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Platinum Priority – Editorial

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Common Genetic Variants Associated with Prostate Cancer Risk: The Need for African Inclusion

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The article by Chen et al. [1] in this issue of *European Urology* is a critical and timely study aimed at identifying genetic variants conferring susceptibility to the risk of prostate cancer (PCa) among males of African ancestry. The authors performed a meta-analysis of ten studies from which common variant genotyping data were available for men of African ancestry, defined as PCa cases (n = 19 378) or controls (n = 61 620), making this the largest African-relevant study of its kind for PCa. The study identified nine novel risk variants, of which seven appear to be African-exclusive/predominant (Table 1). Through African inclusion, the authors were able to expand the repertoire of known PCa risk alleles from 269 [2] to 278. Owing to the significant size and thus the power of the study, it might be argued that identification of a greater number of risk alleles would have been expected. Here we place these significant findings in context with respect to the African diaspora and unravelling of the contribution of inherited risk to the disparity in PCa presentation observed for men of African ancestry.

PCa is a significant health burden for men of African ancestry. In the USA, African American men are 1.7-fold more likely to receive a PCa diagnosis, while mortality rates are 2.3-fold (≥65 yr) and 3.1-fold (<65 yr) greater than for those of European and fivefold greater than for those of Asian ancestry [3]. On December 14, 2020, the International Agency on Research on Cancer released the latest GLOBOCAN 2020 data reporting the estimated age-standardized incidence and mortality rates for all cancers worldwide [4]. Besides the Caribbean, European-predominant ancestral regions of the globe dominate with regard to PCa incidence rates; however, the mortality rates point to a significant burden of disease across the African diaspora, with highest rates for the Caribbean (age-standardized rate 0f 27.9 per 100 000), central Africa (24.8 per 100 000), southern Africa (22.0 per 100 000), and western Africa (20.2 per 100 000). With mortality rates 2.5-fold greater than reported for the USA, lack of prostate-specific antigen (PSA) screening, and limitations in standardized cancer registries across the continent [5], it can be confidently assumed that PCa incidence rates are significantly under-reported. While socioeconomic factors, limited awareness, and the availability of specialist urology care cannot be ignored [6], another factor for this "cancer of the elderly" is that the average life expectancy across Sub-Saharan Africa is 6 yr less than the average age at PCa diagnosis in the USA (66 yr, as reported by the American Cancer Society). As PCa is considered the most heritable of the solid cancers [7], the inherited genetic contribution to the well-documented PCa health disparity among men of African ancestry cannot be ignored.

Although it is the epicentre of African ancestral genetic diversity, populations from Sub-Saharan Africa represent only 0.15% of all genome-wide association studies (GWAS) [8]. PCa is no different. While the meta-analysis by Chen et al. [1] is the largest African-representative PCa GWAS to date, it represents a negligible fraction of the region (Fig. 1), capturing a snapshot from three of 49 countries and accounting for just 16.3% of the cases and 4.1% of the controls from the overall study. Nevertheless, this commendable effort by the authors is the largest study of its kind regarding continental inclusion. Biased towards Afri-

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Table 1 – Nine novel PCa risk alleles identified by Chen et al. [1]

ID	Chromosome	Position (GRCh38)	Risk allele	Alternate allele	Relative allele frequency			Closest gene (distance away)
					African ancestry controls (n = 61 620)[a]	European ancestry controls[a]	Southern African PCa (n = 113)[b]	
rs73923570	Chr2	43324754	G	A	0.115	0	0.106	*THADA*
rs60985508	Chr2	241223950	T	T, C, A	0.307	0.008	0.363	*ANO7*
rs72960383	Chr3	115013663	A	T	0.333	0.028	0.451	*ZBTB20*[c]
rs144842076	Chr4	76871758	C	T	0.965	0.96	0.973	ENSG00000270244 (14.3 kb)[c]
rs13172201	Chr5	1271546	C	T	0.404	0.292	0.451	*TERT*
rs114053368	Chr14	64139414	T	A	0.2	0.064	0.243	*SYNE2*
rs9895704	Chr17	7897764	T	C	0.886	0.999	0.845	*CHD3*
rs73991216	Chr17	31566869	G	A	0.888	1.000	0.836	*RNU6ATAC7P* (3 kb)
rs150947563	Chr20	63809818	C	T	0.984	1.000	0.991	*ZBTB46, ZBTB46-AS1*

PCa = prostate cancer.
[a] Data for African ancestry controls extracted from Chen et al. [1]. Data for rs72960383 (n = 75 718 European controls) and rs144842076 (75 718 European controls) were extracted from gnomAD via the dbSNP database, all other data were extracted from Chen et al. [1] based on European samples from Conti et al. [2] (n = 50 331).
[b] Data extracted from Jaratlerdsiri et al. [13] for men with aggressive PCa from southern Africa.
[c] Novel PCa risk loci.

