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Age Specific Reference Levels of Serum Prostate-Specific Antigen, Prostate Volume and Prostate Specific Antigen Density in Healthy Iranian Men

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ABSTRACT

Background: It is relevant to highlight that there is not a precise and perfect report on either 95 percentile value (upper limit of normal range) or on appropriate reference intervals for serum PSA in Iranian population. **Objective:** To determine age-specific reference ranges for serum prostate-specific antigen (PSA) concentration and PSA density (PSAD) and prostate volumes in a population of healthy Iranian men. **Methods:** Nine-hundred and thirteen healthy Iranian men, aged 50-79 years, underwent a detailed clinical evaluation including a digital rectal examination, a serum PSA determination (DRE) and transrectal ultrasound (TRUS). PSA test was performed on 666 of the subjects and TRUS was done on 633 of them. None of the subjects had any evidence of prostate cancer by any one of the three diagnostic tests and had no history of Lower Urinary Tract Symptoms (LUTS). Age specific ranges for PSA levels, PSA density and prostate volume were determined. **Results:** The serum PSA concentration correlated directly with the subjects' age ($r=0.280$; $p<0.001$) and prostatic volume ($r=0.327$; $p<0.001$). Also prostatic volume was directly proportional to age ($r=0.197$; $p<0.001$). The serum PSA ranges (95th percentile) for each age range in Iranian men were: 0.00-2.61 ng/ml for 50-59 years; 0.00-3.59 ng/ml for 60-69 years; and 0.00-4.83 ng/ml for 70-79 years. The respective prostate volumes were: 14-59, 16-66 and 18-73ml. Also respective PSA densities were: 0.00-0.076, 0.00-0.10 and 0.00-0.14 ng/ml/ml. **Conclusion:** The present study confirms earlier reports that serum PSA levels and prostate volume and PSAD are age- and race- dependent, so it is appropriate to have age- specific reference ranges for these variables in various communities around the world. This will increase the positive predictive value of PSA estimation in the diagnosis of prostate cancer in different communities.

Keywords: Prostate, Prostate-Specific Antigen, ELISA

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INTRODUCTION

Prostate cancer is the fourth most common male malignant neoplasm worldwide. Its incidence varies widely between countries and ethnic populations. The lowest yearly incidence rates occur in Asia (1.9 cases per 100,000 in Tianjin, China) and the highest in North America and Scandinavia, especially in African Americans (272 cases per 100,000) (1-2). PSA is the most clinically useful marker in the diagnosis and management of prostate cancer. Although PSA is prostate-tissue specific, elevations in PSA levels are not prostate cancer specific, but organ specific, therefore, elevated levels may be found in benign prostatic hyperplasia (BPH) and prostatitis (3). Also, PSA levels increase with age mainly because of increases in prostate volume due to BPH (4).

Because PSA is not specific for prostate cancer, the PSA test has a high false positive rate when used as a screening tool (5). Only 26% of men with serum PSA level between 4.1 and 9.9 ng/mL have prostate cancer on biopsy (6).

Strategies to enhance performance of PSA test include PSA density and PSA velocity, measurement of free to total PSA ratio (f/t PSA) and age- and race-specific ranges of PSA (7-9). It is now well established that the utilization of total PSA can be enhanced with the use of age specific reference intervals. These intervals will increase the sensitivity of screening in younger men and increase the specificity of screening in older men (10). It is relevant to highlight that there is no precise and perfect report on either 95 percentile value (upper limit of normal range) or on appropriate reference intervals for serum PSA in Iranian population. Hence it was felt mandatory to establish our own reference range, in particular, the 95 percentile for healthy Iranian men in order to interpret the PSA results in benign as well as malignant disorders of prostate in Iranian patients. Thus we conducted this study to demonstrate serum PSA levels and age specific reference ranges for serum PSA and PSA density and prostatic volume in Iranian men.

