

A130

Association between lung cancer risk and single nucleotide polymorphisms in the first intron and codon 178 of the DNA Repair gene O⁶-alkylguanine-DNA alkyltransferase

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Intragenic polymorphisms influence the expression and function of the DNA repair protein O⁶-alkylguanine DNA alkyltransferase (MGMT) and may influence cancer risk. Here we investigate both the association between lung cancer risk and the allele frequencies of two polymorphisms (Snp3 and K178R) associated with inter-individual differences in MGMT expression levels, in a series of hospital based case-control studies and the functional activity of MGMT variants. Subjects were recruited over a 10 year period in three separate case-control series. Genotyping was carried out on 649 subjects of which 273 had lung cancer. The inactivation of MGMT variants by low molecular weight substrates was examined *in vitro*.

There were differences in allele frequencies between cases and controls for K178R but not for Snp3 polymorphisms. The frequency of the R allele was lower in cases than controls (0.10 versus 0.15; p=0.02), particularly in heavy smokers (0.09 vs 0.17 in cases and controls ; p=0.005). The OR (95%CI) associated with carrying the R allele was 0.64 (0.43-0.93) after adjustment for age, sex and series number. There was evidence of a decreased risk for heterozygotes (OR, 95%CI = 0.70, 0.48-1.03) and a greater decrease for RR homozygotes (0.14, 0.02-1.10: p trend test=0.01). The V143-R178 allele showed a modest but significantly reduced activity towards low molecular weight substrates compared to the I143-K178 allele. Functional difference between the two alleles may contribute to differences in cancer risk.