นิพนธ์ต้นฉบับ

ความถูกต้องในการใช้ BMI และ PSA density ในการคัดกรองมะเร็งต่อมลูกหมากกลุ่มผู้ป่วย PSA ระดับก้ำกึ่ง (4-10 ng/ml)

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บทคัดย่อ

วัตถุประสงค์: เพื่อเปรียบเทียบความไว (sensitivity) และความจำเพาะ (specificity) ของการคัดกรองมะเร็งต่อมลูกหมากด้วย PSA density (PSAD) ในแต่ละกลุ่มดัชนีมวลกาย (body mass index : BMI) และหาค่าจุดตัด (cutoff point) ของ PSAD ค่าใหม่ที่เหมาะสมในแต่ละกลุ่ม BMI เพื่อทำให้เกิดการคัดกรองโรคที่แม่นยำเพิ่มขึ้น อันจะนำมาสู่การลดการตัดชิ้นเนื้อต่อมลูกหมากที่ไม่จำเป็น

ผู้ป่วยและวิธีการศึกษา: การศึกษาแบบ retrospective chart review จากผู้ป่วย 283 คนที่มีค่า PSA ระดับก้ำกึ่ง (diagnostic gray zone) 4-10 ng/ml ได้รับการตัดชิ้นเนื้อต่อมลูกหมากผ่านทางทวารหนักโดยใช้อัลตราซาวน์นำทาง (transrectal ultrasound with prostate biopsy) ในโรงพยาบาลศิริราชระหว่างปี พ.ศ. 2553-2556 แบ่งกลุ่มผู้ป่วยตามเกณฑ์ BMI คนเอเชียโอเชียเนียเป็นสามกลุ่มคือ กลุ่มน้ำหนักปกติ (<23 kg/m^2) กลุ่มน้ำหนักเกิน (23-24.9 kg/m^2) และกลุ่มอ้วน (≥25 kg/m^2) วิเคราะห์ Receiver Operator Characteristics (ROC) curves เพื่อประเมินความถูกต้องของ PSAD ในการคัดกรองมะเร็งต่อมลูกหมากโดยใช้ area under the ROC curve (AUC) คำนวณหาค่าความไว ค่าความจำเพาะของ PSAD ในแต่ละกลุ่ม BMI และหาค่าจุดตัดของ PSAD ค่าใหม่ที่เหมาะสมในแต่ละกลุ่ม BMI

ผลการศึกษา: PSAD ที่จุดตัดมาตรฐาน (standard cutoff point) 0.15 เป็นการทดสอบที่ให้ความไวต่อมะเร็งต่อมลูกหมากเท่ากับร้อยละ 100, 100 และ 78.3 และให้ความจำเพาะเท่ากับร้อยละ 36.7, 44.6 และ 51.5 สำหรับกลุ่มผู้ป่วยน้ำหนักปกติ น้ำหนักเกิน และอ้วนตามลำดับ โดย AUC ของ PSAD ในกลุ่มผู้ป่วยน้ำหนักปกติ น้ำหนักเกิน และอ้วนเท่ากับ 0.79, 0.75 และ 0.71 ตามลำดับ พบว่า PSAD ที่จุดตัดมาตรฐาน 0.15 เป็นจุดตัดที่เหมาะสมสำหรับกลุ่มผู้ป่วยน้ำหนักปกติ และน้ำหนักเกินซึ่งให้ความไวร้อยละ 100 แต่ PSAD ที่จุดตัดมาตรฐานไม่เหมาะเป็นจุดตัดสำหรับกลุ่มอ้วนซึ่งให้ความไวเพียงร้อยละ 78.3 ทำให้พลาดการวินิจฉัยมะเร็งต่อมลูกหมากสูงถึงร้อยละ 21.7 ทั้งนี้ทางผู้เขียนเสนอให้ใช้จุดตัดของ PSAD ใหม่ที่ระดับ 0.06 สำหรับกลุ่มอ้วน ซึ่งจะช่วยเพิ่มความไวของ PSAD เป็นร้อยละ 100

