

## ORIGINAL ARTICLE

# Distributions and characteristics of initial PSA and PSA velocity in Chinese men aged 50 years and younger without prostate cancer: a multi-center study

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## Summary

**Purpose:** To analyze the distributions and characteristics of initial prostate-specific antigen (PSA) and PSA velocity in Chinese men aged 50 years and younger without prostate cancer.

**Methods:** The initial PSA test of men aged 50 years and younger, taken from January 2008 to December 2018 in two medical centers, was retrospectively analyzed. Cases with prostate cancer were excluded. The distributions of initial PSA and PSA velocity, and the correlations between these two values were estimated. Kaplan-Meier and log-rank test were used to estimate significant difference on the risk of PSA $\geq$ 2.5 ng/mL after initial PSA measurement, stratified by median initial PSA (0.6 ng/mL).

**Results:** A total of 9461 men with non-prostate cancer were included in this study. The median initial PSA value was 0.7 ng/mL. A total of 853 men had their PSA meas-

ured two times or more and the median PSA velocity was 0.026 ng $\times$ mL<sup>-1</sup> $\times$ yr<sup>-1</sup>. There was no two-two direct correlation between initial PSA testing age, initial PSA, and PSA velocity. After a follow-up of up to 10 years from the baseline PSA test, the risk of PSA  $\geq$ 2.5 ng/mL, stratified by median initial PSA (0.7 ng/mL), was significantly different (log-rank test,  $p < 0.001$ ).

**Conclusion:** More than 25% of the men aged  $\leq$ 50 years should have regularly PSA screening based on current guidelines. However, the subsequent risk of being diagnosed with prostate cancer in these men is unknown. Men aged 50 years and younger with an initial PSA higher than the median (0.7 ng/mL) have a subsequent higher risk of abnormal PSA value.

**Key words:** initial PSA, prostate cancer, PSA velocity, young men

## Introduction

PSA screening by the United States Preventive Working Group in 2012 is a D-level recommendation. However, PSA screening has become more rational recently, and European Association of Urologists (EAU) guidelines from 2017 to 2018 no longer oppose. PSA screening should be carried out when patients are fully aware of the potential benefits and risks and can help early diagnosis of prostate cancer [1]. Recent studies have shown that

young men ( $\leq$ 50 years) with initial prostate-specific antigen (PSA) levels higher than the median (0.6 or 0.7 ng/mL) have a risk for a significantly high prevalence of prostate cancer [1]. The latest American Urological Association (AUA) and the US National Comprehensive Cancer Network (NCCN) guidelines recommend: 40-year-old men should have PSA (initial PSA) test for the first time and if the initial PSA value is higher than the median

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or PSA velocity  $>1.0 \text{ ng}\times\text{ml}^{-1}\times\text{yr}^{-1}$ , PSA screening should be conducted regularly; and prostate biopsy should be performed when a PSA velocity  $>0.40 \text{ ng}\times\text{ml}^{-1}\times\text{yr}^{-1}$ , prostate biopsy should be performed [2,3]. However, the presence of prostate cancer diagnosis and treatment may differ from eastern to western countries, thus, these guidelines may be not suitable for a Chinese population. To understand the initial PSA and PSA velocity distribution of Chinese young men would be beneficial for establishing a Chinese PSA screening program. In this study, we aimed to explore the distributions and characteristics of initial PSA and PSA velocity in non-prostate cancer Chinese men aged 50 years and younger.

## Methods

From January 2008 to December 2018, there were 9473 asymptomatic men aged 50 years and younger who had their routine health check-up at the Medical Center of Guangzhou First People's Hospital and The Third Affiliated Hospital of SunYet-Sen University were recorded. This health check-up included urinary system examination such as PSA test, digital rectal exam (DRE), and urogenital system ultrasonic examination. A total of 50 cases with elevated serum PSA, abnormal DRE or ultrasound needed a prostate biopsy so as to exclude prostate cancer. Finally, 11 men were diagnosed with prostate cancer and one with prostate sarcoma (Table 1). These 12 cases of prostate malignancy were excluded from further study. Thus 9461 non-prostate cancer young men from 2 medical center aged 17-50 years (mean  $40.3\pm 7.6$ ) were enrolled in our study. Their initial PSA test values were 0.0-77.5 ng/mL (mean 1.0-2.2 ng/mL and median

0.7 ng/mL). There were 853 cases that were tested for PSA from 2 to 11 times. The shortest time from the initial PSA test to the last time PSA test was 3 months, whereas the longest was 10 years; 2.8 years was the average and the median was 2.5 years. Of these 853 cases with multiple PSA tests, the PSA velocity ranged from  $-19.6-25.5 \text{ ng}\times\text{mL}^{-1}\times\text{yr}^{-1}$  (mean [IQR]  $0.03 \text{ ng}\times\text{mL}^{-1}\times\text{yr}^{-1}$ ). There were 820 (96.1%) cases of the 853 cases that had an initial PSA  $<2.5 \text{ ng/mL}$ , and 496 cases (60.5%) had an initial PSA value lower than the median PSA value (0.7 ng/mL), but 324 cases (39.5%) had a PSA value  $>0.7 \text{ ng/mL}$ .

