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Re-Examining PSA Density: Defining the Optimal PSA Range and Patients for Using PSA Density to Predict Prostate Cancer Using Extended Template Biopsy

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CONFLICT OF INTEREST

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ABSTRACT:

OBJECTIVES: To compare the predictive accuracy of PSA density versus PSA across different PSA ranges and by prior biopsy status in a prospective cohort undergoing prostate biopsy.

METHODS: Men from a prospective trial underwent an extended template biopsy to evaluate for prostate cancer at 26 sites throughout the US. The area under the receiver operating curve assessed the predictive accuracy of PSA density versus PSA across three PSA ranges (<4, 4–10, >10 ng/mL). We also investigated the effect of varying the

PSA density cut-offs on the detection of cancer and assessed the performance of PSA density versus PSA in men with or without a prior negative biopsy.

RESULTS: Among 1,290 patients, 585 (45%) and 284 (22%) men had prostate cancer and significant prostate cancer, respectively. PSA density performed better than PSA in detecting any prostate cancer within a PSA between 4-10 ng/ml (AUC: 0.70 vs. 0.53, P<0.0001) and within a PSA >10 mg/ml (AUC: 0.84 vs. 0.65, P<0.0001). PSA density was significantly more predictive than PSA in detecting any prostate cancer in men without (AUC: 0.73 vs. 0.67, P<0.0001) and with (AUC: 0.69 vs 0.55, P<0.0001) a previous history of previous biopsy; however, the incremental difference in AUC was higher among men with a previous negative biopsy. Similar inferences were seen for significant cancer across all analyses.

CONCLUSIONS: As PSA increases, PSA density becomes a better marker for predicting prostate cancer compared to PSA alone. Additionally, PSA density performed best against PSA in men with a prior negative biopsy.

Keywords: PSA Density, Prostate Specific Antigen Density, AUC, Prior Negative Biopsy, Prostate Cancer, Extended Template Biopsy

INTRODUCTION

More than one million men undergo prostate biopsies in the United States annually, with the majority revealing no prostate cancer or low-risk prostate cancer that is unlikely to impact survival.[1] Substantial financial and emotional costs have resulted from the overuse of prostate biopsies.[2,3] An increased risk of medical complications, including pain, bleeding, and sepsis are also associated with prostate biopsies.[4] This has resulted in a need to optimize the utilization of prostate-specific antigen (PSA) testing to reduce the number of unnecessary biopsies and to minimize the harms of over-diagnosis and the over-treatment that follows.[5,6]

Since its inception, studies investigating PSA density have yielded mixed results regarding its utility for prostate cancer prediction.[7–11] Initial investigations showed that PSA density had a better sensitivity and specificity than PSA.[7,9] This is supported by its incorporation into several risk prediction tools and clinical nomograms.[12–14] However, other studies suggest that PSA density adds very little incremental value compared to PSA alone,[10,11] and is only useful in the setting of an abnormal PSA or DRE.[11,15,16] Of note, most of the PSA density literature is older and based on outcomes from sextant biopsy, which are unlikely to generalize to contemporary practice where extended template biopsies are routine.[7–11,17]

PSA density has been investigated within a select PSA range, limiting discoveries about the performance of PSA across a complete spectrum of PSA values. As a result of these limitations, we re-examined the role of PSA density and compared it to PSA for the detection of prostate cancer in a prospective, and contemporary, cohort of men who were undergoing extended template biopsy of the prostate for evaluation of

prostate cancer. Specifically, we looked at the performance of PSA density compared to PSA across a wide range of PSA values, and among men with and without a previous negative biopsy.

