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Single Nucleotide Polymorphisms in Nucleotide Excision Repair Genes, Cigarette Smoking, and the Risk of Head and Neck Cancer

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Abstract

Background—Cigarette smoking is associated with increased head and neck cancer (HNC) risk. Tobacco-related carcinogens are known to cause bulky DNA adducts. Nucleotide excision repair (NER) genes encode enzymes that remove adducts and may be independently associated with HNC, as well as modifiers of the association between smoking and HNC.

Methods—Using population-based case-control data from the Carolina Head and Neck Cancer Epidemiology Study (1,227 cases, 1,325 controls), race-stratified (white, African American) conventional and hierarchical logistic regression models were utilized to estimate odds ratios (OR) with 95% intervals (I) for the independent and joint effects of cigarette smoking and 84 single nucleotide polymorphisms (SNPs) from 15 NER genes on HNC risk.

Results—The odds of HNC were elevated among ever cigarette smokers, and increased with smoking duration and frequency. Among whites, rs4150403 on *ERCC3* was associated with increased HNC odds (AA+AG vs. GG, OR=1.28, 95% I=1.01,1.61). Among African Americans, rs4253132 on *ERCC6* was associated with decreased HNC odds (CC+CT vs. TT, OR=0.62, 95% I=0.45,0.86). Interactions between ever cigarette smoking and three SNPs (rs4253132 on *ERCC*6, rs2291120 on *DDB2*, and rs744154 on *ERCC4*) suggested possible departures from additivity among whites.

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Conclusions—We did not find associations between some previously studied NER variants and HNC. We did identify new associations between two SNPs and HNC and three suggestive cigarette-SNP interactions to consider in future studies.

Impact—We conducted one of the most comprehensive evaluations of NER variants, identifying a few SNPs from biologically plausible candidate genes associated with HNC and possibly interacting with cigarette smoking.

Keywords

Head and neck/oral cancers; DNA damage and repair mechanisms; DNA repair polymorphisms and risk; tobacco

Introduction

Head and neck cancer (HNC) includes tumors, principally squamous cell carcinomas, of the oral cavity, pharynx, and larynx (1). In the United States, an estimated 52,610 incident HNC cases and 11,500 associated deaths occurred in 2012 (2). Cigarette smoking is a major risk factor for HNC incidence with case-control studies consistently reporting elevated odds ratios (ORs) for ever smoking, as well as dose-response gradients with duration and frequency (3). Among non-alcohol drinking HNC cases, 25% of cases are attributed to cigarette smoking (4).

Cigarette smoke contains numerous carcinogens, such as benzo-a-pyrene, that are known to cause DNA damage, including adducts (3, 5-7). Nucleotide excision repair (NER) enzymes are principally responsible for removing bulky DNA adducts, and are therefore hypothesized to be independent risk factors for HNC, as well as important modifiers of the association between smoking and HNC (5-7). Several previous studies have considered associations between variants in NER genes and HNC risk, but studies vary with regard to which specific single nucleotide polymorphisms (SNPs) were investigated and often present inconsistent evidence for analysis of the same SNP (8-49). In general, most previous studies have evaluated only a few SNPs on a single NER gene among a few hundred HNC cases (8-49). Few studies have examined the association of NER SNPs and HNC among African-Americans (16), a group shown to have a stronger association for smoking and HNC (50). Studies of cigarette-SNP joint effects have also been limited by sparse numbers of NER variants and small sample sizes and present varying results, though some studies indicate strong associations among smokers with polymorphisms in NER genes (8, 10-12, 14, 16, 17, 23, 25, 27-29, 31, 32, 34, 36-40, 44).

To comprehensively assess associations between cigarette smoking, NER genes, and HNC risk, we used data from the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study to estimate main and joint effects of cigarette smoking and 84 SNPs across 15 NER genes on HNC risk among a racially diverse population including whites (922 cases and 1074 controls) and African Americans (305 cases and 251 controls).

Methods

Study Population

The CHANCE Study is a population-based case-control study of 1,389 cases and 1,396 controls from 46 of 100 counties in North Carolina (NC) (50-52). Eligible participants were 20 to 80 years of age (50-52). Cases were identified from the NC Central Cancer Registry between January 1, 2002 and February 28, 2006 using rapid case ascertainment (50-52). Tumors were classified according to ICD-O-3 codes; squamous cell carcinomas of the oral cavity (C02.0-C02.3; C03.0-C03.1; C03.9-C04.1; C04.8-C05.0; C06.0-C06.2; C06.8-

C06.9), oropharynx (C01.9; C02.4; C05.1-C05.2; C09.0-C09.1; C09.8-C10.4; C10.8-C10.9), hypopharynx (C12.9-C13.2; C13.8-C13.9); larynx (C32.0-C32.3; C32.8-C32.9), and oral cavity/pharynx not otherwise specified (C02.8-C02.9; C05.8-05.9; C14.0; C14.2; C14.8) were included in the study, while tumors of the salivary glands, nasopharynx, nasal cavity, and nasal sinuses were excluded (50-53). Controls were randomly sampled from the NC Department of Motor Vehicle records and frequency matched to cases within strata of age, race, and sex (50-52).

