Original Article

Prostate-specific antigen age-specific reference ranges and the effect of metabolic syndrome factors in a Thai population

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Abstract

Objectives: An appropriate prostate specific antigen (PSA) cut-off value in Thailand has not been investigated, nor has an age-specific PSA reference range. This study aims to evaluate the correlation between metabolic syndrome, metabolic factors, and age specific PSA level.

Materials and Methods: A cross-sectional study in men who underwent medical checkups from September 2019 to December 2019. The 95th percentile PSA value was applied to the normal age-specific reference range. Correlations between PSA levels and a variety of factors were determined using linear regression.

Results: A total of 507 men met the criteria to be included in the analysis. Age-specific PSA reference ranges for men aged 40-49, 50-59, and 60-70 years were 0-2.3, 0-3.4, and 0-4.2 ng/ml, respectively. The multivariate adjusted geometric mean PSA model indicated that the factors related to PSA were age, higher body mass index (BMI) and serum fasting blood sugar (FBS) ≥ 100 mg/dl. The age group 50-59 and 60-70 have a 43% and 99% increase in mean PSA compared to the age group 40-49, respectively ($p < 0.001$). A higher BMI was associated with lower PSA ($p < 0.001$). And the serum FBS ≥ 100 mg/dl showed a 15% reduction in mean PSA compared to FBS < 100 mg/dl ($p = 0.018$).

Conclusion: The age-specific PSA reference in Thai men was lower than reported in a previous study. Use of the lower PSA cut-off may increase the sensitivity of prostate cancer screening. This study demonstrates that age, BMI, and FBS may all influence the clinical interpretation of serum PSA levels. Screening for prostate cancer using PSA should be carried out with caution in those who have those risk factors.

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Introduction

Prostate cancer is one of the most frequently diagnosed cancers in males globally. In Thailand, prostate cancer is the fourth most common cancer in men, with nearly 6,500 new cases in 2018 and nearly 3,000 deaths in 2018.[1]

Prostate cancer is usually asymptomatic at diagnosis. Early detection of disease whilst still organ-confined would dramatically improve patient outcomes. Prostate cancer screening is carried out via the use of serum prostate specific antigen (PSA) in conjunction with digital rectal examination, followed by biopsy of the prostate when levels of PSA are over 4 ng/ml.[2] However, the PSA level presents several limitations due to the lack of a universal threshold level.[3] In addition, prostate biopsy for cancer diagnosis is an invasive technique with numerous consequences such as bleeding and infection.[4] Two recent studies have shown multiple factors such as age, prostatitis, ejaculation, certain lifestyles, and comorbidities influence PSA level.[5,6]

The age-specific PSA reference ranges were first given by Oesterling et al in 1993.[2] Several studies of age-specific PSA reference ranges have been carried out in populations of different races and have found that racial differences affect the PSA levels.[7,8] Currently, no studies have been conducted on age-specific PSA reference ranges in healthy Thai men.

The metabolic syndrome is a condition consisting of a group of disorders that occur concurrently and significantly increase risk of heart disease, stroke, and type 2 diabetes. These problems include hypertension, diabetes, abdominal obesity, and elevated cholesterol or triglyceride levels. Worldwide, metabolic syndrome and prostate cancer are extremely widespread disorders.[9] Several studies have reported a relationship between metabolic syndrome and prostate cancer.[10-12] A meta-analysis of the effects of metabolic syndrome on the incidence of prostate cancer showed that metabolic syndrome is just a weak and non-significant risk factor for prostate cancer. However, certain components, such as hypertension and greater waist circumference, are related to an increased risk of prostate cancer.[13]

Numerous studies have been undertaken to evaluate the relationship between metabolic syndrome and PSA levels. One study found that PSA level decreased in a group of individuals with metabolic syndrome. The study reported that the metabolic syndrome patients would be less likely to have significantly higher PSA results than the non-metabolic syndrome patients. This meant that they would be less likely to have a prostate biopsy facilitating an early diagnosis for prostate cancer.[14] However, few studies have been conducted to determine the relationship between the metabolic components and PSA levels. Therefore, this study aims to investigate and evaluate the correlation between metabolic syndrome, metabolic components, and age specific PSA level in Thailand.