MATERIAL AND METHODS

Study cohort

The data used for the study was extracted from a prospective, multi-institutional trial initially conducted to investigate the role of a novel biomarker, the 4Kscore, for detecting aggressive prostate cancer across 26 urological centers in the USA between October 2013 and April 2014. All men were referred for a prostate biopsy for suspicion of prostate cancer by a urologist. Every patient underwent a digital rectal examination (DRE) and a trans-rectal ultrasound (TRUS) guided extended template biopsy with a minimum of ten cores. A blood sample was collected immediately prior to biopsy and all samples were shipped to the OPKO laboratory in Nashville, Tennessee, where PSA measurements were ascertained. There were no exclusion based on PSA, and a wide variety of PSA ranges were included in this trial. Prostate volume was measured on TRUS during the biopsy using the formula for an ellipsoid shape.[18] PSA density values were calculated by dividing the total PSA by the prostate volume. Histopathological examination of biopsy specimens were performed according to the established standards at each study site. Significant prostate cancer was defined by a Gleason score of ≥7. All men provided written and informed consent under central and site specific institutional review board approval for participation in this study.

Statistical analysis

A total of 1,370 men were enrolled in the study. Of these participants, 58 were excluded because of delayed shipping of phlebotomy samples and non-adherence to the inclusion and exclusion criteria. In addition, 22 men were excluded because they did not have a reported prostate volume. The performance of PSA density for detecting any prostate cancer and significant prostate cancer was compared to PSA across 3 different PSA ranges (<4, 4 – 10, and >10 ng/mL) using the area under the receiver operating characteristic curve (AUC). The demographic and clinical differences between patients with PSA levels of <4, 4 – 10, and >10 ng/mL were compared using the Kruskal-Wallis test for continuous variables and a chi-square test for categorical variables. Additionally, various PSA density cut-offs were explored to determine the detection rate of any and significant prostate cancer, as well as the number of biopsies avoided and cancers missed. Finally, we used AUC to compare the performance of PSA density and PSA in men who did and did not undergo a previous negative biopsy. All analyses were performed using Stata 12.0 (Stata Corp., College Station, TX, USA).

RESULTS

As of April 2014, a total of 1,290 men formed the final study cohort. Table 1 represents the demographics and the clinical characteristics of the cohort stratified according to PSA ranges. 438 (34%), 725 (56%), and 127 (10%) men had PSA values of <4, 4 – 10, and >10 ng/mL, respectively. 144 (33%), 361 (50%) and 80 (63%) men were diagnosed with any prostate cancer, while 44 (10%), 177 (24%), and 63 (50%)

men were diagnosed with significant prostate cancer within the PSA ranges of <4, 4 – 10, and >10 ng/mL, respectively. Men with prostate cancer were older, had a higher PSA, and had a lower rate of prior negative biopsies compared to those without prostate cancer. The median prostate volume for patients with PSA values of <4, 4 – 10, and >10 ng/mL was 36 (IQR 27 - 51), 46 (IQR 35 – 65) and 50 (35 - 65) cc, respectively (P < 0.0001).

PSA density was significantly more predictive of any and significant prostate cancer when compared to PSA alone in all patients with a PSA >4 ng/mL. In the PSA range of 4 – 10 ng/mL, the AUC of PSA density was significantly greater than that of PSA for any prostate cancer (AUC: 0.70 vs. 0.53, P < 0.0001) and significant prostate cancer (AUC: 0.72 vs. 0.57, P < 0.0001) (Table 2). Similarly, for patients with a PSA >10 ng/mL, the AUC of PSA density was significantly greater than that of PSA for any prostate cancer (AUC: 0.84 vs. 0.65, P < 0.0001) and significant prostate cancer (AUC: 0.82 vs. 0.68, P < 0.0001) (Table 2). However, for men with a PSA <4 ng/ml, we found no significant difference between PSA density and PSA for detecting any prostate cancer (P = 0.63) or significant prostate cancer (P = 0.23).

In Table 3, we looked at the impact of various PSA density cut-offs to decide on the need for biopsy and found that increasing the PSA density cut-off from 0.05 to 0.20 ng/mL/cc resulted in an increased number of biopsies avoided, but at the expense of more cancers being missed. Using a PSA density cut-off of ≥0.15 ng/ml/cc, which has been cited in the literature,[19] 932 (72%) men could be spared a biopsy. However, 329 (56%) and 117 (41%) men would be missed with any and significant prostate cancer, respectively.