For this analysis, we excluded cases and controls who did not provide blood or buccal cell samples, whose samples were insufficient for genotyping, or whose samples did not otherwise meet quality control criteria [115 (8.3%) cases and 53 (3.8%) controls[(52). We further excluded individuals who self-reported race other than white or African American because of sparse data [26 (1.9%) cases and 18 (1.3%) controls] and cases with lip cancers because of etiologic differences [21 (1.5%) cases] (52). Our final sample included 1, 227 HNC cases and 1,325 controls.

Cigarette Smoking

Self-reported demographic and behavioral information was ascertained through nurse-administered questionnaires (50-52). Information on cigarette smoking included ever/never, current/former, frequency (cigarettes/day) and duration (years). Information on environmental tobacco smoke (ETS) included ever/never and duration (years) of exposure in the home and at work (50).

SNP Selection and Genotyping

Blood (~90%) or buccal cell (~10%) samples were collected from cases and controls at the time of interview for DNA extraction (52). An Illumina GoldenGate assay with Sentrix Array Matrix and 96-well standard microtiter platform was used to genotype 1,536 SNPs, including 129 SNPs in 15 NER genes (52, 54). Seventy-one tag SNPs in NER genes were selected based on a case-control study of HNC at MD Anderson Cancer Center, which queried NIEHS-EGP and HapMap databases using selection criteria of $r^2 \geq 0.80$, a minor allele frequency (MAF)≥0.05, 1-2kb flanking regions, and the CEU population (Supplementary Table 1S) (55-57). Another 58 SNPs in NER genes were selected based on several criteria including association in other cancer studies and/or potential function (Supplementary Table 1S). We excluded 14 SNPs for which genotyping resulted in poor signal intensity or genotype clustering (52), as well as SNPs with a minor allele frequency less than 0.05 (31 SNPs among whites and 36 SNPs among African Americans) (Supplementary Table 1S). Most excluded SNPs had been selected based on previous literature and/or function (Supplementary Table 1S). Among the remaining SNPs, genotype frequencies for 7 SNPs in whites and 7 SNPs in African Americans were inconsistent with Hardy-Weinberg equilibrium (HWE; $p<0.05$) (Supplementary Table 1S); however, because genotyping scatter plots showed reasonable genotype clustering, these SNPs were included in analyses but interpreted with caution (58). Our final analysis included 84 SNPs in 14 NER genes among whites and 79 SNPs in 15 NER genes among African Americans.

Statistical Analysis

Cigarette Smoking-HNC Associations—Unconditional logistic regression models were used to estimate odds ratios (ORs) with 95% intervals (I) for the main effects of cigarette smoking and ETS on HNC risk. Adjusted cigarette smoking and ETS models included matching factors (age, sex, race), education, and lifetime consumption of alcohol (categorical milliliters of ethanol). ETS ORs were additionally adjusted for duration of cigarette smoking (continuous years), as well as stratified by ever/never cigarette smoking. Information on human papillomavirus (HPV) infection is not currently available in

CHANCE, and was therefore not considered in analyses. Cigarette smoking and ETS models were considered in the overall study population and stratified by race (white and African American).

SNPs-HNC Associations—For SNPs, race-stratified hierarchical unconditional logistic regression was used to estimate ORs and 95% Is for the main effects of SNPs on HNC risk (as well as tumor site-specific risk) by including a SNP-gene matrix to account for clustering of SNP data by gene (59, 60). Since the conventional logistic regression approach of modeling one SNP at a time with p-values corrected for multiple comparisons using the Bonferroni method is overly conservative because it assumes tests are independent, which is not the case with potentially correlated exposures, we selected a hierarchical approach (59, 60). Results from the conventional approach are provided in supplemental tables.

We used a two-stage hierarchical model:

$$\text{Level 1: } \ln(p_i/1p_i)=\alpha+X_{ij}\beta_j+W_i\gamma$$

where p_i represents the probability of case status in the sample, X_{ij} contains indicators of SNPs, and W_i represents important covariates or potential confounders (59, 60).

$$\text{Level 2:}\beta_j=Z_j\pi+\delta_j$$

where β_j represents the coefficients for the effects of the SNPs, Z_j represents the matrix linking SNPs with their associated genes, and δ_j represents independent errors which are normally distributed with a mean of zero and a variance of τ^2 (59, 60). To avoid over-parameterization by modeling one large SNP-gene matrix (i.e. including all 84 SNPs across 15 genes) in a single model, 15 models, one for each gene, were employed to shrink estimates for SNPs on the same gene towards a common gene effect (i.e. the Z matrix was a single column representing a single gene, with rows of 1's for each SNP). Since SNPs on the same gene were included in the same model, we excluded some SNPs due to extreme colinearity (estimated correlation rho>0.98; 11 SNPs in whites and 5 SNPs in African Americans). A semi-Bayes approach was used to set τ^2 to 0.05, as this corresponded with a plausible range of expected ORs for the association between SNPs and HNC based on previous literature (i.e. 0.6 to 1.6) (59). Sensitivity analyses with τ^2=0.01, τ^2=0.10 and τ^2=1.0 evaluated robustness of this choice.

