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Potential predictive factors of positive prostate biopsy in the Chinese population

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There are numerous arguments for the predictive factors of positive prostate biopsies differing according to race and region. This retrospective study aimed to determine predictive factors for a positive prostate biopsy in Chinese men. Data were collected from 1608 men who underwent a prostate biopsy for suspected prostate cancer. Variables analyzed included age, prostate specific antigen (PSA) level, prostate volume and PSA density (PSAD). Logistic regression analysis estimated relative risk, 95% confidence intervals and p values. Overall, 598 (37.19%) of the 1608 biopsied had prostate cancer. Independent predictors of a positive biopsy result include advanced age, elevated PSA levels, small prostate volume and increased PSAD. Our study showed significant predictors for positive prostate biopsy in Chinese men and a combination of age, PSA, prostate volume and PSAD better defined the probability of a positive biopsy than any factor alone. In the future, we may be able to use our finding to create a nomogram for predicting positive prostate biopsy in Chinese men.

Key words: Prostate biopsy, PSA, prostate volume, prostatic neoplasms.

INTRODUCTION

Prostate cancer (PCa) is now recognized as one of the principal medical problems facing the male population. Widespread use of serum prostate specific antigen (PSA) screening has revolutionized the diagnosis of PCa (Polascik et al., 1999). However, PSA is organ-specific and not cancer-specific (Ablin, 1972), which is elevated not only in patients with PCa, but also in various nonmalignant conditions including infections, and over-the-counter drugs like ibuprofen and benign prostatic hyperplasia (BPH) (Liu et al., 2009). Although debate about the appropriate PSA cut-point for PCa early detection programs continues, a level of total PSA of 4.0 ng/ml has traditionally been used as the threshold for consideration of a prostate biopsy. In general, only approximately 25% of men undergoing biopsy will receive

a diagnosis of PCa (Arcangeli et al., 1997). A large number of men face the prospect of prostate biopsy with limited information about their likelihood of harboring PCa.

In addition to total PSA, other factors have been shown to be associated with the detection of PCa, such as age, digital rectal examination (DRE), transrectal ultrasonography (TRUS), PSA density (PSAD), PSA velocity, transition zone PSAD, free/total PSA (f/T PSA) ratio and age-specific PSA (Catalona et al., 1998; Kamoi and Babaian, 1999). A predictive model that can help counsel patients and their physicians considering prostate biopsy is therefore needed. Several groups have developed models to help predict a positive prostate biopsy among men undergoing evaluation for PCa in the developed countries (Carlson et al., 1998; Eastham et al., 1999; Kamoi and Babaian, 1999; Ohori and Swindle, 2002; Potter et al., 2001). It is generally accepted that PCa incidence is affected by environmental factors, racial, biological, and clinical differences. Therefore, it might be inappropriate that we apply these western models to the Chinese population that has a lower incidence of PCa.

Therefore, this retrospective study aimed to determine predictive factors for a positive prostate biopsy in Chinese men. Our ultimate goal is to develop a simple model   for

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Abbreviations: PCa, Prostate cancer; **PSA,** prostate specific antigen; **BPH,** Benign prostatic hyperplasia; **TRUS,** transrectal ultrasound; **DRE,** digital rectal examination; **PSAD,** PSA density.
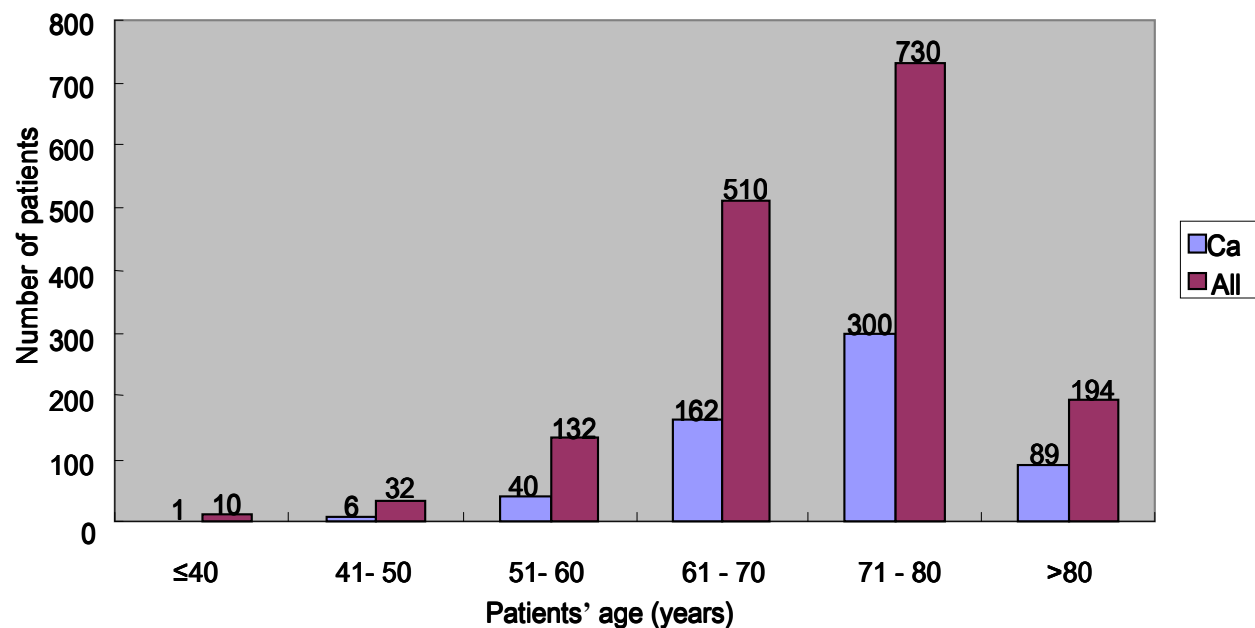
Figure 1. Distribution of age groups in a total of 1608 patients. Mean = 71.20; standard deviation = 8.80; Ca, number of cancer patients; All, total number of patients in each range.

