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ORIGINAL ARTICLE

The likelihood of having a serum PSA level of $\geqslant$2.5 or $\geqslant$4.0 ng ml^{-1} according to obesity in a screened Korean population

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This study aimed to determine if lower serum total prostate-specific antigen (PSA) levels in obese Korean men affect prostate cancer (PCa) screening, as an increased body mass index (BMI) is inversely associated with the PSA level. Between March 2007 and December 2012, 22 208 native Korean men who were eligible to receive a serum PSA test were recruited. Logistic regression was used to estimate the odds of an 'abnormal' PSA ($\geqslant$2.5 or $\geqslant$4.0 ng ml^{-1}) in these men (age: 45–75 years, PSA $<$10 ng ml^{-1}) based on BMI, which was categorized as normal (BMI $<$25 kg m^{-2}) and obese (BMI $\geqslant$25 kg m^{-2}). In all, 20 509 men (92.3%) were included in the study after applying the inclusion criteria. After controlling for age, there was a statistically significant trend towards a lower likelihood of having a serum PSA level $\geqslant$2.5 ng ml^{-1} with an increased BMI, with obese men having an 18% lower likelihood (odds ratio: 0.823, 95% confidence interval: 0.743–0.912; $P<0.001$) compared to men with a normal BMI. Obese men were approximately 82% as likely to have a PSA level $\geqslant$2.5 ng ml^{-1} as men with a normal BMI. These results might affect PCa screening using serum total PSA. Further studies are needed to better define these results in clinical biopsy practice.
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INTRODUCTION

A lower incidence of prostate cancer (PCa) was recently reported in an Asian population when compared with white men.[1] However, PCa has had a rapidly increasing incidence in South Korea over the last 10 years. It has become the fourth most common cancer in men over 65 years old.[2] In 2010, the age-standardized incidence rate of PCa in Korea was 25.3/100 000 man-years, which was somewhat higher compared to Japanese men (17.6/100 000 man-years), although still much lower compared to men in the United States (83.8/100 000 man-years).[3] This increased detection rate reflects not only an aging population, but also the use of more sensitive screening techniques such as serum prostate-specific antigen (PSA) testing.[4]

Although obesity may be a causative factor in the development of PCa, it may also alter the incidence of PCa through its effect on the detection of the disease, i.e., through its influence on serum total PSA levels.[5] Recently, a growing body of evidence has suggested that obese men may have lower serum PSA levels.[6–10] A proposed mechanism for the relationship between obesity and lower PSA is haemodilution. Banez *et al.*[6] reported that PSA significantly decreased with increasing body mass index (BMI) due to the dilution of a fixed amount of PSA in the greater plasma volume of patients with larger bodies. An inverse association could result in fewer screen-detected cancers, decreasing the observed incidence of PCa in obese men.[5] Furthermore, delayed detection of PCa in obese men could explain the association between obesity and worse oncological outcome. The objective of the present study was to investigate whether lower serum PSA levels in obese Korean men affect PCa screening results.

MATERIALS AND METHODS

Data collection and study design

We used data gathered between March 2007 and December 2012 at the health promotion centre attached to Soonchunhyang University Seoul Hospital. All consecutive participants underwent detailed interviews as well as physical and laboratory examinations. This study was approved by our Institutional Review Board.

A total of 22 208 native Korean men were eligible to receive a serum PSA test. For our analyses, only men aged 45–75 years were included, as this age range represents the generally accepted ages for PCa screening. Individuals with a PSA level $\geqslant$10.0 ng ml^{-1} were excluded, under the assumption that they were already likely to have PCa. Other exclusion criteria were as follows: a history of PCa, pyuria or haematuria upon microscopic examination, taking medication such as a 5α-reductase inhibitor, *Serenoa repens*, or testosterone before checking the PSA, and insufficient data. All anthropometric measurements were made by trained observers using standardized techniques. BMI was defined as the weight (kg) divided by the square of the height (m^2). The subjects were then classified as non-obese (BMI $<$25 kg m^{-2}) or obese (BMI $\geqslant$25 kg m^{-2}) according to the Asia-Pacific criteria of obesity.[11]