SNPs were defined using a dominant genetic model given the large portion of SNPs with few cases and controls homozygous for the variant allele (~7% among whites and ~33% among African Americans). The referent allele for both whites and African Americans was assigned to be the major allele based on controls from the overall study population (which was concurrent with the race-specific major allele for 98% of SNPs in whites and 92% of SNPs in African Americans). Because genetic exposures were based on germline DNA, which would not reflect the influences of smoking, drinking or HPV infection, SNP models were only adjusted for matching factors (sex and age) and ancestry (continuous proportion African ancestry), as informed by our directed acyclic graph (DAG) analysis (61). Based on previous studies of cancer among whites and African Americans in North Carolina, 145 ancestral informative markers (AIMS) were selected based on differences in allele frequencies between European and African HapMap populations and used to estimate the proportion of African ancestry in each participant based on Fisher's information criterion (FIC) (52, 62-64).

Joint Effects—Odds ratios and 95% Is for the joint effects of cigarette smoking and SNPs in NER genes were estimated using conventional and hierarchical logistic regression. Joint effects were modeled using disjoint indicator variables for 1) individuals who smoked and had the referent genotype, 2) individuals who did not smoke and had the variant genotype, and 3) individuals who smoked and had the variant genotype (59). As described in Hung et al., hierarchical models included a 3×2 gene-environment matrix to account for clustering of disjoint indicator variables by SNP and cigarette effects (i.e. the Z matrix had two columns, one representing SNP effects and one representing smoking effects, and three rows, each representing the disjoint indicator variables, with 1's and 0's entered according to concordance of rows and columns) (59). A τ^2 of 0.35 was used to correspond to expected ORs between 0.3 and 3.0 for each indicator variable (59). Sensitivity analyses with τ^2=0.05 evaluated robustness of this choice. Joint effects models were stratified by self-reported race. Only joint effect estimates among whites are presented because small cell counts among African Americans prohibited reliable estimation for most SNP-cigarette effects. Joint effects models were adjusted for matching factors (sex and age), education, alcohol drinking, and ancestry since both behavioral and genetic exposures were being modeled. Interactions between SNPs and cigarette smoking were assessed on the additive scale using the relative excess risk due to interaction (RERI), with 95% Is calculated using the Hosmer and Lemeshow method (65). All statistical analyses were performed using SAS 9.3 (Cary, NC) (66).

Results

Study Population

The study population included 922 cases and 1,074 controls who self-reported race as white and 305 cases and 251 controls who self-reported African American (Table 1). The majority of cases (76.4%) and controls (69.7%) were male. Approximately one-third of cases (33.6%) and controls (30.2%) were between the ages of 55 and 65. Controls were more highly educated than cases with 60.7% of controls attending college compared to 38.6% of cases.

Cigarette Smoking-HNC Associations

The adjusted OR for ever compared to never cigarette smoking was elevated in the overall (2.28, 95% I=1.81, 2.88; Table 2) and race stratified study populations (1.97, 95% I=1.54, 2.53 among whites and 7.75, 95% I=3.57, 16.83 among African Americans). Further, the risk of HNC increased with increasing frequency and duration of cigarette smoking (p_{trend}<0.0001). In contrast, we did not observe strong associations between ETS and HNC (Supplementary Table 2s). Adjusted ORs for ever compared to never ETS exposure were not elevated when stratified by race (0.87, 95% I=0.63, 1.19 among whites and 0.91, 95% I=0.45, 1.82 among African Americans) or by active cigarette smoking (0.84, 95% I=0.54, 1.33 among never cigarette smokers and 0.92, 95% I=0.62, 1.37 among ever cigarette smokers). Duration of ETS exposure at work or home was also not associated with HNC risk (Supplementary Table 2s).

SNPs-HNC Associations

Among whites, most ORs were close to the null value for associations between SNPs and HNC (Table 3). The SNP rs4150403 on the excision repair cross-complementing 3 (*ERCC3*) gene, also known as *xeroderma pigmentosum B (XPB)*, however, was statistically significantly associated with elevated HNC risk (AA+AG vs GG, OR=1.28, 95% I=1.01, 1.61). In addition, another SNP on *ERCC3 (XPB)*, rs4150496, suggested a possible reduced HNC risk among whites (AA+AG vs GG, OR=0.80, 95% I=0.62, 1.02). When we considered associations between these SNPs and each tumor site separately, associations between rs4150403 and oral cavity cancer resulted in the largest magnitude OR (1.32, 95%

I=1.01, 1.71; Supplementary Table 3S). For rs4150496, associations with oral cavity and oropharyngeal cancers resulted in the smallest magnitude ORs (OR=0.79, 95% I=0.60, 1.04 and OR= 0.77, 95% I=0.56, 1.06, respectively).

Among African Americans, one SNP on *ERCC6* (also known as Cockayne Syndrome B, *CSB*), rs4253132, was significantly associated with reduced HNC risk (CC+CT vs TT, OR=0.62, 95% I=0.45, 0.86; Table 4). Due to low cell counts, we were unable to assess the association between this SNP and all tumor sites among African Americans. We did find, however, that rs4253132 was significantly associated with reduced risk of laryngeal cancer (OR=0.65, 95% I=0.44, 0.97; Supplementary Table 4S).

