

# PSA Density and Prostate Cancer Detection

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**Objective:** To evaluate the diagnostic value of prostate-specific antigen density (PSAD) and the appropriate cutoff for the detection of prostate cancer.

**Material and Method:** Between January 2008 and March 2011, 292 men with PSA levels between 4 and 10 ng/mL underwent Transrectal Ultrasonography (TRUS) with prostate biopsy. The diagnostic value of PSA levels and PSAD were compared using receiver operating characteristic curves.

**Results:** Prostate cancer was diagnosed in 64 (22%) of the 292 men who had PSA levels 4 to 10 ng/mL. The mean PSA level was 6.96 ng/mL. The mean age was 66 years. The area under the curve (AUC) of PSA and PSAD were 0.475 and 0.665, respectively. The sensitivity and specificity of PSAD at cutoff of 0.15 was 78% and 43%, respectively.

**Conclusion:** PSAD was a better discriminator of prostate cancer than PSA for PSA levels less than 10 ng/ml. Our data suggested that a different PSAD cutoff than previously recommended need to be defined for Thai people.

**Keywords:** Prostate cancer; Prostate specific antigen density

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Prostate cancer is recognized as one of the most important medical problems in the male population<sup>(1)</sup>. Data from Ramathibodi Hospital showed that about 26% of patients who underwent prostate biopsy had histological proof of prostate cancer<sup>(2)</sup>. Serum prostate antigen (PSA) test is the only accepted screening tool available. However, it is organ specific and not cancer-specific, making cancer discrimination difficult. A PSA level of 4.0 ng/mL has been used as the threshold for considering prostate biopsy, and several measures have been proposed to improve the specificity of the PSA test, including PSA density (PSAD), PSA velocity (PSAV) and free-to-total PSA ratio. Zheng et al<sup>(3)</sup> reported that prostate cancer was diagnosed in 19% of 237 men who had PSA levels between 4 and 10 ng/mL. PSAD was a better predictor of prostate cancer in these patients. Ghafoori et al<sup>(4)</sup> also reported that PSAD increased the accuracy in detecting prostate cancer.

The present study was designed to evaluate the diagnostic value of PSAD and to find the appropriate cutoff value for the detection of prostate cancer.

## Material and Method

Between January 2008 and March 2011, 327 men with total PSA levels between 0 and 10 ng/mL underwent Transrectal Ultrasonography (TRUS) with prostate biopsy. These men were part of a group of 660 men, with PSA levels of 0 to 10,489 ng/mL, who had prostate biopsies at our hospital (*i.e.* those with PSA levels of  $\geq 4$  ng/mL, or with abnormal digital rectal examination findings, defined as nodular, irregular or hard consistency prostate) in the same period. Prostate volume was estimated by TRUS. The PSAD was calculated as PSA (ng/mL) divided by the prostate volume (mL). The research project was approved by the Ethics Committee of Ramathibodi Hospital, which conformed to the provisions of the Declaration of Helsinki (as revised in Edinburgh, 2000).

Prior to prostate biopsy, all patients were given antibiotic prophylaxis, which was continued for three days. Prostate biopsies were performed with 12 cores taken from both lobes under TRUS guidance,

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two specimens were obtained from the base of the prostate gland of each side, two from the apex, and two from middle of the gland. Biopsy specimens were reviewed by experienced pathologists.

### Statistical analysis

The statistical analyses were performed using Stata v.9 software (Stata Corp, TX, USA). Continuous variables from different groups with and without prostate cancer were summarized as mean  $\pm$  standard deviation. Comparisons between variables (age, prostate volume, PSA and PSAD) were done using Student's t-test. The receiver operating characteristic curve (ROC) area under the curve (AUC) was used for evaluating the accuracy of PSA and PSAD in the prediction of cancer. AUCs derived from the same sample were compared using the method DeLong, DeLong and Clarke-Pearson as implemented in Stata. P-values less than 0.05 were considered statistically significant.

### Results

Between January 2008 and March 2011, 660 men underwent prostate biopsy. Of these, 204 (31%) were found to have prostate cancer based on biopsy specimens. The mean age was 67.6 years. The median serum PSA was 10.1 ng/mL. The median prostate volume was 44.9 mL. The median PSAD was 0.17. The prevalence of prostate cancer is shown in Table 1, for various ranges of PSA values. The prevalence was 11% (4/35) in men with PSA levels less than 4 ng/mL, 22% (64/292) in men with PSA levels between 4 and 10 ng/mL, and 41% (136/333) in men with PSA levels more than 10 ng/mL. In all, 327 men had PSA levels between 0-10 ng/dL.

