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Age-specific reference ranges for prostate-specific antigen (PSA) in Jordanian patients

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In this study, the normal distribution of total prostate-specific antigen (TPSA) and free prostate-specific antigen (FPSA) values and the appropriate reference ranges for prostate-specific antigen (PSA) in Jordanian patients were established; the values were then compared to those of other studies. Serum TPSA and FPSA levels in 1852 men with no diagnostic prostate cancer, as well as in patients whose PSA value was obtained as part of the clinical work-up of symptoms relating to non-neoplastic urologic conditions, were estimated during the period 1993–2001: 1561 (84.3%) were above 40 y of age or older. We studied the data as a function of age to determine the usefulness of measuring TPSA, FPSA, and their ratio as screening tests for prostate cancer risk patients. Using the 95th percentile, the recommended age-specific reference ranges of TPSA and FPSA values were as follows: for the age group 30–34 y, 2.3 and 0.51 ng/ml, respectively; for the age group 35–39 y, 2.9 and 0.59 ng/ml, respectively; for the age group 40–44 y, 3.2 and 0.63 ng/ml, respectively; for the age group 45–49 y, 3.75 and 0.71 ng/ml, respectively; for the age group 50–54 y, 3.8 and 0.83 ng/ml, respectively; for the age group 55–59 y 3.75 and 0.96 ng/ml, respectively; for the age group >60 y old, 4.3 and 1.26 ng/ml, respectively. There was a continuous increase in TPSA and FPSA means and medians throughout the study period with a significant correlation ($P<0.001$, $P<0.05$) for TPSA and FPSA levels), respectively, and advancing age group. With regard to the ratios of FPSA-to-TPSA for each age group we found no correlation between them. As a result, the appropriate upper limit of normal 95th percentile for all ratios was 0.23 for men for all ages. The establishment of appropriate reference ranges for TPSA and FPSA as well as ratios will allow the practicing urologist to incorporate these new parameters into diagnostic evaluation of men at risk for early, potentially curable prostate cancer.
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Introduction

Today, prostate cancer is the leading cancer in men and the second common cause of men's death in the United States.[1,2] Total prostate-specific antigen (TPSA) is an increasingly popular screening test for prostate cancer.[3,4] The importance of TPSA and free prostate-specific antigen (FPSA) and their ratios as tumor markers in the evaluation of prostate cancer risk patients was well documented.[5–12] The importance of the relation between TPSA or FPSA and age was also reported.[13,14] The increase in incidence of prostate cancer over a period of the last 10 y was related to the increased use of the prostate-specific antigen (TPSA and FPSA) test in diagnosing and screening for prostate cancer risk patients.[12–19]

The TPSA is a serine protease produced by the epithelial cells of normal, hyperplastic, and cancerous prostatic tissues.[20] As the enzyme is not specific for prostate cancer, the TPSA test has a high false-positive rate when used as a screening tool.[21,22] Only 26% of men

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with serum TPSA levels between 4.1 and 9.9 ng/ml have prostate cancer on biopsy.[23] In men without prostate cancer, TPSA levels increase with advancing age, mainly because of the increase in prostate volume due to benign prostate hyperplasia.[22] This fact led Oesterling *et al*[24] to develop age reference ranges for white men from Olmsted County, Minnesota.[24] Other groups[25–28] have reported normal reference ranges similar to theirs, all based on a predominantly white population of men without prostate cancer, and all designed so that the test would have 95% specificity.

By using these ranges, one can reduce the number of prostate biopsies by 22% in men, who are most likely to benefit from treatment.[29]

The usual ranges for TPSA were derived from a community-based population of white men,[24] but they were used for screening on all men on the assumption that the differences between TPSA levels at different racial groups are either small or not clinically significant.[3] Black men in the United States have one of the highest prostate cancer rates worldwide and have a 50% higher age-adjusted incidence of prostate cancer than white men.[3,29] Asian men have the lowest rates of prostate cancer, and there may be as much as a 120-fold difference between rate of prostate cancer in the lowest risk group (Shanghai, China) and the highest risk group (black men in San Francisco, California).[29]

In discussing the importance of age-specific ranges, Oesterling *et al*[24] acknowledge the lack of current information regarding age-specific TPSA levels for black, Asian, and Hispanic men. A study of TPSA levels in Asian men found a lower range of TPSA levels in this population,[24] which suggests that prostate cancer risk may correlate with TPSA levels in that population.

