Editorial

Prediagnostic genetic stratification for aggressive prostate cancer—is the puzzle for genetic variants gaining shape?

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Introduction

Population-based screening for prostate cancer (PCa) using prostate-specific antigen (PSA) has shown to reduce the cancer-specific mortality but was associated with a high rate of overdiagnosis (1). The reason for this is the high prevalence of PCa (2). Thus, 27 men had to be diagnosed with PCa in order to prevent 1 PCa-specific death in the cited mass screening trial. It is important to recognize, that the mentioned screening study was a population-based trial (= every eligible participant providing consent was tested). There was no risk-stratification intended prior to PSA-testing. A PSA cut-off was the only trigger for biopsy irrespective of risk factors. In addition, conditions increasing the PSA-value such as benign prostate enlargement were not considered in the study protocol. The value of PSA screening is higher among individuals defined by particular characteristics, such as family history of PCa, ethnicity, increasing age, or genetic factors. Therefore, a prediagnostic information on the future risk for aggressive PCa might be of important clinical value in order to stratify individuals at risk. In an attempt to categorize men according to their future risk profile, efforts have been made including baseline PSA-values at younger age (3), family history (4) and single nucleotide polymorphism in the kallikrein 6 region (since PSA is a member of the kallikrein-family) (5).

Recently, a new study was published in the *British Medical Journal*. The authors aimed to identify men who might be at risk for PCa development and therefore would be candidates for a more focused (and earlier) PCa screening. More than 200,000 single nucleotide polymorphism (SNP) were analyzed in a development set by performing a stepwise regression framework in order to calculate the individual genetic risk. This yielded 54 SNP that were incorporated in a risk model. Clinical data was obtained from 31,747 men of the international "Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome" (PRACTICAL), which is a collaborative group of researchers investigating the inherited risk of PCa. Aggressive PCa was defined as Gleason Score ≥7, cT3/cT4 disease, PSA ≥10 ng/mL or cN1/cM1-disease). Finally, the model was tested in a validation set of 6,411 men from the ProtecT-Study (6) [1,583 men with an PCa, 632 with aggressive PCa, 220 with very aggressive PCa all diagnosed by transrectal ultrasound biopsy (TRUS) and 4,828 controls]. ProtecT assigned 1,643 men with localized PCa to active monitoring, surgery or radiation therapy. The authors conclude that the "*polygenic hazard scores can be used for personalized genetic risk estimates that can predict for age at onset for aggressive PCa*". Any effort to minimize overdiagnosis should be welcomed with open arms. However, a few questions remain:

Is the polygenic hazard scores safe? Does it reduce the unnecessary biopsy? Does is help preventing overdiagnosis? And finally: Does the polygenic hazard scores reduce PCa-specific mortality? Any combination variants might be used for risk prediction in order to improve screening for lethal disease. However, although there is a plethora of research on SNP`s for aggressive cancer (7-10), the puzzle for genetic variants is still not gaining shape for clinical purposes.

Conclusions

The variable clinical course of aggressive PCa makes the risk prediction difficult. "Proceed with caution!" (11) or in other words "publish these data with care" is one of the dictums standing for the current scientific situation. It is debatable, whether adding more SNPs will help preventing unnecessary biopsies, overdiagnosis or even death from PCa in the future.

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