

Can the Prostate Risk Calculator Based on Western Population Be Applied to Asian Population?

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BACKGROUND. We developed a Korean Prostate Cancer Risk Calculator (KPCRC) for predicting the probability of a positive initial prostate biopsy using clinical and laboratory data from a Korean male population (<http://pcrc.korea.ac.kr>). We compared its performance to prostate-specific antigen (PSA) testing and the Prostate Risk Calculator 3 (PRC 3) based on data from the Dutch part of European Randomized Study of Screening for Prostate Cancer (ERSPC), which predicts biopsy results for previously unscreened men.

METHODS. Data were collected from 602 Korean men who were previously unscreened and underwent initial ten-core prostate biopsies. Multiple logistic regression analysis was performed to determine the significant predictors. Area under the receiver operating characteristic curve (AUC) and calibration plots of both calculators were evaluated.

RESULTS. Prostate cancer (PCa) was detected in 172 (28.6%) men. Independent predictors of a positive biopsy included advanced age, elevated PSA levels, reduced volume of the transition zone, and abnormal digital rectal examination findings. The AUC of the KPCRC was higher than the PRC 3 and PSA alone on internal and external validation. Calibration plots of the KPCRC showed better performance than the other models on internal and external validation. Applying a cut-off of 10% of KPCRC implied that 251 of the 602 men (42%) would not have been biopsied and that 12 of the 172 PCa cases (7%) would not have been diagnosed.

CONCLUSIONS. The KPCRC improves the performance of the PRC 3 and PSA testing in predicting Korean population's risk of PCa. It implies that Asian populations need their own risk calculators for PCa. *Prostate* 72:721–729, 2012. © 2011 Wiley Periodicals, Inc.

KEY WORDS: prostate neoplasms; biopsy; forecasting; validation studies

INTRODUCTION

Statistical and computational models have been developed to predict more accurately an individual's risk of harboring prostate cancer (PCa) at biopsy, mostly because prostate-specific antigen (PSA) and PSA-related measurements have proved to have limited value [1]. In a recent systemic review, 14 direct comparisons between prediction model and PSA testing demonstrated a benefit from nomograms or artificial neural networks over PSA alone varying between 2 and 26% [2]. However, prediction models may not apply well externally since widely varying risk levels are generated for similar patients by different models [1].

The European Randomized Study of Screening for Prostate Cancer (ERSPC) risk calculator has been developed based on 6,288 Dutch, mostly Caucasian, participants in the screening arm of ERSPC study [3]. The Prostate Risk Calculator 3 (PRC 3) of the ERSPC risk

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calculator estimates the chance of positive biopsy in previously unscreened men according to the outcome of transrectal ultrasound (TRUS), the outcome of digital rectal examination (DRE), ultrasound-assessed prostate volume (PV), and PSA level [4].

Up to now, an external validation of the PRC 3 using Western patients was performed in only two studies [1,4], but no studies have investigated its performance in Asian populations. In this study, we developed a Korean Prostate Cancer Risk Calculator (KPCRC) for predicting the probability of a positive initial prostate biopsy using data from a Korean male cohort with ten-core biopsy and compared the performance of the KPCRC, the PRC 3, and PSA testing alone. In addition, our model and the other two models were validated externally using a data set from an affiliated hospital to compare the performance directly.

MATERIALS AND METHODS

Study Population

Between January 2004 and December 2008, a total of 670 cases of TRUS-guided ten-core biopsy were performed when the PSA level was ≥ 4.0 ng/ml, a palpable nodule upon DRE, or a hypoechoic lesion upon TRUS. The procedure was performed after obtaining written informed consent from all the patients. We excluded 15 cases with incomplete medical records, five cases with a PSA level of 1,000 ng/ml or more, and 48 cases of two or more repeated biopsies. Therefore, 602 different cases of initial TRUS-guided biopsy were used to develop the KPCRC. With the same inclusion and exclusion criteria, 240 cases were collected at Korea University Ansan Hospital (KUAH) for external validation.

Developing KPCRC

The factors we evaluated for the risk of a positive biopsy included age, DRE findings, total PSA level, free PSA level, % free PSA, TRUS findings, PV, prostate transitional zone volume (TV), PSA density (PSAD), and PSAD of transition zone volume (PSAD-TZ). DRE was classified as normal or abnormal (any prostatic nodule or induration). Serum PSA and free PSA tests were performed using the automated chemiluminescent microparticle immunoassay analyzer Architect i2000 (Abbott Diagnostic Laboratories, Abbott Park, IL). TRUS findings were classified as normal or abnormal (any presence of hypoechoic lesion). The prostate was measured in three dimensions, and its volume was estimated using a modification of the prolate ellipsoid formula and recorded in cm^3 [0.523 (length (cm) \times width (cm) \times height (cm))]

by TRUS [5]. After identifying the transitional zone by TRUS, the volume was measured by the same method described above. PSAD and PSAD-TZ were calculated by dividing the serum PSA level by the calculated PV and TV, respectively. A member of a urology team performed a DRE on all patients before the TRUS. A minimum of ten cores, including samples from each case, with additional cores when indicated were taken from suspicious areas. The biopsy specimens were examined for the presence of cancer and were categorized using the Gleason score by a pathologist.