Therefore, the aim of this study was to determine the age-specific and prostate-specific ranges (TPSA, FPSA, their ratios and distribution) in Jordanian patients.

Materials and methods

During the period 1993–2001, 1852 Jordanian patients (30 to over 60 y old) were tested for serum TPSA and FPSA levels. Among these, 1561 (84.3%) were over 40 y old. Data on men's TPSA and FPSA values and their ages were maintained in a central computer, and the analysis was based on the results of the first test in each man. Men were grouped into seven age groups at 5-y intervals: 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, and >60 y.

Blood samples (1852) were randomly collected from 59 laboratories out of about 70 laboratories distributed throughout the area of Amman (capital of Jordan). Levels for TSPA and FPSA were estimated using a tumor marker assay analyzer (Mini Vidas, bioMerieux, France and Eleycsys 2010, Roche, Germany; normal range, 0–4.0 ng of TPSA per milliliter), which is an excellent and extremely precise immunoassay system as compared to other available techniques.[30] Patient age, name, and place of the referral were recorded. TPSA and FPSA levels were studied to determine the age-specific range of TSPA and FPSA for this population.

In this study, care was taken to ensure that TPSA and FPSA levels were determined only for patients with no evidence of prostate cancer and for those whose TPSA and FPSA values were obtained as part of screening (based on age), as well as patients whose TPSA and FPSA values were obtained as part of the clinical work-up of symptoms relating to non-neoplastic urologic conditions. This was achieved by using a designed questionnaire filled by the physician ensuring that the men who were tested underwent additional clinical examination that includes digital rectal examination (DRE) and transrectal ultrasound (TRUS) to exclude the presence of prostate cancer.

Centralized registration of blood samples with unique identification numbers ensured that the samples did not enter redundantly and all these men had database registration. Laboratory information (including all TPSA and FPSA test results and the date of the test) was linked with the patient identifier. The age of the patient at the time of the test was computed. The mean of TPSA and FPSA values was calculated as the sum of all TPSA and FPSA values divided by their total number. The median of TPSA and FPSA values (also called the 50th percentiles) was calculated. Likewise, the 90th percentile TPSA and FPSA values were calculated as that value with 90% of the observed TPSA and FPSA values below it and 10% above it. The 95th percentile TPSA and FPSA values were similarly defined.

Statistical analysis

As a result of the lognormal distribution of the TPSA and FPSA concentrations, they were log-transformed in the analysis. The observed 25th, 50th (median), 75th, 95th and standard deviation were calculated on the basis of the empirical distribution of the data in each 5-y age group. Reference ranges were calculated from the 95th percentile of TPSA and FPSA values obtained. One-way ANOVA and LSD tests were used to determine whether TPSA and FPSA concentrations differ significantly according to age or not. A P-value of less than 0.05 was considered to indicate statistical significance.[31]

Results

For every age group studied, valid number, mean, median, standard error, 5th, 25th, 75th, 95th percentile, the −95% and +95% confidence range, and the lower and upper quartile for each of TPSA and FPSA test values are shown in Tables 1 and 2, respectively.

As shown in Tables 1 and 2, there were significant differences for TPSA levels ($P<0.001$) and FPSA levels ($P<0.05$) among all age groups. However, no significant difference was observed between the two age groups 45–49 and 50–54 y) and between the two age groups 50–54 and 55–59 y for TPSA and FPSA. There was a significant difference ($P<0.001$) between the age group >60 y and all other age groups for TPSA and FPSA. The lowest age group exhibited the lowest mean TPSA and FPSA values (1.2 and 0.2 ng/ml, respectively) and the highest age group showed the highest mean TPSA and FPSA levels (3.6 and 0.44 ng/ml, respectively) (Table 3).

Means of TSPA and FPSA levels were significantly different even after adjustment for the age (the mean TPSA and FPSA levels were 2.6 and 0.28 ng/ml,

Table 1 Descriptive statistics for TPSA values according to age groups among healthy Jordanian men during the period 1993–2001

Variable age (y)	Valid no.	Mean ± s.e.	Confid. −95.00%	Confid. 95.000%	Median	5th percentile	95th percentile	Lower quartile	Upper quartile
(1) 30–34	110	1.233a ± 0.06	0.617	0.732	0.575	0.125	2.255	0.660	1.900
(2) 35–39	181	1.719b ± 0.06	0.904	1.000	0.920	0.267	2.900	1.100	2.200
(3) 40–44	214	2.488c ± 0.033	1.339	1.522	1.540	1.745	3.150	2.000	2.900
(4) 45–49	261	2.908dh ± 0.034	1.516	1.799	1.775	2.045	3.750	2.600	3.200
(5) 50–54	311	3.101ehi ± 0.022	1.854	2.108	1.300	2.345	3.800	2.900	3.300
(6) 55–59	362	3.264fi ± 0.017	1.892	2.079	2.000	2.776	3.755	3.100	3.400
(7) >60	413	3.628g ± 0.023	2.153	2.337	2.30	2.845	4.310	3.400	3.870

Means with different letters differ significantly ($P < 0.001$).

