Genetic predisposition to early recurrence in clinically localized prostate cancer.


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Abstract

WHAT’S KNOWN ON THE SUBJECT? AND WHAT DOES THE STUDY ADD?: Currently available nomograms to predict preoperative risk of early biochemical recurrence (EBCR) after radical prostatectomy are solely based on classic clinicopathological variables. Despite providing useful predictions, these models are not perfect. Indeed, most researchers agree that nomograms can be improved by incorporating novel biomarkers. In the last few years, several single nucleotide polymorphisms (SNPs) have been associated with prostate cancer, but little is known about their impact on disease recurrence. We have identified four SNPs associated with EBCR. The addition of SNPs to classic nomograms resulted in a significant improvement in terms of discrimination and calibration. The new nomogram, which combines clinicopathological and genetic variables, will help to improve prediction of prostate cancer recurrence.

OBJECTIVES: To evaluate genetic susceptibility to early biochemical recurrence (EBCR) after radical prostatectomy (RP), as a prognostic factor for early systemic dissemination. To build a preoperative nomogram to predict EBCR combining genetic and clinicopathological factors.

PATIENTS AND METHODS: We evaluated 670 patients from six University Hospitals who underwent RP for clinically localized prostate cancer (PCa), and were followed-up for at least 5 years or until biochemical recurrence. EBCR was defined as a level prostate-specific antigen >0.4 ng/mL within 1 year of RP; preoperative variables studied were: age, prostate-specific antigen, clinical stage, biopsy Gleason score, and the genotype of 83 PCa-related single nucleotide polymorphisms (SNPs). Univariate allele association tests and multivariate logistic regression were used to generate predictive models for EBCR, with clinicopathological factors and adding SNPs. We internally validated the models by bootstrapping and compared their accuracy using the area under the curve (AUC), net reclassification improvement, integrated discrimination improvement, calibration plots and Vickers’ decision curves.

RESULTS: Four common SNPs at KLK3, KLK2, SULT1A1 and BGLAP genes were independently associated with EBCR. A significant increase in AUC was observed when SNPs were added to the model: AUC (95% confidence interval) 0.728 (0.674-0.784) vs 0.763 (0.708-0.817). Net reclassification improvement showed a significant increase in probability for events of 60.7% and a decrease for non-events of 63.5%. Integrated discrimination improvement and decision curves confirmed the superiority of the new model.

CONCLUSIONS: Four SNPs associated with EBCR significantly improved the accuracy of clinicopathological factors. We present a nomogram for preoperative prediction of EBCR after RP.

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