available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Editorial

Referring to the article published on pp. 558–561 of this issue

Further Evidence of Differences in Prostate Cancer Biomarkers Between Caucasian and Asian Men

Alexandre R. Zlotta [a,b,*], *Cynthia Kuk* [a,b]

[a] *Department of Surgery, Urology Division, Sinai Health System, Toronto, Canada;* [b] *Department of Surgical Oncology, Urology Division, University Health Network, Toronto, Canada*

It was long thought that the incidence of prostate cancer (PC) was much lower among Asian men than among Caucasian men living in the Western world. However, a growing body of evidence points to a rapid increase in both PC incidence and mortality rates in some Asian countries in recent years [1]. For instance, the incidence of PC in South Korea jumped rapidly from 8.4 per 100 000 in 1999 to 24.4 per 100 000 in 2011. The ratio between incidence and mortality, in large part due to differences in screening practices, is dramatically different between North America and most Asian countries. In Canada, one in seven Canadian men will be diagnosed with PC during his lifetime, but only one in 29 will die from it (www.cancer.ca/en/cancer-information/cancer-type/prostate/statistics/?region=on), whereas the mortality-to-incidence ratio may be as high as 40% in Asia [1].

Genetic differences in the PC molecular landscape between Asian and Caucasian men have been established. The most prevalent gene fusion in Caucasian men is the well-known *TMPRSS2-ERG* fusion, with a prevalence of approximately 50%, in sharp contrast to the much lower frequency in Asian populations (8–21%) [2,3]. Another interesting point is the absence of a difference in *TMPRSS2-ERG* between metastatic PC and incidental PC, which sheds some light on the possible implication of its absence in metastatic development in Asian men affected by PC [2].

Another important variation is *PTEN* inactivation, reported for 70% of Caucasians but only 34% of Asian men [4]. Genome-wide association studies (GWAS) have identified ~100 genetic loci associated with PC risk, but less than a dozen of these loci have been identified from GWAS in two Asian populations, with new loci specific to PC among Asian men unraveled [5].

Because large-scale prostate-specific antigen (PSA) screening programs have not been launched in Asian countries, partly because of the lower incidence rate and/or financial reasons, men diagnosed with PC in Asian countries are older with a higher PSA level than their Caucasian counterparts. However, this is a fluid situation, with Hong Kong, Macau, and Singapore, for instance, rapidly catching up with a more "classical" presentation of PC and lower PSA levels at the time of diagnosis. Indeed, the PSA distribution for patients undergoing biopsies in these Asian cities may comprise 60% or more of men with PSA <10 ng/ml [1].

In Asian regions with developed economic and health care systems, patients are increasingly found with early PC stages and a favorable Gleason score (GS). For instance, >30% of PC cases in Singapore and Hong Kong and up to 50% in Macau are GS 6 [1]. However, the majority of patients in mainland China are still diagnosed with high-grade PC (GS >7). Whether prostate risk calculators based on Western populations and Caucasian men such as the European Randomized Study of Screening for Prostate Cancer (ERSPC) risk calculator can be applied to Asian populations is an important question. The same holds true for biomarkers [6]. The ERSPC risk calculator had to be recalibrated compared to Caucasian men to perform optimally in Chinese and Korean population [6,7].

In this issue of *European Urology*, results reported by Chiu et al. [8] and their team of co-investigators support the idea that Asian populations need their own risk calculators and Prostate Health Index (PHI) reference ranges for PC. It is not surprising that Chiu et al found that adjustments in PHI, based on data for total PSA, free PSA, and [−2]proPSA, are needed for Caucasian and Asian men. Indeed, all PHI

DOI of original article: https://doi.org/10.1016/j.eururo.2018.10.047.
* Corresponding author. Mount Sinai Hospital and Princess Margaret Cancer Centre, 60 Murray Street, Toronto, Ontario M5T 3L9, Canada.
Tel. +1 416 5864800x3910; Fax: +1 416 5868354.
E-mail addresses: alexandre.zlotta@sinaihealthsystem.ca, azlotta@mtsinai.on.ca (A.R. Zlotta).

https://doi.org/10.1016/j.eururo.2018.12.038

parameters are related to PSA, part of the kallikrein family. If risk calculators such as ERSPC had to be recalibrated for Asian men, fine-tuning the need to consider biopsies for patients on the basis of additional biomarkers from the same family as KLK3 (PSA) would be expected to yield similar results.

