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Original Article

Age-specific PSA reference ranges in Chinese men without prostate cancer

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Abstract

This study is to determine age-specific prostate-specific antigen (PSA) distributions in Chinese men without prostate cancer (PC) and to recommend reference ranges for this population after comparison with other studies. From September 2003 to December 2006, 9 374 adult men aged from 18 to 96 years agreed to participate in the study. After all cases of PC were excluded, 8 422 adult men participated in statistical analysis and were divided into five age groups. Simple descriptive statistical analyses were carried out and quartiles and 95th percentiles were calculated for each age group. The age-specific PSA reference ranges are as follows: 40–49 years, 2.15 ng mL^{-1}; 50–59 years, 3.20 ng mL^{-1}; 60–69 years, 4.10 ng mL^{-1}; 70–79 years, 5.37 ng mL^{-1}. The results indicate that the ethnic differences in PSA levels are obvious. The currently adopted Oesterling's age-specific PSA reference ranges are not appropriate for Chinese men. The reference ranges of this study should be more suitable to Chinese men.

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1 Introduction

Prostate cancer (PC) is now recognized as one of the principal medical problems faced by the male population in China and has already gained increased attention from Chinese urologists owing to its rapidly increasing incidence. Although the incidence rates vary greatly within the same country or region and the incidence rates of PC are generally higher in Western countries than in China [1], many recent reports have indicated that the incidence of PC in China is increasing rapidly. For example, in Shanghai, it is estimated that the incidence of PC increased from 1.8 to 2.4 per 100 000 in 1990 to 4.5–7.7 per 100 000 in 2 000 and to about 10.0 per 100 000 in 2004 [2, 3]. In addition, it is noteworthy that the incidence of PC is influenced by the diagnosis of latent cancers through screening of asymptomatic individuals using prostate-specific antigen (PSA) [4]; such practices can lead to artificially inflated perception of incidence. It is, however, reasonable to assume that the incidence of PC in China is underestimated, as screening for PC using PSA is not a routine practice [5].

PC in China is also characterized by a high rate of advanced tumors at the time of diagnosis. Peyromaure *et al*. [6] found that the majority of PC cases in China were diagnosed after urinary symptoms (75.9%) or bone pain (12.8%). PC was suspected because of increased PSA in only 6.2% of cases. Moreover, only 26% of PC patients had a normal digital rectal examination (DRE). These results differ markedly from Western reports because of the widespread use of PSA-based screening programs in the United States and Europe. In the United States and Europe, PC is usually asymptomatic at diagnosis, the DRE is normal and PC is diagnosed on the sole basis of increased PSA in > 60% of cases [7]. Obviously, detection of organ-confined PC would dramatically improve patient outcome [4]. When cancers are confined to the prostatic capsule and surgically excised, the disease rarely progresses [8].

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In contrast, advanced PC is incurable. Therefore, clinicians advocate that early detection of PC using PSA testing is essential [8, 9].

Urologists in China have thus vigorously appealed for periodic serum PSA testing in all males older than 50 years as practiced in America and Europe. However, the optimal PSA cutoff for detection of PC is unclear in the Chinese population. For example, the median serum PSA was 0.82 ng mL^{-1} in healthy Chinese men aged 50–59 years, 0.93 ng mL^{-1} in those aged 60–69 years and 1.17 ng mL^{-1} in those aged 70 years or older [10, 11]. Although these data have not yet been validated, it should be recognized that serum PSA values in Chinese men older than 50 years are lower than those in other races. As only limited data are available, more studies are needed to confirm the optimal PSA cutoff value for detection of PC.

Age-specific PSA reference ranges represent an attempt to improve the sensitivity and specificity of serum PSA tests by taking into account age-based PSA changes. Oesterling *et al*. [12] proposed that age-specific PSA cutoffs would increase cancer detection (greater sensitivity) in younger men. Simultaneously, age-specific PSA reference ranges could also reduce the number of negative biopsies (greater specificity) in older men. Reissigl *et al*. [13] found that the use of age-specific cutoffs resulted in an 8% increase in biopsies and 8% increase in detected cancers in men aged 45–59 years, whereas 21% fewer biopsies would have been performed in older men, with 4% of cancers not detected.

