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REVIEW

Prostate Cancer

Prostate cancer risk prediction models in Eastern Asian populations: current status, racial difference, and future directions

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Prostate cancer (PCa) risk calculators (RCs) with prostate-specific antigen (PSA) and other risk factors can greatly improve the accurate prediction of potential risk of PCa compared to PSA. The European Randomized Study of Screening for PCa Risk Calculator (ERSPC-RC) and the Prostate Cancer Prevention Trial Risk Calculator (PCPT-RC) are developed on the Western population. However, the Western RCs showed limited diagnostic efficacy in the Eastern Asian population, mainly due to racial differences between the two populations. We aimed to review the application of Western RCs and Eastern Asian RCs in Eastern Asian cohorts and to identify the characteristics and efficacy of these RCs.

INTRODUCTION

Prostate cancer (PCa) is the second most common type of cancer in men worldwide.[1] The PCa risk calculators (RCs) or the nomograms are capable of more accurately predicting potential risk of PCa. A dozen nomograms for PCa detection have been developed to date. The European Randomized Study of Screening for Prostate Cancer Risk Calculator (ERSPC-RC) and the Prostate Cancer Prevention Trial Risk Calculator (PCPT-RC) were well validated. Asian researchers identified that western-developed risk calculators had limited predictive power in the East Asian populations, mainly due to racial differences between the two populations.[2,3] We aimed to summarize the application of Western RCs in Eastern Asian cohorts, to identify the characteristics and efficacy of RCs in Eastern Asian countries, and to illustrate the performance of Eastern Asian RCs. In addition, we intended to illustrate the efforts made by Asian urologists to find better approaches for risk prediction in East Asians, with focus on the potential causes of such racial differences and the possible direction in future.

WESTERN RISK CALCULATORS APPLIED IN EASTERN ASIAN COHORT

Zhu *et al.*[3] evaluated the predictive value of the PCPT-RC and the ERSPC-RC in a Chinese cohort. Their results showed a superior discriminative ability for ERSPC-RC compared to the PCPT-RC. However, the calibration plots showed that the models derived from Western patients overestimated the probability of PCa and high-grade PCa by approximately 20%. Yoon *et al.*[4] validated the ERSPC risk calculator 3 in a Korean cohort. Similar to the study mentioned above, although the accuracy of the predicted probability is significantly better than PSA, the calibration plot showed that the predicted probabilities

were nearly 20% higher than the observed rate of PCa. These results suggested that the probability of biopsy outcome in Chinese and Korean cohorts will be significantly overestimated by the two Western risk calculators.

CHINESE RISK CALCULATORS

We summarized the characteristics of Eastern Asian RCs (**Table 1**). Tang *et al.*[2] first developed a nomogram for the prediction of prostate cancer risk in Chinese men, using a Chinese cohort for internal validation followed by a study by Kuo *et al.*[5] from Taiwan region of China. The RC showed that PSA, age, prostate volume (PV), and digital rectal examination (DRE) were independent variables in predicting a positive initial prostate biopsy. The nomogram's accuracy was better than that by using PSA alone. Another nomogram which was composed of six parameters (PSA, age, PV, DRE, hypoechoic lesions on transrectal ultrasound [TRUS], and percentage of free PSA [%fPSA]) developed by Huang *et al.*[6] exhibited similar predictive efficiency. The advantages of this nomogram were that it could also predict the percentage of positive cores, the percentage of cancer in each positive core, and Gleason score at different risk levels. Despite the merits of these two studies, they were based on single-center data without external validation. Wu *et al.*[7] built the Huashan RCs based on the Chinese population and validated the performance of PSA, PCPT-RC, and Huashan RCs in an additional validation cohort. The authors showed that Huashan RCs which include age, DRE, PV, PSA, %fPSA, and TRUS results outperformed PSA alone and the PCPT-RC in both training and validation cohorts.

The nomograms built by Chen *et al.*,[8] the Chinese Prostate Cancer Consortium Risk Calculator (CPCC-RC), were constructed for predicting initial biopsy results. It was developed in men who

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Table 1: Characteristics of Eastern Asian prostate cancer risk prediction models