However, given the recent evidence suggesting that the PC distribution in developed Asian cities is closer to that of the Western world, it is unexpected to observe such dramatic differences in PC in men with PSA of 2–10 ng/ml who underwent biopsies. Among European and Asian men in this study who had PSA in the "grey" zone and no previous biopsies, only 13% of Asian men were diagnosed with PC, compared to 52% of Caucasians, although the median age did not significantly differ between the cohorts (65 yr for Asians vs 63 yr for Europeans). We previously observed a similar difference, albeit not as drastic, in PC prevalence. In autopsy specimens for men aged 61–70 yr, PC was found for 31% of Asian and 46% of Caucasian men [9]. One possible explanation is that Asian men present with PC later in life. Although biopsy techniques might also account for some differences, this ultra low incidence for PSA <10 ng/ml in the sixth decade of life seems to suggest a delay in PC development in Asian men compared to Caucasians as this was observed in autopsy studies [9].

While there was a marked difference in PC in the study between the two cohorts, the percentage of high-grade PC was the same, at 43%. This is in the same range of high-grade disease we found in our autopsy study in the Asian cohort (51.4% GS 7–10), showing that Asian men present with the same distribution of high-grade disease. In our experience in Toronto, among 3408 biopsies from October 2008 to June 2013, 47% contained PC, in line with what was observed by Chiu et al. in the Caucasian cohort in their study; 57% had intermediate- to high-grade PC [10].

The puzzlingly and intriguingly low number of PCs found among Asian men with PSA <10 ng/ml who underwent biopsy ($n = 151$), for reasons that are still unclear, may suggest that PC develops one or two decades later among Asian men compared to their Caucasian counterparts. Although the study is very interesting, we cannot draw robust and definitive conclusions with respect to the PHI reference range for Asian men, which deserves further evaluation. Pilot PC screening trials among Asian men and a better understanding of PC incidence among men with low PSA levels would also be of utmost interest.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Chen R, Ren S, Chinese Prostate Cancer Consortium, et al. Prostate cancer in Asia: a collaborative report. Asian J Urol 2014;1:15–29.
[2] Koide H, Kimura T, Inaba H, et al. Comparison of ERG and SPINK1 expression among incidental and metastatic prostate cancer in Japanese men. Prostate 2019;79:3–8.
[3] Kimura T, Furusato B, Miki J, et al. Expression of ERG oncoprotein is associated with a less aggressive tumor phenotype in Japanese prostate cancer patients. Pathol Int 2012;62:742–8.
[4] Rubin MA, Maher CA, Chinnaiyan AM. Common gene rearrangements in prostate cancer. J Clin Oncol 2011;29:3659–68.
[5] Wang M, Takahashi A, Liu F, et al. Large-scale association analysis in Asians identifies new susceptibility loci for prostate cancer. Nat Commun 2015;6:8469.
[6] Yoon DK, Park JY, Yoon S, et al. Can the prostate risk calculator based on Western population be applied to Asian population? Prostate 2012;72:721–9.
[7] Chiu P, Roobol M, Nieboer D, et al. Adaptation and external validation of the European Randomised Study of Screening for Prostate Cancer risk calculator for the Chinese population. Prostate Cancer Prostat Dis 2017;20:99–104.
[8] Chiu PKF, Ng CF, Semjonow A, et al. A multicentre evaluation of the role of the Prostate Health Index (PHI) in regions with differing prevalence of prostate cancer: adjustment of PHI reference ranges is needed for European and Asian settings. Eur Urol 2019;75:558–61.
[9] Zlotta AR, Egawa S, Pushkar D, et al. Prevalence of prostate cancer on autopsy: cross-sectional study on unscreened Caucasian and Asian men. J Natl Cancer Inst 2013;105:1050–8.
[10] Bhindi B, Mamdani M, Kulkarni GS, et al. Impact of the U.S. Preventive Services Task Force recommendations against prostate specific antigen screening on prostate biopsy and cancer detection rates. J Urol 2015;193:1519–24.