O14 Urothelial bladder cancer risk patterns according to tumor taxonomic subtypes

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Introduction & Objectives: Urothelial bladder cancer (UBC) is a complex disease with diverse genetic and environmental factors participating and interacting in its development. There are suggestive evidences indicating that UBC is a heterogeneous disease, with pathological and molecular subtypes having been characterized. This study aims to assess the UBC risk factors associated with UBC taxonomic subtypes.

Materials & Methods: Study subjects came from the SBC/EPICURO case-control study. Paraffin embedded tumour tissue were obtained from 1,200 UBC cases and used to assess immunohistochemical protein expression. The expression of KRT5/6, KRT14, FOXA1 and GATA3 was measured using histoscore and unsupervised hierarchical cluster was used to define the UBC subtypes. We analysed the association between subtypes and genetic and non-genetic risk factors. For non-genetic variables, we applied a multinomial logistic regression, adjusting for age, gender, region and smoking status. For genetic variables, we applied multinomial ENET to consider 446,593 SNPs that passed quality control filtering from 1,122,327 genotyped with Ilumina HumanHap1M array. Finally, we ordered the selected SNPs based on their p-values extracted from a univariate multinomial logistic regression.

Results: Three significant clusters were observed according to the four markers: BASQ-like signature (8% of cases: high KRT14-KRT5/6; low GATA3-FOXA1), Luminal-like signature (64% of cases: high GATA3-FOXA1; low KRT14-KRT5/6) and Mixed signature (28% of cases).
Tobacco smoking and risky occupational exposures conferred a lower risk among BASQ-like tumours (OR=6.5; 95%CI: 4.5-9.5 and OR=1.5; 95%CI: 0.7-3.1, respectively) in comparison to the UBC other subtypes. A higher risk of BASQ-like tumours was associated with non-treated bladder infections (OR=4.8, CI95% 1.5-15.1) in comparison to Luminal-like tumours (OR=2.3, CI95% 1.2-4.6). A total of 3,681 SNPs selected by ENET were associated with specific UBC subtypes showing very divers risk patterns for the different subtypes.

Conclusions: This study provides evidence that UBC subtypes display different association patterns with genetic and non-genetic risk factors. Our results provide new insights of UBC aetiology and genetic susceptibility that could help to better define high-risk UBC population.