สรุป: การปรับจุดตัดของ PSAD ให้เหมาะสมตามระดับ BMI กล่าวคือใช้ PSAD ที่จุดตัด 0.15 สำหรับกลุ่มน้ำหนักปกติ น้ำหนักเกิน และใช้ PSAD ที่จุดตัด 0.06 สำหรับกลุ่มอ้วน สามารถลดการตัดชิ้นเนื้อต่อมลูกหมากผ่านทางทวารหนัก (prostate biopsy) ได้ 55 คนจากผู้ป่วย 283 คน (ร้อยละ 19.4) โดยไม่ลดความไวในการคัดกรองมะเร็งต่อมลูกหมากในกลุ่มผู้ป่วย PSA ระดับก้ำกึ่ง (diagnostic gray zone)

คำสำคัญ: การคัดกรองมะเร็งต่อมลูกหมาก ผู้ป่วย PSA ระดับก้ำกึ่ง

Original article

Diagnostic Accuracy of BMI and PSA Density in Screening Prostate Cancer Patients in the PSA Diagnostic Gray Zone (4-10 ng/ml).

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Abstract

Objective: To compare the sensitivity and specificity of prostate cancer screening by PSA density (PSAD) in each body mass index (BMI) group; and, to find an appropriate PSAD cutoff point for each BMI group in order to reduce the number of unnecessary prostate biopsies.

Material and Methods: Retrospective chart review of 283 patients who were in the PSA diagnostic gray zone 4-10 ng/ml and had a transrectal ultrasound with prostate biopsy at Siriraj Hospital from 2010 to 2013. BMI was grouped according to the Asia-Oceania criteria of obesity into the following categories: BMI <23 kg/m^2 (normal weight), BMI 23-24.9 kg/m^2 (overweight) and BMI ≥25 kg/m^2 (obese). Receiver Operator Characteristics (ROC) curves were used to assess PSAD accuracy for predicting overall prostate cancer and then stratified by BMI group using the area under the ROC curve (AUC). The sensitivity and the specificity of PSAD in each BMI group were calculated. New PSAD cutoff points which are appropriate for each BMI group were found.

Results: The sensitivity of prostate cancer at the PSAD standard cutoff point (0.15) is 100%, 100%, and 78.3%, while the specificity is 36.7%, 44.6%, and 51.5% for normal weight, overweight, and obese patients, respectively. AUCs of PSAD for predicting prostate cancer among normal weight, overweight, and the obese are 0.79, 0.75, and 0.71, respectively. PSAD at the standard cutoff point (0.15) is appropriate for normal weight and overweight patients (sensitivity = 100%), but not for the obese (sensitivity = 78.3%), resulting in 21.7% of cancers going undetected. A new PSAD cutoff point at 0.06, not at the standard cutoff point of 0.15, should be used for the obese to increase the sensitivity to 100%.

Conclusions: Adjustment of the PSAD cutoff point according to BMI level, using PSAD at cutoff point 0.15 for normal weight and overweight patients and 0.06 for obese patients, reduced prostate biopsies in 55 of 283 patients (19.4%), without reducing the sensitivity of prostate cancer screening for patients in the PSA diagnostic gray zone 4-10 ng/ml.

Keywords: prostate cancer screening, PSA diagnostic gray zone

Introduction:

The limitation of prostate specific antigen (PSA) is that the specificity for prostate cancer is low. Especially in the patients who are in the PSA diagnostic gray zone 4-10 ng/ml, prostate cancer is found in only 15-32% of this group.[1-4] Therefore, studies of the role of PSA density (PSAD) in prostate cancer screening have been conducted for the purpose of more accurate screening. PSAD level at 0.15 or more than 0.15 is positive prostate cancer screening. PSAD levels are shown to have a strong correlation with the diagnosis of prostate cancer.[5,6] However, the limitation of using PSAD to screen prostate cancer in the patients who are in the PSA diagnostic gray zone is that PSAD has a low sensitivity, just 50-91%[3,4,7,8] Consequently, using PSAD allows many prostate cancer patients to go undiagnosed. That is why PSAD is not widely used to screen for prostate cancer.