PSA density performed better than PSA for detecting prostate cancer in both men who had a previous negative biopsy (AUC 0.69 vs 0.56, P = 0.0001) and those who did not (AUC 0.72 vs 0.67, P = 0.0001) (Figure 1). The same trend was observed for the discrimination of significant prostate cancer, where PSA density outperformed PSA in men who had a previous negative biopsy (AUC 0.81 vs 0.70, P = 0.0042) and those who did not (AUC 0.77 vs 0.73, P = 0.0026). The enhanced predictive accuracy of PSA density over PSA was more pronounced in men that had a prior negative biopsy, compared to those that were biopsy-naïve, for both any prostate cancer (ΔAUC 0.13 vs 0.05) and significant prostate cancer (ΔAUC 0.11 vs 0.04).

COMMENT AND CONCLUSIONS

Screening for prostate cancer using PSA remains a controversial topic, due to its relatively low specificity and the subsequent over diagnosis and overtreatment that invariably ensues. The European Randomized Study of Screening for Prostate Cancer (ERSPC) trial found that although screening with serum PSA afforded a modest reduction in prostate cancer mortality, it resulted in an overwhelmingly large number of men undergoing invasive testing before one life could be saved from prostate cancer death.[20] While it is clear that serum PSA has many limitations for prostate cancer screening, various PSA derivatives have been shown to enhance the performance of PSA for detecting prostate cancer.[21,22] PSA density is one of these derivatives, which adjusts the value of the PSA for the size of the prostate. The PSA density literature is largely based on older practices that did not completely use the current standard of extended template biopsy.[23] Though these results were encouraging, they may not

apply to contemporary practice today.[17] Therefore, we evaluated the performance of PSA density in a prospective and contemporary cohort of men undergoing extended template biopsy of the prostate.

Previous studies have also compared the sensitivity and specificity of PSA density to PSA within discrete PSA ranges. Within a referred population of 3,140 patients, Benson et al. was the first to demonstrate the improved performance of PSA density compared to PSA for differentiating between prostate cancer from BPH within the ranges of 4.1-10 ng/mL and 10.1-20 ng/mL.[7] In another retrospective review of 1809 men referred for having an abnormal prostate cancer screen, Stephan et al. found that at 90 and 95% sensitivity, PSA density detected prostate cancer significantly better than total PSA at a variety of ranges (2-4 ng/mL, 2-10 ng/mL, 4-10 ng/mL, 2-20 ng/mL, 10-20 ng/mL).[24] This same study also found that the ROC analysis for PSAD ran significantly above the total PSA curve within each of these PSA ranges.[24] Although this study did not publish its findings above 20 ng/mL, it was reported that prostate volume had a significantly positive correlation with PSA for those with BPH and those with prostate cancer.[24] The high PSA values associated with large volume prostates often result in unnecessary biopsies for continued suspicion of prostate cancer, even though their PSA level is appropriate for their prostate volume. Our results highlight the utility of PSA density by performing best in the AUC analysis for detecting both any and significant prostate cancer at PSA levels above 10 ng/mL. Although more recent retrospective reviews have noted better AUC results for PSA density compared to PSA across the full PSA range, these studies did not report the isolated performance of PSA density in the highly suspicious range of PSA >10 ng/mL,[23] where this test is perhaps most useful.

By being a highly specific test at elevated PSA levels, PSA density becomes an essential tool for avoiding unnecessary biopsies. Stephan et al. had also noted that the number of suspicious DRE results decreased significantly with increasing prostate volume in patients with prostate cancer.[24] With less of an indication to biopsy large volume prostate patients who may have an appropriately elevated PSA, PSA density emerges as a crucial diagnostic test to prevent cancer due to its enhanced sensitivity in these patients. PSA density's improved specificity and sensitivity better differentiates patients who have a benign elevation in PSA and those who have an inconspicuous cancer.