MATERIALS AND METHODS

Between May 2005 and March 2007, 900 men, 50 to 79 years old, underwent mass screening for prostate cancer in Shiraz Institute for Cancer Research (ICR), Shiraz University of Medical Sciences, Shiraz, Iran. Men were invited through brochures, written press releases, and TV announcements to participate in a prostate cancer screening study. PSA test was requested for all men as the first step in the mass screening. PSA serum level were determined, using a commercial ELISA kit (Can-Ag, Sweden). All PSA determinations were made prior to any prostatic manipulation, including DRE and TRUS. DRE was performed for all men with the patient in the knee-chest position by one experienced urologist. TRUS was also requested to assess the echogenic pattern of the prostate gland and to calculate the prostate volume. The prostate volume was calculated from the formula of a prolate ellipsoid. ($\text{Width} \times \text{length} \times \text{height} \times 0.52$) (11). All TRUS examinations were performed by one radiologist, using a 6 MHz, endorectal transducer. Patients with an elevated serum PSA concentration (>4.0 ng/ml) or abnormal DRE or TRUS findings underwent TRUS-guided extended core biopsy. The men who had a negative biopsy were followed up with a specific screening plan with repeated PSA, DRE and TRUS examinations every 6 months and underwent prostate biopsies up to three times if their PSA level increased or the DRE or TRUS findings were highly suspicious.

The subjects who had a prior diagnosis of prostate cancer, a previous history of prostate surgery or prostatitis or other specific conditions that interfered with voiding function were excluded. Of the 900 men, one-hundred and seventeen men (14.8%) either met exclusion criteria or did not perform PSA test and were excluded from further analysis. Seventy-nine men (8.8%) underwent a TRUS-guided biopsy of the prostate. Seventeen of whom (21.5%) were found to have cancer. They were also excluded from this study. Overall, 766 men, who had no evidence of prostate cancer, participated in the study. Age specific reference range of serum PSA was calculated for all men. Among these subjects, 633 men performed TRUS, so the prostate volume and PSA density (PSAD) were also calculated for them. PSAD was calculated by dividing the serum PSA concentration by the prostatic volume, as determined from TRUS.

The LMS method developed by Cole (12) was applied to calculate smoothed age-related centiles. This is a parametric method and relies on normality of the data of interest. The concept is to use a Box-Cox power transformation to bring the distribution of the data close to normality (the L (t) curve), estimate the mean (the M (t) curve for the transformed data) and the standard deviation (SD) of the transformed data (the S (t) curve) as a function of age and hence derive the required centiles. For this reason, the method is called the LMS method. This method is implemented by a professional software under Windows system (13).

RESULT

With regard to the outcome variable, the mean age \pm standard deviation was 59.03 \pm 6.62 years; 431 (56.3%) were between 50 and 59, 266 (34.7%) between 60 and 69 and 69 (9%) between 70 and 79 years of age. The median (25th, 75th percentiles) serum PSA concentration for the entire study group was 0.9 (0.4, 1.5) ng/ml, the median prostatic volume was 34.0 (25.5, 43.0) mL and the median PSAD was 0.02 (0.01, 0.04) ng/ml/mL.

Serum PSA and Age. In general, the median serum PSA value increased with each decade of age (Table 1). Between 50 and 59 years of age, 5 (1.2%) individuals had a serum PSA level $>$ 4.0 ng/ml, between 60-69 years, 10 (3.8%) and between 70-79 years, 5 (7.2%) individuals had a serum PSA concentration above the standard reference range (0.0-4.0 ng/ml) and no clinical evidence of prostate cancer. Overall, 20 men (2.6%) had a serum PSA level $>$ 4.0 ng/mL.

The age-related serum PSA concentration for all 766 men is presented in Figure 1. The serum PSA concentration generally increases with age, which is more evident for older ages and higher percentiles. The nomogram for serum PSA with regard to patient's age also is shown in Figure 1. Based on these data, the appropriate upper limit of normal (95th percentile) for the serum PSA concentration increases with age, from 2.61 ng/ml for a 55-year-old man to 4.83 ng/ml for a 75-year-old man. The estimated reference range for each 10-year age group is 0.0-2.61 ng/ml for 50-59 years; 0.0-3.59 ng/ml for 60-69 years; and 0.0-4.83 for 70-79 years, as shown in Table 2.

