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Letter to the editor:

IMPACT OF URINARY BLADDER CANCER RISK VARIANTS ON PROGNOSIS AND SURVIVAL

Silvia Selinski

Leibniz Institut für Arbeitsforschung an der TU Dortmund, Leibniz Research Centre for Working Environment and Human Factors (IfADo), Ardeystrasse 67, 44139 Dortmund, Germany; selinski@ifado.de

Dear Editor,

Bladder cancer is one of the most common cancers in men and the 15th most common cancer in European women (Ferlay et al., 2013). Though the prognosis for non-muscle invasive tumours is generally good, a major problem are the frequent relapses (30-80 %) and the risk of progression to muscle invasive tumours (van Rhijn et al., 2009). Development of bladder cancer can be attributed mostly to tobacco smoke and occupational as well as to a genetic predisposition (Brennan et al., 2000; Golka et al., 2002, 2004; Boffetta, 2008; Rushton et al., 2012; Schwender et al., 2012; Bolt, 2013a, b; Burger et al., 2013; Egbers et al., 2014). Polymorphisms of phase II metabolizing enzymes are well-known since many years to modulate bladder cancer risk, in particular, in presence of exposure to bladder carcinogens (Garcia-Closas et al., 2005; Moore et al., 2011). The impact of the deletion variant of *glutathione-S-transferase M1* (*GSTM1*) (Arand et al., 1996; Golka et al., 1997, 2008; 2009; Ovsiannikov et al., 2012) and the polymorphic *N-acetyltransferase 2* (*NAT2*) gene (Garcia-Closas et al., 2005; Golka et al., 1996, 2002; Rothman et al., 2010; Moore et al., 2011; Selinski et al., 2011, 2013a, 2013b, 2014; Blaszkewicz, 2013) is well understood. Since 2008 large genome-wide association studies (GWAS) have discovered a panel of further moderate risk polymorphisms located in twelve regions across the genome (Selinski, 2014b). However, the functional role of these variants is still not clear for most of them (Grotenhuis et al., 2010; Golka et al., 2011; Selinski, 2012, 2013, 2014b; Dudek et al., 2013). Current studies aim to investigate common effects of variants and their interaction with exposure to bladder carcinogens (Schwender et al., 2012; Hammad, 2013; Selinski, 2014a). However, the impact of genetic risk factors on recurrence, progression and survival is poorly understood and a genome-wide search for prognostic polymorphisms is still lacking.

Most studies concentrate on the impact of *glutathione S-transferases* (*GST*), mainly *GSTM1* and *GSTT1*, or on other polymorphic candidate genes. Besides overall survival, often restricted to the subgroup of muscle invasive bladder cancer (MIBC) patients, relapse- and progression-free survival in non-muscle invasive bladder cancer (NMIBC) cases is of main interest due to the high recurrence risk.

Studies on the *GST* polymorphisms show a wide range of positive and negative findings requiring larger studies and careful meta-analyses. In particular, polymorphic *GSTs* might be relevant in patient subgroups (Kang et al., 2014). Recent studies show the following results:

- *GSTT1* positive genotypes were associated with a shorter recurrence and progression free survival time (Ha et al., 2010).
- *GSTM1* negative tumor tissues were associated with shorter recurrence free survival in NMIBC patients (Ha et al., 2011).
- *GSTM1* negative bladder cancer patients from the Copenhagen City Heart Study had a decreased 5-year survival (Nørskov et al., 2011).
- *GSTT1* null genotype was associated with shorter recurrence-free survival time. No association was found in case of *GSTM1*, *NAT2*, and the GWAS SNPs rs710521 (*TP63*) and rs9642880 (*MYC*) (Roth et al., 2012).
- Polymorphic *GSTT1*, *GSTO1* and *GSTO2* were associated with overall survival. No association with survival was found in case of *GSTP1*, *GSTM1* and *GSTA1* (Djukic et al., 2013).
- *GSTT1* null genotype was associated with disease progression and shorter survival time in MIBC cases (Kang et al., 2013).
- *GSTT1* positive genotype was associated with shorter survival time and BCG therapy failure in NMIBC patients (Kang et al., 2014).