Study	Year	n	Population	Mean age (year)	Median PSA (ng ml⁻¹)	Median PV (ml)	PCa%
Tang *et al.*[2]	2013	535	Chinese	72	18.6	54	44.8
Huang *et al.*[6]	2014	1104	Chinese	NA	NA	NA	41.5
Wu *et al.*[7]	2016	682	Chinese	72	23.4 (mean)	55.4 (mean)	45.3
Chen *et al.*[8]	2016	1835	Chinese	67	10.7	44.8	36.6
Suzuki *et al.*[9]	2006	834	Japanese	70	13.1 (mean)	37.7 (mean)	28.9
Park *et al.*[10]	2011	602	Korean	66	6.8	43.6 (mean)	28.6
Yoon *et al.*[4]	2011	602	Korean	66	6.8	38.7	28.6
Kuo *et al.*[5]	2013	893	Chinese	69	28.3 (mean)	43.3 (mean)	34.4

PSA: prostate-specific antigen; PV: prostate volume; PCa%: prostate cancer detection rate; NA: Not applicable

underwent prostate biopsy in two hospitals in Shanghai with validation in three CPCC member hospitals in three different provinces of China.[8] Compared with previous studies, this nomogram was constructed on the basis of a large multicenter cohort (>900 cases) with validation in multiple centers (>900 cases). Two models associated with five risk factors (PSA, age, PV, %fPSA, and DRE) for predicting both PCa and high-grade PCa were constructed. Both models performed better than the ERSPC-RCs and PCPT-RC in the independent validation cohort. In addition to the area under the curve (AUC), CPCC-RC performed better than ERSPC-RC and PCPT-RC in the independent validation cohort in terms of calibration and clinical benefits.[8]

RISK CALCULATORS IN JAPANESE AND KOREANS

Suzuki *et al.*[9] identified age, PSA, %fPSA, PV, and DRE as independent predictors of a positive biopsy based on the Japanese population. Park *et al.*[10] developed and validated a novel Korean prostate cancer risk calculator (KPCRC) for predicting the probability of a positive initial prostate biopsy in a Korean cohort. Variables including age, DRE, PSA, and prostate transitional zone volume were used in this model. The accuracy of the model was higher in the development cohort, but slightly lower in the validation cohort. Yoon *et al.*[4] compared KPCRC with ERSPC in the same Korean cohort. The KPCRC had better performance than ERSPC in both the ROC curve and calibration plot. Another Korean RC named KPCRC-HG aimed specifically at predicting high-grade PCa (biopsy Gleason score ≥7) was developed and externally validated by Park *et al.*[11] KPCRC-HG was shown to have greater predictive accuracy than PCPTRC-HG, but showed a similar performance to ERSPCRC-HG in the same Korean population. KPCRC-HG showed overall better calibration than PCPTRC-HG, while it showed similar calibration with ERSPCRC-HG. It was interesting that the ERSPC-RCs tended to have higher discriminative power and better calibration than the PCPT-RC, both in Korean[11] and Chinese populations.[8] We assumed this is because the characteristics of the cohorts used to develop ERSPC-RCs might be more similar to those of the current East Asian cohorts.

CHARACTERISTICS AND EFFICACY OF EAST ASIAN RCS

Although variables included in different RCs varied, age, PSA, and DRE results were included in all of these RCs (**Table 3**). Prostate volume was included in all RCs except for the Korean RCs; instead, the Korean RCs[10,11] incorporated the prostate transition zone volume as a predictor. TRUS results were involved in some of the RCs, including the Huashan RC[7] and the RC developed by Kuo *et al.*[5] %fPSA was associated with the results by Koreans[12] and Japanese.[13] However, it was not included in the RC by Tang *et al.*,[2] which indicated that %fPSA was not a preferred predictor for biopsy results in the certain proportion of the population. Although we found that %fPSA was not a good predictor

in men with PSA 4–10 ng ml⁻¹ in Chinese,[14] we included %fPSA in the final CPCC-RC because we considered %fPSA to be effective in men with PSA 10–20 ng ml⁻¹.[15] From our perspective, it would depend on the characteristic of the target population, mainly the distribution of PSA level, to include %fPSA or not.

The predictive accuracy of the Asian RCs was summarized (**Table 2**). All of the RCs had a preferred predictive accuracy, with all AUCs over 0.80 and the AUC increase ranging from 0.05 to 0.12 compared to PSA alone. The preferred predictive accuracy might result from the fact that there were more patients with medium to substantial elevated PSA levels compared with the studies carried out in Western countries with PSA screening programs.