China is different from America and Europe because of the lack of optimized age-specific PSA reference ranges for detection of PC. The aim of this study was to determine age-specific PSA distributions in Chinese men, with the goal of recommending optimal values for detection.

2 Patients and methods

From September 2003 to December 2006, 13 237 adult men aged 18–96 years underwent periodic physical examination at our hospital. Among these men, 9 374 agreed to participate in the study and to undergo serum PSA determination, transrectal ultrasound (TRUS) examination and potential prostate biopsy. Although agreements to participate were received from all patients, the vast majority of patients who participated in this study had serum PSA and TRUS examinations at their own expense due to different health insurance systems and limited research funding. Patients also additionally paid for prostate biopsies when it was necessary. The criteria for prostate biopsy were serum PSA > 4.0 ng mL^{-1} and/or prostate nodules found on TRUS. There were 913 (10.11%) patients who underwent TRUS-guided prostate biopsy. Of these, 301 (33.3%) were diagnosed with PC. Of the total of 9 073 patients in the database, 8 422 were included in the statistical analysis. Patients with age < 30 years or ≥ 80 years were not included. The patients were divided into five age groups: 690 were in the 30–39 age group, 1 880 in the 40–49 age group, 2 255 in the 50–59 age group, 1 800 in the 60–69 age group and 1 797 in the 70–79 age group.

2.1 PSA determination method

Specimens were measured using an Elecsys-2010 automated immunoassay instrument (F. Hoffmann-La Roche Ltd., Basel, Switzerland). The electrochemiluminescence immunoassay method was used for measurements. The measurement kit was supplied by Roche (Hoffmann-La Roche Ltd., Basel, Switzerland).

2.2 Statistical analysis

The experimental data were analyzed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA). Simple descriptive statistical analyses were carried out and quartiles and 95th percentiles were calculated for each age group.

3 Results

According to the normality test (Kolmogorov–Smirnov $Z = 31.618$, $P < 0.0001$), the data had a non-normal distribution. A histogram showing PSA value < 10 ng mL^{-1} is provided to show this non-normal distribution more clearly (Figure 1).

The quartiles and 95th percentiles were calculated for each age group. The upper level of PSA in each age-related group was the 95th percentile value, and the lower level was set at 0 ng mL^{-1}.

Table 1 compares the 95th percentiles with those in the study of Oesterling *et al*. [14]. Table 2 compares the 95th percentile of each age group in this study with data from Korean [15], Japanese [16, 17] and Asian Americans

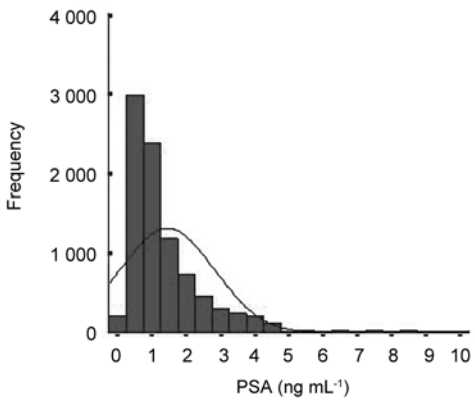

Figure 1. Frequency of prostate-specific antigen (PSA) < 10 ng mL^{-1}.

[18]. The data of Asian Americans were from DeAntoni *et al.*'s study [18]. It is found that age-specific PSA reference ranges for 40–49-year-old Asian Americans were similar to those of other groups, but were significantly higher for age 50 and above.

4 Discussion

Despite the growing awareness of the importance of PSA for early PC screening, optimal reference values of serum PSA for PC screening in Chinese men have still not been determined. Although systematic studies with large samples are lacking in China, some reports performed in other Asian countries such as Korea and Japan suggest that serum PSA levels in Asian people are lower than in other ethnic groups. Therefore, the age-specific PSA reference ranges of Oesterling *et al*. [14] might be too high for Chinese males and are thus not applicable. The current study sought to determine optimal age-specific PSA reference ranges for Chinese men.

