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A Prospective, Multicenter, NCI EDRN Study of [-2]proPSA: Improving Prostate Cancer Detection and Correlating with Cancer Aggressiveness

Lori J. Sokoll¹, Martin G. Sanda², Ziding Feng³, Jacob Kagan⁴, Isaac A. Mizrahi⁵, Dennis L. Broyles⁵, Alan W. Partin¹, Sudhir Srivastava⁴, Ian M. Thompson⁶, John T. Wei⁷, Zhen Zhang¹, and Daniel W. Chan¹

¹ Departments of Pathology and Urology, Johns Hopkins Medical Institutions, Baltimore, MD

² Division of Urology, Beth Israel Deaconess Medical Center, Boston, MA

³ Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA

⁴ Cancer Biomarkers Research Group, Division of Cancer Prevention, National Cancer Institute, Rockville, MD

⁵ Beckman Coulter, Inc., San Diego, CA

⁶ Department of Urology, University of Texas Health Science Center at San Antonio, San Antonio, TX

⁷ Department of Urology, University of Michigan, Ann Arbor, MI

Abstract

Background—The free PSA isoform, [-2]proPSA, has been shown to be associated with prostate cancer. The study objective was to characterize the clinical utility of serum [-2]proPSA for prostate cancer detection and assess its association with aggressive disease.

Methods—From among 669 subjects in a prospective prostate cancer detection study at four NCI Early Detection Research Network clinical validation centers, 566 were eligible. Serum PSA, free PSA, and [-2]proPSA were measured (Beckman Coulter Access 2 Analyzer).

Results—245 (43%) of the 566 participants had prostate cancer on biopsy. At 70% specificity, sensitivity of %[-2]proPSA ([-2]proPSA/fPSA) was 54% (95% CI:48%–61%, null hypothesis 40%). Including %[-2]proPSA in a multivariate prediction model incorporating PSA and %fPSA improved the performance ($p<0.01$). In the 2–4 ng/mL PSA range, %[-2]proPSA outperformed %fPSA (ROC AUC= 0.73 vs. 0.61, $p=0.01$). At 80% sensitivity, %[-2]proPSA had significantly higher specificity (51.6%, 95% CI:41.2%–61.8%) than PSA (29.9%, 95% CI:21.0%–40.0%) and %fPSA (28.9%, 95% CI:20.1%–39.0%). In the 2–10 ng/mL PSA range, a multivariate model had significant improvement (AUC=0.76) over individual PSA forms ($p<0.01$ – <0.0001). At 80% sensitivity, specificity of %[-2]proPSA (44.9%, 95% CI:38.4%–51.5%) was significantly higher than PSA (30.8%, 95% CI:24.9%–37.1%) and relatively higher than %fPSA (34.6%, 95% CI:28.5%–41.4%). %[-2]proPSA increased with increasing Gleason score ($p<0.001$) and was higher in aggressive cancers ($p=0.03$).

Conclusions—In this prospective study, %[-2]proPSA demonstrated potential clinical utility for improving prostate cancer detection and was related to the risk of aggressive disease.

Impact—The addition of %[-2]proPSA could impact the early detection of prostate cancer.

Keywords

proPSA; [-2]proPSA; PSA; detection; prostate cancer

Introduction

A number of approaches have been proposed to improve the clinical utility of prostate specific antigen (PSA) for the early detection of prostate cancer. These approaches have included the use of PSA velocity, PSA density, age-specific reference ranges, artificial neural networks, models and nomograms, and the molecular forms of PSA (1–3). Studies have demonstrated less free PSA and more PSA bound to protease inhibitors among men with prostate cancer (4,5). These observations led to the development of commercial assays for free PSA and complexed PSA (cPSA) (6–8). Although free PSA can improve upon total PSA for cancer detection in the 4–10 ng/mL total PSA range, it is an imperfect marker possibly as it consists of several isoforms that are associated with either prostate cancer or benign prostatic hyperplasia (9).

