Age-related Reference Levels of Serum Prostate-specific Antigen among Taiwanese Men without Clinical Evidence of Prostate Cancer

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Background: To determine the normal distribution of serum prostate-specific antigen (PSA) levels in Taiwanese men without clinical evidence of prostate cancer.

Methods: Between August 2006 and October 2007, healthy Taiwanese men undergoing a routine health examination in our hospital were recruited into the study. All men received a digital rectal examination (DRE) and serum PSA determination and some received a transrectal ultrasound (TRUS). Men with normal DRE findings, and PSA < 4.0 ng/ml, PSA between 4.0 ng/ml and 20 ng/ml with a negative TRUS or abnormal TRUS findings (hypoechoic lesion or others) with a negative biopsy were defined as clinically free of prostate cancer.

Results: A total of 7803 participants without clinical evidence of prostate cancer were included in the study. The median PSA value (95th percentile range) was 0.896 ng/ml (3.329) for men 50-59 years old; 1.151 ng/ml (5.114) for men 60-69 years old; 1.623 ng/ml (6.237) for men 70-79 years old and 1.754 ng/ml (6.613) for men older then 80 years. The serum PSA values correlated with age (r = 0.3078, $p < 0.001$). There were small changes in the median and 95th percentile PSA values in men younger than 50 years old, but large increases in those older than 50 years.

Conclusions: These findings confirm that the serum PSA is directly correlated with age, and offer more efficient PSA reference values for prostate cancer screening tests in Taiwanese men.

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Key words: age, prostate-specific antigen, prostate cancer, Taiwanese

Prostate-specific antigen (PSA) is the most widely used tumor marker for prostate cancer. It is an androgen-regulated protease produced predominantly by the ductal and acinar epithelium of the prostate and is secreted into the lumen.[1,2] An early feature of prostate cancer is invasion of the basal cell layer which allows PSA to increase directly.[3] However, the patient's age contributes to some confusion in the

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use of PSA tests to screen for prostate cancer. The normal upper limit of PSA, 4.0, is not always accurate for all ages.[4] Papers have suggested that age-specific cutoff values for prostate-specific antigen screening are better compared than the currently used single cut-off of 4.0 ng/mL.[5] PSA may increase with prostatic hyperplasia, therefore, one would expect that the PSA level should be lower in younger men. The currently used single cut-off of 4.0 ng/mL underestimates the cancer risk in younger patients, and may also result in unnecessary biopsies in older men with benign prostatic hyperplasia.[6-9]

Age-specific reference ranges for PSA were first presented from a community-based population of 471 healthy American white men by Oesterling et al.[10] There is increasing concern over the general applicability of those reference ranges. Different races have their own reference ranges because of the influence of geographic and ethnic differences.[11] Similar studies have been presented for African Americans,[12] Koreans,[13] Japanese,[11] and Chinese,[14,15] but no large-scale study has been conducted in Taiwanese. To optimize the application of the PSA test in Taiwan, this study was performed to determine cutoff values in different age groups based on clinical evaluation of a large number of patients undergoing health examinations.

METHODS

From August 2006 through October 2007, Taiwanese men without a history of prostate cancer, urinary tract infection, or prostate infection undergoing a routine health checkup in our hospital were recruited into this study. Blood samples were obtained for serum PSA concentration, and a digital rectal examination (DRE) was performed in all participants. Transrectal ultrasound (TRUS) was performed in patients with an abnormal DRE or PSA concentration > 4.0 ng/mL. Men with normal DRE findings, and PSA < 4.0 ng/ml, PSA > 4.0 ng/ml but < 20 ng/ml with a normal TRUS or abnormal TRUS findings (hypoechoic lesion or others) with a negative biopsy were defined as clinically free of prostate cancer.

The PSA values were analyzed with Pearson product-correlation coefficients to measure the association between serum PSA levels and age. Descriptive statistics including the mean, median, 5th, 25th, 75th, and 95th percentiles of the PSA level distribution were calculated for each age group.

RESULTS

During the study period, 7824 participants underwent DRE and serum PSA determination, with 21 cases of proven prostate cancer on prostate biopsy. Ten patients with prostate cancer had PSA values > 4 ng/mL but less than < 10 ng/mL, and 11 had PSA values > 10 ng/mL.