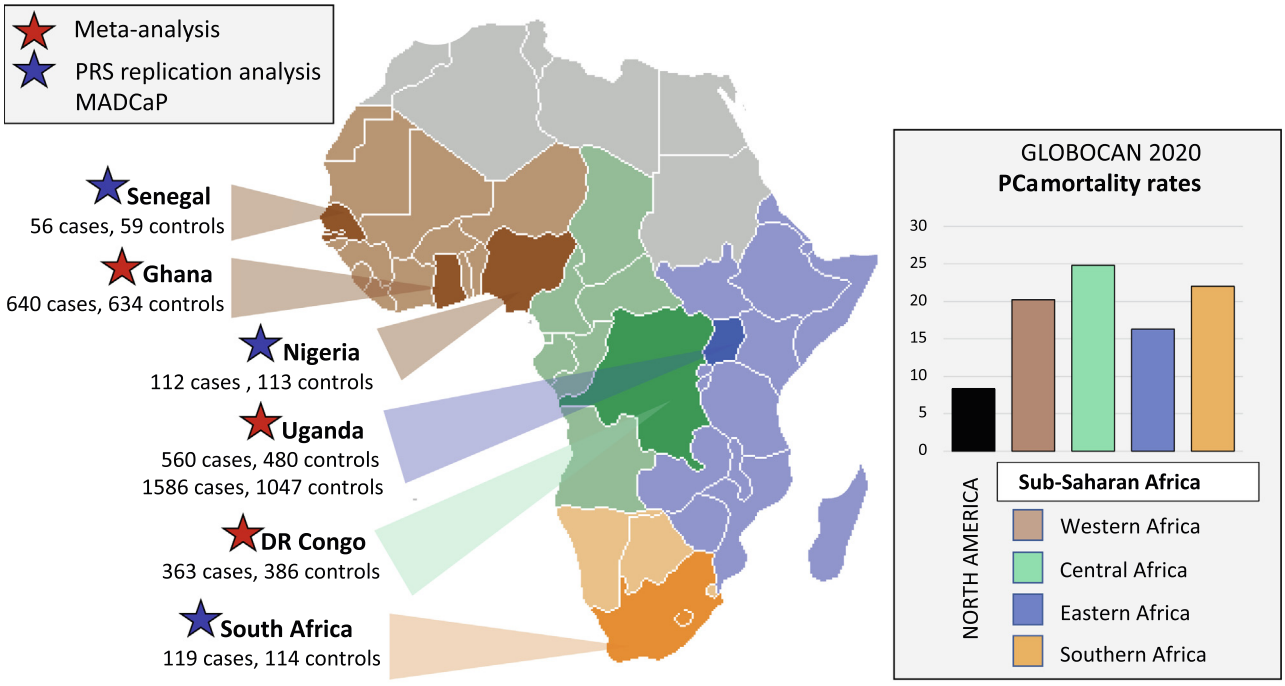

Fig. 1 – Distribution of prostate cancer (PCa) case-control genotype data included in the meta-analysis by Chen et al. [1] (red stars) and the Polygenic Risk Score (PRS) MADCaP validation study (blue stars) across Sub-Saharan Africa with respect to regions as defined by GLOBOCAN 2020 mortality rates.

can American data, the sheer scale allowed the team to generate a multiancestry polygenic risk score (PRS) that provides validated risk stratification (using MADCaP data) and demonstrates effectiveness in distinguishing aggressive disease. However, caution is required when translating PRS data to the majority of Sub-Saharan Africa. As recently demonstrated [9], the more than 2000 representative ethnolinguistic groups provide a reliable proxy for the extent of underappreciated and globally representative genetic diversity. Fatumo and Inouye [10] recently discussed the limitations of current PRS data sets regarding global applicability because of their bias towards European ancestral studies, and highlighted the strength of African inclusion in greatly enhancing the multiancestral applicability of PRS data.