Proenzyme PSA (proPSA) is a cancer associated form of free PSA found primarily in the peripheral zone of the prostate as well as in the circulation (10,11). It contains a 7 amino acid leader peptide sequence and is enzymatically inactive. Enzymatically active PSA results from cleavage of this leader peptide by human kallikrein 2 (hk2) and trypsin. proPSA forms with amino acids of varying lengths also exist in serum including [-2]proPSA, a stable form that is resistant to activation to mature PSA (9,10). An automated assay for [-2]proPSA has been developed and has received European Union (EU) regulatory approval for prostate cancer detection. In the United States, the [-2]proPSA assay is being reviewed by the Food and Drug Administration (FDA) for regulatory approval for clinical use. This assay has been previously examined for prostate cancer early detection (12), including a retrospective study by the NCI Early Detection Research Network (13). Other assays and proPSA forms have also been studied (12,14–27). The purpose of this study was to further characterize the potential clinical utility for [-2]proPSA for prostate cancer detection as well as its association with aggressive cancer in a prospective multi-center study.

Materials and Methods

Subjects

Subjects were enrolled prior to prostate biopsy in a prospective study of prostate cancer detection at four NCI Early Detection Research Network (EDRN) clinical validation centers, approved by Internal Review Boards at each site, that sought to establish an EDRN Prostate Cancer Case-Control ‘Reference Set’ of blood specimens that were collected according to pre-determined standard operating procedures (28). Participants provided written informed consent and specimens were collected prior to prostate biopsy. From among 669 participants in the EDRN reference set cohort, 566 met additional eligibility criteria for this study evaluating the utility of proPSA; these eligibility criteria included over age 40, no prior prostate surgery, biopsy or history of prostate cancer, no use of 5-alpha reductase inhibitors, availability of serum samples with corresponding clinical data, and completion of at least a 10 core template biopsy after enrollment. Exclusions were as follows: 7 lacked samples collected before biopsy or with corresponding clinical data, 6 opted against biopsy after enrollment, 2 had less than a 10 core biopsy, 1 was under 40 years of age, 9 had prior prostate surgery, 55 underwent previous biopsy, and 23 had been treated with 5- α reductase inhibitors.

Specimens and Laboratory Analysis

Blood was collected prior to biopsy and processed using a common protocol (28). Serum was stored at -80°C for between 12 and 30 months prior to analysis. Specimens were analyzed at the EDRN Biomarker Reference Laboratory at Johns Hopkins University in a blinded fashion on the Beckman Coulter Access 2 Immunoassay Analyzer (Beckman Coulter, Inc., Chaska, MN) for total PSA, free PSA (fPSA), and [-2]proPSA (Beckman Coulter Access p2PSA). The commercially available total and free PSA assays, and the investigational use only [-2]proPSA assay all use dual monoclonal antibodies in sandwich assay formats with chemiluminescent detection. Assay design and characteristics have been previously described (12,13,29). There is minimal cross-reactivity of other PSA isoforms in the [-2]proPSA assay. To ensure quality of results, a [-2]proPSA correlation was performed using 52 samples split between the testing site (Johns Hopkins University) and the assay manufacturer (Beckman Coulter, Inc., Chaska, MN). The [-2]proPSA range of values was 1.0–56.8 pg/mL with the relationship of results between the two sites of $y=1.03x+0.04$, $r=0.998$.