### PSA measurement and PSA velocity calculation

PSA measurements tested in these two medical center were done using Roche Elecsys immunity analyzer (Roche, Switzerland). Recent literature reports that there are at least 3 methods to calculate the velocity of PSA but the best method is using linear regression of all PSAs according to the equation:  $p = at + b$ , where "p" is PSA value, "t" is PSA testing time (years), "a" is the slope of regression straight line speed (equivalent PSA velocity), and "b" if the intercept when testing time is zero [4].

### The distributions and characteristics of initial PSA and PSA velocity

First, we used "abnormal" initial PSA (1.0, 2.5, and 4.0 ng/mL) and "abnormal" PSA velocity (0.35, 0.75, and 2.0  $\text{ng}\times\text{mL}^{-1}\times\text{yr}^{-1}$ ) as the critical points to analyze the proportion of initial PSA  $\geq 1.0$ ,  $\geq 2.5$ , and  $\geq 4.0 \text{ ng/mL}$ ; and PSA velocity  $\geq 0.35$ ,  $\geq 0.75$ , and  $\geq 2.0 \text{ ng}\times\text{mL}^{-1}\times\text{yr}^{-1}$  in different age groups ( $\leq 30$  years, 31-39 years, and 40-50 years). Histograms were used to illustrate the distributions and characteristics of initial PSA and PSA velocity in men aged  $\leq 50$  years. We then studied the correlation of initial PSA and age of initial PSA, age of initial PSA

**Table 1.** Results of prostate biopsy in 50 men who met the criteria of biopsy

PSA Value (ng/ml)	DRE(+) n (%)	DRE (-) n (%)	Ultrasound (+) n (%)	Ultrasound (-) n (%)	PCa n (%)	Sarcoma n (%)	Non-cancerous n (%)
<4	13 (39.4)	8 (47.1)	11 (39.3)	10 (45.5)	6 (54.5)	1 (100.0)	14 (36.8)
4-10	10 (30.3)	7 (41.2)	9 (32.1)	8 (36.4)	2 (18.2)	0 (0.0)	15 (39.5)
>10	10 (30.3)	2 (11.7)	8 (28.6)	4 (18.1)	3 (27.3)	0 (0.0)	9 (23.7)
Total	33 (66.0)	17 (34.0)	28 (56.0)	22 (44.0)	11 (22.0)	1 (2.0)	38 (76.0)

**Table 2.** Distributions and characteristics of "abnormal" initial PSA and PSA velocity of non-prostate cancer in men age 50 years old and younger

Age (yr)	Initial PSA (ng/mL)(%)			PSA Velocity ( $\text{ng}\times\text{mL}^{-1}\times\text{yr}^{-1}$ ) (%)		
	$\geq 1.0$ n (%)	$\geq 2.5$ n (%)	$\geq 4.0$ n (%)	$\geq 0.35$ n (%)	$\geq 0.75$ n (%)	$\geq 2.0$ n (%)
$\leq 30$	392 (15.4)	47 (15.2)	45 (19.5)	3 (5.6)	2 (6.9)	3 (15.0)
31-39	691 (27.3)	95 (30.7)	81 (35.1)	20 (37.0)	8 (27.6)	9 (45.0)
40-50	1451 (57.3)	167 (54.1)	105 (45.4)	31 (57.4)	19 (65.5)	8 (40.0)
Total	2534 (26.8)	309 (3.3)	231 (2.4)	54 (6.3)	29 (3.4)	20 (2.3)

and PSA velocity in addition to initial PSA and PSA velocity. Finally, we estimated the difference in the risk of PSA value  $\geq 2.5$  ng/mL between the groups with initial PSA higher or lower than the median (0.7 ng/mL).