Materials and Methods

The study population consisted of men who underwent medical check-ups at the Institute of Pathology Phramongkutklao Medical Center from September 2019 to December 2019. The research protocol was approved by the Ethical Committee of the Faculty of Medicine, Phramongkutklao Medical Center (Protocol Number: R057q/62_Exp).

The inclusion criterion was all men aged 40 to 70 years old. The participants who had a history of prostate cancer, prostate surgery, recent sexual intercourse, or ejaculation (7 days), hematuria and pyuria in urinalysis were excluded.

Anthropometric measurements (height, weight, and waist circumference), a blood test (complete blood cell count, basic chemistry), fasting blood sugar, triglyceride and HDL levels, stool/urine analysis, and details of a full clinical assessment were gathered from participants. In addition, all patients were asked to complete a questionnaire regarding sociodemographic characteristics, comorbidities, the last time they engaged in sexual activity, current or previous medication, and a history of prostate surgery.

Out of the 595 men recruited, 12 men who had engaged in sexual activity in the previous seven-day period were excluded from the study. Fifty-seven with a history of medication for benign prostatic hyperplasia were also excluded, as were 8 with a history of prostate surgery and 3 with known cases of prostate cancer. Data from eight individuals were removed from the study due to the discovery of microscopic pyuria on urinalysis. Consequently, the final population numbered 507.

To diagnose metabolic syndrome, we followed the recommendations by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III).[15] The NCEP ATP III criteria were defined as a person having three or more of the following features:

1. waist circumference in male ≥ 102 cm (≥ 40 inches) or female ≥ 88 cm (≥ 35 inches)
2. triglyceride level ≥ 150 mg/dl
3. HDL cholesterol, male < 40 mg/dl, female < 50 mg/dl
4. Blood pressure (systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg) or persons taking antihypertensive medicine.
5. Fasting blood sugar (FBS) (≥ 100 mg/dl) or previously diagnosed with type 2 diabetes.

The Statistical Package for the Social Sciences (SPSS), Version 20 was used to conduct the statistical analysis (IBM Corp. Chicago, Illinois, USA). For categorical variables, the findings are presented as frequency and percentage, whilst continuous variables are expressed as mean and standard deviation. Correlation between PSA levels and a variety of factors were determined using linear regression, with a significance level of $p < 0.05$ regarded as statistically significant.

Results

Baseline characteristic of the population are shown in Table 1. The mean age and standard deviation (SD) of the population was 53.93±6.9 years old. Overweight status taken from BMI (> 25.0) were 30% and for metabolic syndrome was 15%. Serum PSA more than 4 ng/ml was found in 13 men (3%). As in the study by Oesterling, the 95th percentile PSA value is applied to the normal reference range for the age group.[2] Thus, the PSA levels for men aged 40-49, 50-59, and 60-70 years were 0-2.31, 0-3.44, and 0-4.25 ng/ml, respectively (Table 2).

Demographic and metabolic characteristic data were analyzed to investigate any potential correlation with PSA by linear regression (Table 3). Following analysis, it was determined that increasing age was associated with an increase in the geometric mean PSA. Presence of metabolic syndrome and higher BMI were associated with lower geometric mean PSA levels. The components of metabolic syndrome that correlated with lower geometric mean PSA levels were waist circumference ≥ 90 cm, serum triglyceride concentration ≥ 150 mg/dl, high blood pressure (systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg), and serum FBS ≥ 100 mg/dl.

In building the multivariate adjusted geometric mean PSA model, the factors that were found to be related to PSA were age, higher BMI and serum fasting blood sugar ≥ 100 mg/dl. The age group 50-59 and 60-70 had a 43% and 99% increase in mean PSA compared to the 40-49 age group, respectively ($p < 0.001$). The higher BMI was associated with lower PSA ($p < 0.001$). The serum FBS ≥ 100 mg/dl had a 15% reduction in mean PSA in comparison to FBS < 100 mg/dl ($p = 0.018$).

