SHORT PAPER

Age-Related Prostate Specific Antigen Reference Ranges in Healthy Northern Iranian Men

Shahrzad Rahimifar[1], Adel Montazeri[1*]

[1] Department of Laboratory Sciences, Razi Hospital, Guilan University of Medical Sciences, Rasht, Iran

ABSTRACT

Background: Prostate cancer is the third most common malignancy in men worldwide. Despite being a helpful biomarker in prostate cancer, prostate specific antigen (PSA) is affected by different factors including age, lifestyle, geographical region and ethnicity. **Objective:** To determine the age specific serum PSA level among healthy Northern Iranian men and to compare the results of our study with the findings of other populations in the world. **Methods:** A total of 1271 men who were referred for routine check-up in a multispecialty hospital in the city of Rasht, in Northern Iran, were evaluated for their PSA levels by commercial ELISA method. **Results:** The normal age related prostate specific antigen range (0-95th percentile) in our study was 0.0-0.62 in men younger than 40 yrs; 0.0-0.75 ng/ml in 40-49 yrs; 0.0-0.91 ng/ml in 50-59 yrs; 0.0-1.33 ng/ml in 60-69 yrs; 0.0-1.45 ng/ml in 70-79 yrs group and 0.0-1.93 in subjects older than 80 yrs. **Conclusion:** The present study revealed the lowest upper limit of PSA level in all age groups in comparison to populations from different countries.

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*Corresponding author: Dr. Adel Montazeri, Razi Hospital Laboratory, Guilan University of Medical Sciences, Rasht, Iran, e-mail: montazeri_adel@yahoo.com

INTRODUCTION

Cancer is a serious disease and a prevalent cause of mortality. According to the reports of GLOBOCAN, 14090 new cases of malignancies annually happen; however, it should be further stressed that cancer is the major cause of 8202 deaths per year all over the world (1). PC is the second most frequent malignancy among men worldwide (2), and the first common cancer among European and American men (3). Besides, the prevalence of PC has dramatically augmented in most developing countries over the past two decades (4). In general, susceptibility to prostate cancer rises with age. At higher ages, it is most important to perform routine PSA (prostate specific antigen) test which is a valid tumor marker for a quick detection of prostate cancer while it remains silent (5). Several studies have indicated various age-related reference levels of PSA in different populations (6-8). In this regard, owing to the age-related growth of prostate, the 95th percentile value (upper limit of normal range) of serum PSA (4.0 ng/ml) might not be reliable for all age groups. Age adjusted PSA values might be helpful in reducing unnecessary prostate biopsies in older men and enhancing test sensitivity in younger subjects.

To our knowledge, no research has been done regarding the age-specific reference range of serum PSA level in Northern Iran. The objective of the present study was to determine the age-adjusted cutoff value of serum PSA concentrations among healthy Northern Iranian men in comparison to other populations.

MATERIALS AND METHODS

Subjects. Our study was performed in a multi-specialty hospital in Rasht, Guilan, Iran, from December 2014 to December 2015. During the study period, around 1271 subjects were prescribed for serum PSA levels as a routine health checkup. After obtaining the informed consent, 950 subjects (of 1271) with no history of prostate cancer, prostate infection and surgery were included. Further data of the history of smoking and use of any kind of medication that might affect the serum PSA concentration were included.

The subjects were categorized into 6 age groups: Under 40 (n=70), 40-49 (n=153), 50-59 (n=322), 60-69 (n=234), 70-79 (n=115) and above 80 (n=56). The serum PSA levels were assessed by commercially available ELISA kit (Pishtazteb Co, Iran). All samples were evaluated in one clinical laboratory to eliminate any discrepancy in measurement. PSA levels were determined in nanogram per milliliter (ng/ml) and a comprehensive internal quality control program and External Quality Assurance Scheme (EQAS) (by Pishgam Iranian) were routinely carried out.

Statistical Analysis. The PSA values were analyzed by a statistical software package (Prism v.5.00, GraphPad Software, Inc., San Diego, CA, USA). The data are presented as mean $\pm$ SD, Median, Standard Error of Mean (SEM), and lower and upper 95% confidence intervals (CI).

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RESULTS AND DISCUSSION

Blood samples were collected from 950 non-urologic patients belonging to different age groups. The mean PSA level was around 0.97 ng/ml. Table 1 demonstrates the mean ± SD serum PSA concentration and the estimated upper and lower limit of the PSA level in different age groups.

Table 1. Age-related serum prostate specific antigen (PSA) values in healthy men.

PSA (ng/ml)	Under 40	40-49	50-59	60-69	70-79	Above 80	All ages
N	70	153	322	234	115	56	**950**
Mean ± SD	0.53 ± 0.37	0.66 ± 0.57	0.82 ± 0.71	1.21 ± 0.91	1.28 ± 0.94	1.61 ± 1.19	**0.97 ± 0.84**
Median	0.45	0.5	0.6	1	1.1	1.25	**0.7**
SEM	0.044	0.046	0.04	0.059	0.087	0.159	**0.848**
Lower 95% CI	0.44	0.57	0.75	1.1	1.11	1.3	**0.92**
Upper 95% CI	0.62	0.75	0.91	1.33	1.45	1.93	**1.03**
Min-Max	0.1-2.1	0.1-3.9	0.1-3.7	0.1-3.9	0.1-3.9	0.1-3.9	**0.1-3.9**