### Statistics

Statistical analyses were performed using SPSS 17.0 (Chicago, IL, USA). Values are expressed as means  $\pm$  SD and medians. PSA velocity was analyzed by using linear regression, represented by the slope of the line. The relationship of the initial PSA and the age of the initial PSA, the age of initial PSA and PSA velocity, and the initial PSA and PSA velocity was evaluated using correlation analysis. Using Kaplan-Meier survival curves and log-rank tests we assessed the diversity of risk of PSA value  $\geq 2.5$  ng/mL at a future time between the two groups (initial PSA higher or lower than the median group). P value  $< 0.05$  was considered statistically significant.

## Results

Overall, of the 9461 Chinese young men aged  $\leq 50$  years who had "abnormal" PSA values, there were 2534 (26.8%), 309 (3.3%), 231 (2.4%) cases that had an initial PSA of  $\geq 1.0$ ,  $\geq 2.5$ , and  $\geq 4.0$  ng/mL, respectively. The distributions of "abnormal" initial PSA in each age group are shown in Table 2. Figure 1 shows that the initial PSAs of the vast majority of young men were in the range of 0.0-1.0 ng/mL and 1.1-2.0 ng/mL (73.2% and 23.5%, respectively).

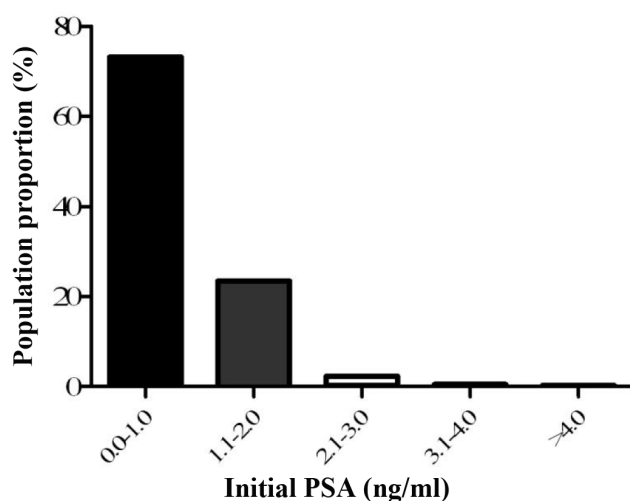
There were 853 (9.0%) cases tested for PSA two or more times among the 9461 men. Of these 853 young men, 820 (96.1%) had initial PSA  $< 2.5$  ng/mL, and 33 had initial PSA  $> 2.5$  ng/mL. There were 54 (6.3%), 29 (3.4%) and 20 (2.3%) cases of PSA velocity  $\geq 0.35$ ,  $\geq 0.75$ , and  $\geq 2.00$  ng/mL $^{-1}$ yr $^{-1}$ , respectively. Table 2 lists the distributions of "abnormal" PSA velocity in each age group. Figure 2

shows 78.6%, 9.2% and 4.3% of young men with PSA velocity distribution of 0.0-0.1 ng/mL $^{-1}$ yr $^{-1}$ , 0.11-0.2 ng/mL $^{-1}$ yr $^{-1}$ , and 0.21-0.3 ng/mL $^{-1}$ yr $^{-1}$ , respectively, while only a handful of PSA velocity values were over this range.

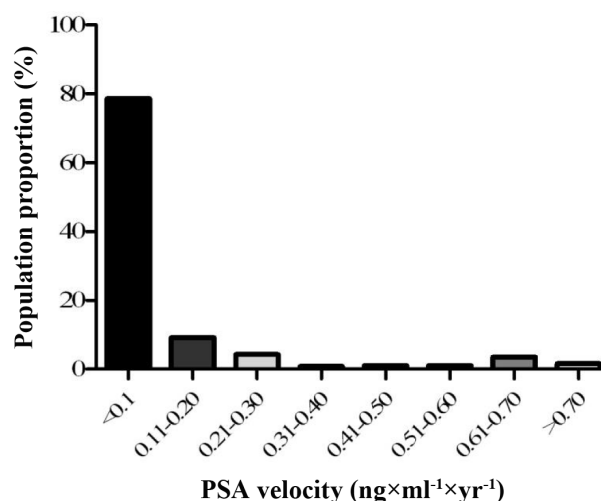
For men aged  $\leq 50$  years, the initial PSA, the age of initial PSA testing, and the PSA velocity had no significant correlation (correlation coefficient  $r=0.021$ ,  $-0.17$  and  $-0.008$ , respectively;  $p=0.223$ ,  $0.759$  and  $0.892$ , respectively). Of the 820 cases with initial PSA  $< 2.5$  ng/mL after a follow-up of up to 10 years from baseline PSA measurement, the risk of PSA  $\geq 2.5$  ng/mL, stratified by median initial PSA (0.7ng/mL) was significantly different (log-rank test,  $p<0.001$ ) (Figure 3).