Of the 7803 men without clinical evidence of prostate cancer, 260 had a serum PSA value > 4.0 ng/mL. These 7803 participants were divided into eight groups according to age, and the serum PSA concentrations are shown in Table 1. The median PSA value (95th percentile range) was 0.703 ng/ml (1.796) for men 20-29 years old; 0.701 ng/ml (1.836) for men 30-39 years old; 0.749 ng/ml (2.167) for men 40-49 years old; 0.896 ng/ml (3.329) for men 50-59 years old; 1.151 ng/ml (5.114) for men 60-69 years old; 1.623 ng/ml (6.237) for men 70-79 years old and 1.754 ng/ml (6.613) for men older then 80 years old. The serum PSA values were correlated with age. ($r = 0.3078$, $p < 0.001$; 95% CI 0.2876 to 0.3277).

The proportion of men with various PSA values according to age is showed in Table 2. Only 105 (1.64%) of the 6390 men < 60 years old had serum PSA levels greater than the cutoff value (4.0 ng/mL). However, 155 (10.97%) of the 1413 men ≧ 60 years old had serum PSA levels greater than cutoff value (4.0 ng/mL). There were only small differences in the median and 95th percentile PSA values in men younger than 50 years old but there were obvious increases in those groups older then 50 years old.

DISCUSSION

PSA is a serine protease produced predominantly by the prostate gland and has been used as a biomarker for prostate cancer detection for decades.[16] It is a useful clinical tool in detecting early prostate cancer and monitoring response to therapy.

As in similar studies conducted among American white and black male populations, Koreans, Japanese, and Chinese men, PSA levels higher than 4.0 ng/mL were rarely found in this study in those under 50 years old (Table 2).[11-15]

Table 1. Serum PSA according to Age in 7803 Taiwanese Men

Age (yr)	N	Serum PSA (ng/ml) Percentile Value					
		5th	25th	Median	75th	95th	Mean PSA
20 ↓	17	0.260	0.509	0.633	0.978	1.712	0.792
20-29	360	0.286	0.486	0.703	0.985	1.796	0.864
30-39	1422	0.298	0.505	0.701	1.013	1.836	0.864
40-49	2333	0.288	0.507	0.749	1.114	2.167	0.942
50-59	2258	0.308	0.571	0.896	1.429	3.329	1.211
60-69	880	0.329	0.690	1.151	2.120	5.114	1.762
70-79	440	0.302	0.750	1.623	2.905	6.237	2.161
80 ↑	93	0.259	0.731	1.754	3.526	6.613	2.500

Abbreviation: PSA: prostate-specific antigen.

Table 2. Proportion of Men with Various Serum PSA Levels according to Age

Age (yr)	N	Serum PSA Level (ng/mL)		
		< 2.50	2.51-4.00	> 4.00
20-29	360	351 (97.5)	6 (1.66)	3 (0.83)
30-39	1422	1390 (97.7)	18 (1.26)	14 (0.98)
40-49	2333	2245 (96.2)	67 (2.87)	21 (0.90)
50-59	2258	2073 (91.8)	118 (5.22)	67 (2.96)
60-69	880	691 (78.5)	114 (12.9)	75 (8.52)
70-79	440	304 (69.0)	77 (17.5)	59 (13.4)
> 80	93	58 (62.3)	14 (15.0)	21 (22.5)

Abbreviation: PSA: prostate-specific antigen.
Values are No. (%).

Therefore, to prevent underestimating the risk of prostate cancer in young men, it is necessary to establish a normal serum PSA distribution. Some hospitals in Japan already use a lower PSA cutoff value of 2.0 ng/mL in screening for prostate cancer in younger men.[17,18] The references from this study can improve the detection rate of prostate cancer in younger patients with PSA lower than the single cut-off of 4.0 ng/mL and reduce the number of negative biopsies in older men with PSA levels > 4.0 ng/mL.[19]

