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Single nucleotide polymorphisms and risk of recurrence of renal-cell carcinoma: a cohort study

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Summary

Background
Germline genetic polymorphisms might affect the risk of recurrence in patients with localised renal-cell carcinoma. We investigated the association between genetic polymorphisms and recurrence of renal-cell carcinoma.

Methods
We analysed germline DNA samples extracted from patients with localised renal-cell carcinoma treated at the Dana-Farber/Harvard Cancer Center (Boston, MA, USA). We selected a discovery cohort from a prospective database at the Dana-Farber/Harvard Cancer Center and selected a validation cohort from department records at the Brigham and Women's Hospital (Boston, MA, USA). We validated the findings from the discovery cohort in the validation cohort. We genotyped 70 genes involved in the pathogenesis of renal-cell carcinoma (including the VHL/HIF/VEGF and PI3K/AKT/mTOR pathways, and genes involved in immune regulation and metabolism) for single nucleotide polymorphisms. We assessed the association between genotype and recurrence-free survival, adjusted for baseline characteristics, with the Cox proportional hazards model, the Kaplan-Meier method, and the log-rank test. We used a false discovery rate q value to adjust for multiple comparisons.

Findings
We included 554 patients (403 in the discovery cohort and 151 in the validation cohort). We successfully genotyped 290 single nucleotide polymorphisms in the discovery cohort, but excluded five because they did not have a variant group for comparison. The polymorphism rs11762213, which causes a synonymous aminoacid change in *MET* (144G→A, located in exon 2), was associated with recurrence-free survival. Patients with one or two copies of the minor (risk) allele had an increased risk of recurrence or death (hazard ratio [HR] 1·86, 95% CI 1·17—2·95; p=0·0084) in multivariate analysis. Median recurrence-free survival for carriers of the risk allele was 19 months (95% CI 9—not reached) versus 50 months (95% CI 37—75) for patients without the risk allele. In the validation cohort the HR was 2·45 (95% CI 1·01—5·95; p=0·048).

Interpretation
Patients with localised renal-cell carcinoma and the *MET* polymorphism rs11762213 might have an increased risk of recurrence after nephrectomy. If these results are further validated in a similar population, they could be incorporated into future prognostic instruments, potentially aiding the design of adjuvant clinical trials of *MET* inhibitors and management of renal-cell carcinoma.

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