Taking a closer look at the nine novel variants identified by Chen et al. [1], seven are at known PCa risk loci (Table 1). Most notably, these include a protein-truncating variant in

the prostate-specific gene anoctamin 7 (*ANO7*; p.Ser914Ter, rs60985508), adding a third functionally relevant variant to the repertoire of known African-exclusive PCa susceptibility genes, along with *CHEK2* p.Ile448Ser (rs17886163) [11], although classified as likely benign in ClinVar, and *HOXB13* p.Ter285Lys (rs77179853) [12], which results in an extended protein. Of the 269 PCa risk variants identified before this study, only 5.6% (15/269) are protein-altering, of which the *CHEK2* nonsynonymous variant is unique to men of African ancestry [2]. This study therefore raises the question of whether African ancestral populations are more likely to carry deleterious PCa-predisposing variants that inadvertently avoided purifying selection because of older age at disease onset. We recently generated whole-genome deep sequenced data for 113 men of southern African ancestry presenting with largely aggressive PCa [13]. While the novel *ANO7* stop-gain variant is represented in this population, neither the *CHEK2* nor the *HOXB13* protein-altering variant was observed in this African ancestral cohort. Notably, a thorough interrogation of the 20 most common genes included in PCa germline testing panels for this cohort revealed that *HOXB13* is highly conserved, with no common or rare variants detected [14].

Taking the evidence together, we are optimistic about the future benefit that African inclusion can deliver in understanding the genetic link to PCa risk and aggressive disease presentation, which has placed African ancestry as one of only three verified risk factors along with elevated age and family history. We commend this team for their efforts and challenge the community to conduct further inclusion- and priority-driven research to reduce PCa health care inequalities.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Chen F, Madduri RK, Rodriguez AA, et al. Evidence of novel susceptibility variants for prostate cancer and a multiancestry polygenic risk score associated with aggressive disease in men of African ancestry. Eur Urol. 2023;84:13–21.

[2] Conti DV, Darst BF, Moss LC, et al. Trans-ancestry genome-wide association meta-analysis of prostate cancer identifies new susceptibility loci and informs genetic risk prediction. Nat Genet 2021;53:65–75.

[3] Taitt HE. Global trends and prostate cancer: a review of incidence, detection, and mortality as influenced by race, ethnicity, and geographic location. Am J Mens Health 2018;12:1807–23.

[4] Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209–49.

[5] Omonisi AE, Liu B, Parkin DM. Population-based cancer registration in Sub-Saharan Africa: its role in research and cancer control. JCO Glob Oncol 2020;6:1721–8.

[6] McGinley KF, Tay KJ, Moul JW. Prostate cancer in men of African origin. Nat Rev Urol 2016;13:99–107.

[7] Hjelmborg JB, Scheike T, Holst K, et al. The heritability of prostate cancer in the Nordic Twin Study of Cancer. Cancer Epidemiol Biomarkers Prev 2014;23:2303–10.

[8] Mills MC, Rahal C. The GWAS Diversity Monitor tracks diversity by disease in real time. Nat Genet 2020;52:242–3.

[9] Atkinson EG, Dalvie S, Pichkar Y, et al. Genetic structure correlates with ethnolinguistic diversity in eastern and southern Africa. Am J Hum Genet 2022;109:1667–79.

[10] Fatumo S, Inouye M. African genomes hold the key to accurate genetic risk prediction. Nat Hum Behav 2023;7:295–6.

[11] Conti DV, Wang K, Sheng X, et al. Two novel susceptibility loci for prostate cancer in men of African ancestry. J Natl Cancer Inst 2017;109:djx084.

[12] Na R, Wei J, Sample CJ, et al. The HOXB13 variant X285K is associated with clinical significance and early age at diagnosis in African American prostate cancer patients. Br J Cancer 2022;126:791–6.

[13] Jaratlerdsiri W, Jiang J, Gong T, et al. African-specific molecular taxonomy of prostate cancer. Nature 2022;609:552–9.

[14] Gheybi K, Jiang J, Mutambirwa SBA, et al. Evaluating germline testing panels in southern African males with advanced prostate cancer. J Natl Compr Cancer Netw 2023;21:289–296.e3.