Statistical Analysis

Total and free PSA were analyzed in one replicate while [-2]proPSA was analyzed in duplicate with the average value used for all analyses. Percent free PSA was calculated as $(\text{fPSA}/\text{PSA}) * 100$ and %[-2]proPSA as $([-2]\text{proPSA}/10)/\text{fPSA}$. Differences between groups were assessed using student's t-test, the Mann-Whitney U Tests and the Chi-square test for categorical variables. The Kruskal-Wallis ANOVA rank test was used to examine the relationship between [-2]proPSA and %[-2]proPSA, and Gleason score. Descriptive statistics and statistical tests were performed using Statistica (v 6.0). Paired ROC analysis was used to assess and compare assay diagnostic clinical utilities (Analyse-it, v2.20). Logistic regression models were generated using MATLAB (v 2.3.1). Serum markers not normally distributed were log-transformed prior to model fitting to correct for skewness. The resulting linear predictor score was used to evaluate the combined markers by ROC analysis.

Study samples were collected using a protocol designed to test the primary hypothesis that at a fixed specificity of 70%, %[-2]proPSA would have a sensitivity of 60% for the detection of prostate cancer which would be an improvement over current PSA derivatives. Statistical significance was tested against the null hypothesis of sensitivity no better than 40% at the same fixed specificity of 70%. This design was to ensure that the corresponding PPV and NPV of %[-2]proPSA would provide clinically meaningful information for a substantial proportion of men in making a biopsy decision. In order to be powered at 90% to detect that the sensitivity is 60% or higher for a test with one-sided type I error 0.05, 171 patients with a positive biopsy for prostate cancer and 256 controls would be needed. The final sample size was inflated to 200 positive biopsy cases and 300 negative biopsy controls. In addition, secondary analyses were performed for clinically meaningful PSA subranges.

Results

The demographic and clinical characteristics of the 566 men in this study are presented in Table 1. Prostate biopsy detected cancer was found in 43% of subjects. The mean age ($\pm$ SD) of the subjects in this study was 61.7 ± 8.6 years (41–93 years) and men in the cancer group (63.3 ± 9.3 years) were slightly older than men in the non-cancer group (60.5 ± 7.9 years, $p < 0.001$). There were no differences between the groups with respect to race, family history of prostate cancer, or DRE findings.

In all subjects ($n=566$), PSA ranged from 0.29 ng/mL to 18.24 ng/mL in the non-cancer group and 0.69 ng/mL to 310.60 ng/mL in the cancer group. Median PSA concentrations and %[-2]proPSA were significantly higher in the cancer group compared to the non-cancer group while

%fPSA was significantly lower (Table 2). Using paired ROC analysis, areas under the curve (AUC) were similarly high for PSA (0.66), %fPSA (0.70), and %[-2]proPSA (0.67) (Figure 1a). At a specificity of 70%, the sensitivity of %[-2]proPSA was 54% (95% confidence interval: 48%–61%) which was significantly better than the null hypothesis of 40% ($p<0.0001$). A logistic regression model was constructed including a base model with clinical and demographic factors (age, race, DRE, and prostate cancer family history) and step-wise selected log transformed laboratory variables (p value of 0.05 for inclusion). PSA ($p<0.0001$), %fPSA ($p=0.001$), and %[-2]proPSA ($p<0.0001$) remained in the model which had an AUC of 0.79 that was greater than the individual markers ($p<0.0001$). The addition of %[-2]proPSA significantly improved the AUC from 0.75 to 0.79 ($p<0.01$). Using the ROC curves, we compared the specificity of each test at a fixed sensitivity of 80%. PSA, %fPSA and %proPSA had similar specificities [41.7% (95% CI: 36.3%–47.4%), 40.2% (95% CI: 34.8%–45.8%), 42.1% (95% CI: 36.6%–47.7%)] while the model had the highest specificity of 61.4% (95% CI: 56.0%–66.7%).