Table 1. Serum PSA concentration, prostatic volume and PSA density as a function of age

Age range (years)	Serum PSA (ng/ml)	Prostatic volume (ml)	PSA density (ng/ml)
50-59	0.75* (0.40;1.30)**	32 (25;40)	0.019 (0.010;0.035)
60-69	1.06 (0.56;1.83)	36 (28;45)	0.024 (0.012;0.045)
70-79	1.46 (0.77;2.51)	39 (30;49)	0.028 (0.014;0.057)

*median value, ** 25th and 75th percentile, respectively

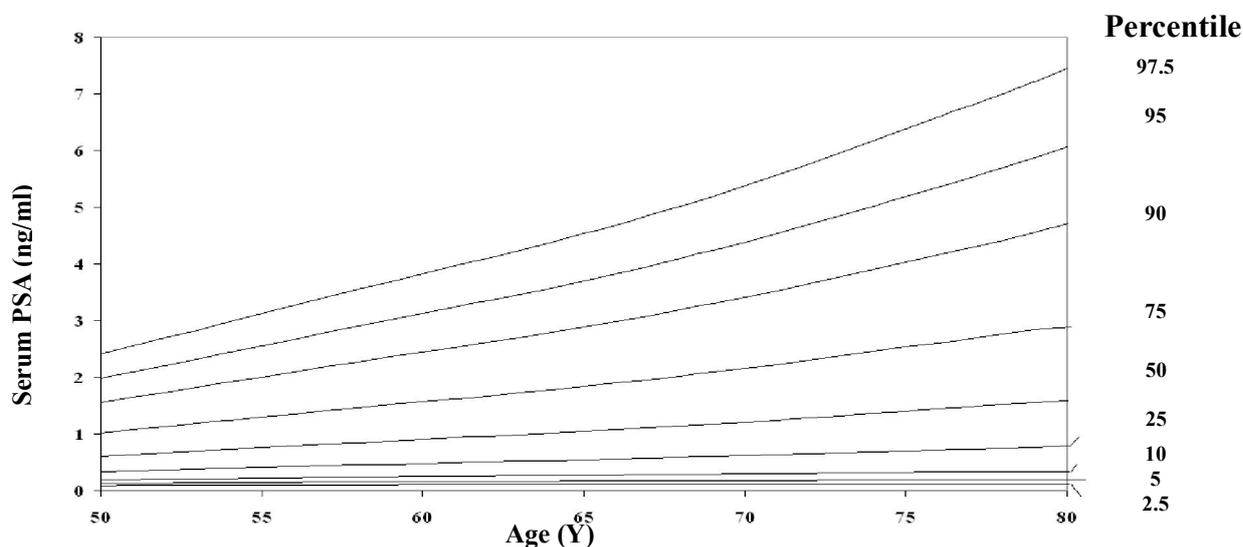


Figure 1. The age-related serum PSA concentration for all 766 men. Nomogram demonstrated the 2.5th, 5th, 10th, 25th, 50th, 75th, 90th, 95th and 97.5th percentiles for serum PSA according to age.

Table 2. Age specific reference ranges* for serum PSA concentration, prostatic volume and PSA density

Age range (years)	Serum PSA (ng/ml)	Prostatic volume (ml)	PSA density (ng/ml)
50-59	0.0-2.61	14-59	0.00-0.076
60-69	0.0-3.59	16-66	0.00-0.100
70-79	0.0-4.83	18-73	0.00-0.140

*For serum PSA concentration and PSA density the upper limit of normal was defined as 95th percentile for the mid point of age range from regression analysis; for prostate volume the 97.5th percentile was used to define the upper limit. The lower limit was set at 0.0 for PSA concentration and PSA density and 2.5th percentile for prostatic volume.

