RESEARCH ARTICLE

Prostate-specific Antigen Velocity (PSAV) and PSAV per Initial Volume (PSAVD) for Early Detection of Prostate Cancer in Chinese Men

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Abstract

Aim: To investigate the utility of prostate-specific antigen velocity (PSAV) and PSAV per initial volume (PSAVD) for early detection of prostate cancer (PCa) in Chinese men. Methods: Between January 2009 and June 2012, a total of 193 men (aged 49–84 years, median 67 years) with at least 2 transrectal ultrasonography (TRUS) procedures and concurrent serum PSA measurements underwent prostate biopsy because of suspicion of PCa. The total group were classified into PCa and non-PCa groups, and the variables of the two groups were compared. Univariate and multivariate analyses were used to investigate which variables were predictove. The diagnostic values of PSAV, PSAVD and prostate-specific antigen density (PSAD) were compared using receiver operating characteristic (ROC) analysis. Results: Prostate cancer was diagnosed in 44 (22.8%) of the 193 men. There were significant differences between the groups in last and initial prostate volumes determined by TRUS, initial age, last serum PSA levels, PSAV, PSAD and PSAVD. After adjusting for confounding factors, the odds ratios of PCa across the quartile of PSAVD were 1, 4.06, 10.6, and 18.9 (P for trend <0.001).The area under the ROC curves (AUCs) of PSAD (0.779) and PSAVD (0.776) were similar and both significantly greater than that of PSA (AUC 0.667). PSAVD was a significantly better indicator of PCa than PSAV (AUC 0.736). There was no statistical significant difference between the AUC of PSAV and that of last serum PSA level. The sensitivity and specificity of PSAVD at a cutoff of 0.023ng in participants with last serum PSA levels of 4.0ng/mL-10.0ng was 73.7% and 70.7%, respectively. Conclusions: The results of this study demonstrated PSAVD may be a useful tool in PCa detection, especially in those undergoing previous TRUS examination.

Keywords: Prostate cancer - prostate biopsy - PSA velocity - PSAV per initial volume

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Introduction

Prostate cancer (PCa) is now recognized as one of the principal medical problems facing the male population. In the United States, PCa accounts for the largest percentage of new male cancer cases and is the second leading cause of cancer death in men. In 2012, there will be an estimated 241,740 new cases and 28,170 deaths from PCa in America (Siegel et al., 2012).

The use of prostate-specific antigen (PSA) as a screening tool has revolutionized the detection of early-stage PCa (Schmid et al., 2004). Since PSA testing has become popular for diagnosis in China, the incidence of PCa is also increasing rapidly, especially in more developed cities (Li et al., 2009).

However, PSA though highly sensitive, it is organ-specific and not cancer-specific, which results in difficulties in discriminating malignant and benign prostatic status (e.g., benign prostatic hyperplasia and prostatitis) in men with slight elevations of PSA. There have been several reports on clinical variables, which may improve the specificity in the early detection of PCa, including PSA density (PSAD), PSA dynamics (velocity and doubling time) and PSA molecular forms as adjuncts to total serum PSA measurements (De Visschere et al., 2010). Some guidelines do incorporate PSA velocity (PSAV) cut points as an indicator for biopsy (Vickers et al., 2009).The utility of PSAV in PCa screening is controversial (Etzioni et al., 2007). Carter et al. and others have shown that PSAV may improve cancer detection (Carter et al., 1992; Vickers et al., 2009), whereas others have been unable to demonstrate an incremental value beyond total PSA alone (Schroder et al., 2006; Thompson et al., 2006). Recently, PSAV per initial volume (PSAVD) has been proposed by Choi et al. as a new indicator for PCa detection (Choi et al., 2011).

The incidence rate of PCa per 100,000 is 152.9 in the United States, but only 11.8 in China (Li et al., 2009; Siegel et al., 2012). Chinese men are expected to have substantially lower prostate volumes than Caucasian men (Chang et al., 2006; Xie et al., 2007). It is thus not clear

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whether the established PCa early detection guidelines from Europe and USA, are also applicable to Chinese. In the present study we evaluated the utility of PSAV and PSAVD for early detection of PCa in Chinese men.

Materials and Methods

Patients

Between January 2009 and June 2012, a total of 1786 patients underwent prostate biopsy by transrectal ultrasonography (TRUS) based on a cancer-detection program at our hospital, in which men with serum PSA levels of ≥4.0ng/mL or abnormal DRE findings were recommended for biopsy. Both asymptomatic men who were referred for PCa screening because of elevated PSA levels, and those symptomatic with benign prostatic hyperplasia (BPH) were included. 193 men had received at least 2 concurrent serum PSA measurements, along with 2 prostate volume (PV) measurements by TRUS before they underwent prostate biopsy. Clinical characteristics of the patients are summarized in Table 1. The study was approved by the institutional review board and written informed consent was obtained from each patient before enrollment. Patients were excluded from analysis if they had received any medication that might influence serum PSA levels, or if they had a history of prostatic surgery.