Discussion

There is a growing awareness regarding prostate cancer screening around the world, including in Thailand. PSA levels have been shown to vary by ethnicity, Asian men having lower levels, whereas European men and African Americans have higher values. In Thailand, prostate cancer screening is based on the American or European guidelines, but the PSA cut-off values of these guidelines may be inappropriate for the Thai population. To date an appropriate PSA cut-off value specific to Thai males has not been investigated,

Table 1. Baseline characteristics of the population (total population = 507)

Characteristic	Number (%) N = 507
Age (years)	53.93±6.9 (mean±SD)
40-49	162 (32)
50-59	216 (43)
60-70	129 (25)
BMI	24.50±2.9 (mean±SD)
Less than 23	226 (45)
23-24.9	125 (25)
25-29.9	117 (23)
30 or greater	39 (7)
PSA (ng/ml)	1.25±1.1 (mean±SD)
Less than 1	269 (53)
1-1.99	156 (30)
2-2.99	44 (9)
3-3.99	25 (5)
4 or greater	13 (3)
Metabolic syndrome	
Yes	78 (15)
No	429 (85)

SD = standard deviation, BMI = body mass index, PSA = prostate specific antigen

Table 2. Mean, median, and 95th percentile PSA among the population

PSA	Age group (years)			
	40-49	50-59	60-70	All
Mean PSA (ng/ml)	0.642	1.285	1.973	1.255
Median PSA (ng/ml)	0.425	0.9770	1.600	0.941
95th percentile PSA (ng/ml)	2.311	3.443	4.250	3.240

PSA = prostate specific antigen

Table 3. Association of PSA with demographic and metabolic characteristics (Linear regression)

Characteristic		Geometric mean				Adjusted geometric mean		
	No (%)	PSA	95%CI	RGM	P-value	95% CI	RGM	P-value
Age (years)								
40-49	162 (32)	0.643		1			1	
50-59	216 (43)	1.286	0.952-1.121	1.033	0.433	1.321-1.565	1.438	< 0.001
60-70	129 (25)	1.974	1.521-1.848	1.676	< 0.001	1.823-2.185	1.996	< 0.001
BMI (kg/m^2)								
< 23	226 (45)	1.758		1			1	
23.0-24.9	125 (25)	0.921	0.667-0.831	0.745	< 0.001	0.51-0.644	0.573	< 0.001
25.0-29.9	117 (23)	0.902	0.58-0.757	0.662	< 0.001	0.482-0.631	0.551	< 0.001
≥ 30.0	39 (7)	0.476	0.35-0.483	0.411	< 0.001	0.32-0.436	0.374	< 0.001
Metabolic syndrome								
Absence	429 (85)	1.337		1			1	
Presence	78 (15)	0.806	0.506-0.703	0.597	< 0.001	0.758-1.036	0.886	0.128
WC								
< 90 cm	408 (80)	1.341		1			1	
≥ 90 cm	99 (20)	0.904	0.535-0.733	0.626	< 0.001	0.938-1.391	1.142	0.185
Triglycerides								
< 150 mg/dl	350 (69)	1.352		1			1	
≥ 150 mg/dl	157 (31)	1.039	0.652-0.834	0.737	< 0.001	0.821-1.048	0.927	0.227
HDL-C								
≥ 40 mg/dl	417 (82)	1.269		1			1	
< 40 mg/dl	90 (18)	1.195	0.743-1.024	0.872	0.094	0.809-1.018	0.907	0.097
Blood pressure								
< 130/85 mmHg	354 (70)	1.292		1			1	
≥ 130/85 mmHg	153 (30)	1.171	0.74-0.95	0.838	0.006	0.856-1.072	0.958	0.452
Fasting blood sugar								
< 100 mg/dl	388 (77)	1.38		1			1	0.018
≥ 100 mg/dl	119 (23)	0.848	0.533-0.703	0.612	< 0.001	0.748-0.973	0.854	

PSA = prostate specific antigen, RGM = relative geometric mean, BMI = body mass index, WC = waist circumference

nor has an age-specific PSA reference range for the Thai population.

Age-specific PSA reference ranges were first given by Osterling et al.[2] The possible benefits of applying age-adjusted PSA criteria include boosting the sensitivity of the test in younger men, facilitating early detection of curable, organ-confined cancers, and decreasing the proportion of negative biopsies in older men.

Table 4. Comparison of age-specific prostate-specific antigen (PSA) reference ranges (95% confidence interval [CI]) with China, Korea, Japan and Singapore.