Prostate Volume and Age. Like PSA, the median prostatic volume increased with each decade of life (Table 1). Between 50-59 years of age, 41(11.1%) men had a prostate >50 ml in size. Between 60 and 69 years, 35(16.4%) men and between 70 and 79 years, 11(21.6%) men had a prostate > 50 ml in size. Overall, 87 men (13.7%) had a prostate > 50 ml in size. The age-related prostatic volume for 633 men for whom TRUS was done is presented in Figure 2. For the entire age group, the prostatic volume correlated directly with age ($r: 0.197, p < 0.001$). The nomogram for prostatic volume with regard to patient's age is also presented in Figure 2. and the calculated reference range (2.5th percentile to 97.5th percentile) for prostatic volume for each 10-year age group is presented in Table 2.

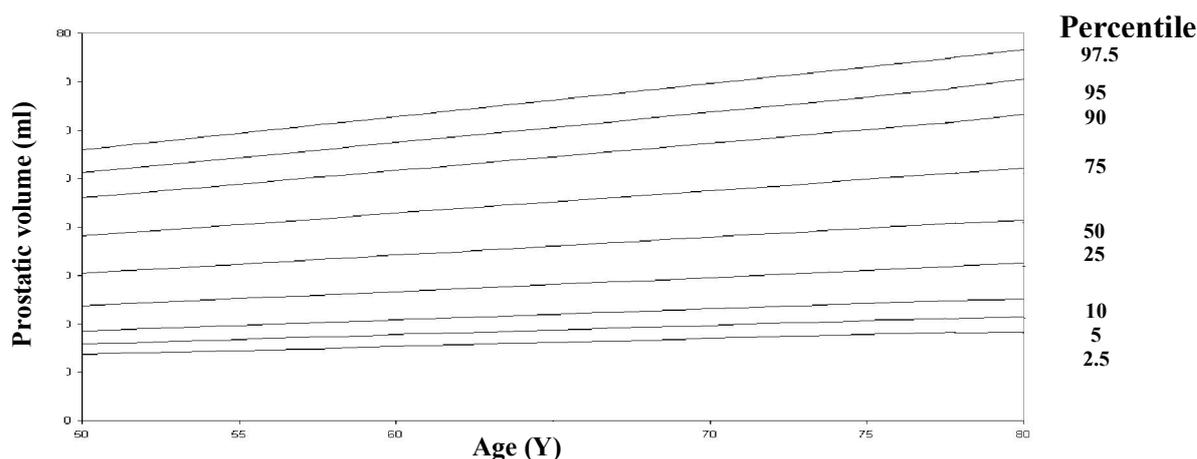


Figure 2. The age-related prostatic volume for all 633 men. Nomogram demonstrated the 2.5th, 5th, 10th, 25th, 50th, 75th, 90th, 95th and 97.5th percentiles for prostatic volume according to age.

PSAD and Age. Similar to PSA and prostatic volume, the median PSAD level increased with each decade of life (Table 1). Between 50 and 59 years of age, 3 men (0.8%) had a PSAD > 0.15 ng/ml/ml. Between 60 and 69 years, 1 (0.5%); and between 70 and 79 years, 2 (3.9%) had a PSAD > 0.15 ng/ml/ml. Overall, 6 (0.9%) men had a PSAD value > 0.15 ng/ml/ml. The PSAD value with regard to the patient's age for 633 men for whom PSAD was calculated is presented in Figure 3. For the entire age group, PSAD is correlated directly with age, as is suggested by the r-value of 0.154 ($p < 0.001$).