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Statistical analysis

The mean and s.d. were used as appropriate to describe the statistical data. All variables were non-parametric variables as determined by the Kolmogorov–Smirnov normality test. A logarithmic transformation of all variables was performed to ensure a more normal distribution, and the data were backtransformed for interpretation. A *P* value was calculated using the independent *t*-test for continuous variables and the Pearson Chi-square test for categorical variables. Two separate PSA thresholds, 2.5 and 4.0 ng ml^{-1}, were used to categorize PSA values as 'normal' or 'abnormal' for the analyses. To describe the association between obesity and the likelihood of a certain serum total PSA level, logistic regression analyses were used after dichotomising men as having a PSA level $\geqslant$2.5 or $\geqslant$4.0 ng ml^{-1}, respectively. The odds ratio of having an 'abnormal' PSA level for each threshold was then calculated, using men with a normal BMI as the reference group. The SPSS (Statistical Package for the Social Science) 14.0 software (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses and $P<0.05$ were considered statistically significant for all analyses.

RESULTS

Of the 22 208 men considered, 20 509 men (92.35%) remained after applying the inclusion criteria. Sixty-four were excluded for having a PSA level of $\geqslant$10 ng ml^{-1}, 12 for known PCa, 745 because of a pyuria or haematuria upon microscopic examamination, 583 for taking medication that can influence the PSA level and 295 for data loss.

Table 1 provides the demographics of the study population. The mean age was 52.4 years and did not significantly differ between the non-obese and obese groups. The mean PSA was significantly lower in the obese group (1.22 ng ml^{-1}) compared to the non-obese group (1.31 ng ml^{-1}) ($P<0.001$). In all, 1723 (8.40%) and 552 (2.69%) men had serum total PSA levels $\geqslant$2.5 and $\geqslant$4.0 ng ml^{-1}, respectively. Univariate analyses revealed that the likelihood of having a PSA level $\geqslant$2.5 ng ml^{-1} in the non-obese group (9.00%) was significantly higher than that in the obese group (7.53%) ($P<0.001$). A similar finding was also observed regarding the likelihood of having a PSA level $\geqslant$4.0 ng ml^{-1} ($P<0.05$) (**Table 1**).

After controlling for age, there was a statistically significant trend towards a lower likelihood of having a serum total PSA level $\geqslant$2.5 ng ml^{-1} with increased BMI, and obese men had an 18% lower likelihood (odds ratio: 0.823, 95% confidence interval: 0.743–0.912; $P<0.001$) compared to men with a normal BMI (**Table 2**). Although there was similar trend towards a lower likelihood of having a serum PSA level $\geqslant$4.0 ng ml^{-1} with increased BMI, with obese men having a 14% lower likelihood, this trend was not statistically significant ($P=0.082$) (**Table 2**).

Table 1 Demographics of the study population

	Non-obese (n=12 193)	*Obese (n=8316)*	P
Age (mean±s.d.), year	52.4 (6.2)	52.4 (6.1)	0.777[a]
BMI (mean±s.d.), kg m^{-2}	22.8 (1.6)	26.9 (1.7)	<0.001[a]
PSA (mean±s.d.), ng ml^{-1}	1.31 (1.06)	1.22 (1.03)	<0.001[a]
N (%), PSA $\geqslant$2.5 ng l^{-1}	1097 (9.00%)	626 (7.53%)	<0.001[b]
N (%), PSA $\geqslant$4.0 ng ml^{-1}	348 (2.85%)	204 (2.45%)	<0.05[b]

Abbreviations: BMI, body mass index; *N*, numbers; PSA, prostate-specific antigen.
[a] Independent *t*-test.
[b] Pearson Chi-square test.

Table 2 The OR of having a serum PSA level $\geqslant$2.5 or $\geqslant$4.0 ng ml^{-1} according to obesity

	OR	*95% CI*	P
PSA threshold 2.5 ng ml^{-1}			
Non-obese	Reference		
Obese	0.823	0.743–0.912	<0.001[a]
PSA threshold 4.0 ng ml^{-1}			
non-obese	Reference		
obese	0.856	0.718–1.020	0.082[a]

Abbreviations: CI, confidence interval; OR, odds ratio; PSA, prostate-specific antigen.
[a] Logistic regression analyses.

