

Association between Head and Neck Cancer and Microsomal Epoxide Hydrolase Genotypes  
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Squamous cell cancer of the head and neck (SCCHN) is a group of epithelial cancers of the upper aerodigestive tract which are mainly caused by smoking and other lifestyle factors. Polycyclic aromatic hydrocarbons (PAH), a tobacco smoke constituent, are metabolized in a cytochrome P450-mediated process to highly reactive epoxides which are converted by human microsomal epoxide hydrolase (mEH) to trans-dihydrodiols. Sequence variations in the gene EPHX1 encoding for mEH may alter the enzyme activity and thus modulate the risk of PAH for tobacco-related cancer, especially in smokers. mEH has polymorphic variants with either a Tyr (Y) or His (H) substitution in codon 113 and either a His (H) or Arg (R) substitution in codon 139. EPHX1 genotype combinations, according to in-vitro expression studies of cDNA published in 1994, were used in literature to predict a putative low, medium and high mEH activity. We conducted a case-control study with 280 SCCHN cases and 289 non-cancer controls to estimate the SCCHN risk of the Y113H and H139R EPHX1 polymorphisms with respect to smoking habits and putative enzyme activity. Genomic DNA isolated from whole blood was genotyped with a LightCycler™ instrument (Roche, Mannheim, Germany). We found allele frequencies of 31% for the 113H allele and of 21% for the 139R allele in controls which correspond to literature. We could not detect overall SCCHN risks of the genotypes (for 113YH OR 0.83, 95% CI 0.56-1.23; for 113HH OR 0.89, 95% CI 0.45-1.75, for 139HR OR 0.75, 95% CI 0.51-1.12, for 139RR OR 1.38, 95% 0.50-3.80), but a lower risk of the 139HR genotype in smokers (OR 0.57; 95% CI 0.34-0.95). There was no SCCHN excess risk for genotype combinations according to a putative medium or high enzyme activity, but heterogeneity within these categories among smokers using the 113HH/139HH genotype combination, assigned to the putative low enzyme activity category, as reference (Wald  $\chi^2$  test P=0.02). With the exception of 113YY/139RR, the other genotype combinations were associated with a lower risk than 113HH/139HH. Especially the putative high genotype combinations 113YY/139HR and 113YH/139RR were associated with a significantly lower risk (OR 0.30; 95% CI 0.09-0.97 and OR 0.10; 95% CI 0.01-0.93 respectively). The two variant amino acids are far away from the catalytic center of the protein. Meanwhile, new sequence variations and data on mEH expression and enzyme activity have been reported. We conclude that the impact of the EPHX1 sequence variations on the enzyme activity is still not yet conclusive for genotype-phenotype relations.