THE DIFFERENCES BETWEEN WESTERN RCS AND EASTERN ASIAN RCS

There were substantial differences between these Eastern Asian nomograms and Western nomograms for the following reasons. First, the PCa detection rates between Eastern Asia and Western countries were remarkably different when stratified by PSA, mainly due to racial and clinical differences.[8,16] Because lower chances of PCa were observed in Chinese compared with Western populations, this explanation helped illustrate the overestimation of risk in Eastern Asian by Western RCs. Supported by the Asian collaborative report, it had been illustrated that the estimated PCa detection rate ranged from 15% to 26% in Eastern Asian populations for men with PSA 4–10 ng ml⁻¹.[16] Second, the Eastern Asian RCs were mainly based on clinical cohorts, while the majority of Western RCs were based on screening populations. Furthermore, the variables in nomograms developed by the Western population were not all proper in Eastern Asian clinical practice. For instance, the family history of PCa is an important predictor in some Western RCs such as PCPT-RC.[17] Family history was important in Western countries for the high incidence rate of PCa. In contrast, the incidence rate of PCa in Eastern Asia was quite low in the past decades which led to the very low rate of positive family history. Thus, none of the Eastern Asian RCs involved family history as an indicator thus far.

FUTURE OF RCS IN EASTERN ASIAN POPULATION

Despite some drawbacks of RCs in Asians, these Asian RCs were built more recently in contemporary cohorts. This advantage guaranteed that the study population was managed with the current standard care. For instance, the included patients tended to receive 10 or 12 cores rather than 6 or 8 cores during the biopsy. It is predicted that Asian RCs will improve based on this advantage.

It is important to realize the influence of racial differences and heterogeneity (*e.g.*, different clinical settings) on the risk prediction of the RCs. Some researchers compared their RC with other RCs or

Table 2: Area under the curve of East Asian risk prediction models

Study	AUC of model	AUC of PSA	AUC increase	Validation
Tang *et al.*[2]	0.848	0.797	0.051	Internal
Huang *et al.*[6]	0.853	0.761	0.092	NA
Wu *et al.*[7]	0.849	0.827	0.022	External
Chen *et al.*[8]	0.801	0.705	0.096	External
Suzuki *et al.*[9]	0.818	0.698	0.120	NA
Park *et al.*[10]	0.910	0.830	0.080	NA
Yoon *et al.*[4]	0.800	0.720	0.080	NA
Kuo *et al.*[5]	0.888	0.747	0.141	External

AUC: area under the curve; PSA: prostate-specific antigen; NA: Not applicable

Table 3: Variables used in model construction

Study	Age	PSA	PV	DRE	%fPSA	Other
Tang *et al.*[2]	+	+	+	+	-	-
Huang *et al.*[6]	+	+	+	+	+	Hypoechoic lesions on TRUS
Wu *et al.*[7]	+	+	+	+	+	TRUS result
Chen *et al.*[8]	+	+	+	+	+	-
Suzuki *et al.*[9]	+	+	+	+	+	-
Park *et al.*[10]	+	+	-	+	-	Prostate transitional zone volume
Yoon *et al.*[4]	+	+	-	+	-	Prostate transitional zone volume
Kuo *et al.*[5]	+	+	+	+	-	TRUS echogenicity

PSA: prostate-specific antigen; PV: prostate volume; DRE: digital rectal examination; TRUS: transrectal ultrasound; +: include; -: not include

validated their RCs in a different population. For instance, the ERSPC study group had already made a calibrated version of the prediction model by calibration with a Hong Kong (China) cohort.[18] It is expected that, in future, we will see more Western-derived RCs with racial options that can enhance its applicability in other populations. As research continues, the differences in RCs between Eastern Asian and Western countries may be diminished by establishing internationally adapted RCs.

In addition, with progress in imaging techniques, imaging results have the potential to be added into the RCs as predictors. For instance, magnetic resonance imaging (MRI) has been one of the most exciting advances in PCa diagnosis. Especially for a certain risk group, the MRI information could improve the estimation of risk, as it was reported that MRI could improve the prediction of high-grade PCa with estimated risk ≤10%.[19] Moreover, molecular biomarkers, including prostate cancer gene 3 (PCA3) and 4K score, have been shown to have added value to the DRE-based ERSPC-RC in detecting PCa in prescreened Western men.[20,21] In the near future, these biomarkers may be incorporated into Asian RCs.

CONCLUSION

It was recognized that the Western RCs are likely to overestimate the PCa risk in Eastern Asia when comparing to Asian RCs, due to the racial and clinical difference of these two populations. It suggests that the RCs incorporate race factors should be applied, for increasing the accuracy of cancer detection. Eastern Asia RCs and Western RCs had improved substantially in recent years, and they might further improve with incorporation of MRI results and novel molecular biomarkers.

AUTHOR CONTRIBUTIONS

BMH and RC reviewed the literature and drafted the manuscript. TQS, YY, CLZ, and SCR edited the manuscript. XG and YHS supervised the whole work. All authors read and approved the final manuscript.

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