No other significant SNP-HNC associations were detected, including none of the extensively studied associations between SNPs in *ERCC2* (also known as *XPD*), *ERCC1*, or ligase 1 (*LIG1*) and HNC risk. In particular, we did not find an association between rs13181 in *ERCC2 (XPD)* and HNC among whites (GG+TG vs TT, OR=1.05, 95% I=0.76, 1.45; Table 3) nor among African Americans (OR=1.01, 95% I=0.75, 1.37; Table 4). In sensitivity analyses, results from tables 3 and 4 were robust to further adjustment for cigarette smoking and alcohol drinking and variation of τ^2 (i.e. results were similar when adjusting for cigarette smoking and alcohol drinking or when τ^2=0.01, 0.10 and 1.0 rather than 0.05, though the OR for rs4150403 among whites was non-significantly elevated when adjusting for cigarette smoking and alcohol drinking or when τ^2=0.01, data not shown). Compared to the hierarchical model, ORs (95% Is) for the conventional model were similar though less stable, with a few additional SNP-HNC associations implicated at 0.05 alpha level but none at a Bonferroni corrected significance level of 0.0006 (Supplementary Tables 5S and 6S).

Joint Effects

Using the conventional method (Table 5), interactions between ever cigarette smoking and 3 SNPs suggested possible departures from the null on the additive scale at an uncorrected 0.05 alpha level among whites. Specifically, the interaction between cigarette smoking and rs4253132 on *ERCC6* (*CSB*, RERI=0.70, 95% I=0.14, 1.26) and rs2291120 on *DDB2* (*XPE*, RERI=0.68, 95% I=0.11, 1.26) appeared to be more than additive, while the interaction between cigarette smoking and rs744154 on *ERCC4* (*XPF*, RERI=-1.02, 95% I=-2.02, -0.02) appeared to be less than additive. However, RERI estimates were generally imprecise and none were significant at a Bonferroni corrected significance level (Table 5). Further, genotype frequencies for rs4253132 on *ERCC6* among whites appeared inconsistent with HWE at a 0.05 alpha level, although the genotype clustering plot appeared reasonable, and should therefore be cautiously interpreted. ORs (95% Is) for joint effects from the hierarchical model (Table 6) were similar to estimates from the conventional method. RERI point estimates were also similar between the two methods, but we were unable to estimate 95% Is for RERI estimates using hierarchical regression. Joint effects of SNPs and former/current cigarette smoking as well as SNPs and ETS among whites are provided in Supplementary Table 7S and 8S, respectively, and highlight a few other potential gene-environment interactions. Among African Americans, no significant ever cigarette-SNP interactions were noted; however, estimates were unreliable due to relatively low cell counts and are therefore not presented.

Discussion

Consistent with extensive literature, we found a positive association between cigarette smoking and HNC risk (3). In particular, we found noticeably larger ORs among African Americans compared to whites. A detailed analysis of smoking-HNC associations by race using CHANCE data has been previously published (50). Briefly, elevated HNC ORs among African American cigarette smokers were noted even when accounting for frequency

and duration of smoking, mentholated vs. non-mentholated cigarettes, and tumor site (50). Racial differences in carcinogen metabolism and smoking cessation patterns may be contributing factors (50).

Our study identified associations between two SNPs in the same NER gene and HNC among whites. Specifically, we detected elevated HNC risk associated with rs4150403 and possibly reduced HNC risk with rs4150496. These SNPs are in intron 3 and 11, respectively, of *ERCC3 (XPB)*, responsible for encoding a component of the transcription factor II H (TFIIH) subunit which unwinds the double helix surrounding a DNA adduct, and are not in linkage disequilibrium (LD) with each other, but are in LD with untyped SNPs near or in introns or the 3'UTR of the gene (r^2>0.80, CEU population) (6, 67-70). Previous epidemiologic studies of HNC have not considered these SNPs. Only one previous study has examined the effects of any variant in *ERCC3 (XPB)*, finding reduced HNC risk associated with rs4233583 (AA vs. CC, OR=0.37, 95% CI=0.15, 0.90), a 3'UTR SNP which is correlated with rs4150496 (r^2=0.96, CEU population) (32, 68, 69).

An association between rs4253132 and reduced HNC risk was detected among African Americans in our study. This SNP occurs in intron 10 of *ERCC6*, which operates in transcription-coupled NER, and is in LD with about a dozen other untyped intronic SNPs (r^2>0.80, YRI population) (6, 67-70). Two previous studies have collectively reported on associations between 5 SNPs in *ERCC6* and HNC risk; however, neither study evaluated rs4253132 nor considered an African American population. One study reported reduced HNC risk associated with rs4253211 (Arg/Pro+Pro/Pro vs. Arg/Arg, OR=0.53, 95% CI=0.34, 0.85) and no association with rs2228527 (Arg/Gly+Gly/Gly vs. Arg/Arg, OR=0.87, 95% CI=0.61, 1.20) (8). Another study found elevated HNC risk associated with rs2228528 (GA+AA vs. GG, OR=1.43, 95% CI=1.02, 2.01) and no association with rs2228526 (AG+GG vs. AA, OR=0.82, 95% CI=0.50, 1.34) and rs2228529 (AG+GG vs. AA, OR=0.79, 95% CI=0.49, 1.26) (14). Our study also evaluated rs2228527, rs2228528, and rs2228529 finding near null associations among whites and African Americans (ORs~0.9). While rs2228526, rs2228527, and rs2228529 are correlated (r^2=1.0, CEU population), rs4253132, rs4253211, or rs2228528 are not (69).