Statistical Analysis

Continuous variables were expressed as either the mean \pm standard deviation (SD), median [interquartile range], or numbers (percentage) of cases. Categorical variables were reported as the number of occurrences and frequency. Student's *t*-test and the Pearson's χ^2 test were used for statistical comparisons of continuous and categorical variables, respectively. Simple and multiple logistic regressions with a backward variable selection procedure were performed to identify independent predictors of PCa in the model-building set. PSA level, PV, and TV were log-transformed prior to analysis. A prediction equation for positive biopsy was developed based on this analysis.

The area under the receiver operating characteristic curve (AUC) was calculated for the KPCRC, the PRC 3, and PSA for the Korean male cohort (583 patients) whose PSA value was 3 ng/ml or more because the PSA values of population cohort for developing the PRC 3 were within this range [6]. Differences in predictive accuracy estimates were tested for statistical significance with the method proposed by Hanley and McNeil [7].

Performance characteristics of the risk calculators were examined by calibration plots, where the x-axis represents the predicted probability and the y-axis represents the actual observed proportion of positive biopsy [1]. Calibration was assessed by grouping patients whose PSA value was 3 ng/ml or more into 11 groups (each comprising 48 or 49 patients in the model-developing cohort and 21 or 22 in the cohort for the external validation) with respect to their predicted probabilities and then comparing the mean of each group with the observed proportion of men with cancer. The sum of squares of the residuals (SSR) was used to assess the deviation from perfect prediction (the 45° line).

The models were externally validated using KUAH data set of which PSA value was 3 ng/ml or more in regard to predictive accuracy and

performance characteristics with the ROC curves and calibration plots, respectively.

Finally, the number of biopsies saved, positive predictive value, total and clinically significant (defined as Gleason score ≥ 7) PCa lost according to threshold probability for both calculators were counted and compared with the expected number for each case if a PSA-based decision was undertaken. The number of biopsies saved means the number of negative biopsy cases of which the predicted probability are below the threshold probability.

All statistical outcomes were presented as the odds ratio and the 95% confidence interval (CI) based on a two-sided test using the SAS statistical package (Version 9.1; SAS Institute, Cary, NC). We regarded a *P*-value < 0.05 as statistically significant.

RESULTS

The characteristics of the Korean male population are shown in Table I. PCa was diagnosed in 172 men

(28.6% of 602 cases), with 120 (19.9% of 602 cases) being clinically significant. Among the cases with a positive biopsy result, the assigned Gleason score was 2–4 in 5 cases (2.9%), 6 in 47 cases (27%), 7 in 35 cases (20%), and 8–10 in 85 cases (50%). Age, PSA, PSAD, and PSAD-TZ were significantly higher for positive-biopsy patients ($P < 0.001$). In contrast, PV and TV were significantly lower in PCa-diagnosed patients ($P < 0.001$). DRE and TRUS findings were also significantly different in both groups ($P < 0.001$). The remaining 430 cases included 393 cases of benign prostatic hyperplasia, 34 of prostatitis, and 3 of high-grade prostatic intraepithelial neoplasia. The characteristics of KUAH data set for external validation are shown in Table II.

In the simple logistic regression analysis, all of the variables listed above were statistically significant predictors of PCa upon needle biopsy (all $P < 0.001$) (Table III). In the multiple logistic regression analysis with a backward variable selection procedure, the significant predictors of a positive prostate biopsy for all

TABLE I. Clinical Characteristics of the Study Population Used to Develop the Korean Prostate Cancer Risk Calculator

Variable	All cases (602 cases)	Cancer group (172 cases)	Non-cancer group (430 cases)	<i>P</i> -value
Age (years)	65.67 ± 9.11	68.69 ± 7.50	64.46 ± 9.42	<0.001
Age, no. (%)				
<40 yr	8 (1.3)	0 (0.0)	8 (1.9)	<0.001
40–49 yr	22 (3.7)	2 (1.2)	20 (4.6)	
50–59 yr	90 (15.0)	11 (6.4)	79 (18.4)	
60–69 yr	282 (46.8)	87 (50.6)	195 (45.4)	
70–74 yr	118 (19.6)	40 (23.2)	78 (18.1)	
≥75 yr	82 (13.6)	32 (18.6)	20 (11.6)	
No. of abnormal DRE finding	149 (24.8%)	94 (54.7%)	55 (12.8%)	<0.001
PSA (ng/ml)	6.77 [4.41:12.19]	20.31 [8.72:79.24]	5.72 [3.95:8.33]	<0.001
PSA level, no. (%)				
<2.5 ng/ml	40 (6.6)	2 (1.2)	38 (8.8)	<0.001
2.5–3.99 ng/ml	83 (13.8)	8 (4.6)	75 (17.4)	
4–9.99 ng/ml	286 (47.5)	39 (22.7)	247 (57.5)	
10–19.99 ng/ml	83 (13.8)	37 (21.5)	46 (10.7)	
≥20 ng/ml	110 (18.3)	86 (50.0)	24 (5.6)	
Free PSA (ng/ml)	1.05 [0.67:1.91]	1.96 [0.95:7.77]	0.92 [0.56:1.40]	<0.001
No. of abnormal TRUS findings	241 (40.0)	110 (64.0)	131 (30.5)	<0.001
Prostate volume (cm ³)	38.7 [28.4:52.6]	33.8 [25.4:48.3]	40.3 [30.0:54.1]	<0.001
Prostate volume, no. (%)				
<30 cm ³	175 (29.1)	69 (40.1)	106 (24.6)	0.005
30–59 cm ³	320 (53.2)	79 (45.9)	241 (56.1)	
60–89 cm ³	89 (14.8)	19 (11.1)	70 (16.3)	
90–119 cm ³	10 (1.6)	3 (1.7)	7 (1.6)	
≥120 cm ³	8 (1.3)	2 (1.2)	6 (1.4)	
Prostate transitional zone volume (cm ³)	17.1 [10.6:27.0]	13.9 [9.0:21.0]	19.1 [11.8:29.0]	<0.001
PSAD (ng/ml/cm ³)	0.17 [0.11:0.34]	0.61 [0.26:2.02]	0.13 [0.09:0.21]	<0.001
PSAD-TZ (ng/ml/cm ³)	0.39 [0.22:0.87]	1.82 [0.63:4.62]	0.30 [0.19:0.49]	<0.001