Parameters and prostate biopsy

Serum PSA level was determined beforehand using the EIA method. Ultrasonographic images of the prostate were obtained by TRUS using a commercially available device. The volume of the whole prostate was calculated using the ellipsoid volume formula (Terris et al., 1991).This formula is defined by measuring the height(H), width(W), and length(L) of the prostate from two selected orthogonal views and calculating the PV as that of the corresponding ellipsoid: $PV=\pi/6\times W\times H\times L$ (Xie et al., 2007).

PSAV, PSAD and PSAVD were defined as [PSAV= (serum PSA level of last visit –serum PSA level of initial visit)/follow-up years] (McLaren et al., 1998), [PSAD=last serum PSA level/last PV] (Bretton et al., 1994), [PSAVD = PSAV /initial PV] (Choi et al., 2011).

Prostate biopsy was performed in a transrectal fashion using a commercially available TRUS system. Biopsy samples were taken at 8-10 cores guided by the same experienced physician in urological ultrasonography. One experienced urological pathologist reviewed the biopsy specimens.

Statistical analysis

Analysis was performed using the Statistical Package for Social Sciences software program (SPSS 19 for Windows). The total group were divided into PCa group and non-PCa group according to prostate biopsy result. Differences in continuous variables between groups were tested by the Mann-Whitney U tests. PSAV, PSAD and PSAVD were divided into quartiles, and we investigated the trends to determine which PSA derivatives were significant predictors for detecting PCa using univariate and multivariate logistic regression analysis. The diagnostic performance of these PSA-associated variables for detecting PCa was evaluated by a receiver operating characteristic (ROC) curve using MedCalc version 11.4.2. The area under the curves (AUC) of these indicators was compared by the chi-square test. Differences with a P-value less than 0.05 were considered significant.

Results

PCa was diagnosed in 44(22.8%) of the 193 men who had biopsies, characteristics of men with and without cancer are shown in Table 1. There were significant differences between two groups in initial and last PV determined by TRUS, initial age , last serum PSA levels, PSAD, PSAV and PSAVD, whereas there was no significant difference in initial serum PSA level and follow-up period.

PSAV, PSAD and PSAVD were divided into quartiles (Table 2). Multivariate analysis was adjusted for initial age, initial serum PSA level, and initial PV for PSAV. For PSAVD and PSAD multivariate analysis was adjusted for initial age and initial serum PSA level. All of those indicators showed a positive trend for detecting PCa on

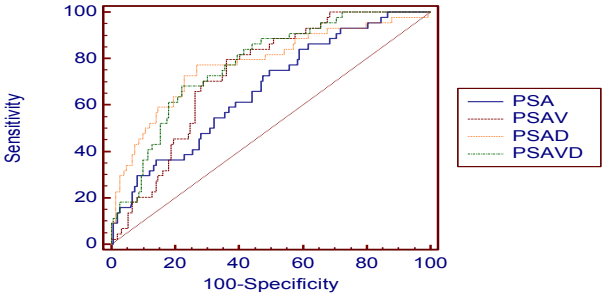

Figure 1. ROC Curves for PSA, PSAV, PSAD and PSAVD. Subjects were all participants in this study. The AUC and the P values for the differences among each variable are shown in the Table 3

Table 1. Patient Characteristics of 193 Study Participants

Parameter	Total Group		PCa Group	Non-PCa Group	P Vlaue
	Mean±SD	Median (range)	(n=44)	(n=149)	
Age(y)	67.4±7.5	67 (49-84)	70.8±6.3	66.3±7.5	0.001
Initial PSA(ng/mL)	8.0±4.8	7.0 (0.9-38.6)	8.5±4.3	7.9±4.9	0.326
Last PSA(ng/mL)	10.0±6.6	8.6 (0.7-39.5)	13.2±8.3	9.0±5.7	0.001
Initial PV(cc)	40.2±19.4	35.4 (11.3-110.1)	30.1±16.4	43.3±19.3	<0.001
Last PV(cc)	43.0±22.1	37.1 (11.3-117.1)	31.9±20.9	46.0±21.6	<0.001
PSAD(ng·mL-1·cc-1)	0.30±0.28	0.21 (0.02-1.62)	0.54±0.41	0.23±0.18	<0.001
PSAV(ng·mL-1·y-1)	0.67±4.29	0.72 (-27.46-30.00)	2.68±4.60	0.07±4.03	<0.001
PSAVD(ng·mL-1·y-1·cc-1)	0.024±0.128	0.017(-0.777-0.885)	0.110±0.164	-0.001±0.104	<0.001
Time interval(y)	1.7±0.9	1.3 (1.0-6.3)	1.8±1.0	1.6±0.8	0.172