Among all previous studies of NER variants and HNC, SNPs in *ERCC2 (XPD)* have been the most commonly investigated, particularly rs13181. *ERCC2 (XPD)* encodes a protein component of the TFIIH subunit which denatures the double helix of DNA in preparation for excision of bulky DNA adducts (6, 67). Over 20 previous case-control studies have studied rs13181 and HNC risk, with the majority finding null associations (8-12, 15, 17, 18, 20-23, 25, 26, 30, 31, 33-35, 37, 38, 45, 48). The largest study, based on data from the International Head and Neck Cancer Epidemiology Consortium, found no association between rs13181 and HNC risk (Gln/Gln vs. Lys/Lys, OR=1.03, 95% CI=0.88, 1.21) (15). Likewise, we did not find strong evidence for an association between rs13181 and HNC risk among whites or African Americans. Further, several previous studies have found inconsistent associations for rs13181 within strata of cigarette smoking (10-12, 17, 23, 31, 34, 37, 38). In our study, we did not find an additive effect for smoking and rs13181.

Interactions between ever cigarette smoking and 3 SNPs, rs4253132 (intron 10 of *ERCC6*, in LD with other untyped intronic SNPs, r^2>0.80, CEU population), rs2291120 (intron 1 of *DDB2*, not in LD with other SNPs), and rs744154 (intron 1 of *ERCC4*, in LD with other untyped intronic SNPs and synonymous SNP rs1799801), were suggestive of possible super- or sub-additive effects among whites in our study (68-70). Using the conventional method, RERIs for these SNPs were significant at an uncorrected 0.05 alpha level, but not at a Bonferroni corrected level. Using hierarchical regression, RERI point estimates were similar to those obtained from the conventional method. Although no previous studies

considered interactions between cigarette smoking and rs4253132, rs2291120, or rs744154, four studies did investigate the effects of other SNPs, though not in LD with implicated SNPs in our study, in *ERCC6* and *ERCC4 (XPF)* within strata of cigarette smoking (8, 14, 27, 44, 69). Studies of rs4253211 in *ERCC6* and rs1800067 and rs2276466 in *ERCC4* reported similar SNP-HNC associations across strata of cigarette smokers (8, 27, 44), while other studies found rs2228528 on *ERCC6* was associated with elevated HNC risk among ever smokers (GA+AA vs. GG, OR=2.36, 95% CI=1.36, 4.10), but not among never smokers (OR=0.99, 95% CI=0.64, 1.55) (14) and rs3136038 on *ERCC4* was associated with reduced HNC risk among nonsmokers (TT vs. CC+CT, OR=0.55, 95% CI=0.34, 0.88), but not smokers (OR=0.96, 95% CI=0.66, 1.39) (44).

Differences in joint effect results between the present and past studies may in part stem from differences in analytic approaches. Namely, most previous studies examined the effects of SNPs on HNC stratified by cigarette smoking but did not consider the ORs for singly and doubly exposed individuals (i.e. individuals who had the variant allele or smoked cigarettes or both) which would have allowed testing the interaction on the additive scale by calculating a RERI (8, 10-12, 14, 16, 17, 23, 25, 27-29, 31, 32, 34, 36-40, 44). Additional studies which assess interactions on the additive scale among large study populations are needed to follow-up our suggestive findings.

The present study builds upon the existing literature by 1) including one of the largest study populations to date, 2) estimating race-stratified effects, and 3) evaluating more NER genes, including more SNPs, than any single previous study. Besides two studies which evaluated a limited number of SNPs in NER genes (13, 15), this is the largest candidate gene study to evaluate the independent and joint effects of cigarette smoking and SNPs in NER genes with respect to HNC. Most previous studies included a hundred to a thousand cases and controls (8-49). Further, our study included more African Americans than any previous study. Only one previous study reported race-specific associations for a NER variant and upper aerodigestive cancers among 119 African Americans (16). Consideration of race-specific estimates is an important contribution of this study since HNC incidence, including patterns of risk factors such as cigarette smoking, varies by race, and SNP LD patterns vary by ancestry (57, 71, 72). Despite our large overall and race-specific sample sizes, exploration of gene-environment interactions among African Americans was limited. HNC tumor site-specific estimates were also limited by sparse numbers.

In addition to including more individuals than previous studies, our analysis also examined more SNPs in NER genes than any previous study. Previous candidate gene studies have collectively examined approximately 60 SNPs in 10 NER genes and HNC risk (8-49). Our study alone included 84 SNPs across 15 NER genes. Although our study included the largest array of NER variants to date, it should be noted that selection of SNPs was based on a variety of approaches which limited the variation captured across some genes, especially among African Americans. Specifically, tagging SNPs were not selected for all genes and SNPs were selected based on only the CEU population. For this reason, we did not consider haplotypes. It is also important to note that SNPs found to be associated with HNC risk in this study occur in noncoding intronic regions and were not found to be in LD with SNPs in coding regions (with the exception of rs744154 which is in LD with rs1799801) (68-70). Although intronic SNPs can be located within regulatory regions (e.g., splice sites) (73), further research regarding the exact function of these SNPs will further elucidate potential associations with HNC.