A recent study revealed that the correlation between PSAD and body mass index (BMI) is negative9. The people with high BMI tend to have low PSAD, whereas the people with low BMI tend to have high PSAD. Because BMI correlates with PSAD, the author hypothesized that BMI may affect the sensitivity and specificity of PSAD in prostate cancer screening, and using only one PSAD cutoff point at 0.15 for all patients, with both high and low BMI, may not be appropriate. The cutoff point must be changed to make the screening more accurate.

Material and Methods

From a prostate cancer screening population of 2,613 men, 283 were studied retrospectively. Criteria for selection were patients in the PSA diagnostic gray zone 4-10 ng/ml; patients who had a TRUS with prostate biopsy at Siriraj Hospital from 2010 to 2013; and patients whose prostate volume, body weight, height and biopsy result were available.

BMI was calculated as body weight in kilograms divided by height in meters squared (kg/m^2). BMI was grouped according to the Asia-Oceania criteria of obesity into the following categories: BMI <23 kg/m^2 (normal weight), BMI 23-24.9 kg/m^2 (overweight) and BMI ≥25 kg/m^2 (obese)[10].

The prostate length, width, and height were measured by transrectal ultrasound. Prostate volume was calculated using a modification of the ellipsoid formula: Prostate volume = 0.523 x length (cm) x width (cm) x height (cm). PSAD is defined as the quotient of serum PSA level divided by the prostate volume.

Baseline patient characteristics in each BMI group were analyzed and compared. The correlation between BMI and PSAD was found by Pearson's correlation coefficient. Receiver operator characteristics (ROC) curves were plotted for all cutoff values in the range of PSAD values observed. The area under the ROC curve (AUC) was used to measure the performance accuracy of PSAD as a predictor of prostate biopsy results within each BMI category. An AUC of 1.0 represents error-free prediction of cancer status in all samples, whereas an AUC of 0.50 represents a fifty percent likelihood of a correct prediction of cancer status similar to a coin toss. Sensitivity and specificity of PSAD in each BMI group were calculated. New PSAD cutoff points that are appropriate for each BMI group were also found, making screening more accurate.

Results

Baseline characteristics of the study population (overall and stratified by BMI group)

Overall baseline characteristics of the study sample and clinical features of each BMI group are listed in Table 1. Ninety-four patients (33%) of the 283 study samples were normal weight, 67 patients (24%) were overweight, and 122 patients (43 %) were obese. Mean age was 66.4 years, mean PSA was 6.99 ng/ml and mean PSAD was 0.209. Adenocarcinoma of the prostate was found in 17.3% of the entire study sample.

After baseline patient characteristics in each BMI group were analyzed and compared, it was found that the average prostate volumes in normal weight , overweight, and obese patients are 38.0 ml, 38.2 ml, and 45.2 ml respectively (P value= 0.008). There were no significant differences concerning age, PSA, PSAD and biopsy results across the three BMI categories.

Correlation between BMI, PSAD, and the other variables

BMI had a negative correlation with PSAD (coefficient = -0.141, *P* value = 0.018), and BMI had a positive correlation with prostate volume (coefficient = 0.176, *P* value = 0.003). BMI had no correlation with PSA, and age had no correlation with the other variables (PSA, prostate volume, and PSAD) (Table 2).