We observed that the 95th percentiles of serum PSA levels in Chinese men increased with age. The average annual increase was 2.66%, which was significantly lower than the average annual increase of 3.20% observed by Oesterling *et al*. [14]. The age-specific PSA reference range for each age group in this study was also significantly lower than those observed by Oesterling *et al.* [14] (Table 1). This difference was relatively small for the 40–49-year-old age group (2.15 *vs.* 2.50), but gradually increased with age and was greatest for the 70–79-year-old age group (5.37 *vs.* 6.50). It is therefore likely that the current commonly adopted (in China) age-specific PSA reference range of Oesterling *et al*. [14] might cause errors in PC screening by increasing specificity and decreasing sensitivity. This error would be especially obvious in the 70–79-year-old age group if serum PSA > 6.5 ng mL^{-1} is used as the criterion for prostate biopsy for the 70–79 age group. Then patients with PC but with serum PSA between 5.37 and 6.5 ng mL^{-1} are likely to be missed.

Table 1. Comparison of age-specific prostate-specific antigen (PSA) reference ranges (95% confidence interval [CI]).

Age (years)	Current study	Oesterling *et al.* [14]
40–49	2.15	2.5
50–59	3.20	3.5
60–69	4.10	4.5
70–79	5.37	6.5

The table compares the 95th percentile, that is, the upper limit of the age-specific PSA reference ranges of each age group in this study, with those of Oesterling *et al*. [14], which have been commonly adopted in China. The upper limits of the age-specific PSA reference ranges of the Chinese patients in this study were similar to those of Oesterling *et al*. [14] in the 60–69 age group, but in the other age groups the upper limits of the age-specific PSA reference ranges were lower; the difference was especially large in the 70–79 age group.

Table 2 shows no significant differences among Asian people in the 40–49-year-old age group; participants included Chinese, Japanese, Korean and Asian Americans. With increased age, however, the serum PSA increased at a significantly greater rate in Asian Americans (1.32 ng mL^{-1} per 10 years) [18] than in Chinese (1.16 ng mL^{-1} per 10 years), Koreans (1.13 ng mL^{-1} per 10 years) [15] or Japanese (1.14 ng mL^{-1} per 10 years) [16]. These results suggest that above age 50, when the prostate gland begins to show hyperplasia or tumorigenesis, environmental, dietary or other unknown factors might affect PSA levels. It is generally known that Asian Americans have a lower incidence of PC than African Americans and Caucasians, but exhibit a higher incidence than men in Asia. For example, the incidence of PC in Japanese men is 1/30 of that in North American men. However, after Japanese immigrants live in North America for one or two generations, the incidence of PC in their descendants reaches 1/2 that of local residents. This phenomenon suggests that dietary and environmental factors might play a more important role in the development of PC than genetic factors. A diet composition study associated certain food components with increased risk of PC, and other components with decreased risk of PC. These components included fats,

Table 2. Comparison of age-specific prostate-specific antigen (PSA) reference ranges (95% confidence interval [CI]) with Korean, Japanese and Asian Americans.

Age (years)	Current study	Korean [15]	Japanese [16]	Japanese [17]	Asian Americans [18]
40–49	2.15	2.00	2.10	2.00	2.00
50–59	3.20	2.40	2.90	3.00	4.50
60–69	4.10	3.90	4.00	4.00	5.50
70–79	5.37	6.30	5.20	5.00	6.80

The table compares the 95th percentiles of each age group in this study with data from Korean [15], Japanese [16, 17], and Asian-Americans [18]. The data of Asian Americans were obtained from DeAntoni *et al*.'s study [18]. That study included Asian Americans (n = 900), Caucasians (n = 70 772), African Americans (n = 4 485) and Latinos/Hispanics (n = 1 543). All of the studies were selected because their data collection methods were identical to ours.

vitamin A and its precursors, vitamin D metabolites and plant estrogen. The Western diet is rich in animal fats, protein and refined carbohydrates, but lacking in fiber. The Asian diet includes bean products, cereals and vegetables. This dietary difference might give rise to the different incidences of PC.

Collectively, this study showed clear ethnic differences in PSA levels. Even for the same race, PSA is affected by dietary and environmental factors. Therefore, age-specific PSA reference ranges should be population-specific. The age-specific PSA reference ranges for Chinese men should be lower than the reference ranges of Oesterling *et al*. [14] currently used in China and are more in line with the reference ranges of this study.

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