Null Results in Brief

No Association between the XPD (Lys751G1n) Polymorphism or the XRCC3 (Thr241Met) Polymorphism and Lung Cancer Risk

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Introduction

DNA repair helps to protect the genome from tobacco-induced damage. Reduced DNA repair capacity may predispose individuals to lung cancer (1). Polymorphisms in genes encoding DNA repair proteins may modulate susceptibility to tobacco lung carcinogens.

Bulk DNAs adducts induced by chemical carcinogens in cigarette smoke are repaired through the nucleotide excision repair pathway that includes the XPD gene. An XPD variant in exon 23 leading to a Lys751G1n amino acid substitution has been associated with reduced DNA repair capacity (2). DNA strand breaks generated by reactive oxygen species in tobacco smoke may be repaired through the homology-directed double-stranded DNA break repair pathway that includes XRCC3. A nucleotide substitution in exon 7 of the XRCC3 gene results in an amino acid change Thr241Met. There are few data on these polymorphisms in relation to lung cancer (3, 4).

To investigate the possible association between the XPD Lys751G1n and XRCC3 Thr241Met polymorphisms and the risk of lung cancer among Caucasians and African Americans, we analyzed DNA samples from a case-control study of 331 incident lung cancer cases and 687 population controls in Los Angeles County, California.

Materials and Methods

Detailed descriptions of the methods of subject enrollment and study population have been published previously (5). The XPD codon 751 genotypes were determined using a PCR-RFLP technique as described previously (2). The XRCC3 codon 241 genotypes were also determined using PCR-RFLP. The XRCC3 polymorphic site was amplified from 50 ng of DNA using 0.8 M of each primer (forward primer, 5'-TTGAGGCTTCTT-GAGA-3'; reverse primer, 5'-AACGCGTAGGCTTTCTCTT-3'), 200 μM of each deoxynucleotide triphosphate, 0.5 unit of Taq polymerase (Promega), Madison, WI) and Taqstart antibody (Sigma Chemical Co., St. Louis, MO), and 2 mM MgCl2 in 1× PCR buffer (Promega). The PCR cycling conditions consisted of initial denaturation at 94°C for 4 min followed by 30 cycles of 94°C for 30 s, 60°C for 30 s, and 72°C for 1 min, and a final step at 72°C for 7 min. The products were digested with NlaIII (New England Biolabs, Beverly, MA) and resolved on 3% metaphor agarose gels (BioWhittaker Molecular Applications, Rockland, ME). The three possible genotypes are defined by distinct banding patterns: (a) Thr/Thr (239 and 313 bp); (b) Thr/Met (105, 208, 239, and 313 bp); and (c) Met/Met (105, 208, and 239 bp). As a quality control, both assays were repeated on 5% of the samples, and the replicates were 100% concordant.

ORs and 95% CIs were calculated by unconditional logistic regression using SAS version 8 (SAS Institute, Cary, NC). All ORs are adjusted for age and sex and for smoking (the natural logarithm of pack-years and a product term for pack-years and years since quitting smoking). Results in all subjects were also adjusted for ethnicity.

Results and Discussion

The frequency of the XPD Gln-751 allele was 0.347 for Caucasians and 0.250 for African Americans. The XRCC3 Met-241 allele frequency was 0.382 for Caucasians and 0.231 for African Americans. The frequencies were consistent with previous studies (2–4) and were in Hardy-Weinberg equilibrium among controls in both ethnic groups.

Our data do not support any appreciable association between XPD codon 751 or XRCC3 codon 241 genotypes and lung cancer risk in either ethnic group (Table 1). We combined the data for Caucasians and African Americans because we had good power for these modest associations with these common polymorphisms. Our data in African Americans and Caucasians are in agreement with two recent studies showing no substantive evidence of a differential risk for lung cancer ac-
cording to XPD codon 751 (3, 4) or XRCC3 codon 241 (4) polymorphisms.

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References


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