the detection of PCa based on readily available parameters (age, PSA level, prostate volume and PSAD) in the Chinese men. This model would potentially offer a robust tool that could improve the prediction of PCa.

MATERIALS AND METHODS

Patients

Between April 1996 to October 2009, 2365 Chinese patients suspected of having prostate cancer underwent transrectal ultrasound (TRUS) prostate biopsies for the first time in our department. They were first referred to our department because of one or more of the following indications: abnormal digital rectal examination (DRE) findings, abnormal computed tomographic or magnetic resonance imaging finding, and/or serum prostate specific antigen (PSA) level greater than 4 ng/ml. Of these, we studied 1608 patients with all necessary data and at least six core biopsy specimens. The patients were 30 to 97 years of age (mean ± SD, 71.20 ± 8.80 years). Age was defined as the subject's age on the day of the serum PSA measurement. All TRUS examinations were performed in real time. Each gland was examined in both axial and sagittal projections. Prostate volume was calculated as follows: volume equals 0.52 × length × width × height, with length being measured in the longitudinal view and width and height being measured in the transaxial view (Terris and Stamey, 1991). PSA density (PSAD) was calculated by dividing serum PSA by prostate volume.

Moreover, all patients received an enema and a combination tablet of ciprofloxacin, norfloxacin and metronidazole for antibiotic prophylaxis before biopsy procedures. The biopsies were performed with an automatic core biopsy device (Biopsy; Bard Peripheral Technologies, Covington, GA) and 18- gauge Tru-Cut–type needles. Informed consent was obtained from all patients. All patients were placed in the left lateral decubitus position with knees and hips flexed 90 degrees. Digital rectal examination was performed before

the probe was placed into the rectum. In patients with hypoechoic lesions, TRUS guided biopsies were performed in each of these lesions in axial and longitudinal sections, two biopsies per site, and then additional TRUS-guided sextant biopsies were performed. In patients that did not have hypoechoic lesions, only TRUS guided sextant biopsies were performed. All biopsy specimens were labeled according to the sites of origin and submitted separately in individual containers with 10% formaldehyde to the Department of Pathology at our hospital.

Statistical analysis

The factors we evaluated for the risk of a positive biopsy included age, total PSA level, prostate volume and PSAD, which were analyzed and categorical variables with the following categories: age (younger than 67, 67 to 72, 73 to 77, or 77 years and older), serum PSA (< 6.5, 6.5 to 12, 12.1 to 24, or >24 ng/ml), prostate volume (<30.01, 30.01 to 44.88, 44.92 to 69.46, or >69.46 ml), and PSAD (<0.116, 0.116 to 0.239, 0.239 to 0.544, or >0.544 ng/ml^2). The selected categories represent quartiles of the distribution.

We conducted both univariate and multivariate analyses. The significance of each factor was assessed by univariate logistic regression analyses. Multivariate stepwise logistic regression analysis was used to determine which factors were independent predictors of PCa. Relative risks (RR) and 95% confidence intervals (95% CI) were also derived. Analysis was performed using the Statistical Package for Social sciences software program (SPSS 12.0 for Windows).