Table 2. Comparison of PSAV, PSAD and PSAVD Quartiles in PC Detection

Variable	n	PC Patients, n (%)	Univariate OR(95%CI)	Multivariate OR(95%CI)
PSAV(ng·mL-1·y-1)				
1 (<-0.513)	49	1 (2.0)		
2 (-0.513-0.716)	47	7 (14.9)	8.400 (0.991-71.177)	10.317 (0.998-106.633) *
3 (0.716-1.784)	49	17 (34.7)	25.500 (3.231-201.242)	27.725 (2.910-264.108) *
4 (≥1.784)	48	19 (39.6)	31.448 (3.996-247.503)	30.496 (3.418-272.080) *
P for trend			0.001	0.005*
PSAD (ng·mL-1·cc-1)				
1 (<0.128)	49	3 (6.1)		
2 (0.128-0.206)	48	6 (12.5)	2.191 (0.515-9.317)	2.705 (0.616-11.884) **
3 (0.206-0.356)	48	9 (18.8)	3.539 (0.895-13.989)	4.046 (0.997-16.425) **
4 (≥0.356)	48	26 (54.1)	18.121 (4.945-66.401)	17.113 (4.488-65.259) **
P for trend			<0.001	<0.001**
PSAVD (ng·mL-1·y-1·cc-1)				
1 (<-0.015)	48	2 (4.2)		
2 (-0.015-0.017)	47	6 (12.8)	3.366 (0.643-17.610)	4.060 (0.720-22.913) **
3 (0.017-0.056)	49	13 (26.5)	8.306 (1.761-39.182)	10.602 (2.036-55.213) **
4 (≥0.056)	49	23 (46.9)	20.346 (4.437-93.293)	18.911 (3.888-91.977) **
P for trend			<0.001	<0.001**

* Adjusted for initial age, initial serum PSA, and initial prostate volume; ** Adjusted for initial age and initial serum PSA

Table 3. The AUC and the P values for the Differences among Each Parameter (n=193)

	AUC	PSA	PSAV	PSAD
PSA	0.667			
PSAV	0.736	0.06		
PSAD	0.779	0.001	0.3234	
PSAVD	0.776	0.0054	0.0042	0.9498

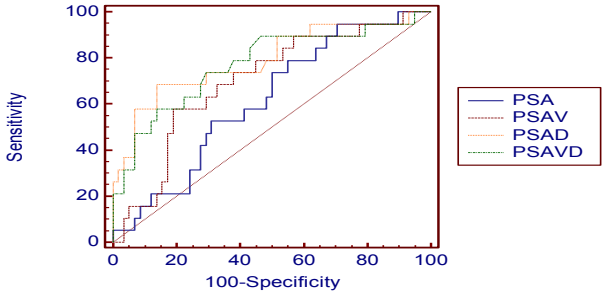

Figure 2. ROC Curves for PSA, PSAV, PSAD and PSAVD. Subjects were participants with last serum PSA levels of 4.0ng/mL-10.0ng/mL. The AUC and the P values for the differences among each variable are shown in the Table 4

univariate and multivariate analysis.

ROC analysis (Figure 1 and Table 3) showed that PSAD and PSAVD were significantly better predictors of PCa than serum PSA. ROC analysis showed the cutoff of PSAVD was >0.023 ng·mL-1·y-1·cc-1, of which sensitivity, specificity, positive and negative predictive values was 73.7%, 70.7%, 45.2% and 89.1%, respectively. The diagnosis value of PSAVD was significantly higher than that of PSAV. However, the difference between PSAD and PSAVD was not significant. There was no statistical significant difference between the AUC of PSAV and that of last serum PSA level.

Figure 2 and Table 4 show ROC analysis of participants with last serum PSA levels of 4.0ng/mL -10.0ng/mL. The diagnosis utility of PSAD and PSAVD was similar, and PSAVD performed significantly better than PSAV in PCa detection. Table 5 shows sensitivity, specificity, positive and negative predictive values of each variable, while

Table 4. The AUC and the P values for the Differences among Each Parameter (n=77)

	AUC	PSA	PSAV	PSAD
PSA	0.617			
PSAV	0.699	0.2423		
PSAD	0.792	0.0101	0.2802	
PSAVD	0.773	0.0254	0.0239	0.7949

Subjects were participants in this study who had last serum PSA levels of 4.0ng/mL-10.0ng/mL

Table 5. Specificity at Fixed Sensitivities and Predictive Values at Inflexion Points for Each Variable