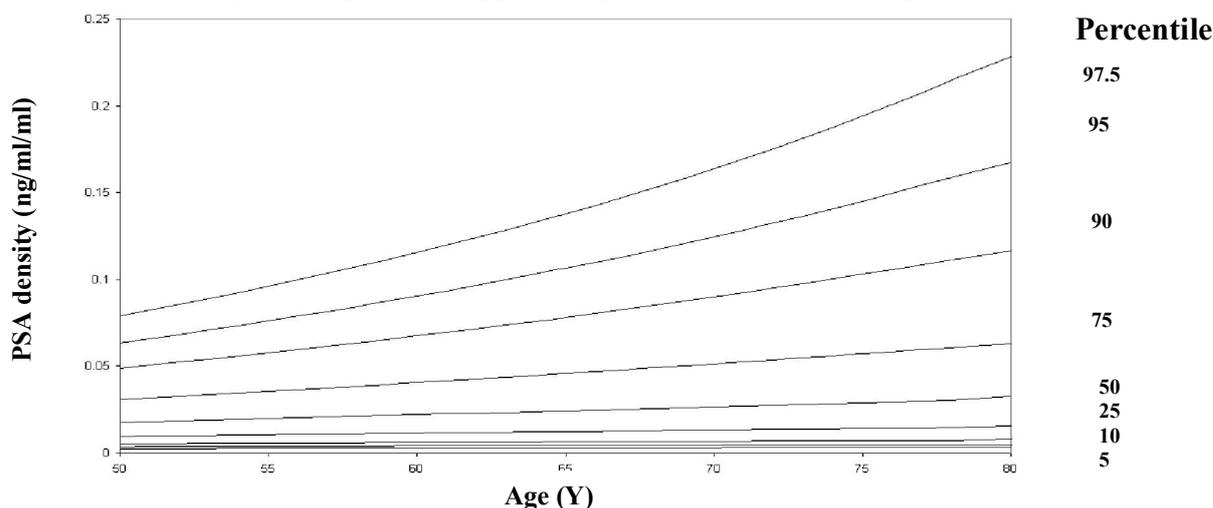


Figure 3. The age-related prostate-specific antigen density for all 633 men. Nomogram demonstrated the 2.5th, 5th, 10th, 25th, 50th, 75th, 90th, 95th and 97.5th percentiles for PSAD according to age.

Serum PSA and Prostatic Volume. The individual serum PSA value with regard to the prostatic volume is displayed in Figure 4. Over the entire range of prostatic size, the serum PSA concentration correlated directly with prostatic volume ($r: 0.327$, $p < 0.001$). The nomogram for serum PSA concentration with regard to prostatic volume is also given in Figure 4.

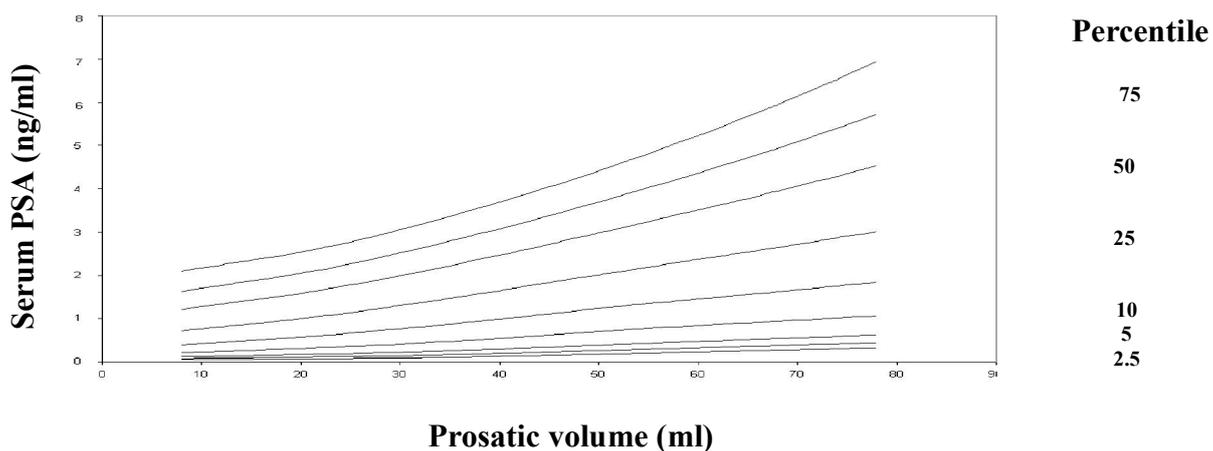


Figure 4. The prostatic volume-related serum PSA for all 633 men. Nomogram demonstrated the 2.5th, 5th, 10th, 25th, 50th, 75th, 90th, 95th and 97.5th percentiles for serum PSA according to prostatic volume.