## Discussion

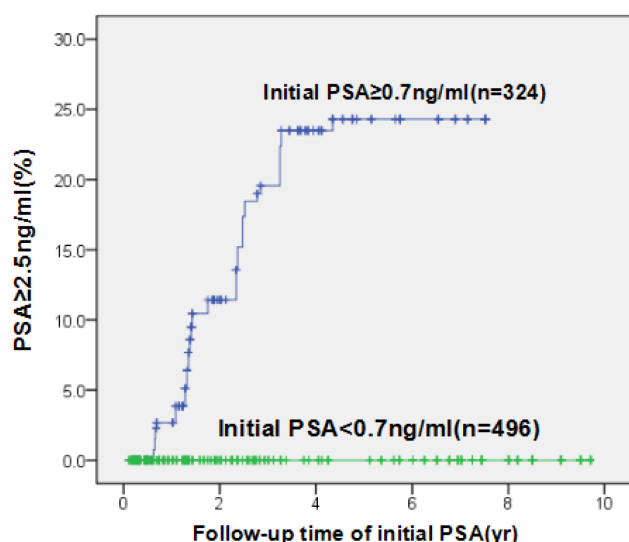
PSA measurement is widely used as an important tool for early diagnosis of prostate cancer. Whether PSA screening can reduce prostate cancer mortality or not remains controversial [5,6], but it is still highly recommended by domestic and overseas guidelines. In 2000, the American Urological Association (AUA) guidelines recommended that PSA testing for prostate cancer should begin at the age of 50. For high-risk groups, such as family history of prostate cancer or African ethnicity, PSA measurement should begin at the age of 45 [7]. Studies have increasingly shown that the initial PSA levels of young men and the future risks of prostate cancer are clearly related. Fang et al. [8] reported that for 40-49 year-old young men if their initial PSA was greater than the median PSA (0.6 ng/mL), the risk was 3.75 fold greater than for men with their initial PSA less than 0.6 ng/mL at the same age-stage. This finding was confirmed



**Figure 1.** Distributions of initial PSA in men aged  $\leq 50$  years without prostate cancer (n=9461).



**Figure 2.** Distributions of PSA velocity in men aged  $\leq 50$  years without prostate cancer (n=853).



**Figure 3.** Comparison of cumulative risk of future PSA  $\geq 2.5$  ng/mL between the initial PSA levels above and below the median initial PSA (0.7 ng/mL). Log-rank test,  $p < 0.001$ .

by subsequent studies [9,10]. Accordingly, the latest AUA Prostate Cancer Guideline Update recommends that all men aged 40 years should be tested for initial PSA, and if the initial PSA is greater than the median PSA (0.6 ng/mL or 0.7 ng/mL), PSA screening should be regularly performed [2]. But for young men, although controversially, regular PSA screening should begin when initial PSA is higher than the critical initial PSA values. Also, the latest NCCN guidelines recommend initial PSA greater than 1.0 ng/mL should trigger regular PSA screening in young men [3]. Our recent study reported that the initial PSA of Caucasian whites and African-Americans in young men was 0.7 ng/mL. After 9 years of follow-up, we found that the incidence of prostate cancer in the group with 0.7-1.5 ng/mL at initial PSA testing was not higher than the group with initial PSA of less than 0.7 ng/mL (median PSA). But the group of initial PSA greater than 1.5 ng/mL had significantly increased incidence of prostate cancer. Thus, our study suggested that young men should begin regular PSA screening when initial PSA is greater than 1.5 ng/mL as an appropriate recommendation, and that this could reduce the number of young men subjected to unnecessary PSA testing [10].

This study found that the initial PSA was 0.7 ng/mL, and the rate of 26.8% of men aged  $\leq 50$  years with an initial PSA  $\geq 1.0$  ng/mL was similar to the rates reported in other races/ethnicities. According to the aforementioned guidelines, at least 25% of our Chinese young men ( $\leq 50$  years) should have PSA screening regularly. However, in our study, after a follow-up of up to 10 years from baseline PSA measurement, men from the group with PSA

greater than the median (0.7 ng/mL) had an increased risk of PSA  $\geq 2.5$  ng/mL than men from the group with PSA  $< 0.7$  ng/mL. Furthermore, overall, the risk of diagnosing prostate cancer is increasing. However, there are significant racial differences reported in the incidence of prostate cancer. The incidence of prostate cancer reported for the Asian races was significantly lower than many other races in western countries [11]. Chinese guidelines for prostate cancer also recommend PSA screening in men aged  $\geq 50$  years [12]. Still, so far, there is no strong evidence to support this recommendation. In actual clinical work, a variety of factors (such as routine physical examination, blood testing, and packaged items) have led to a lot of men aged  $\leq 50$  years also having PSA tests; however the rationale for this testing needs further study. In addition, further study is needed to determine whether initial PSA testing is needed for Chinese young men  $\leq 50$  years and to determine further screening of high-risk groups.