DISCUSSION

Catalona *et al.*[12] proposed lowering the PSA cutoff from 4.0 to 2.5 ng ml^{-1} for performing a prostate biopsy to increase the detection rate of curable PCa. Kobayashi *et al.*[13] reported a 23.6% cancer detection rate in a Japanese sample, with PSA levels between 2.0 and 4.0 ng ml^{-1}. In Korea, Park *et al.*[14] found that the cancer detection rate in a sample of Korean men with a PSA level between 3.0 and 4.0 ng ml^{-1} was 26%. The PCa detection rate for non-palpable lesions among Korean men was 21.8% in those with a PSA level of 2.5–4.0 ng ml^{-1} and 20.2% in those with a PSA level of 4.0–10.0 ng ml^{-1}, with no statistically significant difference between groups.[15] The pathologic characteristics of prostatectomy specimens were also similar between the two groups.[15] Many Korean institutions have adopted a PSA cutoff value of 2.5 ng ml^{-1} to prompt prostate biopsy.

This study showed that there was a statistically significant trend towards a lower likelihood of having a serum total PSA level $\geqslant$2.5 ng ml^{-1} with increasing BMI and that obese men had an 18% lower likelihood compared to men with a normal BMI. When we considered this threshold, there was an observable trend of a decreasing PSA level with increasing BMI, indicating significant differences in the point estimates of 'abnormal' PSA risk among BMI groups.[5] Although there was a similar trend towards a lower likelihood of having a serum PSA of $\geqslant$4.0 ng ml^{-1} with increasing BMI, with obese men having a 14% lower likelihood in the present study, the trend was not statistically significant. We believe that this finding may be due to a lack of statistical power.

Culp and Porter[5] first quantified the potential effect of the inverse association between the serum total PSA level and BMI on PCa screening in 3152 men in the United States. Using a threshold of 4.0 ng ml^{-1}, they found that obese men had a significantly decreased odds ratio (46%) of having an abnormal PSA test compared to men with a normal BMI; however, this effect was restricted to non-Hispanic whites when stratified by race.[5] They failed to show an inverse relationship between the serum total PSA level and BMI in African-Americans or Hispanic men, but they noted that these observations may have been due to a lack of power.[5]

Because obesity and PCa screening affect a substantial proportion of the male population, our findings have public health significance. Obese men are known to suffer PCa death at a significantly higher rate and to have lower serum PSA concentrations compared to non-obese men.[16,17] It has therefore been suggested that obese men experience a detection bias, minimising or even reversing the association between obesity and PCa risk (i.e., obesity becomes 'protective'), as demonstrated by several recent large prospective cohort studies.[18–20] However, we hypothesize that the association between obesity and advanced disease will persist if obesity is biologically linked with aggressive disease.[21] Indeed, a meta-analysis of multiple prospective

studies found that although obesity has a null or slightly protective effect in localized disease, it is associated with an increased incidence of advanced PCa.[22] It is known that there is no single PSA threshold that can accurately classify PCa risk from a screening standpoint.[23] However, the probability of finding cancer upon prostate biopsy is strongly related to the serum PSA level.[21] If PSA screening is to be applied with equal effect to native Korean men with differing BMIs, PSA should likely be corrected for BMI.

The International Association for the Study of Obesity proposed a criterion for obesity as a BMI $\geqslant$30 kg m^{-2} based on data from a Caucasian population. However, for people from the Asia-Oceania region, for whom the main form of energy intake is carbohydrates, obesity has been defined as a BMI $\geqslant$25 kg m^{-2}.[11] This difference in BMI cutoff is quite large and could have had affected the study results. If we had used the Western criteria for obesity in the current study, only 2.3% (472 of 20 509) of the participants would have been classified as obese. Therefore, we believe that our results might not be applicable to populations in other countries. The current study was not community-based, and we had no additional evidence that these men were perfectly healthy. Moreover, PCa was not excluded by biopsy. These points highlight the limitations of this study.

In conclusion, obese men are approximately 82% as likely to have a PSA level $\geqslant$2.5 ng ml^{-1} as men with normal BMI. These results might affect PCa screening efficiency using serum total PSA. Further studies are needed to better define these results in clinical biopsy practice.

AUTHOR CONTRIBUTIONS

WJY designed and performed experiments, analysed the data and wrote the paper.

COMPETING FINANCIAL INTERESTS

The author declares no competing financial interests.

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