

題名:Joint Effects of Cigarette Smoking and Individual Susceptibility on Risk of Urothelial Carcinoma.

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摘要:Nucleotide excision repair (NER) is critical for protecting against damage from carcinogens in tobacco smoke. We evaluated the influence of common genetic variation in the NER pathway on bladder cancer risk by analyzing 22 single nucleotide polymorphisms (SNP) in seven NER genes (XPC, RAD23B, ERCC1, ERCC2, ERCC4, ERCC5, and ERCC6). Our study population included 1,150 patients with transitional cell carcinoma of the urinary bladder and 1,149 control subjects from Spain. Odds ratios (OR) and 95% confidence intervals (95% CI) were adjusted for age, gender, region, and smoking status. Subjects with the variant genotypes for SNPs in four of the seven genes evaluated had small increases in bladder cancer risk compared to subjects with the homozygous wild-type genotypes: RAD23B IVS5-15A>G (OR, 1.3; 95% CI, 1.1-1.5; P = 0.01), ERCC2 R156R (OR, 1.3; 95% CI, 1.1-1.6; P = 0.006), ERCC1 IVS5+33A>C (OR, 1.2; 95% CI, 1.0-1.5; P = 0.06; P(trend) = 0.04), and ERCC5 M254V (OR, 1.4; 95% CI, 1.0-2.0; P = 0.04). A global test for pathway effects indicated that genetic variation in NER characterized by the 22 SNPs analyzed in this study significantly predicts bladder cancer risk (P = 0.04). Pairwise comparisons suggested that carrying variants in two genes could result in substantial increases in risk. Classification tree analyses suggested the presence of subgroups of individuals defined by smoking and NER genotypes that could have substantial increases in risk. In conclusion, these findings provide support for the influence of genetic variation in NER on bladder cancer risk. A detailed characterization of genetic variation

in key NER genes is warranted and might ultimately help identify multiple susceptibility variants that could be responsible for substantial joint increases in risk.