Table 1. Baseline characteristics of the study population (overall and stratified by BMI group)

	Overall	Normal weight (BMI <23 kg/m^2)	Overweight (BMI 23-24.9 kg/m^2)	Obese (BMI ≥25 kg/m^2)	Obese
Number (%)	283 (100)	94 (33.2)	67 (23.7)	122 (43.1)	
Mean BMI (SD) kg/m^2	24.5 (3.2)	21.1 (1.6)	24.1 (0.5)	27.3 (2.1)	
Mean age (95%CI) years	66.4 (65.6-67.3)	67.5 (66.0-69.0)	65.4 (63.6-67.3)	66.2 (64.9-67.4)	0.174
Mean PSA (95%CI) ng/ml	6.99 (6.80-7.19)	7.02 (6.68-7.36)	6.92 (6.52-7.32)	7.01 (6.72-7.31)	0.917
Mean PV (95%CI) ml	41.1 (38.9-43.3)	38.0 (34.5-41.4)	38.2 (33.9-42.5)	45.2 (41.5-48.9)	0.008
Mean PSAD (95%CI)	0.209 (0.196-0.223)	0.224 (0.198-0.250)	0.221 (0.191-0.251)	0.192 (0.173-0.211)	0.093
Biopsy results, n(%)					0.835
Benign	234 (82.7)	79 (84.0)	56 (83.6)	99 (81.1)	
Cancer	49 (17.3)	15 (16.0)	11 (16.4)	23 (18.9)	

BMI body mass index, *PSA* prostate specific antigen, *PV* prostate volume, *PSAD* prostate specific antigen density, *SD* standard deviation, *CI* confidence interval

Table 2. Pearson's correlation among PSA, PSAD, PV, age and BMI

Variable		Age	PSA	PV	PSAD
Age	Coefficient	-	0.047	0.066	0.023
	P value	-	0.435	0.266	0.701
BMI	Coefficient	-0.046	-0.024	0.176	-0.141
	P value	0.440	0.692	0.003*	0.018*

BMI body mass index, PSA prostate specific antigen, PV prostate volume, PSAD prostate specific antigen density

Predictive accuracy of PSA and PSAD and diagnostic performance of PSAD in the overall study population

In the overall study sample, the AUCs of serum PSAD and PSA for predicting prostate cancer from the biopsy were 0.75 and 0.53, respectively (*P* value <0.001) (Fig. 1). Therefore, using PSAD to predict prostate cancer is significantly more accurate than using PSA.

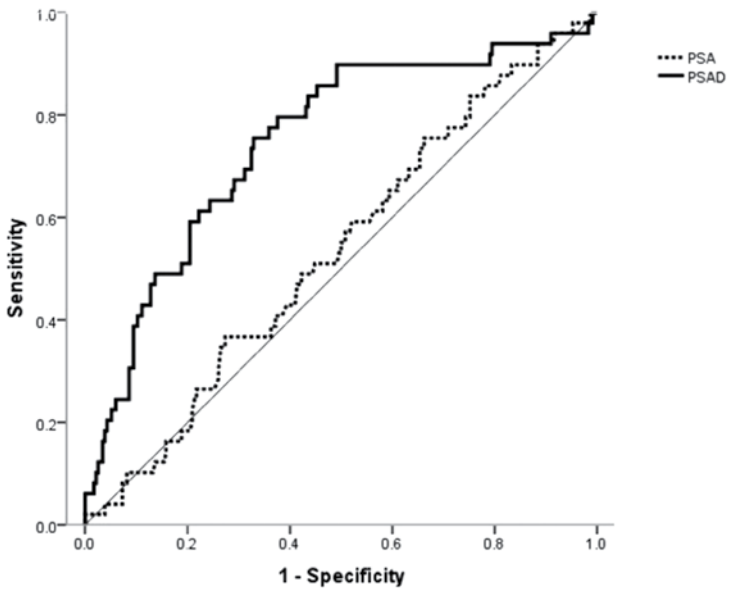
However, after analyzing the diagnostic performance of PSAD in prostate cancer screening, it was found that PSAD at the standard cutoff point of 0.15 had a sensitivity of only 89.8%; as a result, 10.2% of cancers were not detected (Table 3). Therefore, PSAD is not widely used to screen for prostate cancer.