The utility of %[-2]proPSA for the early detection of prostate cancer was also examined in clinically relevant total PSA ranges. In the 2–4 ng/mL PSA range (Table 2), median %fPSA was significantly lower in the cancer group (non-cancer: 22.0%; cancer: 17.3%, $p=0.02$) and %[-2]proPSA was significantly higher in the cancer group (non-cancer: 1.36%; cancer: 1.75%, $p<0.0001$). %[-2]proPSA had the best overall performance using ROC analysis (Table 2, Figure 1b) with an AUC (0.73) significantly greater than the AUC for PSA (0.58, $p=0.01$) and %fPSA (0.61, $p=0.01$). The AUC for the logistic regression model (0.76) was similar to the AUC for %[-2]proPSA which was expected since log %[-2]proPSA ($p<0.0001$) was the only variable remaining in addition to the base model. The specificity at a fixed sensitivity of 80% showed similar results for PSA [29.9% (95% CI: 21.0%–40.0%)] and %fPSA [28.9% (95% CI: 20.1%–39.0%)] while both %proPSA and the model had significantly higher specificities of 51.6% (95% CI: 41.2%–61.8%) and 53.1% (95% CI: 43.1%–63.1%).

Similar to the group of all subjects, in both the 4–10 ng/mL PSA range and the 2–10 ng/mL PSA range, median PSA concentrations and %[-2]proPSA were significantly higher in the cancer group compared to the non-cancer group while %fPSA was significantly lower (Table 2). In contrast, as shown in Figures 1c and 1d, the diagnostic utility of %[-2]proPSA (AUC=0.70) in the 4–10 ng/mL and of %fPSA (AUC=0.66) and %[-2]proPSA (AUC=0.70) in the 2–10 ng/mL range were significantly better than PSA (both ranges AUC=0.58, $p<0.05$). Further improvement in diagnostic utility was observed with a logistic regression model with an AUC of 0.76 for both ranges (Table 2, Figures 1c and 1d) which was significantly larger than the AUCs of the 3 individual PSA forms (PSA, $p<0.0001$; %fPSA, $p<0.001$; %[-2]proPSA, $p<0.01$). In the 2–10 ng/mL range the log transformed laboratory results for PSA ($p=0.03$), %fPSA, ($p=0.002$) and %[-2]proPSA ($p<0.0001$) remained in the model when a p value of 0.05 was used for inclusion, while PSA was eliminated and %fPSA and %[-2]proPSA (both $p<0.0001$) remained in the model for the 4–10 ng/mL range. For the specificity at a fixed sensitivity of 80%, both %proPSA and the model had higher specificities of 44.9% (95% CI: 38.4%–51.5%) and 58.6% (95% CI: 52.2%–64.9%) as compared to PSA and %fPSA with 30.8% (95% CI: 24.9%–37.1%) and 34.6% (95% CI: 28.5%–41.4%) in the PSA range of 2–10 ng/mL. Both %fPSA [43.8% (95% CI: 35.3%–52.5%)] and %[-2]proPSA [44.5% (95% CI: 36.0%–53.3%)] had significantly higher specificity than PSA [23.4% (95% CI: 16.6%–31.3%)], while the model had the highest specificity of 55.8% (95% CI: 47.5%–64.1%) in the PSA range of 4–10 ng/mL.

In the 245 men with cancer, aggressiveness was examined by comparing [-2]proPSA and %[-2]proPSA with Gleason score as shown in Figure 2. Both [-2]proPSA and %[-2]proPSA increased with increasing Gleason Score ($p<0.001$). A similar relationship between [-2]proPSA and %[-2]proPSA and Gleason score was observed in men with a total PSA between 2 and 10

ng/mL (n=195) although only [-2]proPSA was statistically different with respect to disease significance ($p=0.02$) which likely reflects the smaller sample size (n=118; %[-2]proPSA, $p=0.05$). In addition, [-2]proPSA and %[-2]proPSA were evaluated using the Epstein criteria for insignificant cancer defined as men with T1c disease with a Gleason score < 7 , PSA density ≤ 0.1 , no more than 2 biopsy cores positive for tumor and no more than 50% cancer in any one core (30). There were 148 of the 245 men in the cancer group who had T1c disease and sufficient pathologic data to evaluate based on the Epstein criteria. Both [-2]proPSA and %[-2]proPSA were significantly higher ([-2]proPSA medians: 12.0 pg/mL vs. 8.0 pg/mL, $p<0.001$; %[-2]proPSA medians: 1.66% vs. 1.40%, $p=0.03$) in men with significant disease (86%) compared to men with insignificant disease (14%).

