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Molecular epidemiology and cancer susceptibility - Genetic polymorphisms and susceptibility to urothelial cancer -

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Arylamines are suspected to be the primary causative agent of urothelial cancer in tobacco smoke. In the human liver, arylamines are *N*-hydroxylated by a cytochrome P450 (CYP) 1A2-catalyzed reaction, which produces a substrate for *O*-esterification that can be catalyzed by *N*-acetylatransferases (NAT) or sulfotransferases (SULT). Recently, several polymorphisms of *CYP1A2*, *SULT1A1* and *NAT2* that affect their activities have been reported. In this study, 306 Japanese patients with urothelial transitional cell carcinoma and 306 healthy controls were compared for frequencies of *CYP1A2*, *SULT1A1* and *NAT2* genotypes. The frequencies of *NAT2* intermediate or slow acetylator genotype were significantly higher in the urothelial cancer patients than in the healthy control subjects (OR=1.49, 95% CI, 1.06-2.09, OR=3.23, 95% CI, 1.72-6.08, individually). Stratifying by amount of smoking, among subjects who consumed $\geqq$40 pack-years and carried the *SULT1A1* $^{*}1/^{*}1$ or *NAT2* slow acetylator genotype, the OR was 1.87 (95% CI, 1.07-3.26) or 6.53 (95% CI, 1.69-25.28) with non-smokers who carried the homozygous wild genotype, respectively. The relationships between *CYP1A2*, *SULT1A1* and *NAT2* polymorphisms and clinical findings including differentiation, stage, survival time and recurrence rate were analyzed. Only associations between *NAT2* genotype and pathological finding were admitted, and the higher OR of *NAT2* slow acetylator genotype was more likely to

present to a low grade tumor (G1) or a superficial tumor among heavy smokers. Our results suggest that *SULT1A1* *1/*1 and *NAT2* slow acetylator genotype might modulate the effect of carcinogenic arylamines contained in tobacco smoke, and the modulation of *NAT2* slow acetylator genotype has a tendency to present a higher risk for highly differentiated and superficial tumors among heavy smokers.