Predictive accuracy and diagnostic performance of PSAD by BMI category

The AUCs of PSAD for predicting prostate cancer from a biopsy were 0.79, 0.75, and 0.71 for normal weight, overweight, and obese men, respectively. There was no difference in the predictive accuracy of PSAD in predicting the presence of cancer across the BMI groups (*P* value = 0.70) (Fig. 2).

After analyzing the diagnostic performance of PSAD in each BMI group, it was found that PSAD at the standard cutoff point of 0.15 had 100%, 100%, and 78.3% sensitivity and 36.7%, 44.6%, and 51.5% specificity for normal weight, overweight, and obese patients, respectively (Table 4).

PSAD at the standard cutoff point of 0.15 has 100% sensitivity in normal weight and overweight groups, meaning no cancer no cancers went undetected using PSAD at the standard cutoff point led to 54 fewer prostate biopsies in the 161 normal weight and overweight patients combined (33.5%).



	PSA	PSAD	*P*
AUC (95 % CI)	0.53 (0.45-0.62)	0.75 (0.67-0.83)	<0.001*

Fig. 1 Receiver operator characteristics (ROC) curves for PSA and PSAD predicting cancer status among patients in the PSA diagnostic gray zone (4-10 ng/ml). Note:using PSAD to predict prostate cancer is significantly more accurate than using PSA (P value <0.001). (PSA prostate specific antigen, PSAD prostate specific antigen density, AUC area under the ROC curve, CI confidence interval)

Table 3. Diagnostic performance of PSAD with respect to multiple cutoff levels. Note the unacceptable rate of undetected cancers when the standard cutoff point of 0.15 is used as criterion for biopsy.

PSAD cutoff	% Sensitivity	% Specificity	Cancers missed	% Positive predictive value	% Negative predictive value
0.05	100	0.4	0/49	17.4	100
0.06	100	0.9	0/49	17.4	100
0.07	95.9	1.7	2/49	17.0	66.7
0.08	95.9	3.8	2/49	17.3	81.8
0.09	95.9	6.0	2/49	17.6	87.5
0.10	95.9	9.0	2/49	18.1	91.3
0.11	93.9	14.1	3/49	18.6	91.7
0.12	91.8	20.5	4/49	19.5	92.3
0.13	89.8	29.9	5/49	21.2	93.3
0.14	89.8	38.0	5/49	23.3	94.7
0.15	89.8*	44.9	5/49	25.4	95.5
0.16	85.7	52.1	7/49	27.3	94.6
0.17	83.7	54.7	8/49	27.9	94.1
0.18	79.6	57.7	10/49	28.3	93.0
0.19	79.6	61.5	10/49	30.2	93.5
0.20	75.5	64.5	12/49	30.8	92.6