Discussion

Since the discovery a decade ago that free PSA is comprised of an isoform (10,11) that may be specific for cancer, several assays of differing formats recognizing full-length and truncated forms of proPSA have been developed and evaluated for the improved detection of prostate cancer. There is less consensus on the utility of an automated assay measuring [-5, -7]proPSA (14,20,22,27) compared to the automated assay measuring [-2]proPSA used in this study, or to manual assays measuring [-2]-, [-4]-, and [-7]proPSA evaluated individually or summed to form total proPSA (12,13,15,18,21,24,25). Potential roles for [-2]proPSA and proPSA improving the diagnostic ability of %fPSA when %fPSA is $>25\%$ (21) or $<15\%$ (19), identifying aggressive prostate cancer (16,17), and aiding in treatment decisions for men on expectant management (31) have also been investigated.

In the overall study population, %[-2]proPSA was equivalent to PSA and %fPSA using ROC analysis. Moreover, it was complementary and provided independent value to PSA and %fPSA when the three PSA markers were combined with demographic and clinical parameters in a logistic regression model. This model had improved performance over the individual markers. It should be noted that since PSA concentration is the most common indication for prostate biopsy, many of the men in this study were pre-selected by total PSA. It should also be noted that there was higher than usual representation of biopsy Gleason score ≥ 7 in this multicenter cohort. However, patients were consecutively enrolled in a prospective fashion at four geographically distributed sites and thus we do not believe any biases were introduced that would affect the observed results.

In previous studies, %[-2]proPSA has shown utility in clinically important PSA ranges from 2–20 ng/mL where PSA loses specificity (12,13,15,24). In this study, %[-2]proPSA had the best diagnostic utility in the 2–4 ng/mL range where it is now recognized that 25% of men may have cancer (32,33) and where cutoffs lower than 4 ng/mL for PSA have been suggested (34). We found that %[-2]proPSA was significantly better than %fPSA in overall diagnostic efficacy (AUC 0.73 vs. 0.61) and has higher specificity at a fixed sensitivity of 80%, a trend reported in two previous studies for %[-2]proPSA and %proPSA which showed the potential to spare unnecessary biopsies (16,25). The better performance of %[-2]proPSA compared to the other PSA derivatives was also evidenced by the logistic regression model (AUC=0.76) whereby only %[-2]proPSA remained in the model using a backwards elimination approach.

In the 4–10 ng/mL and 2–10 ng/mL PSA ranges, logistic regression models incorporating clinical and demographic factors and PSA derivatives had the highest discriminatory value for prostate cancer detection (ROC AUC = 0.76). In this study, the AUCs for %[-2]proPSA were slightly larger than for %fPSA, although statistical significance was not achieved. In a previous, EDNRN study using samples from 89 men collected pre-biopsy (13), %[-2]proPSA (AUC=0.73) performed significantly better than %fPSA (AUC=0.53) in the 2–10 ng/mL PSA range. Differences between studies include retrospective versus prospective collection, as well as

slightly more stringent eligibility criteria and consistent specimen collection and processing procedures in the current study. As we have shown, and others have reported (12,18,24), [-2]proPSA as part of multivariate models, algorithms, or combinations of markers, may be an ideal approach to improve differentiation of prostate cancer from benign disease compared to individual PSA molecular forms. Successful approaches have included a multivariate logistic regression model with total PSA, %fPSA, and sum-proPSA (18), the ratio [-2]proPSA/(fPSA-sum proPSA) (24), and artificial neural networks and logistic regression models with age, total PSA, %fPSA, and %[-2]proPSA (12).

