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Original Article

An inverse association of body mass index and prostate-specific antigen in northwest men of China: a population-based analysis

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Abstract: Objectives: To examine the relationship between body mass index (BMI) and prostate-specific antigen (PSA) in Chinese men and to investigate whether this relationship was independent of other factors. Methods: Cross-sectional analysis was in men aged 19 to 82 years old (N=12,964) who without prostate cancer and had health examination between 2008 and 2013 in a clinical center in Xi'an, China. Obesity and overweight were classified according to the WHO criterion. Mean PSA level was calculated by categories (normal weight, overweight, and obesity) and age group (≤ 40, 41-59, ≥ 60 years old). The association between BMI and PSA was examined using multivariate regression models and stratified by age. Results: The crude prevalence was 38.42% for overweight and 3.47% for obesity in the study population. Mean PSA level increased with age at each BMI category. BMI was negatively associated with PSA level at each age group, independent of fasting plasma glucose (FPG) and prostate volume. Per unit increase in BMI was associated with a decrease of PSA by 0.03 (P=0.05), 0.11(P < 0.001), and 0.15 (P < 0.001) in men aged ≤ 40, between 41 to 59, and > 60 years old, respectively. Conclusions: Our results indicate that a higher BMI is associated with a lower level of PSA in healthy Chinese men across all age group, independent of prostate volume and FPG. With the current obesity epidemic, individual's BMI should be considered when PSA test is used to screen or diagnose prostate cancer.

Keywords: Prostate-specific antigen, body mass index, northwest men, China, population-based analysis

Introduction

Prostate cancer is the second most common cancer in men worldwide and it is estimated that every one in six men will develop prostate cancer in their lifetime [1]. The incidence of prostate cancer in China, although lower than Western countries, was significantly increased in recent years. In Beijing, the incidence of male prostate cancer increased from 55.3 per million in 2001 to 166.2 per million in 2010, with an average annual growth rate of 9.2% [2]. This increased in the prostate incidence in Chinese population reflects not only the aging of the population, but also the use of more sensitive screening techniques such as serum prostate-specific antigen (PSA) testing [3]. Recently, PSA test was widely adopted in many countries as a screening tool for prostate cancer [4, 5].

To date, studies conducted to establish normal serum PSA values have involved populations in North America, Europe, Japan, Korea and China. Recently, some studies reported that obese men may have lower normal serum PSA level than non-obese men [6]. However, it is unclear whether there is a direct link between obesity and PSA because many factors associated with obesity also have been linked with PSA, including age, fasting plasma glucose (FPG), and prostate volume (PV) [7-9]. Currently, obesity rate is growing at an alert level globally, including China. As a result, a large number of obese individual without cancer may test positive in PSA screening, which will significantly increase the rate of false positive and cost of health care. Therefore, there is an urgent need to understand the relationship between obesity and PSA in healthy and cancer population [10, 11].

Table 1. Characteristics of study participants (N=12,964)

Variables	Mean ± SD
Age, years	54.94 ± 14.70
PSA, ng/mLt	2.14 ± 1.72
PV, mL	25.07 ± 8.25
Height, cm	171.0 ± 5.90
Weight, kg	73.18 ± 10.23
BMI, kg/m^2	24.45 ± 2.94
BMI category, N (%)	
Normal weight	7556 (58.29)
Overweight	4958 (38.24)
Obese	450 (3.47)

PSA: prostate specific antigen; PV: prostate volume; BMI: body mass index.

The objective of the current study was to examine the association between body mass index (BMI) and serum PSA in healthy Chinese men and to investigate whether this relationship was independent of other factors.