Table 2 Descriptive statistics for FPSA values according to age groups among healthy Jordanian men during the period 1993–2001

Variable age (y)	Valid no.	Mean ± s.e.	Confid. −95.00%	Confid. 95.000%	Median	5th percentile	95th percentile	Lower quartile	Upper quartile
(1) 30–34	110	0.209a ± 0.12	0.184	0.233	0.340	0.102	0.521	0.110	0.220
(2) 35–39	181	0.215b ± 0.008	0.199	0.230	0.140	0.087	0.590	0.130	0.270
(3) 40–44	214	0.220c ± 0.013	0.194	0.246	0.215	0.040	0.633	0.110	0.230
(4) 45–49	261	0.235dh ± 0.017	0.202	0.268	0.200	0.005	0.714	0.110	0.195
(5) 50–54	311	0.241ehi ± 0.01	0.211	0.271	0.105	0.050	0.830	0.095	0.330
(6) 55–59	262	0.380fi ± 0.016	0.348	0.411	0.210	0.090	0.962	0.270	0.430
(7) >60	413	0.435g ± 0.03	0.376	0.494	0.200	0.104	1.264	0.110	0.400

Means with different letters differ significantly ($P < 0.05$).

Table 3 Distribution of serum TPSA and FPSA levels according to age groups among controls in Jordanian men in 1993–2001

Age group	Mean	Median	5th percentile	95th percentile
30–34				
TPSA	1.233	1.200	0.125	1.821
FPSA	0.21	0.21	0.01	0.792
35–39				
TPSA	1.720	1.890	0.267	1.900
FPSA	0.22	0.22	0.087	0.67
40–44				
TPSA	2.489	2.550	1.745	3.155
FPSA	0.220	0.200	0.400	1.500
45–49				
TPSA	2.908	3.000	2.045	3.955
FPSA	0.240	0.140	0.010	0.54
50–54				
TPSA	3.101	3.150	2.345	3.800
FPSA	0.24	1.10	0.100	0.800
55–59				
TPSA	3.264	3.300	2.700	3.755
FPSA	0.38	0.34	0.1	0.41
>60				
TPSA	3.628	3.625	3.845	4.310
FPSA	0.440	0.200	0.104	1.450

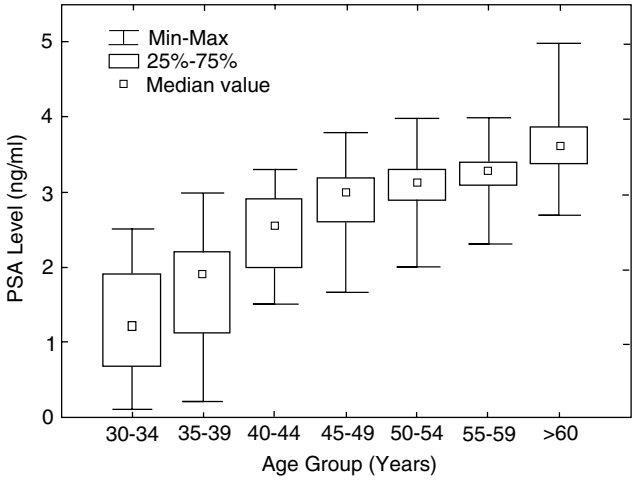

Figure 1 *Serum concentrations of TPSA as a function of age in Jordanian healthy men with no clinical evidence of prostate cancer. The lower and the upper ends of the 'whiskers' represent the minimum and maximum TPSA ranges, respectively. The lower and the upper ends of the boxes represent the 25th and 75th percentiles. The inside box represents the median.*

respectively). The average confidence rates for TPSA and FPSA levels were 1.47, 1.65 and 0.25, 0.31, respectively ($P < 0.001$). There was more variation in TPSA and FPSA values with advancing age as shown by the difference in the interquartile range between the 25th and 75th percentiles (Tables 1 and 2). The lowest TPSA and FPSA reference ranges were observed in the lowest age group (1.3 and 0.5 ng/ml, respectively), and the highest reference ranges (4.3 and 1.3 ng/ml) were shown in the highest age group. The average median TPSA and FPSA levels were 1.5 and 0.2 ng/ml, respectively.