In addition to the need for biomarkers to identify prostate cancer at an early, curative stage, it is also important to identify aggressive cancers for which treatment may be most beneficial. [-2]proPSA may be helpful since both [-2]proPSA and %[-2]proPSA correlated with Gleason score. Higher [-2]proPSA and %[-2]proPSA values were also highly associated with significant disease using the Epstein criteria (30). A recent study (12) incorporating the same assay for [-2]proPSA used in this study showed %[-2]proPSA and [-2]proPSA/%fPSA could distinguish between Gleason sum <7 and ≥ 7 as well as organ-confined versus non-organ confined disease. Makarov et al (31) found that [-2]proPSA/%fPSA at diagnosis was able to predict which men in an expectant management program for prostate cancer would require treatment based on development of an unfavorable biopsy. [-2]proPSA and proPSA (sum -2, -4/-5, -7) analyzed with microtiter-plate based assays have also been associated with aggressive prostate cancer characteristics (16,17) while screening studies (14,20) evaluating the automated [-5, -7]proPSA assay failed to find an association with stage or grade.

In summary, we have further validated the utility of %[-2]proPSA for the early detection of prostate cancer showing potential utility in the 2–10 ng/mL total PSA range and demonstrated the utility of combining %[-2]proPSA with other PSA forms in logistic regression models. Our observation that [-2]proPSA and %[-2]proPSA may be associated with aggressive and significant prostate cancer is worthy of further investigation. The EDRN-NCI standardized prostate cancer reference set is available for the validation of other prostate cancer markers, allowing both comparisons of marker performance as well as the creation of multiple-marker panels.

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Figure 1a

Figure 1b

Figure 1c

Figure 1d

Figure 1.

1a. ROC analysis for all subjects (n=566) comparing PSA (AUC=0.66), %fPSA (AUC=0.70), %[-2]proPSA (AUC=0.67), and a logistic regression model with age, race, DRE, prostate cancer history (base), log PSA, log %fPSA, and log %[-2]proPSA (AUC=0.79). 1b. ROC analysis for the 2–4 ng/mL PSA range (n=161) comparing PSA (AUC=0.58), %fPSA (AUC=0.61), %[-2]proPSA (AUC=0.73), and a logistic regression model with base components and log %[-2]proPSA (AUC=0.76). 1c. ROC analysis for the 4–10 ng/mL PSA range (n=268) comparing PSA (AUC=0.58), %fPSA (AUC=0.67), %[-2]proPSA (AUC=0.70), and a logistic regression model with base components, log %fPSA, and log %[-2]proPSA (AUC=0.76). 1d. ROC analysis for the 2–10 ng/mL PSA range (n=195) comparing PSA (AUC=0.58), %fPSA (AUC=0.66), %[-2]proPSA (AUC=0.70), and a logistic regression model with age, race, DRE, prostate cancer history (base), log PSA, log %fPSA, and log %[-2]proPSA (AUC=0.76).

Figure 2.

Relationship between [-2]proPSA (left open bars) and %[-2]proPSA (right filled bars) with increasing Gleason score (both $p < 0.001$).

Table 1

Demographic and Clinical Characteristics

	Non-Cancer		Cancer	
	N	%	N	%
Subjects	321	57	245	43
Age (yrs)				
mean $\pm$ SD (range)	60.5 $\pm$ 7.9 (42–80) *		63.3 $\pm$ 9.3 (41–93) *	
40–49	24	7	16	6
50–59	128	40	74	30
60–69	127	40	98	40
70–79	40	12	45	18
80+	2	1	12	5
Race				
White	273	85	212	86
Black	24	7	20	8
Asian	9	3	1	1
Other	9	3	7	3
Unknown	6	2	5	2
Family history of prostate cancer				
No	230	72	168	69
Yes	75	23	64	26
Unknown	16	5	13	5
Digital rectal examination				
Negative (non-suspicious for cancer)	259	81	185	76
Positive	58	18	60	24
Unknown	4	1	0	0
Biopsy Gleason Score				
6			107	44
7 (3+4)			65	26
7(4+3)			31	13