DRE, digital rectal examination; PSA, prostate-specific antigen; TRUS, transrectal ultrasound; PSAD, PSA density; PSAD-TZ, PSAD of transition zone volume; yr, years.

TABLE II. Clinical Characteristics of KUAH Data Set for External Validation

Variable	All cases (240 cases)	Cancer group (88 cases)	Non-cancer group (152 cases)	P-value
Age (years)	66.38 ± 10.80	69.4 ± 9.40	64.61 ± 11.19	<0.001
Age, no. (%)				
<40 yr	4 (1.7)	0 (0.0)	4 (2.6)	0.006
40–49 yr	11 (4.6)	1 (1.1)	10 (6.6)	
50–59 yr	43 (17.9)	11 (12.5)	32 (21.1)	
60–69 yr	78 (32.5)	32 (36.3)	46 (30.2)	
70–74 yr	50 (20.8)	15 (17.1)	35 (23.0)	
≥75 yr	54 (22.5)	29 (33.0)	25 (16.5)	
No. of abnormal DRE finding	29 (12.1%)	21 (23.9%)	8 (5.3%)	<0.001
PSA (ng/ml)	8.67 [5.63–14.32]	11.00 [8.30–28.83]	7.12 [5.02–10.78]	<0.001
PSA level, no. (%)				
<2.5 ng/ml	0 (0.0)	0 (0.0)	0 (0.0)	<0.001
2.5–3.99 ng/ml	8 (3.3)	1 (1.1)	7 (4.6)	
4–9.99 ng/ml	137 (57.1)	36 (10.9)	101 (66.5)	
10–19.99 ng/ml	55 (22.9)	23 (26.2)	32 (21.0)	
≥20 ng/ml	40 (16.7)	28 (32.8)	12 (7.9)	
Free PSA (ng/ml)	1.18 [0.73–2.31]	1.50 [0.92–3.21]	1.05 [0.70–1.83]	0.004
No. of abnormal TRUS findings	78 (32.5)	37 (42.1)	41 (27.0)	0.016
Prostate volume (cm ³)	32.0 [24.5–45.0]	29.0 [23.0–40.9]	34.0 [25.0–49.7]	0.026
Prostate volume, no. (%)				
<30 cm ³	105 (43.8)	46 (52.3)	59 (38.8)	0.017
30–59 cm ³	109 (45.4)	40 (45.4)	69 (45.4)	
60–89 cm ³	17 (7.1)	2 (2.3)	15 (9.9)	
90–119 cm ³	6 (2.5)	0 (0.0)	6 (3.9)	
≥120 cm ³	3 (1.3)	0 (0.0)	3 (2.0)	
Prostate transitional zone volume (cm ³)	14.8 [9.0:22.0]	13.6 [9.0:18.0]	15.8 [9.8:27.5]	0.015
PSAD (ng/ml/cm ³)	0.29 [0.16:0.49]	0.49 [0.29:0.96]	0.22 [0.13:0.34]	<0.001
PSAD-TZ (ng/ml/cm ³)	0.69 [0.32:1.18]	1.05 [0.72:2.12]	0.48 [0.25:0.87]	<0.001

DRE, digital rectal examination; PSA, prostate-specific antigen; TRUS, transrectal ultrasound; PSAD, PSA density; PSAD-TZ, PSAD of transition zone volume; yr, years.