There was a linear progressive increase in TPSA and FPSA reference ranges with advancing age (Table 1 and 2). The concentrations of TPSA and FPSA as a function of age in healthy men are shown in Figures 1 and 2, respectively, where the maximum, the minimum, the median TPSA and FPSA ranges, and the 25th and 75th percentiles are illustrated. Using the 95th percentile, the

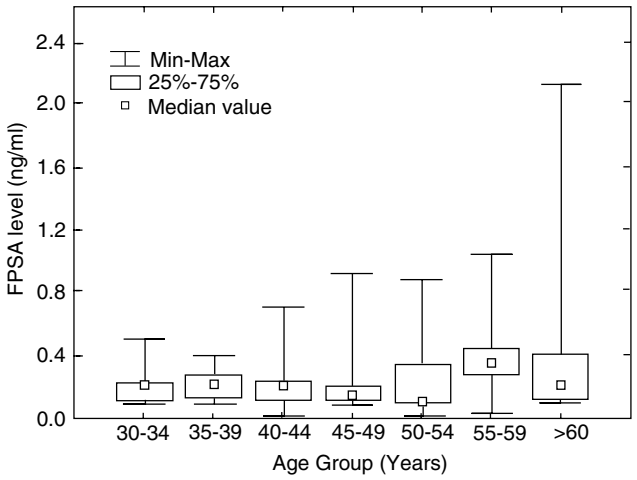

Figure 2 *Serum concentrations of FPSA as a function of age in Jordanian healthy men with no clinical evidence of prostate cancer. The lower and the upper ends of the 'whiskers' represent the minimum and maximum PSA range. The lower and the upper ends of the boxes represent the 25th and 75th percentiles. The inside box represents the median.*

recommended age-specific reference ranges for FPSA-to-TPSA were as follows: 0.51, 0.59, 0.63, 0.71, 0.83, 0.96, and 1.26 ng/ml for the age group,[1–7] respectively. No significant correlation was observed among them. With regard to the ratios of FPSA-to-TPSA for each age group, we found no correlation between them. As a result, the appropriate upper limit of normal (95th percentile) for all ratios was 0.23 for men of all ages.

Discussion

Serum TPSA and FPSA levels increased with advancing age, which agrees with the findings of other studies conducted on white and black men in the United States and Japan.[23,32,33] However, Jordanian patients exhibited higher TPSA values when compared to values observed in the above reports and were more widely distributed, particularly among older men. Therefore, if the usual 95th percentiles were used in patients with prostate cancer, we may expect that many cases would go unidentified. In populations with no clinical evidence of prostate cancer, racial differences may play an important role in affecting TPSA estimates. The highest TPSA values observed in this study might be due to some genetic factors or racial causes as has been suggested by Catalona *et al*.[23] Serum testosterone levels were reported to have a significant effect on estimating TPSA level.[34] Higher levels of TPSA were observed in black men as compared to white men, which may be due to the higher level of testosterone observed in black men.[34] Therefore, we may speculate that Jordanian patients might have greater androgen activity or androgenicity and therefore would have high TPSA and FPSA levels. Alternatively, these high levels might indicate that Jordanian men without prostatic cancer may have a high incidence of prostatic hyperplasia, increased PSA 'leakiness', an increased incidence of prostatic infarction, or any non-neoplastic condition that might elevate PSA spuriously.[3]

The age-specific reference ranges derived from the 95th percentiles of the distributed TPSA and FPSA levels were different from those derived from other studies.[23,25,32] Nonetheless, serum TPSA and FPSA screening and age-specific reference ranges are powerful tools that may suggest risk of prostate cancer in patients with urologic conditions, and when properly applied on an individual basis will improve the clinical value of such screening.

In this study, men were allocated to different age groups with a 5-y interval; therefore, we may expect that our age-specific reference ranges for TPSA and FPSA, and ratios would give a better value for clinicians to maximize the detection of prostate cancer risk patients.

Conclusions

The establishment of appropriate reference ranges for TPSA and FPSA, as well as ratios, will allow the practicing urologist to incorporate these new parameters into a diagnostic evaluation of men at risk for early, potentially curable prostate cancer.

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