A PSA of 4.0-10.0 ng/mL with a PSA velocity of  $\geq 0.75$  ng $\times$ mL $^{-1}\times$ yr $^{-1}$  is a currently recognized indication for prostate biopsy [2]. Some authors found that using PSA velocity  $\geq 0.4$  ng $\times$ mL $^{-1}\times$ yr $^{-1}$  as a biopsy indication could significantly improve the detection rate of prostate cancer for young men aged  $\leq 50$  years or PSA  $\leq 4.0$  ng/mL [13]. Orsted et al. reported that when PSA velocity was  $\geq 0.35$  ng $\times$ mL $^{-1}\times$ yr $^{-1}$  in the first 10-15 years, the death risk of prostate cancer 25 years later was 4.7 fold greater than for those whose PSA velocity was  $< 0.35$  ng $\times$ mL $^{-1}\times$ yr $^{-1}$  [14]. D'Amico et al. [15] and Kim et al. [16] demonstrated that the risk of death of prostate cancer was significantly high with PSA velocity  $\geq 2$  ng $\times$ mL $^{-1}\times$ yr $^{-1}$  before radical prostatectomy. The aforementioned results showed that PSA velocity can be used as an important basis for the diagnosis and prognosis for prostate cancer. The number of PSA velocity value of the 417 young men aged  $\leq 50$  years were: 25 cases (6.0%)  $\geq 0.35$  ng $\times$ mL $^{-1}\times$ yr $^{-1}$ ; 13 cases (3.1%)  $\geq 0.75$  ng $\times$ mL $^{-1}\times$ yr $^{-1}$ ; and 8 cases (1.9%)  $\geq 2.0$  ng $\times$ mL $^{-1}\times$ yr $^{-1}$ . Although the proportion of PSA velocity in young men aged  $\leq 50$  years was greater than the "abnormal" range, the difference was not large; thus, we should take their young-age PSA velocity into account while assessing this part of the patient's future PSA measurement and risk of prostate cancer. In this way, we could get a more accurate and reliable evaluation of the prostate cancer risk.

As it has been reported in the literature, PSA and PSA velocity increase with age and there is significant correlation between these two values [17-19]. Our study showed that PSA and PSA velocity had no correlation with age, PSA, or PSA

velocity. We analyzed the main reasons: benign prostatic hyperplasia (BPH) is an important reason for high PSA. Prostatic hyperplasia is not obvious in most young men aged  $\leq 50$  years; BPH is considered a disease of old age. Recent studies have reported that there is a significant relationship between PSA, PSA velocity and age, though these studies involved mainly elderly populations, and these results may be not be extrapolated to younger men. Loeb et al. [13] reported that the effectiveness of PSA velocity for diagnosing prostate cancer in young men is significantly higher than in old men. Therefore, using PSA and PSA velocity characteristics in a young man for predicting future risk of prostate cancer may be more reliable.

Above all, by retrospectively analyzing the young men aged  $\leq 50$  years who have an initial PSA test, we reported distribution characteristics of initial PSA and PSA velocity of Chinese young men for the first time, which was very important to assess the change and development of PSA in a Chinese cohort. However, there were several limitations in this study: 1) This was a single-center retrospective study; 2) The proportion of prostate biopsies and the diagnosis of prostate cancer in our study were so small that the morbidity of prostate cancer

with higher initial PSA in the future was hard to evaluate. But we predicted the risk of their future PSA was greater than the "abnormal" range of PSA value by comparing the two groups stratified by median initial PSA (0.6 ng/mL), which indirectly showed that the risk of prostate cancer in the future should be higher in the group of initial PSA higher than the median; 3) All the participants came from the same hospital. Though it was a large-sample size study, it might not fully represent the normal population. These results still need to be confirmed in a large-sample community or population-based multi-center prospective study.

## Conclusions

More than 25% of the men aged  $\leq 50$  years should have regularly PSA screening based on current guidelines. However, the subsequent risk of being diagnosed with prostate cancer in these men is not known. Men aged  $\leq 50$  years with an initial PSA higher than the median (0.7 ng/mL) have a subsequent higher risk of abnormal PSA value.

## Conflict of interests

The authors declare no conflict of interests.

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