TABLE III. The Simple and Multiple Logistic Regression Model Analyzing the Predictors of Prostate Cancer Detection Upon Initial Prostate Biopsy

Variable	Simple logistic regression		Multiple logistic regression ^a	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	1.06 (1.04–1.08)	<0.001	1.05 (1.02–1.08)	0.003
DRE	8.22 (5.44–12.4)	<0.001	4.90 (2.79–8.61)	<0.001
Log(PSA)	4.31 (3.29–5.65)	<0.001	4.62 (3.38–6.32)	<0.001
Log(free PSA)	2.74 (2.12–3.40)	<0.001		
Abnormal TRUS findings	4.05 (2.79–5.88)	<0.001		
Log(P-volume)	0.46 (0.30–0.70)	<0.001		
Log(T-volume)	0.51 (0.39–0.68)	<0.001	0.23 (0.15–0.34)	<0.001
Log(PSAD)	5.75 (4.24–7.80)	<0.001		
Log(PSAD-TZ)	5.04 (3.83–6.62)	<0.001		

OR, odds ratio; CI, confidence interval; DRE, digital rectal examination; PSA, prostate-specific antigen; TRUS, transrectal ultrasound; P-volume, prostate volume, T-volume, prostate transitional zone volume; PSAD, PSA density; PSAD-TZ, PSAD of transition zone volume.

^aBackward variable selection procedure was applied.

patients were age, DRE findings, the logarithmic transformations of PSA level, and TV (Table III). The prediction equation and its variables were described previously [8]. As for continuous variables such as age, PSA, and TV, the value itself was put into the equation. The age range was 36–89 years, the PSA range was 0.45–893, and the range of TV was 3–120. As for the categorical variable of DRE finding, 0 was used in the equation when normal, and 1 was used when abnormal. Using this equation, we developed a novel KPCRC. The calculator is available on the following website: <http://pcrc.korea.ac.kr>.

A significantly higher AUC was observed for the KPCRC and the PRC 3 compared with PSA testing alone, with the KPCRC achieving the highest predictive accuracy (Fig. 1). The accuracy of the predicted probability (AUC of each model) was 0.90 (95% CI = 0.89–0.92), 0.88 (95% CI = 0.86–0.90), and 0.83 (95% CI = 0.83–0.4) for the KPCRC, the PRC 3, and PSA, respectively.

The calibration plots for the entire cohort showed that the PRC 3 tends to overestimate risk, with the KPCRC showing overall better calibration (SSR of 0.02 for the KPCRC vs. 0.03 for PSA and 0.42 for the PRC 3). The KPCRC showed very good calibration for all over the predicted probabilities (Fig. 2).

These models were externally validated using the KUAH data set. A higher AUC was observed for the KPCRC than the PRC 3 and PSA testing alone, which did not reach clinical significance (Fig. 3). The accuracy of the predicted probability (AUC of each

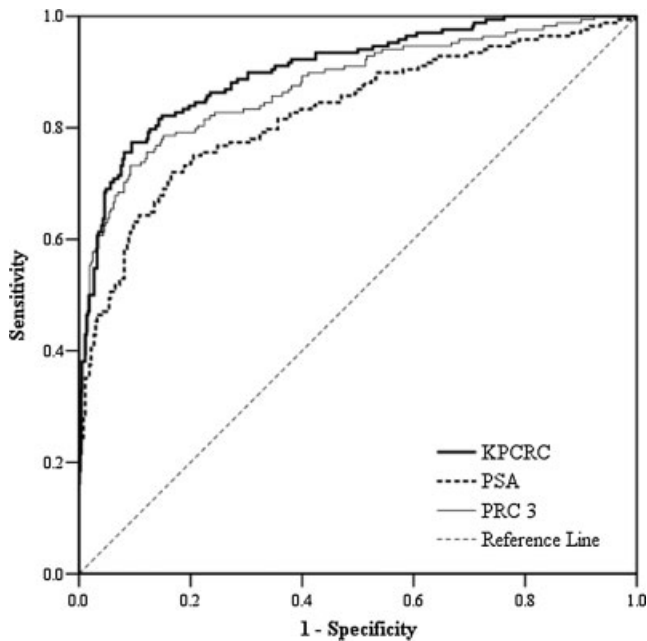


Fig. 1. Receiver operating characteristic curves of the KPCRC, PRC 3, and PSA alone on the model-developing cohort of PSA ≥ 3.0 ng/ml.

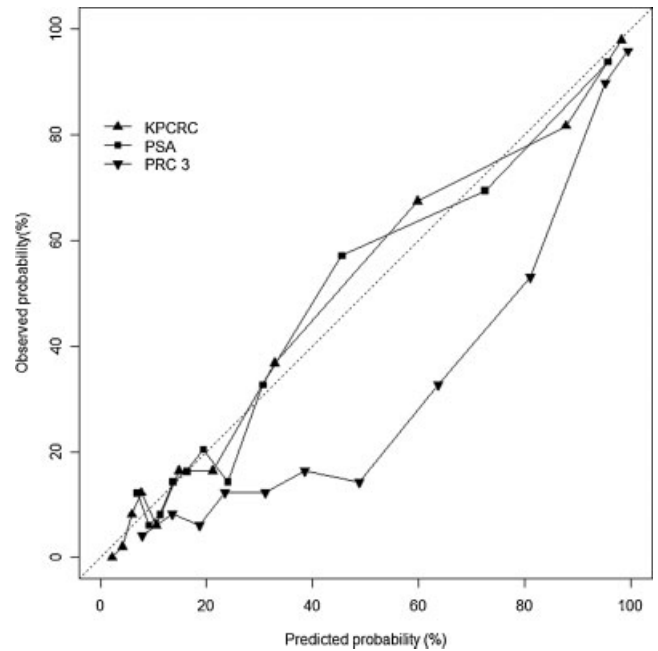


Fig. 2. Calibration plots depicting the agreement between predicted and observed probabilities of positive biopsy of the KPCRC, PRC 3, and PSA alone on the model-developing cohort of PSA ≥ 3.0 ng/ml.

