Interpretation of free prostate-specific antigen clinical research studies for the detection of prostate cancer. J Urol 1998; 159: 5–12.
21. Vashi AR, Wojcie KJ, Henriwks W, England BA, Vessella RL, et al. Determination of the “reflex range” and appropriate cutpoints for percent free prostate-specific antigen in 413 men referred for prostate evaluation using the AxSYM system. Urology 1997; 49: 19–27.
22. Hara N, Kitamura Y, Saito T, Komatsubara S. Total and free prostate-specific antigen indexes in prostate cancer screening: value and limitation for Japanese populations. Asian J Androl 2006; 8: 429–34.
23. Sun J, Tao S, Gao Y, Peng T, Tan A, et al. Genome-wide association study identified novel genetic variant on SLC45A3 gene associated with serum levels prostate-specific antigen (PSA) in a Chinese population. Hum Genet 2013; 132: 423–9.
24. Terao C, Terada N, Matsujo K, Kawaguchi T, Yoshimura K, et al. A genome-wide association study of serum levels of prostate-specific antigen in the Japanese population. J Med Genet 2014; 51: 530–6.
25. Agnihotri S, Mittal RD, Kapoor R, Mandhani A. Raising cut-off value of prostate specific antigen (PSA) for biopsy in symptomatic men in India to reduce unnecessary biopsy. Indian J Med Res 2014; 139: 851–6.
26. Na R, Wu Y, Xu J, Jiang H, Ding Q. Age-specific prostate specific antigen cutoffs for guiding biopsy decision in Chinese population. PLoS One 2013; 8: e67585.
27. Lee R, Localio AR, Armstrong K, Malkovich SB, Schwartz JS, et al. A meta-analysis of the performance characteristics of the free prostate-specific antigen test. Urology 2006; 67: 762–8.
28. Foj L, Filella X, Alcover J, Augé JM, Escudero JM, et al. Variability of assay methods for total and free PSA after WHO standardization. Tumour Biol 2014; 35: 1867–73.