RESULTS

PCa was diagnosed in 598 (37.19%) of the 1608 men who had biopsies. The patients' age and PSA distributions for the 1608 men are shown in Figures 1 and 2, respectively. We divided age into ranges   of   ten   years
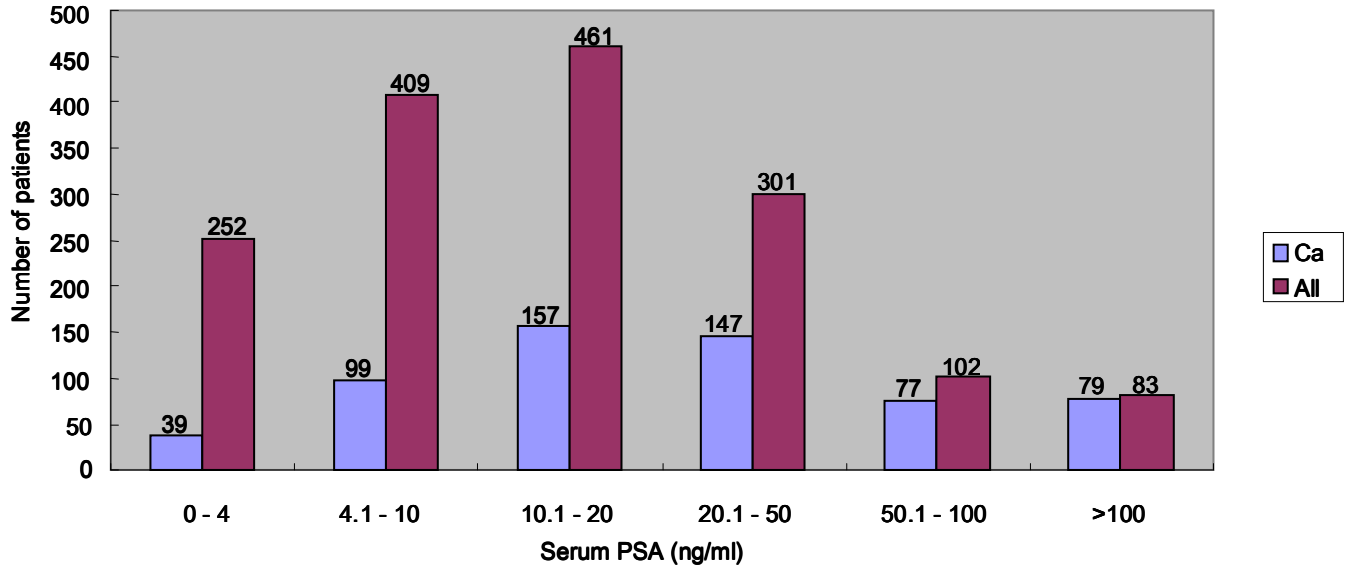
Figure 2. Distribution of serum PSA groups in a total of 1608 patients. Mean = 27.00; standard deviation = 61.80; Ca, the number of cancer patients; All, total number of patients in each range.

each, and divided PSA into ranges on the basis of the clinical significance and established cut-points. Most men were between 61 and 80 years of age; the median age of the patients was 72 years (range, 30 to 97 years). The median serum PSA level was 12 ng/ml (range, 0.05 to 1714 ng/ml). In the logistic regression analysis, the stepwise multivariate logistic regression analysis showed that the statistical significance of all four risk factors for the detection of PCa in the study cohort was $p < 0.01$ (Table 1). Independent analyses using forward and backward stepwise procedures also yielded identical results.

Table 2 shows the significant predictors for a positive prostate biopsy in the order of statistical significance that was determined on univariate logistic regression analysis: age (73 to 77 years, $p = 0.011$; >77 years, $p < 0.0001$), PSA (6.5 to 12 ng/ml, $p = 0.002$; 12.1 to 24 ng/ml, $p < 0.0001$; >24 ng/ml, $p < 0.0001$), prostate volume (44.92 to 69.46 ml, $p = 0.002$; >69.56 ml, $p < 0.0001$), PSAD (0.116 to 0.239 ng/mL^2, $p = 0.002$; 0.239 to 0.544 ng/mL^2, $p < 0.0001$; >0.544 ng/mL^2, $p < 0.0001$).

DISCUSSION

The use of PSA for PCa early detection is ubiquitous. The sensitivity of PSA for signaling the presence of cancer is better than DRE, but both of these two modalities are limited by poor specificity and thus trigger the perfor-mance of many potentially unnecessary biopsies (Carlson et al., 1998; Cooner et al., 1990). Recently, a large randomized trial evaluating the impact of PSA screening on PCa mortality has been published (Andriole et al., 2009). In the United States, after seven to ten years of

follow-up, the rate of death from prostate cancer was very low and did not differ significantly between the screening groups and control groups. New strategies are therefore needed to predict which patients will have possible finding on prostate biopsies to avoid un- necessary biopsy procedures and to identify PCa accurately.