DISCUSSION

Prostate cancer is a significant public health issue worldwide. Its incidence varies widely between countries. PSA is the most clinically useful marker in the diagnosis and management of prostate cancer. PSA level, also varies between ethnics.

In a recent study in Iran, the rate of prostate cancer was 3.6% and mean \pm Standard deviation for PSA was 1.6 ± 1.1 ng/ml in all men without prostate cancer. Mean \pm SD of PSA for normal men aged 40-49, 50-59, 60-69 and ≥ 70 years 1.3 ± 0.7 , 1.4 ± 0.8 , 1.8 ± 1 and 2.2 ± 1.6 ng/ml, respectively. In this study, age-reference level of PSA was not calculated. (14)

There was only one study that determined age-reference ranges of serum PSA in Iranian men in Yasuj, Iran. The PSA reference levels were 0-1.35, 0-1.85, 0-3.20 and 0-4.40 ng/ml for men aged 40-49, 50-59, 60-69 and ≥ 70 years, respectively (15).

In the above study, the patients who were referred to the hospital for blood cell count due to various reasons were randomly selected. This case selection may cause a problem because some patients may have a disorder or might have received some medication which could interfere with serum PSA level. Also in the above study, the patients were not examined for the evidence of prostate cancer, and digital rectal examination and TRUS or biopsy were not performed for them. Also, age specific reference ranges for serum PSAD and prostate volume were not calculated.

Thus, we conducted this investigation, based on a community population of healthy Iranian men with no clinical evidence of prostate cancer, to define 'normal levels' for serum PSA level as well as for prostate volume and PSAD among Iranian men.

In the current study, the serum PSA concentration was found to correlate with patient's age ($r=0.280$) and with prostate volume ($r=0.327$). Also PSAD and prostatic volume correlated directly with patient's age, to a lesser degree ($r=0.154$ and 0.197 , respectively). These findings are in agreement with the results of previous investigations (7,10,16). In addition, the issue of PSA variation among different races has been repeatedly investigated. Racial differences in serum PSA distribution were observed in African-American (4), Japanese (7), Korean (15), Arab (1), Chinese (18), Taiwanese (19), Singaporean (20)

and USA White men (10). The 95th percentiles of serum PSA concentrations for specific age groups were greater for African-American and USA White men but lower for Asian men. Also, Asian men living in different areas have different PSA levels. Taiwanese men had the highest PSA levels (19), while the lowest were among the Chinese men (18), suggesting that potential dietary and environmental-gene interaction may contribute to the difference in PSA levels within and outside a given racial background. The present study revealed that the serum PSA concentration for Iranian men also differed from that of African-American and USA White men, confirming that the serum PSA level for Asian races are lower than that of USA White men (Table 3). For each age group, from 50-79 years, the upper limit of normal for serum PSA levels for Iranian men are lower than those for African-American or USA White men and are higher than those for Chinese men (Table 3). The clinical implication of this finding is that the serum PSA value for an Iranian man has a different clinical meaning than the same value for a similarly aged USA White or Chinese man. Thus, a serum PSA concentration of 4.2 ng/mL would be considered elevated for a 65-year-old Iranian man, whereas it would be normal for the same-aged white American man. Also, a serum PSA concentration of 4.5 ng/ml would be normal for a 75-year-old Iranian man and would be elevated for the same-aged Chinese man. Therefore, it is necessary to establish the normal serum PSA distribution for the screening of prostate cancer on a racial basis. Also age-specific reference intervals are now of prime importance in improving the sensitivity and specificity of prostate cancer diagnosis in men (21). Establishing PSA reference ranges that are race-specific as well as age-specific are intended to produce reference ranges with similar levels of specificity in different racial groups. However, the positive predictive value of these PSA reference ranges will still be higher in white men than in Asian men, because the prevalence of clinically significant prostate cancer is much higher among the former. Thus a serum PSA value that is elevated above the appropriate race-specific, age-specific serum PSA reference range is more likely to represent prostate cancer in the white men than in the Asian man. Also, a prospective study indicated that, in men with no prostate cancer at initial screening, the risk of developing prostate cancer in any given 4-year period is greater for Dutch men aged 55-69 years than for their Japanese counterparts, because the former have higher normal PSA levels (22).