model) was 0.80 (95% CI = 0.74–0.86), 0.78 (95% CI = 0.71–0.84), and 0.72 (95% CI = 0.65–0.79) for the KPCRC, the PRC 3, and PSA, respectively. The KPCRC showed overall better calibration than the other models (SSR of 0.08 for the KPCRC vs. 0.09 for

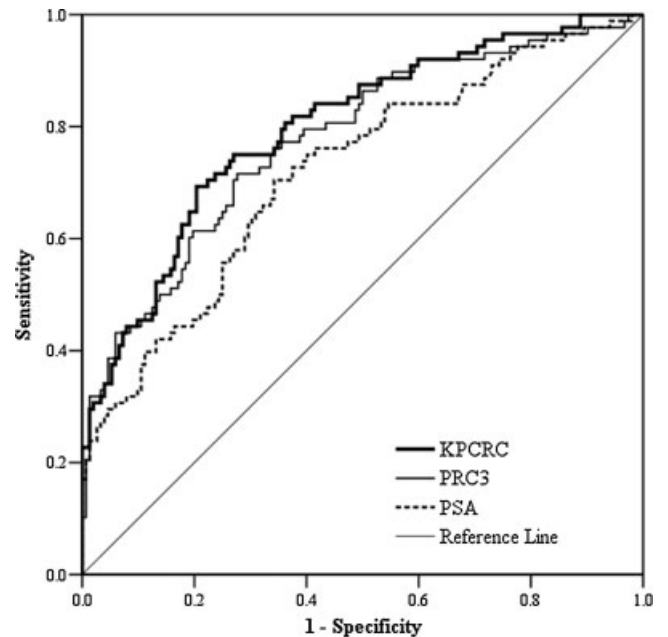


Fig. 3. Receiver operating characteristic curves of the KPCRC, PRC 3, and PSA alone on KUAH data set of PSA ≥ 3.0 ng/ml.

PSA and 0.16 for the PRC 3, Fig. 4). Taken together, the KPCRC showed better predictive accuracy than the PRC 3 and PSA testing alone.

Table IV shows the number of biopsies saved, positive predictive value, and the number of total and high-grade cancers missed according to threshold probability for both calculators, along with the missed cancers if a PSA-based decision was undertaken using 602 Korean patients data for developing the KPCRC. In the threshold probability of 5% in the KPCRC group (numbers of biopsies were 467), the number of biopsies saved and positive predictive value (PPV) in the KPCRC group were better than those in the threshold probability of 15% in the PRC 3 group (numbers of biopsies were 468). Applying PSA cut-off ≥ 4.0 ng/ml would result in 479 biopsied cases; however, the number of PCa cases lost would be considerably higher (10 PCa lost vs. two in the KPCRC group). In the threshold probability of 10% in the KPCRC group (numbers of biopsies were 338), the number of biopsies saved was similar in both groups and PPV in the KPCRC group was better than that in the threshold probability of 30% in the PRC 3 group (numbers of biopsies were 330).

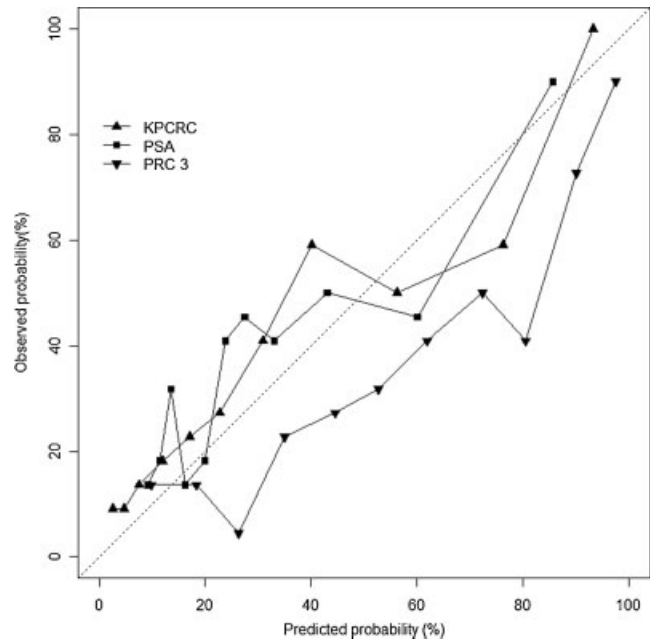


Fig. 4. Calibration plots depicting the agreement between predicted and observed probabilities of positive biopsy of the KPCRC, PRC 3, and PSA alone on KUAH data set of PSA ≥ 3.0 ng/ml.