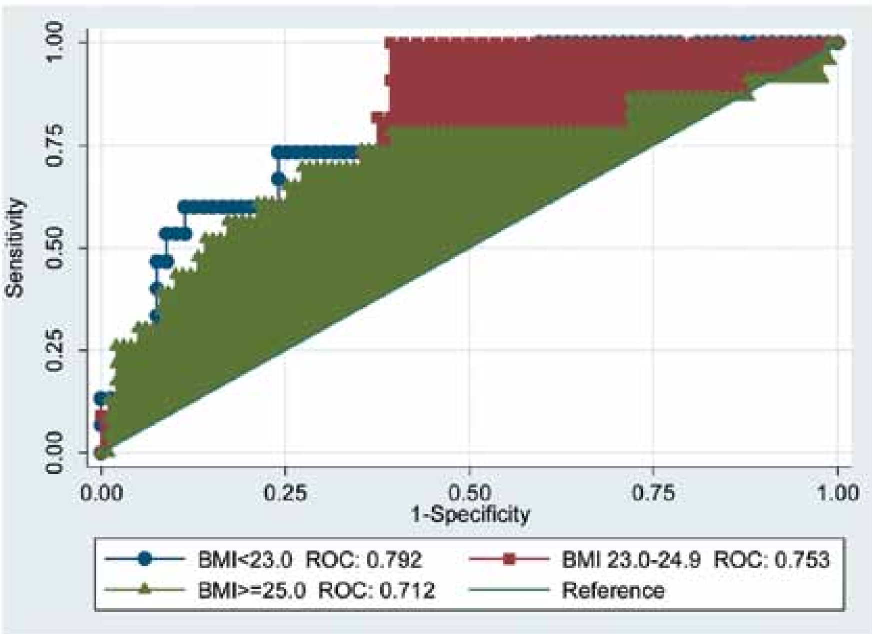


Fig. 2 Receiver operator characteristics (ROC) curves for PSAD predicting cancer status among normal weight, overweight, and obese men. (AUC area under the ROC curve, CI confidence interval)

	Normal weight (BMI<23 kg/m^2)	Overweight (BMI 23-24.9 kg/m^2)	Obese (BMI ≥25 kg/m^2)	*P*
AUC (95 % CI)	0.79 (0.67-0.91)	0.75 (0.63-0.87)	0.71 (0.57-0.85)	0.70

Table 4. Diagnostic performance of PSAD, when the standard cutoff point (0.15) is used, with respect to BMI groups. Note the unacceptable rate of undetected cancers that occur when PSAD are used for the obese.

BMI	Number	% Sensitivity	% Specificity	Cancers missed	No. Test positive (%)	No. Test negative (%)
Normal weight (BMI<23 kg/m^2)	94	100	36.7	0/15	65 (69.1)	29 (30.9)
Overweight (BMI 23-24.9 kg/m^2)	67	100	44.6	0/11	42 (62.7)	25 (37.3)
Obese (BMI ≥25 kg/m^2)	122	78.3*	51.5	5/23	66 (54.1)	56 (45.9)

For the obese patients, PSAD at the standard cutoff point of 0.15 had a sensitivity of only 78.3%, meaning that many cancers were not diagnosed. Therefore, PSAD at the standard cutoff point of 0.15 is not appropriate for the obese and should be adjusted to make the screenings more sensitive.

Diagnostic performance of PSAD with respect to multiple cutoff levels in the obese patients and new cutoff point.

After analyzing the diagnostic performance of PSAD in the obese patients, it was found that PSAD at the standard cutoff point of 0.15 had a sensitivity of only 78.3%. Changing the PSAD cutoff point to 0.06 made the sensitivity 100% (Table 5), resulting in 1 fewer prostate biopsy in 122 patients (0.8%).

Discussion

This research revealed that 17.3% of the patients whose PSA was in the diagnostic gray zone 4-10 ng/ml were diagnosed with cancer of the prostate (Table 1). This figure is in accordance with previous studies revealing that only 15-32% of the patients whose PSA was in the diagnostic gray zone 4-10 ng/ml were diagnosed with cancer of the prostate[1-4]. This information emphasizes that PSA in the diagnostic gray zone leads to many unnecessary prostate biopsies.

After analyzing ROC curves, it was found that predicting prostate cancer by using PSAD was significantly more accurate than by using PSA (Fig. 1). AUCs of PSAD and PSA were 0.75 and 0.53, respectively (*P* value <0.001). These figures are in accordance with a recent study in Thailand. That research also studied the patients whose PSA were in the diagnostic gray zone 4-10 ng/ml, and it was found that AUCs of PSAD and PSA were 0.78 and 0.43, respectively[4].

Because predicting prostate cancer by using PSAD is significantly more accurate than by using PSA, it indicates that PSAD may help reduce the number of unnecessary prostate biopsies when an appropriate cutoff point is used.

In this study, it was found that PSAD at the standard cutoff point of 0.15 has only 89.8% sensitivity, resulting in more than 10% of cancers going undetected (Table 3). Because PSAD has a low sensitivity, PSAD at the standard cutoff point of 0.15 is not appropriate for prostate cancer screenings; and, a new cutoff point that increases sensitivity should be found.

