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Somatic Genetic Mutations in Urogenital Tumors.

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The present study was aimed at investigating the somatic genetic alterations in two non-hormonally driven urological cancers (bladder and kidney cancer). The non-coding somatic mutations in the *TERT* promoter region were investigated in bladder and kidney cancer. Somatic mutations in the *FGFR3* gene were also investigated in bladder cancer. The results from this study showed that the *TERT* promoter mutations in conjunction with common allele for the rs2853669 polymorphism define bladder cancer patients that are at an increased risk of recurrence and poor survival. *FGFR3* mutations, in contrast, were not independently associated with either disease recurrence or cause-specific patient survival in bladder cancer. Tumors with *TERT* promoter and/or *FGFR3* mutations carried shorter telomeres than those without mutations, thus indicating mechanistic relevance of telomere biology in etiology of the disease. In clear cell renal cell carcinoma of the kidney, relatively low frequencies of *TERT* promoter mutations were present. Nevertheless, patients with the mutations, particularly in the absence of the rs2853669 polymorphism showed the worst disease-specific survival. Thus, both in bladder and kidney cancer, the *TERT* promoter mutations define a small subset of tumors that are at an increased risk and can be used as a potential biomarker for predicting disease recurrence and patient survival.

The investigation of somatic mutations in the two non-hormonally driven urogenital cancer types led to the following major findings in this study:

(1) *TERT* promoter mutations are the most common somatic genetic alterations in bladder cancer with even distribution across all tumor stages and grades; (2) association of the *TERT* promoter mutations with poor patient survival and disease recurrence, through an interaction with a common polymorphism (rs2853669) in the same locus; (3) association of the mutations in increasing *TERT* promoter activity in bladder cancer cell lines; (4) co-occurrence of *TERT* promoter and *FGFR3* mutations in the low grade bladder tumors; (5) association of the *TERT* promoter and/or *FGFR3* mutations with shorter relative telomere length in bladder cancer; (6) low frequency *TERT* promoter mutations in kidney cancer and its association with poor patient survival.