Material and methods

Subjects

This is a cross-sectional analysis in men aged 19 to 82 years old who had health examination between 2008 and 2013 in a clinical center in Xi'an, China. After obtaining institutional review board approval, we abstracted clinical information retrospectively from a self-administered questionnaire assessing age, race, medication history, diabetes mellitus history, prostate cancer history, and current height and weight. The consecutive participants volunteered for screening consisting of a PSA, FPG, urine routine test and a digital rectal examination (DRE) performed by the urologist. Individuals with a history of prostate cancer, prostate surgery, have active infection or prostate or inflammation with abnormal urinalysis, have undergone a DRE in the previous 7 days, have undergone a cystoscopy or prostate needle biopsy within a month of testing, a FPG more than 15 mmol/L, a BMI less than 15 kg/m^2, PSA levels > 15 ng/mL because of a potential data registration error or a high chance of prostate cancer and inflammatory prostate disease. We excluded the men suspected of having prostate cancer or prostatitis on basis of DRE and ultrasonography, too. We also excluded the men who were taking prostate related medication, such as finasteride, which affects PSA [12]. A total of 12,964 men were included in the final analysis. This study protocol was approved by our local clinical research ethics committee.

Measurement

BMI was calculated as weight in kilograms divided by squared height in meters squared. Limosis vein blood sample was drawn from cubital vein when the men was in quiet state after 10-h fasting in the morning to assay FPG and serum PSA, and serum PSA was measured from serum drawn before DRE (Access Hybritech PSA assay; Beckman Coulter, Inc., Fullerton, Calif). Prostate volume was measured by ultrasonography using the formula for an elliptic volume (π/6 × height × width × length).

Statistical analysis

Descriptive data on study participants' characteristics were expressed as means ± standard deviations (SD) for continuous variables and percentage (%) for categorical variables. Student's *t*-test and one way analysis of variance (ANOVA) were applied to compare continuous variables were applied to compare categorical variables. Overweight (25 ≤ BMI < 30 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) were classified according to the WHO criterion. Mean (SD) PSA level was calculated by BMI categories (normal weight, overweight, and obesity) and age group (≤ 40, 41-59, ≥ 60 years old). The association between BMI (both as a continuous variable and a categorical) and PSA was examined using multivariate regression models and stratified by age. Statistical significance was defined as $P<0.05$. All statistical analyses were performed using computer software (17.0; SPSS Inc., Chicago, IL, USA).

Results

There were 12,964 men included in current analysis. Baseline characteristics of study participants are shown in **Table 1**. The mean age was 54.01 ± 14.03 years old with a range from 19 to 82. The man BMI was 24.45 ± 2.94 kg/m^2 and the mean PSA was 2.04 ± 1.63 ng/mL. Of all participants, 58.29% (N=7,556) were normal weight, 38.24% (N=4,958) were overweight, and 3.47% (N=450) were obese. Enrolled men were classified into BMI categories of normal: 55.69% (N=7993), overweight: 40.32%

Table 2. Mean PSA concentration by BMI and age (N=12,964)

Age group (years)	≤ 40 (N=3,758)	41-59 (N=4,894)	≥ 60 (N=4,362)	*P* value
Normal weight	1.76 ±1.04	1.85 ± 1.17	2.70 ± 2.33	0.075[c], < 0.001[d]
Overweight	1.61 ± 0.90	1.73 ± 1.11	2.52 ± 2.10	0.014[c], < 0.001[d]
Obese	1.43 ± 0.82	1.61 ± 0.80	2.63 ± 2.26	0.141[c], < 0.001[d]
P value	< 0.001[a]	< 0.001[a]	0.01[a]	
	0.001[b]	0.01[b]	0.30[b]	

PSA: prostate specific antigen; PV: prostate volume; BMI: body mass index; [a]Difference between overweight and normal weight values; [b]Difference between obese and normal weight values; [c]Difference between 41-59 and ≤ 40 years old values; [d]Difference between over 59 and ≤ 40 years old values.