Variable	Specificity at 90% sensitivity	Specificity at 95% sensitivity	PPV	NPV
PSA	32.8(>5.3)	10.3 (>4.6)	29.8	90.5
PSAV	43.1 (>0.31)	22.4 (>-0.14)	34	92.6
PSAD	48.3 (>0.16)	37.9 (>0.13)	36.2	93.3
PSAVD	53.5 (>0.012)	20.7 (>-0.005)	38.6	93.9

Subjects were participants with last serum PSA levels of 4.0ng/mL-10.0ng/mL;Values are percentages; thresholds are indicated in parentheses; PPV and NPV indicate positive and negative predictive values at 90% sensitivity

maintaining 90% sensitivity, PSAVD (threshold>0.012 ng·mL-1·y-1·cc-1) enabled a one-half reduction in unnecessary biopsies.

Discussion

Widespread PSA-based screening has contributed to the improvement in PCa detection. In the United States, the incidence of PCa peaked in 1992 that was 5 years after the introduction of serum PSA test into PCa screening, since then the incidence has been decreasing slowly (Siegel et al., 2012). However, the reference range for serum PSA level in normal men and PCa patients may overlap with each other. Consequently, several PSA-associated variables have been proposed in order to improve PCa detection, such as PSAV, PSAD and PSAVD.

PSAV is the rate of change in serum PSA level in a specified period. Carter et al. suggested that in men with a serum PSA level generally less than 4.0ng/mL, a PSAV above 0.35 ng·mL-1·y-1 may indicate clinically significant PCa when they are potentially curable (Carter et al., 2006). It has been suggested by the same author that for men with indolent tumors or those men with BPH with a serum PSA level of greater than 4.0ng/mL to be identified, a cut point for PSAV less than 0.75ng·mL-1·y-1 should be recommended (Carter et al., 1992).

Nevertheless, application of PSAV is limited by the necessity of using equipment and reagents from the same manufacturer (Smith et al., 1994). Some studies do not confirm the usefulness of PSAV in diagnosing PCa in prescreened population. The study by Ulmert et al. (2008) suggested that, although PSAV had a strong association with a subsequent diagnosis of PCa, the predictive accuracy of PSA alone was not improved by adding PSAV. The Prostate Cancer Prevention Trial found that there was no increased value in predictive accuracy of detecting prostate cancer using PSAV (Thompson et al., 2006). Schroder et al. (2006) suggested that PSAV does not improve the positive predictive value of a PSA cutoff of 4.0ng/mL in PCa screening. The European Randomized Study of Screening for Prostate Cancer suggested that using PSAV for predicting which men should undergo prostate biopsy would miss a large number of significant tumors with rising PSAV cut point (Wolters et al., 2009). In the present study there was no statistical significant difference between the AUC of PSAV and that of last serum PSA level.

PSAD has been shown to correlate with PCa presence, aggressiveness, pathologic tumor stage and progression-free survival after treatment (Bretton et al., 1994; Allan et al., 2003). Therefore, PSAD should be considered in PCa detection, especially those who have had prior TRUS measurements of PV (Zheng et al., 2008; Kawachi et al., 2010). However, the optimal PSAD cutoff is still a controversy. Catalona et al. suggested that the commonly used PSAD cutoff of 0.15 detected only 59% of cancers (Catalona et al., 2000).

Recently, Choi et al. (2011) put forward PSAVD as a new indicator in PCa detection and this proposal was mainly based on two reasons. First, they found a correlation between initial PV and prostate volume velocity (PVV) in the non-PCa group, which implied the larger prostate grew faster. Therefore they believed that initial PV could substitute for the PV change. Furthermore, Rhodes et al. (1999) reported a prostate growth rate of 1.6% per year among men residing in Olmsted County after 5 years of follow-up, which actually agrees with the first reason. The second reason was that TRUS is an uncomfortable and invasive procedure. Once patients take TRUS measurements of PV, the use of PSAVD will not require extra measurements before prostate biopsy, which is indeed much more convenient than the utility of PSAD. Compared with PSAV, PSAVD performed better in the diagnosis of PCa in the present study and the study carried out by Choi et al., although a previous TRUS measurement of PV is necessary in the application of PSAVD.

Several limitations of our study should be mentioned. First, PV measurements in present study were carried out by TRUS, which has a disadvantage in that the results can vary depending on the individual sonographer performing the examination. The second limitation is that the data in present study was from only one hospital, which may introduce a selection bias and limit the general application of the conclusion. Therefore, subsequent studies with a greater number of individuals from various medical centers are necessary.

In conclusions, in present study, PSAVD could be applied clinically to improve the diagnosis accuracy in PCa detection. PSAVD may be a better indicator of PCa than PSAV when previous PV measured by TRUS is available.

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