		Non-Cancer		Cancer	
		N	%	N	%
Subjects		321	57	245	43
8-10				42	17

* p<0.001

Participating EDNRN Prostate Clinical Epidemiology and Validation Centers sites and their contribution of cases to the cohort included: Beth Israel Deaconess Medical Center (BIDMC), Boston MA (33%); Johns Hopkins University (JHU), Baltimore, MD (13%); University of Michigan (UM), Ann Arbor, MI (44%), and the University of Texas Health Science Center at San Antonio (UTHSCSA), San Antonio, TX (11%).

Table 2
Comparison of mean and median serum values for the non-cancer and cancer groups and ROC analysis.

All Subjects (n=566)							
	Non-Cancer (n=321)		Cancer (n=245)		ROC AUC	95% Confidence Interval	
	Mean±SD	Median	Mean±SD	Median			
PSA, ng/mL	4.48±3.12	3.93	9.90±25.1	5.35***	0.66	0.62–0.71	
%tPSA	23.3±10.6	21.6	16.9±9.0	14.8***	0.70	0.65–0.74	
%[-2]proPSA	1.46±0.63	1.34	2.00±1.26	1.66***	0.67	0.62–0.71	
Base [†] logistic regression model + log PSA +log %tPSA + log %[-2]proPSA					0.79	0.75–0.82	
2–4 ng/mL PSA Range (n=161)							
	Non-Cancer (n=97)		Cancer (n=64)		ROC AUC	95% Confidence Interval	
	Mean±SD	Median	Mean±SD	Median			
PSA, ng/mL	3.02±0.56	3.05	3.16±0.54	3.28	0.58	0.49–0.67	
%tPSA	22.9±8.8	22.0	20.1±9.8	17.3*	0.61	0.52–0.70	
%[-2]proPSA	1.45±0.49	1.36	2.00±0.92	1.75***	0.73	0.65–0.81	
Base [‡] logistic regression model + %[-2]proPSA					0.76	0.68–0.84	
4–10 ng/mL PSA Range (n=268)							
	Non-Cancer (n=137)		Cancer (n=131)		ROC AUC	95% Confidence Interval	
	Mean±SD	Median	Mean±SD	Median			
PSA, ng/mL	5.78±1.42	5.51	6.19±1.56	5.88*	0.58	0.51–0.65	
%tPSA	20.2±8.5	18.8	15.5±6.5	13.6***	0.67	0.61–0.74	
%[-2]proPSA	1.32±0.61	1.20	1.81±0.89	1.58***	0.70	0.64–0.76	
Base [‡] logistic regression model + log %tPSA + log %[-2]proPSA					0.76	0.71–0.82	
2–10 ng/mL PSA Range (n=429)							
	Non-Cancer (n=234)		Cancer (n=195)		ROC AUC	95% Confidence Interval	
	Mean±SD	Median	Mean±SD	Median			
PSA, ng/mL	4.63±1.78	4.42	5.20±1.94	4.95***	0.58	0.53–0.64	
%tPSA	21.3±8.7	20.3	17.0±8.0	15.0***	0.66	0.61–0.71	

All Subjects (n=566)						
		Non-Cancer (n=321)		Cancer (n=245)		
		Mean±SD	Median	Mean±SD	Median	ROC AUC
						95% Confidence Interval
%[-2]proPSA		1.38±0.56	1.28	1.87±0.90	1.66***	0.65-0.75
Base [‡] logistic regression model + log PSA +log %fPSA + log %[-2]proPSA						0.72-0.81

* p<0.05.
** p<0.001,
*** p<0.0001,
[‡] Age, race, DRE, and prostate cancer family history