Of the 327 men with PSA levels between 0 and 10 ng/mL, the mean age was 66.3 years, the median serum PSA and PSAD value were 6.5 ng/mL and 0.16, respectively. The diagnosis of prostate cancer was made in 68 (21%) men. The median prostate volume was 39.3 mL. The characteristics of patients with PSA levels less than 10 ng/mL are shown in Table 2.

The ROC curves and analysis showed that both PSA and PASD were fair discriminators of prostate cancer for PSA levels less than 10 ng/ml, and PSAD was a better discriminator than PSA. The AUC values for PSA and PSAD were 0.509 and 0.670, respectively.

In all, 151 men underwent digital rectal examination (DRE); 16 of 54 men (30%) with abnormal DRE were detected as having prostate cancer.

From Table 3, PSA level was a good discriminator of prostate cancer when PSA levels were greater than 10 ng/ml (see below).

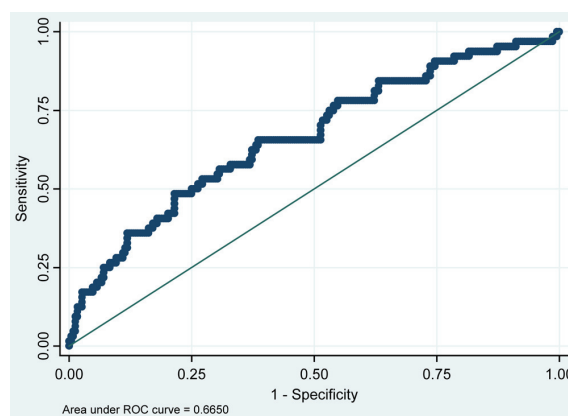
The characteristics of patients with PSA between 4 and 10 ng/mL are shown in Table 4. There were 292 men with a mean age of 66.0 years, median serum PSA and PSAD of 6.96 ng/mL and 0.19, respectively. The diagnosis of prostate cancer was made in 64 (22%) men. The median prostate volume was 44.8 mL.

The ROC curve and analysis showed that PASD was a fair discriminator for prostate cancer for PSA levels between 4 and 10 ng/ml (Fig. 1). The AUC of PSAD was 0.665. The sensitivity and specificity of PSAD are shown in Table 5. The PSAD cut-off value of 0.15 was associated with a sensitivity of 78% and a specificity of 43% in the present study.

After adjusting for the effect of PSA density, the age, prostate volume, DRE findings and the free-to-total PSA ratio were not significantly associated with the detection or diagnosis of prostate cancer in patients with PSA between 4 to 10 ng/mL (see Table 6).

### Discussion

The prevalence of prostate cancer increased with the PSA level as expected (Table 1), with an overall prevalence of 31%. The prevalence was 22% (64/292) in men with PSA levels between 4 and 10 ng/mL. Statistical analyses showed that PSA level would be a good discriminator of prostate cancer if it were greater than 10 ng/ml. PSAD was a better discriminator for prostate cancer than PSA for PSA levels less than



**Fig. 1** Receiver operating characteristic (ROC) curve for PSA density in detecting prostate cancer, for PSA 4 to 10 ng/mL (n = 292)

**Table 1.** Characteristics of all patients who underwent prostate biopsy

Characteristics	Summary (n = 660, unless stated otherwise)
Age (years): mean (SD)	67.6 (7.9)
Serum PSA (ng/mL): median (range)	10.1 (0.62 to 10,489)
Prostate cancer prevalence	
Overall (n = 660; 100%)	204/660 (31%)
PSA < 4 (n = 35; 6%)	4/35 (11%)
PSA ≥ 4 & ≤ 10 (n = 292; 44%)	64/292 (22%)
PSA > 10 (n = 333; 50%)	136/333 (41%)
Proportion with missing PSA density data	293/660 (44%)
Prostate volume (mL): median (range) (n = 367)	44.9 (8.1 to 144)
PSA density: median (range) (n = 367)	0.17 (0.01 to 6.23)
Gleason score for prostate cancer: mean (SD) (n = 200)	6.86 (1.2) (range: 3 to 10)

**Table 2.** Characteristics of patients with PSA ≤ 10 ng/ml and the discriminatory abilities of PSA and PSA density with respect to prostate cancer detection/diagnosis