Table 5. Diagnostic performance of PSAD with respect to multiple cutoff levels in the obese patients. Note: at PSAD cutoff point 0.06, the sensitivity is 100%.

PSAD cutoff	% Sensitivity	% Specificity	Cancers missed	% Positive predictive value	% Negative predictive value
0.05	100	1.0	0/23	19.0	100
0.06	100*	1.0	0/23	19.0	100
0.07	91.3	2.0	2/23	17.8	50
0.08	91.3	4.0	2/23	18.1	66.7
0.09	91.3	7.1	2/23	18.6	77.8
0.10	91.3	12.1	2/23	19.4	85.7
0.11	87.0	18.2	3/23	19.8	85.7
0.12	82.6	28.3	4/23	21.1	87.5
0.13	78.3	34.3	5/23	21.7	87.2
0.14	78.3	46.5	5/23	25.4	90.2
0.15	78.3	51.5	5/23	27.3	91.1
0.16	73.9	61.6	6/23	30.9	91.0
0.17	69.6	64.6	7/23	31.4	90.1
0.18	69.6	66.7	7/23	32.7	90.4
0.19	69.6	71.7	7/23	36.4	91.0
0.20	60.9	74.7	9/23	35.9	89.2

After the diagnostic performance of PSAD in each BMI group was analyzed, it was found that PSAD at the standard cutoff point of 0.15 had 100%, 100%, and 78.3% sensitivity for normal weight, overweight, and obese patients, respectively (Table 4). Because PSAD at the standard cutoff point of 0.15 has 100% sensitivity, without missing any cancers, in normal weight and overweight patients, PSAD at the standard cutoff point is appropriate for prostate cancer screening in normal weight and overweight patients; and, using PSAD at the standard cutoff point led to 54 fewer prostate biopsies in 161 normal weight and overweight patients combined (33.5%).

After analyzing the diagnostic performance of PSAD in the obese patients (Table 5), it was found that PSAD at the standard cutoff point of 0.15 had only 78.3% sensitivity, meaning that more than 20% of the cancer patients were not diagnosed. Therefore, a standard cutoff point of 0.15 is not appropriate for the obese patients, and the cutoff point should be adjusted to make the screening more sensitive. In this study, it was found that a PSAD at a cutoff point of 0.06 made the sensitivity for the obese patients 100% (Table 5), and this cutoff point allowed for one fewer prostate biopsy in 122 obese patients (0.8%).

The fact that PSAD at the standard cutoff point of 0.15 tends to decrease the sensitivity in the obese patients (100%, 100%, and 78.3% in the normal weight, overweight, and obese patients, respectively), and tends to increase the specificity in the obese (36.7%, 44.6%, and 51.5% in the normal weight, overweight, and obese patients respectively) can be explained by the negative correlation between PSAD and BMI (coefficient = -0.141, P value = 0.018) (Table 2).

The negative correlation between BMI and PSAD leads to the obese patients (high BMI) tending to have lower PSAD than other people. Low PSAD made the test in the obese more negative (Table 4 : 30.9%, 37.3%, and 45.9% of test negative in the normal weight, overweight, and obese patients respectively), more false negative (Table 4: 0,0, and 5 undetected cancer in the normal weight, overweight, and obese patients respectively), and fewer sensitivity (Table 4 : 100%, 100%, and 78.3% of sensitivity in the normal weight, overweight, and obese patients respectively).

The tendencyofthe obese patients to have false negative results and a low sensitivity can be solved by decreasing the cutoff point for them. In this study, it was found that for the obese a cutoff point of 0.06 made the sensitivity 100%, and did not lead to any undetected cancers.

Conclusions:

Adjustment of the PSAD cutoff point according to BMI level, using PSAD at cutoff point 0.15 for normal weight and overweight patients and 0.06 for obese patients, reduced prostate biopsies for 55 of 283 patients (19.4%), without reducing the sensitivity of prostate cancer screening for the patients in the PSA diagnostic gray zone 4-10 ng/ml.

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