Age (years)	95th percentile PSA values (ng/ml)					
	Study group	Oesterling[2] (US)	China[15]	Korea[16]	Japan[17]	Singapore[18]
40-49	2.3	2.5	2.15	2.0	2.0	2.3
50-59	3.4	3.5	3.20	2.4	3.0	4.0
60-70	4.2	4.5	4.10	3.9	4.0	6.3

The age-specific PSA reference range uses a 95th percentile PSA value for each profile. The standard values from the reference study for men aged 40-49, 50-59, 60-69, and 70-79 years, respectively, are 0-2.5 ng/ml, 0-3.5 ng/ml, 0-4.5 ng/ml, and 0-6.5 ng/ml.[2] According to this study, the age-specific PSA reference ranges for Thai men aged 40-49, 50-59, and 60-70 years were 0-2.3, 0-3.4, and 0-4.2 ng/ml, respectively. It was found that the age-specific PSA reference range obtained in this study was lower than the reference study.

Comparing age-specific serum PSA values in Asian populations from other studies suggests that men of Asian ethnicity have lower total PSA and age-specific PSA values than those of American men and demonstrates that race, nationality, and environment may have an influence on PSA values.[16-19] As a result, incorporating age-specific PSA results for each ethnicity would increase the sensitivity and specificity of PSA testing in the screening of men over the age of 40 for prostate cancer.

The results of this study showed a correlation of the reduction in PSA with higher BMI, and FBS ≥ 100 mg/dl after adjusting for confounding factors such as age and BMI. In addition, higher BMI levels were associated with significantly lower PSA levels. With regard to the metabolic components, there was a clear correlation between FBS ≥ 100 mg/dl with decreased serum PSA.

A previous study was carried out in obese men and PSA, dihydrotestosterone (DHT), and testosterone levels and found that obese males had lower PSA, DHT, and testosterone levels.[20] It was hypothesized that the lower PSA levels were the result of reduced circulating DHT and testosterone. Additionally, the dilution of serum as a result of increased plasma volume in obese men could be another cause of lower PSA levels. This study result agrees with the study by Werny DM et al, which concludes that PSA levels are lower in obese men than in men with weight within normal limits, which could be due to obesity-related hemodilution or a decrease in circulating androgens in obese men.[21] In the obese men, the PSA density cut-off for prostate biopsy was lower than in males with a normal BMI.[22]

To explain the causes of PSA reduction in the high FBS group, studies have shown that there are several potential causes. The diabetic patients have low testosterone levels, which can lead to a lower PSA than that in the non-diabetic group.[23,24] Another study found that in men with diabetes with poor glycemic control, based on their HbA1C levels, there was a correlation between higher HbA1C levels and lower PSA levels.[25] This association was found to be independent of age, BMI, androgen levels, medication use, and severity of diabetes, implying that parameters associated with glycemia may have a direct effect on PSA levels. Another study concluded that lower PSA levels in diabetics appear to be related to factors such as duration of diabetes, disease severity, or use of either oral diabetes medication or insulin rather than an actual diagnosis of diabetes.[26]

There are several limitations to our study. For example, this study excluded prostate volume and digital rectal examination as potential predictors of PSA levels. Secondly, the study did not assess testosterone levels, which would have been beneficial in determining the relationship between various factors and PSA levels. Finally, the study demonstrates a correlation between risk variables and PSA levels but does not demonstrate a difference in the likelihood of high-grade prostate cancer across groups due to a lack of follow-up PSA and prostate biopsy for cancer diagnosis.

Conclusions

This study adds weight to the findings of prior studies that serum PSA levels vary in accordance with age, race, and ethnic origin. The age-specific PSA reference ranges reported in this study may be more appropriate for Thai men than the ones

currently used based on men, for example, of American ethnicity. The identification of a specific reference range could increase the sensitivity of prostate cancer screening and decrease the need for prostate biopsy in Thailand.

This study demonstrates that age, BMI, and FBS may all influence the clinical interpretation of serum PSA levels. Screening for prostate cancer should be interpreted with caution in those who have the risk factors identified in this study. The PSA threshold levels may need to be re-evaluated for men of Thai ethnicity, however additional research is essential to identify the extent of the effect of these factors on the prognosis of prostate cancer.

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Conflict of Interest

The authors declare no conflict of interest.

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