Editorial

Development and validation of a polygenic hazard score for aggressive prostate cancer identification

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Prostate cancer (PCa) is a major health issue that affects over a million men globally every year (1). Although screening men for PCa using prostate specific antigen (PSA) estimates, over the past three decades, resulted in a significant improvement in quantity and quality of life, two major problems reduce the value of early screening using this method: (I) inaccuracy of test results (i.e., the receipt of false positive results), and (II) unnecessary aggressive treatment for low-risk PCa that could be managed via active surveillance or observation (2). These two major issues limited the global enthusiasm for early screening of PCa and influenced health policies supporting the utility of PCa screening tests in several countries. However, the need for a more efficient screening test to reduce disease burden and improve survival rates in men at risk of PCa because of genetic vulnerability or increasing age remained a challenge.

To address this unmet need, Seibert and colleagues conducted a well-designed and methodologically sound study to examine whether, with a combination of risk information from an array of single nucleotide polymorphisms (SNPs), polygenic models can estimate individualized genetic risk for developing PCa. To examine this hypothesis, the authors used data from 21 global studies of European ancestry from the international PRACTICAL consortium to develop this polygenic hazard score (PHS) for predicting age related risk of developing aggressive PCa. The goal of the utility of the PHS was to ensure screening efficacy using standard methods (e.g., PSA) for vulnerable men because of their inherent genetic risk for developing PCa in their lifetime.

The PHS was developed as a parsimonious survival analysis model to predict the age of onset of PCa using Cox proportional hazards regression. Exclusively focusing on prediction of aggressive PCa, the authors included only data from men with Gleason score ≥7, stage T3-4, PSA concentration ≥10 ng/mL, nodal metastasis, or distant metastasis. Men with low Gleason score and low PSA concentration but stage T2b or T2c were considered low-risk in the data analyses to ensure that no low-risk tumors were included as cases of aggressive cancer. The term "very aggressive disease", was defined by the authors as any case with Gleason score ≥8, stage T3-4, positive nodes, or distant metastases. The dataset included 18,868 men with any PCa, 10,635 with aggressive PCa, 5,406 with very aggressive PCa, and 12,879 controls of genotypic European ancestry. Age was reported either at PCa diagnosis or at follow-ups. Genotyping was performed with a custom Illumina array (iCOGS) resulting in 201,043 SNPs. Men were excluded from data analyses (n=4,803) if they had incomplete staging information to ensure accuracy of prediction models.

The authors reported that 2,415 nucleotide polymorphisms were significantly associated with increased risk of PCa. Of these, 54 were identified by means of stepwise regression series and combined with individual genotype to generate the PHS. As a first step of ensuring its validity, the model was tested using data from the ProtecT-Study because of the availability of staging data and PSA results [n=6,411; 1,583 men with a PCa, 632 with aggressive PCa, 220 with very aggressive PCa, all diagnosed by transrectal ultrasound biopsy (TRUS) and 4,828 controls]. According to the study results, the genetic-based prediction model for aggressive PCa was significant with most SNPs associated with aggressive disease also revealing significant associations with any PCa stage.

As an additional step, the authors examined whether family

history of PCa improves the value of PHS for prediction of onset of aggressive PCa using the same Cox model approach. Models were constructed with family history alone, hazard score alone, or with both. Interestingly the study results showed that family history did not improve prediction of onset of aggressive PCa over and above the PHS value.

In summary, the authors concluded that unlike PSA test results, the PHS is representative of a man's fixed genetic risk, which can be calculated long before onset of PCa, and substantially inform the decision of whether he should undergo PCa screening. This is a significant advancement as previous tools often included PSA concentrations as a variable in their analysis, thus limiting their use in PSA-screening. Given the recent recommendation of not using PSA screening to reduce over diagnosis and over treatment, the personalized PHS can be used to suggest screening for PCa in men who might be at high-risk at a younger age. If confirmed by future trials, this will have several implications for men's health and PCa health care and related polices. Utility benefits could include improved understating of biological pathways of onset and PCa progression, reduced overdiagnosis and overtreatment of low-risk disease, informed patient decision about PCa screening, and reduced screening costs and patient's financial distress.

The study, however, has some limitations that reduce the generalizability and applicability of the utility of PHS in a global PCa population. Major among these is the lack of data on most venerable PCa population (i.e., African ancestry). Including data from European ancestry from the international PRACTICAL consortium limit the understating of the applicability of risk model based on the identified 54 nucleotide polymorphisms. It is not clear whether the same set of nucleotide polymorphisms will be significantly associated with increased risk of PCa in other races especially men of African descendant. Additionally, according to the authors, family history did not improve prediction of onset of aggressive PCa. The authors justified the lack of significance of a well-established risk factors of PCa onset by the small validation data set used in this study. Alternatively, the familial genetic risk factors could be part of the nucleotide polymorphisms build PHS. Further analysis is warranted in this regard as the PCBaSe study identified age-specific risk of any, non-low, and high-risk PCa using family history factors from 51,897 brothers of 32,807 men with PCa (3).

In conclusion, the genetic risk model applied in this study is promising and might play a significant role in the future in guiding clinical and patient-provider shared decisions about PCa management. Future trials are needed to confirm the accuracy and applicability of this model in PCa, especially in ethnically diverse populations.

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Footnote

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