Genetic Markers and the Risk of Developing Prostate Cancer

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In the current issue of European Urology, Aly et al. [1] reported on a study that investigated if a panel of 35 single nucleotide polymorphisms (SNPs) associated with prostate cancer could be used to determine whether biopsy of the prostate should be performed. They found that a genetic model may reduce the number of biopsies compared with a nongenetic model, but they also concluded that the clinical significance of this finding requires further evaluation.

Prostate cancer screening using a threshold based on a prostate-specific antigen (PSA) of 3 ng/ml as an indication for prostate biopsy lacks specificity. For values between 3 and 10 ng/ml, the estimated risk of being diagnosed with prostate cancer is only about 20–25% [2]. The lifetime risk of prostate cancer diagnosis is estimated at about 18%, whereas that for death from prostate cancer is only about 3%. Thus it is well established that the ubiquitous application of PSA screening has led to considerable overdetection and overtreatment in this group of patients.

A number of risk calculators (or nomograms) are being developed to predict a positive prostate biopsy and to support physicians in clinical decision making with respect to individual patients and reduce the number of unnecessary biopsies with a marginal loss of potentially aggressive tumours [3]. Using multivariable logistic regression analysis, the European Randomised Study of Screening for Prostate Cancer (ERSPC) section in Rotterdam developed the ERSPC risk calculator, which provides a clinically useful tool for any decision threshold compared with a model with PSA only, PSA and digital rectal examination (DRE), or biopsying all men. Limitations are that the model is based on sextant biopsy results, which is no longer up to date, and the fact that the model was developed from a screening population.

There is an urgent need to improve prediction models, not only to increase our ability to better identify patients with an increased risk of having prostate cancer but also to help clinicians distinguish between fatal and indolent prostate cancers.

Such attempts were recently presented by Vickers et al. [4], who showed an improved accuracy to predict biopsy outcome by the measurement of several forms of PSA. They developed a statistical model that predicts prostate biopsy outcomes based on age, DRE, and a panel of four kallikrein markers: total PSA, free PSA, intact PSA, and human kallikrein 2. Using data from the Swedish branch of the ERSCP screening study, they estimated that for every 1000 previously unscreened men with elevated total PSA, use of their model to determine biopsy would reduce biopsy rates by 573 while missing only a small number of cancers (31 of 152 low-grade cancers and 3 of 40 high-grade cancers). These findings were subsequently replicated in an independent cohort [5], and taken together, this model in addition to age and DRE substantially improved the predictive accuracy of a base model (composed of total PSA, age, and DRE) for both low- and high-grade cancers.

A family history of prostate cancer is one of the strongest risk factors, and twin studies suggest that heritable factors can explain as much as 42% of the disease risk [6].

Genome-wide association studies (GWASs) have recently emerged as a powerful method to identify genomic low-risk susceptibility regions for complex diseases including cancer [7]. New SNPs associated with prostate cancer risk are continuously being discovered [8]. Such risk SNPs are being measured today with high accuracy and at low cost using high-throughput technology. The question now raised by Aly et al. [1] whether in addition to a hereditary component a panel of SNPs associated with prostate cancer will improve the accuracy of an existing model to predict biopsy outcome is therefore both relevant and timely.

The study population (the Stockholm-1 cohort; \(n = 5241\)) consisted of men who underwent prostate biopsy...
from 2005 to 2007. Thirty-five validated SNPs were analysed and converted into a genetic risk score. Two prediction models were built to determine whether the genetic risk score could improve the prediction of prostate cancer diagnosis. The nongenetic model included total PSA, free-to-total PSA ratio, age at biopsy, and family history of prostate cancer (yes or no); the genetic model also included the genetic risk score. Associations between prostate cancer diagnosis and evaluated risk factors were explored in logistic regression analysis. The authors restricted their subsequent analyses to a subgroup of 2542 men having PSA values <10 ng/ml representing the grey zone, where it is debated whether or not a biopsy should be performed.

The strongest association was the combined genetic score \( (p < 0.0001) \), although all risk factors evaluated were significantly associated with biopsy outcome. When using the nongenetic model, the area under the curve (AUC) was 0.62 compared with 0.55 for PSA only. The full model, including the genetic score, increased the predictive performance further to an AUC of 0.67. Thus adding the genetic score modestly but significantly improved the prediction model. The authors performed additional analyses to investigate if the genetic model required significantly fewer biopsies than the nongenetic model, and they found that 480 biopsies (22.7%) could be avoided, at a cost of missing a prostate cancer diagnosis in only 3% of patients characterised as having aggressive disease. However, the genetic model could not discriminate between aggressive and nonaggressive prostate cancers.

For a biomarker (in this case a genetic signature) to be potentially clinically useful, it must show that adding the biomarker to an existing model based on the most important clinical and pathologic factors improves the predictive accuracy (discrimination and calibration) of the model \([9]\). In the current study \([1]\), Aly et al are to be congratulated for their attempt to incorporate the genetic score in a model that also includes standard clinical data (including PSA) and to judge the clinical usefulness of the genetic model in terms of the number of biopsies to be avoided in men with a PSA level <10 ng/ml.

Although the current study by Aly et al. \([1]\) represents a relatively new concept, there are other recent studies with a similar setup. Johansson et al. \([10]\) conducted a case-control study nested within a prospective cohort in northern Sweden consisting of 520 cases and 988 controls, and they used receiving operating characteristic curves with AUC estimates as measures of prostate cancer prediction. They found a marginal but significant improvement in the prediction of prostate cancer by adding the information on 33 common genetic risk variants to measures of PSA. The AUC for their genetic risk score was 0.64 compared with 0.86 for total PSA in combination with the ratio of free to total PSA. A full model including the genetic risk score, total PSA, and the ratio of free to total PSA increased the AUC to 0.87. Despite achieving relatively high AUC values, they concluded that the improvement in predictive accuracy did not appear useful for clinical risk assessment.

Although we hope to find a genetic signature that will prove even more useful in this context, we are clearly still in the early phase of adding signatures of genetic risk factors to prediction models. There are numerous publications on new promising biomarkers in prostate cancer, but the only biomarker used routinely to predict biopsy outcome in prostate cancer is PSA. Hence we cannot expect to find the perfect genetic signature very soon.

Major concerns about the usefulness of known risk-associated SNPs in the prediction of outcome in prostate cancer patients was recently discussed in a review article by Wiklund \([8]\), who made it clear that these SNPs in general perform poorly in discriminating cases from controls as judging from low AUC values. It is a common opinion that currently identified risk-associated SNPs only represent a small fraction of all possible risk-associated SNPs, and risk prediction models based on risk-associated SNPs known this far may therefore be unreliable and likely to change as new SNPs of interest are identified. Prostate cancer risk variants with a great capacity to discriminate between indolent and aggressive forms of prostate cancer are also urgently needed. To discover inherited genetic variants associated with aggressive and nonaggressive prostate cancers, we need studies with optimal design and large well-defined cohorts.

Prostate cancer is one of the most heritable cancers in men, indicating that risk-associated genetic factors should be included in an optimised model to predict the risk of developing prostate cancer. Recent GWASs have revealed numerous genetic variants associated with an increased risk of being diagnosed with prostate cancer, and genetic signatures are now ready to be evaluated in existing prediction models. This approach may help address the significant issue of overscreening and overdiagnosis of prostate cancer. However, future studies should aim at detecting strong genetic risk factors useful to identify fatal variants of prostate cancer. The ultimate goal, then, is a genetic-based targeted PSA screening strategy to reduce both overdiagnosis and mortality by identifying those men at risk for fatal prostate cancer at a curable stage.

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**References**