PSA values were measured with different techniques in previous investigations but Jacobsen et al. (23) showed that PSA is fairly stable, especially if the serum has been separated early after blood sample collection and stored appropriately. This implies that the assay technique should not substantially affect the values of PSA measured. This was also confirmed by Junker et al. (24), who compared four different total and free PSA assays and found no significant difference in the mean values obtained, especially when the total PSA level was <25 ng/ml.

Table 3. Reference ranges of serum PSA levels (ng/ml) in different populations

Age range, years	Serum PSA range*, ng/ml								
	USA White (10)	African-American (4)	Japanese (7)	Chinese (18)	Korean (17)	Singaporean (20)	Arab (2)	Taiwanese (19)	Our study
40-49	0-2.5	0-2	0-2	0-1.23	0-2	0-1.7	0-0.9	-	-
50-59	0-3.5	0-4	0-3	0-2.35	0-2.5	0-2.3	0-1.6	0-4	0-2.61
60-69	0-4.5	0-4.5	0-4	0-3.20	0-3.9	0-4	0-2.9	0-6	0-3.59
70-79	0-6.5	0-5.5	0-5	0-3.39	0-5.8	0-6.3	0-5.5	0-6	0-4.83

* The upper limit of normal was defined as the 95th percentile for the midpoint of each age range using polynomial regression analysis. The lower limit was set at 0.0

The most likely explanation for the difference in the age-specific reference ranges for PSA relates to the prostate volume in different races. Prostate volume in all age groups for Iranian men is higher than for Japanese or Arab men but it seems to be similar for American White men. Also Japanese and Arab men have smaller prostates than White men (Table 4). However, the difference in serum PSA concentration among races does not seem to be dependent on prostate size alone. Oesterling et al. (7) demonstrated that the difference in serum PSA concentration between white and Japanese men remained, even after adjusting for prostate size. The higher level of serum PSA beyond that which can be accounted for by prostate size alone might also reflect the difference in the cellular composition of the prostate glands in different communities. This has clinical implications for prostate pathology. For example, while the autopsy prevalence of latent prostate cancer shows little racial or geographical variation, the autopsy prevalence of 'proliferative' (more extensive and less well differentiated) latent prostate cancer shows racial and geographical variation similar to those seen for clinically diagnosed prostate cancer (25, 26). With regard to PSAD, the values obtained for the Iranian men are lower than those observed for the Japanese men (Table 4). This is due to the fact that the prostate glands of Iranian men are significantly larger for the corresponding serum PSA values as compared with Japanese men. As a result, the age-specific reference ranges for PSAD are lower for Iranian men. When compared with the standard reference range for PSAD (0.0-0.15 ng/ml/ml), these age-specific reference ranges for Iranians make PSAD a more sensitive parameter.

Table 4. Reference ranges* for prostate volume and PSA density in different populations

Age range ,years	Prostate volume range, ml				PSA density range (ng/ml/ml)		
	USA White (10)	Japanese (7)	Arab (2)	Our study	USA White (10)	Japanese (7)	Our study
40-49	13-51	9-33	8-22	-	0.0-0.08	0.0-0.10	-
50-59	15-60	9-35	9-27	14-59	0.0-0.10	0.0-0.12	0.0-0.076
60-69	17-70	10-37	9-30	16-66	0.0-0.11	0.0-0.15	0.0-0.100
70-79	20-82	11-40	10-33	18-73	0.0-0.13	0.0-0.18	0.0-0.140

*For PSA density, the upper limit of normal was defined as the 95th percentile for the midpoint of age range from regression analysis; for prostate volume, the 97.5th percentile was used to define the upper limit. The lower limit was set at 0.0 for PSA density and 2.5th percentile for prostate volume.

In conclusion, the present study confirms earlier reports that serum PSA levels, prostate volume and PSAD are age- and race-dependent, so it is appropriate to have age-specific reference ranges for these variables in various communities around the world. This will enhance the positive predictive value of PSA estimation in the diagnosis of prostate cancer in each community.

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