Re-examining Prostate-specific Antigen (PSA) Density: Defining the Optimal PSA Range and Patients for Using PSA Density to Predict Prostate Cancer Using Extended Template Biopsy

Joshua S. Jue, Marcelo Panizzutti Barboza, Nachiketh S. Prakash, Vivek Venkatramani, Varsha R. Sinha, Nicola Pavan, Bruno Nahar, Pratik Kanabur, Michael Ahdoot, Yan Dong, Ramgopal Satyanarayana, Dipen J. Parekh, and Sanoj Punnen

OBJECTIVE To compare the predictive accuracy of prostate-specific antigen (PSA) density vs PSA across different PSA ranges and by prior biopsy status in a prospective cohort undergoing prostate biopsy.

MATERIALS AND METHODS Men from a prospective trial underwent an extended template biopsy to evaluate for prostate cancer at 26 sites throughout the United States. The area under the receiver operating curve assessed the predictive accuracy of PSA density vs PSA across 3 PSA ranges (<4 ng/mL, 4-10 ng/mL, >10 ng/mL). We also investigated the effect of varying the PSA density cutoffs on the detection of cancer and assessed the performance of PSA density vs PSA in men with or without a prior negative biopsy.

RESULTS Among 1290 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 of 4-10 ng/mL (area under the receiver operating characteristic curve [AUC]: 0.70 vs 0.53, $P < .0001$) and within a PSA >10 mg/mL (AUC: 0.84 vs 0.65, $P < .0001$). PSA density was significantly more predictive than PSA in detecting any prostate cancer in men without (AUC: 0.73 vs 0.67, $P < .0001$) and with (AUC: 0.69 vs 0.55, $P < .0001$) a 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.

CONCLUSION As PSA increases, PSA density becomes a better marker for predicting prostate cancer compared with PSA alone. Additionally, PSA density performed better than PSA in men with a prior negative biopsy. UROLOGY 105: 123–128, 2017. © 2017 Elsevier Inc.

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 overdiagnosis and the overtreatment 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 with PSA alone,[10,11] and is only useful in the setting of an abnormal PSA or

Financial Disclosure: *The authors declare that they have no relevant financial interests.*

From the Department of Urology, University of Miami Leonard M. Miller School of Medicine and Sylvester Cancer Center, Miami, FL; the Urology Clinic, Department of Medical, Surgical and Health Science, University of Trieste, Trieste, Italy; and the OPKO Diagnostics, LLC, Miami, FL

Address correspondence to: Sanoj Punnen, M.D., M.S., Department of Urology, University of Miami Leonard M. Miller School of Medicine and Sylvester Cancer Center, Miami, FL. E-mail: s.punnen@miami.edu

Submitted: March 13, 2017, accepted (with revisions): April 11, 2017

digital rectal examination (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 with 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 with PSA across a wide range of PSA values, and among men with and without a previous negative biopsy.

MATERIALS AND METHODS

Study Cohort

The data used for the study were 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 urologic centers in the United States 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 DRE and a transrectal ultrasound (TRUS)-guided extended template biopsy with a minimum of 10 cores. A blood sample was collected immediately before 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. Histopathologic examination of biopsy specimens was 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 1370 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 with PSA across 3 different PSA ranges (<4 ng/mL, 4-10 ng/mL, 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 ng/mL, 4-10 ng/mL, 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 cutoffs 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).

RESULTS

As of April 2014, a total of 1290 men formed the final study cohort. Table 1 represents the demographics and the clinical characteristics of the cohort stratified according to PSA

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 (y)	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)
n (%)			
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)

DRE, digital rectal examination; PSA, prostate-specific antigen; TRUS, transrectal ultrasound.
Continuous data are presented as median (interquartile range) and categorical data as n (%).