TABLE IV. Number of Biopsies Saved, Positive Predictive Value, Total and Clinically Significant (Defined as Gleason Score ≥ 7) Prostate Cancers Lost According to Threshold Probability in the Range of 5–30% for the KPCRC and PRC 3, Compared With the Expected Results When the Cut-Off of a PSA Level was 4.0 ng/ml

Threshold probability (%)	Biopsies, no. (A)	Biopsies saved, no. (B) (% , B/602)	PCa detected, no. (C)	PPV (% , C/A)	PCa lost, no. (D) (% , D/172)	Clinically significant lost, no. (E) (% , E/172)
5						
KPCRC	467	132 (21.9)	170	36.4	2 (1.2)	2 (1.2)
PRC 3	580	21 (3.49)	171	29.5	1 (0.58)	1 (0.58)
10						
KPCRC	338	251 (41.7)	160	47.3	12 (7.0)	4 (2.3)
PRC 3	533	67 (11.1)	170	31.9	2 (1.2)	1 (0.58)
15						
KPCRC	275	306 (50.8)	152	55.3	20 (11.6)	10 (5.8)
PRC 3	468	128 (21.3)	166	35.5	6 (3.5)	3 (1.7)
20						
KPCRC	228	344 (57.1)	143	62.7	29 (16.9)	16 (9.3)
PRC 3	413	177 (29.4)	160	38.7	12 (7.0)	6 (3.5)
25						
KPCRC	203	366 (60.8)	140	69.0	32 (18.6)	16 (9.3)
PRC 3	364	224 (37.2)	158	43.4	14 (8.1)	7 (4.1)
30						
KPCRC	175	384 (63.8)	130	74.3	42 (24.4)	20 (11.6)
PRC 3	330	253 (42.0)	153	46.4	19 (11.0)	8 (4.7)
PSA cut-off ≥ 4.0	479	113 (18.8)	162	33.8	10 (5.8)	5 (2.9)
Total	602		172	28.6		

KPCRC, Korean Prostate Cancer Risk Calculator; PRC 3, Prostate Risk Calculator 3; PSA, prostate-specific antigen; no., numbers; PCa, prostate cancer; PPV, positive predictive value.

DISCUSSION

There has been a substantial body of evidence demonstrating that PSA has predictive value for PCa detection [9]. However, PSA levels depend on other clinical factors such as age and the prostate size [10,11]. Therefore, it would be reasonable to make a decision whether to perform prostate biopsy based on statistical model incorporating other clinical factors than PSA alone. Many efforts have been attempted to develop predictive models for PCa based on clinical, laboratory, and/or ultrasound parameters in order to improve the rates of PCa detection [12–17]. However, a recent systematic review of nomograms showed that many of them were not validated externally although the performance of nomograms improved that of PSA alone [2].

Nomograms are useful only for populations of men who resemble closely the population from which the nomogram was derived [2]. Therefore, the nomogram or risk calculator based on data from Western population should be validated externally when applied to other population than Western, especially Asian population. To the best of our knowledge, no study has been performed addressing this topic. Without considering the characteristics of the study cohort and the cohort from which the risk calculator was derived, it might be unreasonable to say one calculator is superior to another. For this reason, it should be certified that the characteristics of Western and Asian populations are comparable before assessing which one is better between the KPCRC and the PRC 3. One study revealed that PSA levels in Singapore-Chinese men were higher than that in US Whites and that PCa incidence in Singapore-Chinese men were lower than that in US Whites [18]. Although the studies comparing Asian and Western patients in PCa are rare, many articles have been published about racial differences between Blacks and Whites [19,20]. Another study analyzing 2004–2005 data from the Surveillance, Epidemiology, and End Results Program reported that between Whites and Blacks, there were statistically significant differences in clinical characteristics of PCa patients such as age, PSA level, Gleason score, and tumor stage [21]. Taking these results into consideration, it can be expected that there are major differences in the characteristics of patients with PCa among races. Of course, there is some possibility that the characteristics of study patients in our model and the ERSPC may be different.

The major different point in the study cohort between the KPCRC and the PRC 3 is the numbers of biopsy cores (10 cores in this study vs. six in ERSPC) [3]. Because the patients in our study were enrolled

since 2004, 10 or more cores were taken from the biopsy procedure according to the extended biopsy schemes. It was reported that the sextant protocol leaves some portion of cancers undetected compared with results obtained from a more extensive biopsy protocol [22]. In addition, some authors suggested that increasing the numbers of biopsy cores would improve the detection of clinically significant PCa and the predictive accuracy of the Gleason score, while not increasing the detection of potentially insignificant cancer [23–25].

In the evaluation using calibration plots, risk underestimation would be expected from the PRC 3 since significantly higher numbers of cores were taken in our study. Nevertheless, the PRC 3 showed definite overestimation for predicted probabilities from 20 to 80%. Several reasons could account for its discrepancy, mainly due to difference in predictive variables of each calculator. First, TV was one of the variables of the KPCRC while PV was one of the variables of PRC 3. In the statistical model, a small PV resulted in a higher predicted probability [3,9]. It has been reported that, for any given age or PSA level, total PV is lower in Japanese than in Caucasian men [26,27]. Therefore, smaller PV in our cohort resulted in a higher probability in PRC 3. In addition, Gupta et al. [28] suggested that Asian men might produce more PSA per unit PV than Caucasian men. As a result, the PRC 3 with a relatively higher value of PSA level may give higher predicted probability than the observed one. Finally, TRUS finding was included in variables of the PRC 3, not in the KPCRC. In our cohort, hypo-echoic lesion was detected in about 30% of patients in non-cancer group. This result may contribute to the risk overestimation of PRC 3.