Although we did not find associations between previously studied SNPs in NER genes and HNC risk, we identified two new associations. Among whites, rs4150403 on *ERCC3 (XPB)* was associated with increased HNC risk. Among African Americans, rs4253132 on *ERCC6*

was associated with decreased HNC risk. Three suggestive ever cigarette smoking-SNP interactions were also identified. Although our study was one of the largest to date, studies with even larger sample sizes are needed to confirm these results, especially to estimate gene-environment interactions more precisely. Further studies focusing on African American and other diverse populations are recommended.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic Characteristics of Study Population, Carolina Head and Neck Cancer Epidemiology (CHANCE) Study

Characteristic	Cases N	%	Controls N	%
Total	1227		1325	
Sex				
Male	938	76.4	924	69.7
Female	289	23.6	401	30.3
Race/Ethnicity				
White	922	75.1	1074	81.1
African American	305	24.9	251	18.9
Age				
20-49	239	19.5	151	11.4
50-54	189	15.4	156	11.8
55-59	207	16.9	199	15.0
60-64	205	16.7	202	15.2
65-69	168	13.7	237	17.9
70-74	135	11.0	216	16.3
75-80	84	6.8	164	12.4
Education				
High school or less	754	61.5	520	39.2
Some college	294	24.0	395	29.8
College or more	179	14.6	410	30.9
Tumor Site				
Oral Cavity	172	14.0		
Oropharynx	333	27.1		
Hypopharynx	55	4.5		
NOS	224	18.3		
Larynx	443	36.1		

Table 2

Odds Ratios for Cigarette Smoking and Head and Neck Cancer in the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study

	Overall			Whites			African Americans		
Cigarette Smoking	**Cases N**	**Controls N**	**OR (95% I)[a]**	**Cases N**	**Controls N**	**OR (95% I)[b]**	**Cases N**	**Controls N**	**OR (95% I)[b]**
Never	163	508		150	409		13	99	
Ever	1064	817	2.28 (1.81, 2.88)	772	665	1.97 (1.54, 2.53)	292	152	7.75 (3.57, 16.83)
Missing	0	0		0	0		0	0	
Former/Current									
Never	163	508		150	409		13	99	
Former	361	557	1.51 (1.17, 1.94)	292	467	1.32 (1.01, 1.73)	69	90	4.98 (2.17, 11.43)
Current	703	260	3.87 (2.97, 5.04)	480	198	3.44 (2.58, 4.58)	223	62	10.61 (4.73, 23.76)
Missing	0	0		0	0		0	0	
Duration (years)									
Never Smokers	163	508		150	409		13	99	
1-19	110	280	0.98 (0.72, 1.35)	92	228	0.88 (0.63, 1.23)	18	52	2.54 (0.94, 6.87)
20-39	465	320	2.34 (1.79, 3.07)	305	256	1.95 (1.46, 2.62)	160	64	7.62 (3.38, 17.21)
40+	485	214	5.30 (3.94, 7.13)	373	178	4.75 (3.45, 6.53)	112	36	16.28 (6.52, 40.62)
Missing	4	3		2	3		2	0	
p_{trend}[c]			<0.0001			<0.0001			<0.0001
Frequency (cigarettes/day)									
Never Smokers	163	508		150	409		13	99	
1-19	211	322	1.39 (1.05, 1.85)	115	230	1.14 (0.83, 1.57)	96	92	4.78 (2.12, 10.82)
20+	850	495	2.99 (2.33, 3.84)	654	435	2.56 (1.96, 3.33)	196	60	13.16 (5.73, 30.23)
Missing	3	0		3	0		0	0	
p_{trend}			<0.0001			<0.0001			<0.0001

OR odds ratio, I interval estimates

[a] Odds ratios adjusted for matching factors (age, sex, and race, including pairwise interactions), education, and alcohol drinking. 122 individuals missing alcohol drinking, and therefore dropped from models.

[b] Odds ratios adjusted for matching factors (age and sex, including pairwise interactions), education, and alcohol drinking. 122 individuals missing alcohol drinking, and therefore dropped from models.

[c] p-value for linear trend obtained from modeling the continuous forms of the frequency, duration, and cumulative variables.

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Table 3

Odds Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Head and Neck Cancer Using Hierarchical Logistic Regression, the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, Whites

		Coded Allele		Cases/Controls N					
Gene	**SNP**	**Referent (A)**	**Variant (B)**	**AA**		**AB + BB**		**OR (95% I)[a]**	**p-value[b]**
ERCC3 (XPB)	rs4150496	G	A	401	392	518	682	0.80 (0.62, 1.02)	0.08
	rs1011019	C	T	462	548	459	526	0.94 (0.72, 1.24)	0.68
	rs4150434	G	A	546	670	373	404	1.00 (0.81, 1.24)	0.97
	rs4150416	T	G	410	481	509	593	0.89 (0.68, 1.17)	0.40
	rs4150407	A	G	318	311	601	763	0.94 (0.72, 1.23)	0.65
	rs4150403	G	A	733	904	186	170	1.28 (1.01, 1.61)	0.04
XPC	rs2228001	A	C	335	375	584	698	0.90 (0.72, 1.12)	0.35
	rs3731143	T	C	816	957	103	116	1.05 (0.81, 1.36)	0.72
	rs2228000	C	T	524	598	395	475	0.93 (0.70, 1.25)	0.64
	rs3731124	A	C	519	598	400	475	0.88 (0.68, 1.15)	0.35
	rs13099160	A	G	811	961	108	112	1.03 (0.75, 1.40)	0.87
	rs3731089	G	A	775	918	144	155	1.03 (0.75, 1.40)	0.86
	rs2733537	A	G	416	480	503	593	0.95 (0.72, 1.25)	0.69
	rs3731068	C	A	622	731	297	342	1.05 (0.83, 1.33)	0.70
	rs2607755	T	C	242	284	677	789	1.04 (0.82, 1.32)	0.75
ERCC8	rs3117	T	C	337	397	585	677	1.02 (0.84, 1.22)	0.87
CDK7	rs2972388	A	G	266	335	656	739	1.12 (0.92, 1.36)	0.25
XPA	rs3176757	C	T	580	684	303	352	0.98 (0.75, 1.29)	0.90
	rs3176748	A	G	421	490	462	546	0.89 (0.71, 1.12)	0.32
	rs2808667	C	T	781	915	102	121	1.11 (0.84, 1.47)	0.46
	rs2805835	G	C	692	817	191	219	0.96 (0.76, 1.22)	0.75
	rs3176689	A	T	595	703	288	333	0.92 (0.74, 1.15)	0.48
	rs3176683	T	C	784	909	99	127	0.88 (0.68, 1.16)	0.37
	rs3176658	C	T	678	762	205	274	0.81 (0.62, 1.07)	0.14
	rs1800975	G	A	420	473	463	563	0.99 (0.76, 1.29)	0.93
RAD23B	rs1805330	C	T	764	870	158	204	0.94 (0.75, 1.18)	0.60