Table 3. Regression results on the association of PSA (ng/mL) with BMI, stratified by age

Age group (years)	Normal weight	Overweight		Obese		Per BMI increase (treat BMI as a continuous variable)	
		β (95% CI)	*P* Value	β (95% CI)	*P* Value	β (95% CI)	*P* Value
≤40							
Model 1	referent	-0.08 (-0.19, -0.04)	0.002	-0.062 (-0.486, 0.198)	0.406	-0.031 (-0.009, 0.000)	0.056
Model 2	referent	-0.08 (-0.19, -0.04)	0.002	-0.054 (-0.441, 0.205)	0.471	-0.030 (-0.008, 0.000)	0.062
Model 3	referent	-0.08 (-0.19, -0.04)	0.002	-0.086 (-0.555, 0.147)	0.254	-0.032 (-0.009, 0.000)	0.05
41-59							
Model 1	referent	-0.102 (-0.162,-0.066)	<0.001	-0.004 (-0.275, 0.262)	0.960	-0.100 (-0.007, -0.004)	< 0.001
Model 2	referent	-0.101 (-0.163,-0.065)	<0.001	0.008 (-0.252, 0.278)	0.921	-0.104 (-0.007, -0.004)	< 0.001
Model 3	referent	-0.104 (-0.161,-0.067)	<0.001	0.010 (-0.269, 0.308)	0.894	-0.105 (-0.007, -0.004)	< 0.001
≥60							
Model 1	referent	-0.062 (-0.066,-0.006)	0.02	0.050 (-0.136, 0.221)	0.636	-0.148 (-0.005, -0.003)	< 0.001
Model 2	referent	-0.051 (-0.059,0.001)	0.056	0.038 (-0.157, 0.228)	0.716	-0.151 (-0.005, -0.003)	< 0.001
Model 3	referent	-0.052 (-0.057,0.000)	0.049	0.026 (-0.155, 0.199)	0.805	-0.149 (-0.004, -0.003)	< 0.001
All men							
Model 1	referent	-0.081 (-0.092, -0.045)	< 0.001	-0.010 (-0.140, 0.112)	0.831	-0.221 (-0.023, -0.020)	< 0.001
Model 2	referent	-0.080 (-0.085, -0.038)	< 0.001	-0.012 (-0.147, 0.113)	0.797	-0.222 (-0.022, -0.019)	< 0.001
Model 3	referent	-0.080 (-0.082, -0.039)	< 0.001	-0.010 (-0.139, 0.104)	0.778	-0.242 (-0.022, -0.019)	< 0.001

Model 1: crude model; Model 2: adjusted for fasting blood glucose; Model 3: adjusted for prostate volume.

(N=5786) and obese: 3.99% (N=572). We divided men into 3 age groups: ≤ 40, 41-59, and ≥ 60 years old. The means serum PSA levels by BMI and age groups are shown in **Table 2**. In both age groups of ≤40 and 41-59 years old, overweight and obese men had significantly lower serum PSA (P < 0.001, P=0.001 and P < 0.001, P=0.008, respectively) than normal weight men. In age group of ≥ 60, there were no significantly different in PAS levels between obese group and normal weight group (P= 0.303). However, the overweight group had significantly lower PSA as compared to the normal weight group (P=0.013). At 41-59 group both normal (P for trend=0.075) and overweight groups (P for trend=0.014), PSA level was significantly increased with age, and in obese group, PSA level also increased with age, but the trend was not statistically significant (P for trend =0.141). PSA levels were statistically higher in men with ≥ 60 years old as compared to those ≤ 40 years old in each group (P for trend < 0.001, respectively).

Table 3 shows the multivariate regression results of BMI and PSA, stratified by age. At age group of ≤ 40 years old, being overweight was significantly associated with lower level of PSA as compared to normal weight, independent of FPG and PV. Obese individuals also had lower PSA levels as compared to normal weight individuals, however, the difference was not statistically significant in both crude and FPG or PV adjusted models. Similar results were found in men at age group of 41-59, ≥ 60 years old and all men group. When BMI was treated as a continuous variable, per unit increase in BMI was associated with a decrease of PSA by 0.03 (P=0.05), 0.11 (P < 0.001), and 0.15 (P < 0.001) ng/mL in men aged ≤ 40, between 41 to 59, and ≥ 60 years old, respectively (model 3). This inverse association between BMI and PSA is independent of FPG and PV.