Characteristics	Summary (n = 327, unless stated otherwise)
Age (years): mean (SD)	66.3 (7.5)
Serum PSA (ng/mL): median (range)	6.5 (0.62 to 10)
Prostate cancer prevalence	68/327 (21%)
Prostate volume (mL): median (range)	39.3 (8.1 to 135)
PSA density (PSAD): median (range)	0.16 (0.01 to 0.71)
Area under the ROC curve (AUC) for PSA: mean (SE)	0.509 (0.038)*
Area under the ROC curve (AUC) for PSAD: mean (SE)	0.670 (0.038)*
Area under the ROC curve for PSAD < 4 ng/mL (n = 35)	0.723 (0.105)
Area under the ROC curve for PSAD between 4-10 ng/mL (n = 292)	0.665 (0.040)
Abnormal per rectum exam (hard, nodular, irregular) (n = 151)	54/151 (36%)
CaP in Abnormal DRE (n = 54)	16/54 (30%)
Free-to-total PSA ratio: median (range) (n = 67)	0.15 (0.06 to 0.39)
Gleason score for prostate cancer: mean (SD) (n = 68)	6.20 (0.8) (range: 3 to 10)

\* The AUC difference between PSA and PSAD is statistically significant, with approximate Chi-square p-value < 0.001; SE: standard error

**Table 3.** Discriminatory ability of PSA with respect to prostate cancer diagnosis

Classification variable	Area under ROC curve (SE)
PSA, all observations (n = 660)	0.700 (0.024)
PSA, for PSA > 10 ng/mL (n = 333)	0.782 (0.027)
PSA, for PSA ≤ 10 ng/mL (n = 327)	0.509 (0.038)

SE: standard error

10 ng/mL (Table 2). However, the discriminatory ability of PSAD was moderately good (area under ROC curve = 0.67). Zheng et al<sup>(3)</sup> reported that prostate cancer was diagnosed in 19% of the 237 Chinese men who had

PSA levels between 4 and 10 ng/mL, and PSAD was a better predictor of prostate cancer, while Ghafoori et al<sup>(4)</sup> also reported that PSAD increased the accuracy in detecting prostate cancer.

For PSA levels between 4 and 10 ng/mL, the discriminatory ability of PSAD was also moderately good (area under ROC curve = 0.665; Table 4). The PSAD cut-off value of 0.15 was associated with a sensitivity of 78% and a specificity of 43% in the present study. A study by Kotb et al<sup>(5)</sup> reported that although a low PSAD (< 0.15) might suggest an insignificant risk of prostate cancer, PSAD might be used as an additional clinical marker of indolent disease, as shown by future PSAV values and repeat biopsy over time. Lam et al<sup>(6)</sup> reported that the PSAD

**Table 4.** Characteristics of patients with PSA 4 to 10 ng/mL, and cancer-discriminating properties of PSA and PSAD

Characteristics	Summary (n = 292, unless stated otherwise)
Age (years): mean (SD)	66.0 (7.4)
Serum PSA (ng/mL): median (range)	6.96 (4.03 to 10)
Prostate cancer prevalence	64/292 (22%)
Prostate volume (mL): median (range)	44.8 (8.1 to 120)
PSA density (PSAD): median (range)	0.19 (0.04 to 0.71)
Gleason score for prostate cancer: mean (SD) (n = 64)	6.17 (0.78) (range: 3 to 10)
Abnormal per rectum exam (hard, nodular, irregular) (n = 129)	33/129 (26%)
Serum free PSA (ng/mL): median (range) (n = 67)	0.99 (0.06 to 3.84)
Free-to-total PSA ratio: median (range) (n = 67)	0.15 (0.06 to 0.39)
Area under the ROC curve (AUC) for PSA: mean (SE)	0.475 (0.041)*
Area under the ROC curve (AUC) for PSAD: mean (SE)	0.665 (0.040)*

\* The AUC difference between PSA and PSAD is considered statistically significant, with approximate Chi-square p-value < 0.001; SE: standard error

**Table 5.** Cut off values of PSA density and their sensitivities and specificities in detecting prostate cancer, for PSA 4 to 10 ng/mL (n = 292)

PSA density cutoff value	Sensitivity (%)	Specificity (%)	Correct classification (%)
0.05	98.4	44.0	22.3
0.1	93.8	14.9	32.2
0.15	78.1	43.0	51.0
0.2	53.1	71.5	67.5
0.25	35.9	85.1	74.3
0.3	25.0	92.1	77.4
0.4	12.5	97.4	78.8
0.5	6.3	98.7	78.4

