Specificity of a Polygenic Score for Aggressive Prostate Cancer

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ABSTRACT

Background
To address the concern that polygenic hazard scores for prostate cancer (PCa) might not distinguish between indolent and aggressive disease, we performed case-only analyses using a 601-variant polygenic score (PHS601). Among men who eventually developed PCa, we hypothesized that those with higher PHS were more likely to develop aggressive disease.

Methods
We analyzed genetic and phenotypic data from a diverse, national cohort of men diagnosed with PCa (Million Veteran Program, n = 69,901, 6413 metastatic). We used Cox proportional hazards models to examine the association of PHS601 with both age at onset of metastatic PCa (birth-to-met) and time from localized to metastatic diagnosis (localized-to-met). We also examined the association of PHS601 with age at diagnosis of intermediate/high-risk PCa in two independent population-based cohorts from the PRACTICAL Consortium (COSM and ProtecT).

Results
PHS601 was associated with both birth-to-met and localized-to-met within MVP. The HRs for men in the highest quintile of PHS601 vs. those in the lowest quintile ($HR_{80/20}$) were 1.74 [1.65-1.84] and 1.41 [1.31-1.51] for birth-to-met and localized-to-met, respectively. A similar association was observed for intermediate/high-risk PCa in two external cohorts.

Conclusions
Men with high PHS601 are diagnosed with PCa at a younger age and are more likely to develop aggressive disease.

DATA AVAILABILITY STATEMENT

The data used in this study were obtained from the U.S. Department of Veterans Affairs Million Veteran Program (MVP), a national research program to study how genes, lifestyle, and military exposures affect health and illness. Due to the sensitive nature of the data, including protected health information and genetic data, access is limited to approved investigators with appropriate ethical and regulatory approvals.

Data are not publicly available due to participant confidentiality and federal regulations, but may be made available upon reasonable request and following the appropriate data access procedures.

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