In this study, it was obvious that the serum PSA level correlated directly with age. In addition, this study also determined the upper limit of age-related serum PSA levels. However, the present study revealed that serum PSA levels for Taiwanese men are slightly different from those in other Asian countries, but are closer to the levels in African-American men, American white men, and Chinese men in Shanghai (Table 3). Interestingly, although the Taiwanese male population is ethnically similar to men in mainland China, we found that age-related serum PSA levels among men in Taiwan were higher than those in Shaanxi but closer to the levels in Shanghai. These findings suggest that dietary differences and the living environment may affect age-related PSA reference levels in those with a similar ethnic background.[11] The present results also found that in the 60 -69 year age group, the 95th percentile in Taiwanese men (5.11 ng/mL) was higher than that in white men (4.5 ng/mL) but lower than in Asian-Americans (5.5 ng/mL). Asian-American men had higher PSA levels than men in Asian countries, which could show dietary and environmental effects.[20]

With age-related PSA reference levels, some prostate cancers could be identified at early and curable stages, and there would be fewer unnecessary diagnostic procedures. However, with the increased upper limit of the reference range for men older than 60 years old, it is possible that some curable cancers

Table 3. Comparison of Serum PSA Levels among African-Americans,[20] White Americans,[10] Asian-Americans,[20] Taiwanese, Japanese,[11] Korean,[13] and Chinese[14,15]

Age (year)	95th Percentile Value (ng/mL)							
	African-American	White	Asian-American	Taiwanese	Japanese	Korean	Chinese Shaanxi	Chinese Shanghai
20-29	–	–	–	1.86	–	–	1.20	
30-39	–	–	–	1.85	–	1.8	1.21	
40-49	2.7	2.5	2.0	2.17	2.0	2.0	1.23	2.15
50-59	4.4	3.5	4.5	3.32	3.0	2.5	2.35	3.2
60-69	6.7	4.5	5.5	5.01	4.0	3.9	3.20	4.3
70-79	7.7	6.5	6.8	6.20	5.0	6.3	3.39	5.37

Abbreviation: PSA: prostate-specific antigen.

could be neglected.

There were some limitations of this study. First, it was not a community-based study. However, all participants came for a health checkup and were not recruited because they had prostatic disease or symptoms. Second, prostate biopsy was performed only in patients with PSA levels > 4.0 ng/mL. There could have been prostate cancer cases in patients with PSA levels < 4.0 ng/mL. Only 21 men with PSA levels > 4 ng/mL were confirmed to have prostate cancer, we expect that prostate cancer would be detected in fewer men with PSA < 4.0 ng/mL.

In conclusion, serum PSA concentration correlates with age, and the PSA cut-off levels in Taiwanese men are different from those in other races and also in China. Our results may help us to increase the sensitivity and specificity in detection of prostate cancer in different age groups.

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台灣無前列腺癌的男性前列腺特異指數依年齡分布的參考值

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背 景： 於臨床上未證實有前列腺癌的台灣男性建立起依年齡分布的前列腺特異指數參考值。

方 法： 於 2006 年八月至 2007 年十月，收納至本院健康檢查的台灣男性作爲參加者。參加者皆接受肛門指診及前列腺特異指數抽血檢查，部分參加者另外有再做經直腸超音波檢查或前列腺切片檢查。定義臨床上無證實有前列腺癌者爲肛門指診無異常，前列腺特異指數小於 4.0 ng/ml，或指數介於 4 ng/ml 到 20 ng/ml 但是經直腸超音波檢查正常，或超音波檢查異常但前列腺切片檢查正常。

結 果： 共有 7803 位參加者爲臨床上無證實有前列腺癌的男性。依年齡分爲八組，其中 50-59 歲的中位數 (第 95 百分位數) 爲 0.896 ng/ml (3.329 ng/ml)，60-69 歲爲 1.151 ng/ml (5.114 ng/ml)，70-79 歲爲 1.623 ng/ml (6.237 ng/ml)，80 歲以上爲 1.754 ng/ml (6.613 ng/ml)。前列腺特異指數和年齡是有相關的 ($r = 0.3078$, $p < 0.001$)。在年齡小於 50 歲的男性，他們的中位數及第 95 百分位數變化較小，但在 50 歲以後就有較多的增加。

結 論： 我們發現確認前列腺特異指數與年齡是相關，不但如此，這些資料也爲台灣男性提供隨年齡分布的前列腺特異指數參考值以供前列腺癌篩檢使用。

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關鍵詞： 年齡，前列腺特異指數，前列腺癌，台灣人

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