		Coded Allele		Cases/Controls N					
Gene	**SNP**	**Referent (A)**	**Variant (B)**	**AA**		**AB + BB**		**OR (95% I)[a]**	**p-value[b]**
	rs1805329	C	T	590	711	332	363	1.10 (0.92, 1.33)	0.30
ERCC6	rs2228529	A	G	596	661	313	396	0.87 (0.72, 1.05)	0.15
	rs4253132	T	C	714	815	195	242	0.90 (0.73, 1.12)	0.36
	rs2228528	G	A	627	733	282	324	0.96 (0.79, 1.17)	0.71
DDB2 (XPE)	rs2029298	A	G	425	478	497	596	1.02 (0.82, 1.27)	0.85
	rs4647709	C	T	766	902	156	172	1.01 (0.79, 1.30)	0.93
	rs2291120	T	C	685	812	237	262	1.00 (0.81, 1.22)	0.97
	rs1685404	G	C	418	502	504	572	1.01 (0.83, 1.22)	0.95
	rs2957873	A	G	643	711	279	363	1.00 (0.75, 1.33)	0.99
	rs326224	G	A	683	761	239	313	1.08 (0.79, 1.46)	0.64
	rs2306353	G	A	696	762	226	312	0.81 (0.59, 1.13)	0.21
	rs326222	C	T	484	526	438	548	0.96 (0.76, 1.21)	0.70
ERCC5 (XPG)	rs2296147	T	C	279	302	636	764	0.96 (0.76, 1.21)	0.73
	rs4771436	T	G	558	652	357	414	0.95 (0.71, 1.26)	0.71
	rs1047768	C	T	315	371	600	695	1.01 (0.77, 1.34)	0.93
	rs4150351	A	C	591	687	324	379	0.86 (0.67, 1.11)	0.24
	rs4150355	C	T	400	427	515	639	0.85 (0.67, 1.09)	0.21
	rs4150360	T	C	271	310	644	756	0.89 (0.66, 1.19)	0.43
	rs4150383	G	A	624	742	291	324	1.09 (0.84, 1.41)	0.52
	rs4150386	A	C	718	831	197	235	1.01 (0.81, 1.25)	0.96
	rs17655	C	G	550	651	365	415	1.05 (0.79, 1.40)	0.74
	rs873601	A	G	459	532	456	534	0.97 (0.74, 1.25)	0.80
	rs4150393	A	G	698	839	227	217	1.16 (0.89, 1.52)	0.26
	rs1051677	T	C	729	853	186	213	1.02 (0.83, 1.25)	0.87
	rs1051685	A	G	732	824	183	242	0.91 (0.74, 1.11)	0.34
ERCC4 (XPF)	rs3136038	C	T	402	490	520	584	1.00 (0.78, 1.28)	1.00
	rs1799798	G	A	757	901	165	173	1.16 (0.93, 1.44)	0.20
	rs744154	C	G	480	582	442	492	0.97 (0.70, 1.33)	0.83
	rs1800067	G	A	778	920	144	154	1.06 (0.83, 1.34)	0.64
	rs3136172	A	G	458	566	464	508	1.15 (0.84, 1.55)	0.38