Several PSA derivatives have been used to improve the specificity of PSA, such as PSAD. Initially, PSAD was used to differentiate high PSA levels in men with large prostate volumes who did not have prostate cancer. Furthermore, PSAD has been demonstrated to correlate with prostate cancer presence, aggressiveness, patho-logic tumor stage and progression-free survival after treatment (Allan et al., 2003). In addition, it has been reported that serum p53 antibodies were superior to PSA parameters to discriminate non palpable PCa from benign prostatic disease, but it is not yet available for general use and needs validation to define its role as a marker to detect non-palpable PCa (Suzuki et al., 2004). In this study, we analyzed age, PSA, PSAD and prostate volume. Prostate volume was also included in order to investigate the relationship between a positive biopsy and not only PSAD, but also prostate volume itself. Although total PSA has been reported to be a poor predictor of positive biopsy result (Carlson et al., 1998; Catalona et al., 1998; Roobol et al., 2007), in our study, we still included total PSA in order to evaluate the validity of PSA for positive biopsy predictor because those are most from North America.

Although some models have been developed for predicting the probability of a positive prostate biopsy, however, PCa is thought to differ epidemiologically and biologically between western and Asian men (Chuang et al., 2007; Peyromaure et al., 2005). Thus, models

Table 1. Multivariate testing (logistic regression test).

Parameter	$\chi 2$	P-value	95% CI[a]
Age	41.675	0.000	1.034 - 1.065
PSA	11.822	0.001	1.010 - 1.035
Prostate volume	23.442	0.000	0.983 - 0.993
PSAD	11.166	0.001	1.478 - 4.481

[a]CI, Confidential interval.

Table 2. Patient distribution in each variable and univariate analysis evaluating risk of positive biopsy.

Variable	Patient	Positive biopsy	RR	95% CI	P-value
Age (year)					
<67	404	125 (30.9%)	1		
67 to 72	430	144 (33.5%)	1.124	0.840-1.503	0.432
73 to 77	394	156 (39.6%)	1.463	1.092-1.959	0.011
>77	380	173 (45.5%)	1.865	1.393-2.497	0.000
PSA (ng/ml)					
<6.5	402	69 (17.2%)	1		
6.5 to 12	407	107 (26.3%)	1.721	1.224 - 2.419	0.002
12.1 to 24	403	152 (37.7%)	2.922	2.104 - 4.058	0.000
>24	396	270 (68.2%)	10.340	7.400 - 14.449	0.000
Prostate volume (ml)					
<30.01	403	191 (47.4%)	1		
30.01 to 44.88	401	185 (46.1%)	0.951	0.721 - 1.254	0.720
44.92 to 69.46	403	147 (36.5%)	0.637	0.481 - 0.845	0.002
>69.56	401	75 (18.7%)	0.255	0.186 - 0.351	0.000
PSAD (ng/ml^2)					
<0.116	402	44 (10.9%)	1		
0.116 to 0.239	402	76 (18.9%)	1.897	1.271 - 2.831	0.002
0.239 to 0.544	402	167 (41.5%)	5.782	3.991 - 8.376	0.000
>0.544	402	311 (77.4%)	27.807	18.815 - 41.096	0.000

developed in Western countries cannot be directly applied to the Chinese male population in which the incidence of PCa is lower. To our knowledge, this is the first study that combines these four risk factors into a comprehensive clinical instrument that determines an individual's risk for PCa in China. We evaluated four independent risk factors that are readily available to urologists in general practice. According to the multivariate logistic regression analysis, the independent factors associated with a positive biopsy were more advanced age, elevated total PSA level, smaller prostate volume and higher PSAD. Furthermore, we could use these factors to generate a predictive model for the diagnosis of prostate cancer to reduce the number of unnecessary prostate biopsies. One limitation of this study is the potential for missed diagnosis of cases. It has been showed that patients with an initial negative biopsy can have cancer at repeat biopsies (up to 25%) (Djavan et al., 2001; Nam et al., 2004). However, we did not assess repeat biopsies.

Our study shows significant predictors for positive prostate biopsies in Chinese men. After conducting the studies with more cases, confirming and validating our finding in other centers, we may be able to use these findings to create a nomogram for predicting positive prostate biopsy in Chinese patients.

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