Discussion

In this large study of 12,964 Chinese men without prostate cancer, we observed an inverse association between BMI and serum PSA level in Chinese men, independent of FPG and PV. And when BMI was treated as a continuous variable, per unit increase in BMI was associated with a decrease of PSA. This inverse association was found in all age groups, even for men older than 60.

Although how obesity related to PSA or prostate cancer is unclear, previous studies have shown an inverse relationship between serum PSA levels and BMI in other populations. A recent in 3,000 healthy men from the San Antonio Center for Biomarkers of Risk of prostate carcinoma (SABOR) reported that high BMI was associated with lower PSA levels after controlling for age and race [13]. Two studies in Asian populations also reported an inverse association between BMI and PSA [4, 14]. However, the study conducted in Korea only found such inverse association in men younger than 60 years of age. As compared to previous studies, our study had much larger sample size and was able to control for other factors such as FPG and prostate volume. In addition, the inverse relationship between BMI and PSA was found in young, middle-aged and old (over 60 years old) Chinese men in this study.

The mechanisms behind the inverse association of BMI and PSA are unclear. Obesity is featured with multiple metabolic disorders and may influence PSA in several pathways. The first one is hemodilution hypothesis which suggests that obesity increased plasma volume, hemodilution, and then make circulation PSA levels reduce [15]. This hypothesis is based on the premise that blood PSA concentration is a function of plasma volume as well as PSA expression and PSA leakage into circulation [16]. The second one is steroid hormone metabolism hypothesis. It is highly likely that obesity influence the PSA level through multiple pathways. Obesity might alter levels of multiple hormones and growth factors (e.g. testosterone, estrogens, leptin, insulin and insulin-like growth factor 1) with competing effects on prostate growth and size [17]. For obese individuals, a high amount of adipose tissue could improve aromatase activity so as to make cyclic estrogen levels increase [18]. We speculate that this result might be due to regulating via androgen, estrodiol from adipose tissue, growth factors for obesity.

In current study, we observed an inverse association between BMI (as a continuous variable) and PSA in all age groups of men. However, when divided the study participants by weight category, only overweight men had statistically significantly lower level of PSA as compared to normal weighted men in crude and FPG or PV adjusted models. One possible reason might be the small sample size of obese men we have in this study. It is also possible that other factors such as functional androgen levels, race and other diseases/health conditions in obese individuals influence the relationship between BMI and PSA [19, 20].

Our study had several strengths. First, the sample size is large. We had data from 13,084 healthy men with aged range from 18 to 82. Such a large sample size and wide age range allow us to have good power for stratified analysis, particular by age groups. Second, important factors may influence the relationship between BMI and PSA, including FPG and PV, were collected. So we were able to explore influence from these factors. As we known, no previous studies have controlled the influence of FPG, PV, or both in their analyses. Third, we choose the data of ≤ 40 years old men for the control, which has been published. It plays an important role on clarifying the inverse association between BMI and serum PSA because the men suffer from prostate cancer nearly impossibly. Several limitations also exist, including the cross-sectional design, no information on important lifestyle factors, and other medical history, such as blood pressure medication. And it may not be possible to generalize our results to all races because only the northwest men of China, almost all Han race, were sampled, and BMI tends to be lower in Asian men than in Western men [21]. However, the trends in BMI and PSA level are not different in Western men [22, 23] so a more general application of our results might be acceptable. In addition, we may not have excluded all subjects with prostate cancer, because biopsies were not taken for all participants. However, the prevalence of prostate cancer in eastern Asia is not high [24]. We excluded subjects with PSA levels > 15 ng/mL, and 98% of the study population had a PSA level < 4 ng/mL. We also excluded people with

abnormal ultrasound findings result from ultrasonographic imaging with all participants undergone. The probability that men with cancer were included is very low.

Conclusion

A higher BMI is associated with a lower level of PSA in healthy northwest men of China across all age groups, the inverse association is a continuous variable, independent of FPG and PV. When PSA is used to screen prostate cancer, BMI must be taken into account to avoid a missed diagnosis.

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Disclosure of conflict of interest

None.

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