The upper limit of normal range was defined as 95th percentile value. Therefore, the normal range of prostate specific antigen (0-95th percentile) is 0.0-0.62 in healthy males younger than 40, 0.0-0.75 ng/ml between 40-49, 0.0-0.91 ng/ml ranging 50-59; 0.0-1.33 ng/ml in 60-69 category, 0.0-1.45 ng/ml in 70-79 group and 0.0-1.93 in subjects older than 80 (Table 1). In the present study, the normal upper limit of PSA value increased from 0.6 to 1.9 ng/ml in proportion to age; the mean, on the other hand, was recognizably lower than the international standard cutoff value in all age groups (4 ng/ml). The distribution of PSA values (ng/ml) with regard to age are illustrated in Figure 1.
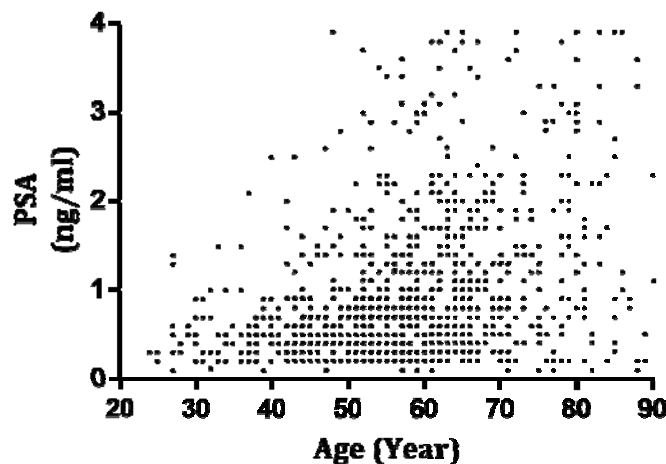

Figure 1. Distribution of serum PSA concentration (ng/ml) in subjects of all groups (yrs).

Table 2 summarizes the present study's results in comparison with the previous reports. The association between PSA and age is evident in different countries, particularly Asians (7,9,12,15). On the basis of previous findings, the majority of diagnosed cases are older than 60 years (23). A join point analysis by Pakzad *et al.* in 2016 revealed a dramatic increase in the incidence of prostate cancer in Iran (24).

Table 2. Age-specific serum prostate specific antigen (PSA) values among different healthy populations.

Population	Year	N	95 percentile PSA level (ng/ml) in age groups (yr)						Ref
			<40	40-49	50-59	60-69	70-79	>80	
Caucasians	1993	471	-	2.5	-	-	6.5	-	9
Whites	1993	471	-	2.5	3.5	4.5	6.5	-	9
Japanese	1995	286	-	2	3	4	5	-	10
US Whites	1996	1082	-	2.1	3.6	1.3	5.8	-	11
US (African-American)	1996	1673	-	2.4	6.5	11.3	12.5	-	11
Korean	2000	5805	1.8	2	2.4	3.9	6.3	-	12
Singaporeans	2000	513	1.4	1.7	2.3	4	6.3	6.6	13
Saudi Arabian	2003	543	-	2.8	3.9	5.4	6.2	-	14
South Indian	2004	583	0.9	1.3	1.48	1.6	2.0	2.4	15
Turkish	2005	257	-	4.5	4.3	6.1	10.1	-	16
Gujarati	2007	1899	-	2.1	3.4	4.2	5	-	17
Chinese	2008	8422	-	2.1	3.2	4.1	5.3	-	7
Spanish	2010	63926	1.4	1.7	3.3	5.1	-	-	18
Taiwan	2010	7803	-	-	3.3	5.1	6.2	6.6	19
Iraqi	2011	130	1.6	2	4.6	4.8	-	-	20
Syrian	2012	3000	-	1.7	-	-	5.8	-	21
Indian	2014	1253	0.7	0.8	1.1	1.4	1.8	2.3	6
South Iranian	2005	650	-	1.3	1.8	3.2	4.4	-	22
North Iranian*	2016	950	0.62	0.75	0.91	1.33	1.45	1.93	

* Our report.

The present study is among the first studies to draw attention to the age-related normal range of PSA, as an initial diagnostic test, in healthy men in Guilan, Iran. It is worth noting that our results are consistent with the widely accepted opinion among scientists that the serum PSA concentration is directly related to age. Furthermore, this investigation revealed the lowest upper limit of age-specific PSA levels in comparison to global populations. The lowest PSA upper limit shown in our report might stem from genetic factors, environmental etiology, nutrition, geographical district or other unknown factors. The root cause of serum PSA variation has not been clarified yet. In a study from India, Muslims and South Indian men had the same serum PSA concentration while Hindu males had slightly lower levels (25), which is closer to our findings. In another investigation on healthy multiethnic Asian populations (from India, Malaysia and China), various baseline PSA values were established among different ethnicities in all age groups (26). Different studies in south Iran and Yasuj have shown that the PSA level in healthy Iranian men is lower compared to American, European and

Japanese subjects. Apart from all the differences, the PSA values defined for Iranian men were closer to Asian races, Japanese subjects in particular (27,28). Based on such findings, it can be deduced that decreasing the PSA cutoff value in all age groups, might help improving survival rates via the early detection of confined tumors. The limitation of the present research was the lack of participant document on DRE (digital rectal examination), and prostate biopsy.

In conclusion, this study shows that serum PSA level correlates with age. Interestingly, for the first time, we revealed the significance of determining age-specific PSA values in healthy Northern Iranian men. The typical lower age-specific reference range of serum PSA level in comparison with other populations also underlines the need for more research on different regions of every country.

ACKNOWLEDGEMENTS

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