Accounting for Genetic Factors May Improve Accuracy of Prostate Cancer Detection

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Accounting for Genetic Factors that Cause Normal Variations in PSA Levels May Improve the Accuracy of Prostate Cancer Detection

The accuracy of prostate-specific antigen (PSA) screening for prostate cancer could be improved by accounting for genetic factors that cause changes in PSA levels that are not associated with cancer, according to data presented during the AACR Annual Meeting 2022, held April 8-13.

“PSA levels represent the main diagnostic biomarker for prostate cancer. This test is widely used but not currently implemented as part of a formal screening program,” said presenter Linda Kachuri, MPH, PhD, a postdoctoral scholar in the Department of Epidemiology & Biostatistics at the University of California, San Francisco. “Because of its poor sensitivity and specificity, PSA testing can often lead to detecting latent disease or, in some cases, missing aggressive tumors.”

Kachuri and colleagues studied whether certain genetic factors could cause variations in the levels of PSA that are not attributable to cancer, and whether accounting for such normal variations could help improve the diagnostic potential of this biomarker. They conducted a large genome-wide association study of PSA in more than 95,000 men without diagnosed prostate cancer using data from five cohorts from the United States, United Kingdom, and Sweden.

The researchers identified 128 PSA-associated variants, including 82 new ones, which they used to build a polygenic score for PSA levels. The polygenic score provided a combined measure of each individual’s genetic predisposition to high PSA levels.

The authors validated the polygenic score by applying it to two cohorts of individuals enrolled in the PCPT and SELECT cancer prevention trials, involving 5,737 and 22,247 participants, respectively. The PSA polygenic score accounted for 7.3 percent and 8.7 percent of the variation in baseline PSA levels in the PCPT cohort and the SELECT cohort, respectively. Importantly, it was not

associated with prostate cancer in either of the cohorts, confirming that it reflects benign PSA variation.

To examine whether the polygenic score could improve the detection of clinically significant disease and reduce overdiagnosis, the researchers applied the polygenic score correction factor to a real-world Kaiser Permanente cohort and estimated the effects of this adjustment on the PSA thresholds used for biopsy referrals.

“We adjusted each person’s PSA values based on his unique polygenic score,” explained Kachuri. “PSA values personalized in this way are more likely to reveal changes in PSA due to prostate cancer because they are corrected for the influence of inherited genetics.”

Applying a correction to the PSA levels appeared to improve the accuracy of the referral decisions, as it would have avoided 20% of negative biopsies in non-prostate cancer cases. It would have also resulted in 15.7% fewer biopsies in cases with low-grade disease, which accounted for 71% of all patients who would have avoided a biopsy. Furthermore, in both the PCPT and the SELECT cohorts, genetically adjusted PSA was more robustly associated with aggressive prostate cancer than unadjusted PSA levels.

“We showed that genetic correction of PSA levels has the potential to both reduce unnecessary biopsies and improve our ability to detect tumors with a more aggressive profile,” commented Kachuri. “We hope that our findings represent a step forward in developing informative screening guidelines and reducing the diagnostic gray area in PSA screening.”

While the study was very large, almost 90% of the participants were of predominantly European ancestry. According to Kachuri, this represents a key limitation because the composition of the study doesn’t reflect the patient population impacted by prostate cancer. “We hope to be able to share findings soon from our efforts to conduct larger and more diverse studies of PSA genetics,” she said.

This study was funded by the National Cancer Institute (R01CA241410). John S. Witte, PhD, principal investigator on the study, is a non-employee cofounder of Avail Bio and a consultant for Sanofi.

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