A number of recent studies concentrate on polymorphisms in selected candidate genes. Validation by an independent research group is still lacking though the authors often replicated their findings in further study groups. Candidate genes are usually cancer-related but also miRNA polymorphisms.

- miR-146a SNP rs2910164 was associated with bladder cancer risk and recurrence in a large Chinese study (Wang et al., 2012).
- In a study of miRNA biogenesis genes *DDX20* (*DEAD (Asp-Glu-Ala-Asp) box polypeptide 20*) missense SNP rs197412 was associated with longer recurrence-free survival in NMIBC patients. Two *DGCR8* (*DGCR8 microprocessor complex subunit*) SNPs rs2073778 and rs720012 were associated with tumor progression (Ke et al., 2013).
- In a study of *regulator of G-protein signaling* (*RGS*) gene variants *RGS5* (*regulator of G-protein signaling 5*) intron SNP rs2344673 was associated with survival in MIBC patients. Rs1323291, rs3795617 and rs16829458 were associated with risk of recurrence in NMIBC patients. Rs1323291, rs10917690, rs6678136 and rs11585883 were associated with risk of progression from NMIBC to MIBC (Lee et al., 2013).
- *TERT* (*telomerase reverse transcriptase*) promotor mutations were associated with survival and recurrence (Rachakonda et al., 2013).
- Five SNPs in the *XRCC1* (*X-ray repair complementing defective repair in Chinese hamster cells 1*) repair gene were associated with better survival (Sacerdote et al., 2013).
- *TSP-1* (*thrombospondin-1*) SNP rs2169830 was associated with recurrence time and *TSP-1* mRNA expression (Yang et al., 2013).
- The largest study so far on candidate SNPs was just published by Andrew et al. (2014) investigating the association of 1367 SNPs from about 400 potentially cancer-related genes, e. g. from apoptosis, proliferation, DNA repair, hormone regulation, immune surveillance, and cellular metabolism pathways. *ALDH2* (*aldehyde dehydrogenase 2 family (mitochondrial)*) SNP rs2238151 and *IGF1* (*insulin-like growth factor 1 (somatomedin C)*) SNP rs5742714 were associated with a shorter recurrence-free time. *XRCC4* (*X-ray repair complementing defective repair in Chinese hamster cells 4*) SNP rs2662238, *DRD4* (*dopamine receptor D4*) SNP rs4987059 and *RB1CC1* (*RB1-inducible coiled-coil 1*) SNP rs35402311 were associated with overall survival in NMIBC patients (Andrew et al., 2014).

So far, only one study investigated the complete panel of candidate variants from GWAS.

- Grotenhuis et al. (2014) investigated twelve confirmed bladder cancer polymorphisms with regard to recurrence and progression in NMIBC patients and to overall survival in MIBC patients. The *MYC* near SNP rs9642880 was associated with progression-free but not with recurrence-free survival in NMIBC patients or with overall survival in MIBC cases. The *TACC3-FGFR3* (*transforming, acidic coiled-coil containing protein 3 - fibroblast growth factor receptor 3*) SNP rs798766 was associated with recurrence-free survival in non-smoking NMIBC cases. The *NAT2* tagSNP rs1495741 was associated with recurrence in ever smoking NMIBC cases and progression-free survival in non-smoking NMIBC cases. No association with recurrence- or progression-free survival or with overall survival was found in case of the *GSTM1* deletion, the *UGT1A* (*UDP glucuronosyltransferase 1 family, polypeptide A6*) SNPs rs11892031 and rs17863783, *TP63* (*tumor protein p63*) near rs710521, the *CLPTM1L-TERT* (*CLPTM1-like telomerase reverse transcriptase*) SNPs rs401681 and rs2736098, the *PSCA* (*prostate stem cell antigen*) SNPs rs2294008 and rs2978974, rs1058396 (*SLC14A1, solute carrier family 14 (urea transporter), member 1*), rs8102137 (*CCNE1, cyclin E1*) and rs1014971 (*CBX6-APOBEC3A, chromobox homolog 6 - apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3A*) (Grotenhuis et al., 2014).

Most of the studies comprise more than 200 cases similar to the validation case-controls series in the GWAS. Thus, reasonable validation case groups are available and special emphasis should be placed on a systematic genome-wide search for prognostic variants.

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