We can just increase the cut-off level of the predicted probability in order to increase PPV in the statistical model detecting PCa. However, increasing the cut-off level necessarily coincides with missing cancer diagnoses. A key question is whether the numbers of clinically significant cancers missed with this multivariate approach was acceptable. In our PCa cohort, 70% of patients had Gleason scores 7 or more. In the range of threshold probability 5–30% calculated by either KPCRC or PRC 3, proportion of clinically significant cancers occupied about half of the total PCa lost (Table IV). It was reported that the proportion of Korean patients with Gleason scores 7 or higher was more than half of each subgroup throughout the clinical stages and PSA ranges [29]. It seems that PCa in Korean men exhibit poor differentiation regardless of the initial serum PSA level or clinical stage at presentation unlike Western population. This may be due to smaller PV of an Asian population, which was suggested by another study [30].

Considering these results, it would be appropriate that the cut-off be set not to miss PCa diagnosis for Korean patients. In the threshold probability of 15% in the KPCRC group, more than 50% of total biopsy cases would be saved. However, more than 10% of PCa would be missed. In the threshold probability of 10% in the KPCRC group, 42% of total biopsy cases would be saved and 7% of PCa lost. These expected numbers were better or similar compared to PSA cut-off of 4 ng/ml and the threshold probability of 30% in the PRC 3 group.

The web-based calculator necessarily needs special equipments such as a desktop computer and internet access. Now that internet access is easily available throughout Korea and most of the physicians use the electronic medical records in their office, this web-based calculator can be used by both physicians and patients without any difficulty. It constitutes the first study comparing the performance of the PRC 3 based on Western data with that of KPCRC based on Asian data by the ROC curves and the calibration plots. Knowing that performing biopsy purely based on the PSA level lacks specificity, predictive models incorporating prebiopsy risk factors can improve the detection of PCa and reduce unnecessary biopsy simultaneously. These risk factors may differ among populations. Therefore, it would be necessary to investigate the characteristics of each population when considering a prostate biopsy. Predictive models do not replace clinical judgment or patient preference, but it may be useful in providing valuable information before a prostate biopsy [1]. As a consequence of the improved predictive accuracy, more individualized screening could be achieved.

CONCLUSIONS

As a conclusion, the calculators developed by regression analysis improved the performance of PSA alone in predicting PCa. In addition, the KPCRC outperformed the PRC 3 in estimating individual risk of PCa in Korean male population and deciding the need for initial prostate biopsy. This may be due to the difference between the populations, on which the calculators were based. The KPCRC is freely available on the internet; therefore, it can provide physicians and patients with practical information that can be used in deciding whether to undergo prostate biopsy.

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REFERENCES

1. Cavadas V, Osorio L, Sabell F, Teves F, Branco F, Silva-Ramos M. Prostate cancer prevention trial and European randomized study of screening for prostate cancer risk calculators: a performance comparison in a contemporary screened cohort. *Eur Urol* 2010;58:551–558.
2. Schroder F, Kattan MW. The comparability of models for predicting the risk of a positive prostate biopsy with prostate-specific antigen alone: a systematic review. *Eur Urol* 2008;54:274–290.
3. Van Den Bergh RC, Roobol MJ, Wolters T, Van Leeuwen PJ, Schröder FH. The prostate cancer prevention trial and european randomized study of screening for prostate cancer risk calculators indicating a positive prostate biopsy: A comparison. *BJU Int* 2008;102:1068–1073.
4. Roobol MJ, Kranse R, Maattanen L, Schröder FH. External validation of the Riskindicator[®]. ERSPC Rotterdam, Helsinki and Tampere. *Eur Urol Suppl* 2009;8:192.
5. Kawamura K, Suzuki H, Kamiya N, Imamoto T, Yano M, Miura J, Shimbo M, Suzuki N, Nakatsu H, Ichikawa T. Development of a new nomogram for predicting the probability of a positive initial prostate biopsy in Japanese patients with serum PSA levels less than 10ng/ml. *Int J Urol* 2008;15:598–603.
6. Roobol MJ, Steyerberg EW, Kranse R, Wolters T, van den Bergh RCN, Bangma CH, Schröder FH. A risk-based strategy improves prostate-specific antigen-driven detection of prostate cancer. *Eur Urol* 2010;57:79–85.
7. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* 1983;148:839–843.
8. Park JY, Yoon S, Park MS, Cho DY, Park HS, Moon DG, Yoon DK. Initial biopsy outcome prediction in Korean patients-comparison of a noble web-based Korean Prostate Cancer Risk Calculator versus prostate-specific antigen testing. *J Korean Med Sci* 2011;26:85–91.
9. Roobol M, Schroder F, Crawford E, Freedland S, Sartor A, Fleshner N, Andriole G. A framework for the identification of men at increased risk for prostate cancer. *J Urol* 2009;182:2112–2122.
10. El-Galley R, Petros J, Sanders W, Keane T, Galloway N, Cooner W, Graham S. Normal range prostate-specific antigen versus age-specific prostate-specific antigen in screening prostate adenocarcinoma. *Urology* 1995;46:200–204.
11. Nadler R, Humphrey P, Smith D, Catalona W, Ratliff T. Effect of inflammation and benign prostatic hyperplasia on elevated serum prostate specific antigen levels. *J Urol* 1995;154:407–413.
12. Carlson GD, Calvanese CB, Partin AW. An algorithm combining age, total prostate-specific antigen (PSA), and percent free PSA to predict prostate cancer: Results on 4298 cases. *Urology* 1998;52:455–461.
13. Ross PL, Scardino PT, Kattan MW. A catalog of prostate cancer nomograms. *J Urol* 2001;165:1562–1568.
14. Garzotto M, Hudson RG, Peters L, Hsieh Y-C, Barrera E, Mori M, Beer TM, Klein T. Predictive modeling for the presence of prostate carcinoma using clinical, laboratory, and ultrasound parameters in patients with prostate specific antigen levels < or = 10ng/ml. *Cancer* 2003;98:1417–1422.
15. Garzotto M, Beer TM, Hudson RG, Peters L, Hsieh Y-C, Barrera E, Klein T, Mori M. Improved detection of prostate cancer using classification and regression tree analysis. *J Clin Oncol* 2005;23:4322–4329.