The first study to explore various PSA density cut-offs on the detection of prostate cancer established 0.15 ng/ml/cc as the best threshold to optimize cancer detection for men with a PSA between 4.1 – 10 ng/mL.[19] Most studies on PSA density cut-offs have shown that higher thresholds afford more biopsies to be avoided, but at the expense of more missed cancer[11,15,16] – similar to what we saw in this trial. In accordance with prior findings, we also found that a cut-off between 0.15-0.20 ng/ml/cc allowed the lowest number needed to biopsy to detect one cancer; however, this strategy missed an unacceptable number of significant cancers (41%-58%, respectively). Rather than a fixed PSA density cut-off value to apply to all men, we propose the use of a continuous score that is tailored to the individual goals and values of each patient relative to the concerns of a missed cancer versus the fear of an unnecessary biopsy. For example, in an elderly patient with many comorbidities, a high cut-off like 0.20 ng/ml/cc may be appropriate to avoid the detection and treatment of an indolent cancer. In relatively young, healthy males, a low PSA density cut-off like 0.05

ng/ml/cc may be more appropriate to allow the lowest chance of missing a significant prostate cancer (4%).

Our study found that the incremental gain in performance between PSA density and PSA was highest in men who had a prior negative biopsy, suggesting that the best improvement in cancer detection was found in this population. With prostate cancer detection rates between 10% and 35% on rebiopsy,[25] a more specific test would save many patients from a likely negative biopsy. These results are in line with other studies that found PSA density to be a better predictor of prostate cancer than other PSA derivatives in patients with a PSA 4 – 10 ng/mL and a prior negative biopsy.[21,26] However, with these studies being based on a sextant biopsy scheme, it is not clear that this would generalize to men undergoing an extended template biopsy, as previous studies have suggested big differences in cancer detection between the two biopsy approaches.[17] To our knowledge, this is the first study to confirm a much better performance of PSA density over PSA in men with a previous negative biopsy. Men with a large prostate, who are likely to have an elevated PSA, are often biopsied more than once. Our results confirm that PSA density would allow much more men whose PSA values, while elevated, are appropriate for their gland size, to avoid an unnecessary biopsy of the prostate. Given these men have already undergone a previous biopsy, an accurate assessment of prostate volume should readily be available for calculation of PSA density.

Although PSA density has been well-investigated in the past, our study is one of the few to use an extended template biopsy scheme within a contemporary cohort of patients to yield results that are more generalizable to clinical practice today. Similarly,

patients were prospectively accrued, while many prior studies were retrospective and limited to selection bias. Perhaps the most significant limitation to this study is that histopathological examination of biopsy specimens and prostate volume measurements on TRUS biopsy were not standardized across locations. While this may lead to differences solely due to the interpretation, the resultant variability is likely small, since study sites followed current national standards and guidelines. Another limitation is that there were no standardized criteria applied for the referral of patients for biopsy. However, this may make the results more generalizable to clinical practice, where prostate biopsy is a joint decision between the patient and the physician.

PSA density proved to be a more sensitive and specific test than PSA in detecting insignificant and significant prostate cancer in PSA levels >4 ng/mL, performing best in PSA levels >10 ng/mL. PSA density also performed best against PSA in patients who had a prior negative biopsy, preventing this patient population from unnecessarily being subjected to repetitive, invasive testing. While screening for prostate cancer with serum PSA can result in an alarming number of men to undergo unnecessary testing, the use of PSA density helps avoid biopsies in men whose PSA may be elevated, but appropriate for the size of the prostate.

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Figure 1a: AUC of PSA vs PSA density without prior negative biopsy detecting any prostate cancer

AUC comparing PSA and PSA density in men without prior negative biopsy for the discrimination of any prostate cancer.

Figure 1b: AUC of PSA vs PSA density with prior negative biopsy detecting any prostate cancer

AUC comparing PSA and PSA density in men with a prior negative biopsy for the discrimination of any prostate cancer.

Table 1: Patient demographics and clinical variables among the patients in the cohort by PSA level.