**Table 6.** Factors associated with prostate cancer, adjusted for log PSA density, for PSA between 4 and 10 ng/mL; multiple logistic regression

Factor (sample size)	Odds ratio (95% confidence interval)	p-value
Age (n = 292)	1.01 per year increase (0.97 to 1.05)	0.560
Prostate volume (mL) (n = 292)	0.98 per unit increase (0.95 to 1.01)	0.201
Abnormal per rectal exam (yes) (n = 129)	1.93 (0.80 to 4.70)	0.144
Free-to-total PSA ratio (n = 67)	0.96 per percent increase (0.87 to 1.06)	0.421

cutoff of 0.15 was recommended in earlier studies, which spared 50% of these patients from unnecessary biopsies. But Catalona et al<sup>(7)</sup> found that half the tumors were missed by using a PSAD cutoff point of more than 0.15. Thus, Lotfi et al<sup>(8)</sup> suggested that a PSAD cutoff of 0.15 was not inclusive enough in patients with PSA levels between 4 and 10 ng/mL, and we proposed a PSAD cutoff of 0.1 as a better threshold.

Cao et al<sup>(9)</sup> reported that in China the sensitivity and specificity of PSAD at a cutoff 0.13 was 92% and 47%, respectively. Therefore, they suggested that PSAD at this cutoff was a good predictor of prostate cancer. A study by Zhao et al<sup>(10)</sup> found the sensitivity and specificity of PSAD at a cutoff of 0.10 to be 100% and 11%, respectively, although Yamamoto et al<sup>(11)</sup> found that the cancer detection rate in Japanese patients with PSAD of less than 0.10 was

only 6%. In our study, to increase sensitivity, the PSAD cut-off value should be lowered to 0.1, in which case the sensitivity would increase to 94% but the specificity would be lowered to 15% (Table 5).

On multivariable logistic regression analysis, after adjusting for the effects of PSA density, no other factors (age, prostate volume, DRE findings, or free-to-total PSA ratio) were significantly associated with the detection or diagnosis of prostate cancer in patients with PSA between 4 and 10 ng/mL.

### Conclusion

PSA level was found to be a good discriminator of prostate cancer when PSA levels were greater than 10 ng/mL, but PSAD was a better discriminator of prostate cancer than PSA for PSA levels less than 10 ng/mL. The discriminatory ability of PSA density was only moderately good, however. Our data suggested that a different PSAD cutoff value other than 0.15, such as 0.1, would probably be needed for Thai people.

### Potential conflicts of interest

None.

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## PSA Density และการตรวจหามะเร็งต่อมลูกหมาก

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**วัตถุประสงค์:** เพื่อประเมินความสามารถของ PSAD และค่า PSAD ที่เหมาะสมในการช่วยตรวจหามะเร็งต่อมลูกหมาก  
**วัสดุและวิธีการ:** รวบรวมข้อมูลย้อนหลังตั้งแต่เดือน มกราคม พ.ศ. 2551 ถึง มีนาคม พ.ศ. 2554, ผู้ป่วยชายจำนวน 292 คน ที่มีค่า PSA ระหว่าง 4 ถึง 10 ng/mL ที่ได้รับการตรวจชิ้นเนื้อต่อมลูกหมากด้วยวิธี transrectal ultrasonography with prostate biopsy ในโรงพยาบาลรามาริบัติ ประเมินความสามารถของ PSA, PSAD และค่า PSAD ที่เหมาะสมในการช่วยตรวจหามะเร็งต่อมลูกหมาก

**ผลการศึกษา:** พบมะเร็งต่อมลูกหมากในผู้ป่วย 64 คน จากทั้งหมด 292 คน ที่มีค่า PSA ระหว่าง 4 ถึง 10 ng/mL คิดเป็นร้อยละ 22 ค่า PSA เฉลี่ยคือ 6.96 ng/mL มีอายุเฉลี่ย 66 ปี ค่า PSAD ที่ 0.15 จะมี sensitivity และ specificity เท่ากับร้อยละ 78 และร้อยละ 43 ตามลำดับ

**สรุป:** PSAD มีความสามารถช่วยตรวจหามะเร็งต่อมลูกหมากได้ดีในช่วง PSA น้อยกว่า 10 ng/mL ค่า PSAD ที่เหมาะสมจะมีค่า sensitivity และ specificity ที่แตกต่างกันไป

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