16. Karakiewicz PI, Benayoun S, Kattan MW, Perrotte P, Valiquette LUC, Scardino PT, Cagiannos I, Heinzer H, Tanguay S, Aprikian AG, Huland H, Graefen M. Development and validation of a nomogram predicting the outcome of prostate biopsy based on patient age, digital rectal examination and serum prostate specific antigen. *J Urol* 2005;173:1930–1934.
17. Suzuki H, Komiya A, Kamiya N, Imamoto T, Kawamura K, Miura J, Suzuki N, Nakatsu H, Hata A, Ichikawa T. Development of a nomogram to predict probability of positive initial prostate biopsy among Japanese patients. *Urology* 2006;67:131–136.
18. Cheng I, Yu M, Koh W, Pike M, Kolonel L, Henderson B, Stram D. Comparison of prostate-specific antigen and hormone levels among men in Singapore and the United States. *Cancer Epidemiol Biomarkers Prev* 2005;14:1692.
19. Smith D, Bullock A, Catalona W. Racial differences in operating characteristics of prostate cancer screening tests. *J Urol* 1997;158:1861–1866.
20. Morton RA Jr. Racial differences in adenocarcinoma of the prostate in North American men. *Urology* 1994;44:637–645.
21. Shao YH, Demissie K, Shih W, Mehta AR, Stein MN, Roberts CB, DiPaola RS, Lu-Yao GL. Contemporary risk profile of prostate cancer in the United States. *J Natl Cancer Inst* 2009;101:1280–1283.
22. Norberg M, Egevad L, Holmberg L, Sparén P, Norlén BJ, Busch C. The sextant protocol for ultrasound-guided core biopsies of the prostate underestimates the presence of cancer. *Urology* 1997;50:562–566.
23. Makhlouf A, Krupski T, Kunkle D, Theodorescu D. The effect of sampling more cores on the predictive accuracy of pathological grade and tumour distribution in the prostate biopsy. *BJU Int* 2004;93:271–274.
24. Singh H, Canto EI, Shariat SF, Kadmon D, Miles BJ, Wheeler TM, Slawin KM. Improved detection of clinically significant, curable prostate cancer with systematic 12-core biopsy. *J Urol* 2004;171:1089–1092.
25. Chan TY, Chan DY, Stutzman KLRE, Epstein JI. Does increased needle biopsy sampling of the prostate detect a higher number of potentially insignificant tumors? *J Urol* 2001;166:2181–2184.
26. Masumori N, Tsukamoto T, Kumamoto Y, Miyake H, Rhodes T, Girman CJ, Guess HA, Jacobsen SJ, Lieber MM. Japanese men have smaller prostate volumes but comparable urinary flow rates relative to American men: Results of community based studies in 2 countries. *J Urol* 1996;155:1324–1327.
27. Oesterling J, Kumamoto Y, Tsukamoto T, Girman C, Guess H, Masumori N, Jacobsen S, Lieber M. Serum prostate specific antigen in a community based population of healthy Japanese men: Lower values than for similarly aged white men. *Br J Urol* 1995;75:347–353.
28. Gupta A, Aragaki C, Gotoh M, Masumori N, Ohshima S, Tsukamoto T, Roehrborn C. Relationship between prostate specific antigen and indexes of prostate volume in Japanese men. *J Urol* 2005;173:503–506.
29. Song C, Ro JY, Lee MS, Hong SJ, Chung BH, Choi HY, Lee SE, Lee E, Kim CS, Ahn H. Prostate cancer in Korean men exhibits poor differentiation and is adversely related to prognosis after radical prostatectomy. *Urology* 2006;68:820–824.
30. Briganti A, Chun FKH, Suardi N, Gallina A, Walz J, Graefen M, Shariat S, Ebersdobler A, Rigatti P, Perrotte P, Saad F, Montorsi F, Huland H, Karakiewicz PI. Prostate volume and adverse prostate cancer features: Fact not artifact. *Eur J Cancer* 2007;43:2669–2677.