	PSA < 4 ng/mL 438 (34)	PSA 4 – 10 ng/mL 725 (56)	PSA > 10 ng/mL 127 (10)
Median (Interquartile Range)			
Age at Blood Draw (yrs)	63 (56 - 68)	64 (60 - 69)	67 (61 - 73)
PSA (ng/mL)	2.8 (1.7 - 3.5)	5.5 (4.6 - 6.8)	13.7 (11.3 - 19.8)
TRUS-Estimated Prostate Volume (cc)	36 (27 - 51)	46 (35 - 65)	50 (35 - 65)
PSA Density (ng/mL/cc)	0.06 (0.04 - 0.09)	0.12 (0.09 - 0.17)	0.31 (0.21 - 0.56)
Number (%)			
Ethnicity			
Caucasian	380 (87)	637 (88)	100 (79)
African - American	31 (7)	53 (7)	20 (16)
Hispanic	21 (4.5)	20 (3%)	6 (4.5)
Other	4 (1)	11 (1.5)	1 (0.5)
Unknown	2 (0.5)	4 (0.5)	0 (0)
Abnormal DRE	146 (33)	146 (20)	31 (24)
Prior Negative Biopsy	44 (10)	161 (22)	40 (31)
Any Prostate Cancer	144 (33)	361 (50)	80 (63)
Biopsy Gleason Grade			
6	100 (23)	184 (25)	17 (13)
3+4	23 (5.3)	97 (13)	16 (13)
4+3	12 (2.7)	43 (5.9)	18 (14)
8	7 (1.6)	24 (3.3)	12 (9.4)
9	1 (0.2)	11 (1.5)	16 (13)
10	1 (0.2)	2 (0.3)	1 (0.8)

PSA = prostate-specific antigen; PSA density = PSA density; DRE = digital rectal examination; TRUS = trans-rectal ultrasound; continuous data are presented as median (interquartile range) and categorical data as *n* (%)

Table 2: Discrimination of any and significant prostate cancer comparing PSA vs PSA density within the PSA ranges of 4 – 10 and >10 ng/mL

		PSA (AUC, 95% CI)	PSA density (AUC, 95% CI)	ΔAUC (PSA density – PSA)	p value
PSA <4 ng/mL	Any prostate cancer	0.64 (0.58, 0.69)	0.62 (0.57, 0.68)	-0.02	0.6344
	Significant prostate cancer	0.70 (0.62, 0.77)	0.64 (0.56, 0.72)	-0.06	0.2327
PSA 4 – 10 ng/mL	Any prostate cancer	0.53 (0.49, 0.57)	0.70 (0.66, 0.74)	+0.17	<0.0001
	Significant prostate cancer	0.57 (0.52, 0.62)	0.72 (0.68, 0.77)	+0.15	<0.0001
PSA >10 ng/mL	Any prostate cancer	0.65 (0.56, 0.75)	0.84 (0.77, 0.91)	+0.19	<0.0001
	Significant prostate cancer	0.68 (0.58, 0.77)	0.82 (0.75, 0.89)	+0.14	<0.0001

AUC = area under the receiver operating characteristic curve; CI = confidence interval; PSA = prostate-specific antigen; PSA density = PSA density;

Table 3: Detection of any and significant prostate cancer and the effect on biopsies using various PSA density cut-off values

PSA density cut-off	Any prostate cancer found N (%)	Any prostate cancer missed N (%)	Significant prostate cancer found N (%)	Significant prostate cancer missed N (%)	Biopsies that could be avoided N (%)	Number needed to biopsy
Not using PSAD	585 (100)	0 (0)	284 (100)	0 (0)	0 (0)	-
≥0.05	537 (92)	48 (8)	273 (96)	11 (4)	191 (15)	2.1
≥ 0.10	394 (67)	191 (33)	227 (80)	57 (20)	630 (49)	1.7
≥ 0.15	256 (44)	329 (56)	167 (59)	117 (41)	932 (72)	1.4
≥ 0.20	169 (29)	416 (71)	118 (42)	166 (58)	1072 (83)	1.3