		Coded Allele		Cases/Controls N					
Gene	**SNP**	**Referent (A)**	**Variant (B)**	**AA**		**AB + BB**		**OR (95% I)[a]**	**p-value[b]**
RAD23A	rs2974752	A	G	333	424	561	617	1.16 (0.96, 1.40)	0.11
ERCC2 (XPD)	rs13181	T	G	379	435	532	632	1.05 (0.76, 1.45)	0.79
	rs238418	C	A	374	420	537	647	0.91 (0.66, 1.26)	0.58
	rs1799787	C	T	464	538	447	529	1.06 (0.82, 1.35)	0.67
	rs3916874	G	C	471	542	440	525	1.01 (0.83, 1.25)	0.90
	rs238416	G	A	364	468	547	599	1.10 (0.88, 1.38)	0.39
	rs50872	C	T	525	583	386	484	0.91 (0.76, 1.08)	0.27
	rs50871	T	G	239	257	672	810	0.91 (0.75, 1.11)	0.36
	rs238407	A	T	261	338	650	729	1.05 (0.82, 1.35)	0.71
	rs3810366	C	G	176	232	735	835	1.08 (0.84, 1.40)	0.54
ERCC1	rs735482	A	C	688	796	234	277	0.92 (0.74, 1.14)	0.44
	rs3212955	A	G	528	607	394	466	0.93 (0.71, 1.23)	0.63
	rs3212948	C	G	382	458	540	615	1.17 (0.91, 1.50)	0.22
	rs3212930	T	C	576	657	346	416	0.92 (0.73, 1.17)	0.50
LIG1	rs156641	G	A	370	440	552	634	1.02 (0.81, 1.29)	0.86
	rs20580	C	A	237	293	685	781	1.02 (0.79, 1.31)	0.87
	rs20579	C	T	691	826	231	248	1.09 (0.87, 1.35)	0.45

OR odds ratio, I interval estimates

[a]Odds ratios adjusted for matching factors (age and sex including pairwise interactions) and proportion African ancestry.

[b]Significant associations using a dominant genetic model (p<0.05) highlighted in gray.

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2014 August 01.

Table 4

Odds Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Head and Neck Cancer Using Hierarchical Logistic Regression, the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, African Americans

		Coded Allele		Cases/Controls N					
Gene	**SNP**	**Referent (A)**	**Variant (B)**	**AA**		**AB + BB**		**OR (95% I)[a]**	**p-value[b]**
ERCC3 (XPB)	rs4150496	G	A	177	136	125	115	0.85 (0.61, 1.20)	0.35
	rs4150459	G	A	188	164	114	87	1.04 (0.74, 1.48)	0.81
	rs1011019	C	T	180	143	122	108	0.85 (0.60, 1.20)	0.35
	rs4150434	G	A	230	186	72	65	0.94 (0.65, 1.36)	0.73
	rs4150416	T	G	84	76	218	175	1.04 (0.74, 1.47)	0.81
	rs4150407	A	G	83	68	219	183	0.95 (0.68, 1.35)	0.79
XPC	rs2228001	A	C	180	134	125	117	0.88 (0.63, 1.23)	0.46
	rs2228000	C	T	251	205	54	46	0.99 (0.69, 1.43)	0.95
	rs3731124	A	C	252	212	53	39	0.97 (0.68, 1.37)	0.84
	rs3731089	G	A	263	208	42	43	0.91 (0.62, 1.34)	0.64
	rs2733537	A	G	212	164	93	87	0.91 (0.66, 1.28)	0.60
	rs2607755	T	C	111	109	194	142	1.15 (0.85, 1.56)	0.37
	rs1902658	G	A	53	51	252	200	1.02 (0.71, 1.46)	0.93
ERCC8	rs3117	T	C	126	94	179	157	0.82 (0.57, 1.17)	0.27
CDK7	rs2972388	A	G	160	132	145	119	1.05 (0.74, 1.49)	0.78
CCNH	rs2266691	A	G	257	220	48	30	1.35 (0.88, 2.09)	0.17
	rs2266692	G	T	237	202	68	48	1.26 (0.85, 1.87)	0.25
XPA	rs3176757	C	T	227	181	66	53	1.00 (0.69, 1.44)	0.99
	rs3176753	T	C	218	173	75	61	0.97 (0.68, 1.37)	0.86
	rs3176748	A	G	238	195	55	39	1.05 (0.72, 1.52)	0.81
	rs3176658	C	T	249	194	44	40	0.99 (0.67, 1.45)	0.95
	rs1800975	G	A	187	141	106	93	0.92 (0.66, 1.28)	0.62
RAD23B	rs1805330	C	T	183	160	122	91	1.16 (0.81, 1.67)	0.43
ERCC6	rs2228529	A	G	233	189	69	60	0.85 (0.58, 1.22)	0.37
	rs2228527	A	G	217	175	85	74	0.91 (0.65, 1.29)	0.61
	rs4253132	T	C	189	124	113	125	0.62 (0.45, 0.86)	0.005

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2014 August 01.

		Coded Allele		Cases/Controls N					
Gene	**SNP**	**Referent (A)**	**Variant (B)**	**AA**		**AB + BB**		**OR (95% I)[a]**	**p-value[b]**
	rs2228528	G	A	210	180	92	69	0.92 (0.65, 1.30)	0.62
DDB2 (XPE)	rs2029298	A	G	90	88	214	163	1.16 (0.86, 1.56)	0.33
	rs1685404	G	C	164	140	140	111	1.10 (0.82, 1.48)	0.51
	rs2957873	A	G	90	82	214	169	1.07 (0.75, 1.53)	0.71
	rs326224	G	A	80	63	224	188	0.87 (0.62, 1.24)	0.45
	rs2306353	G	A	105	97	199	154	1.14 (0.80, 1.61)	0.47
	rs326222	C	T	54	50	250	201	1.09 (0.75, 1.59)	0.64
	rs901746	A	G	65	58	239	193	0.97 (0.68, 1.40)	0.89
ERCC5 (XPG)	rs2296147	T	C	192	147	111	100	0.90 (0.65, 1.23)	0.51
	rs2296148	C	T	227	189	76	58	1.04 (0.74, 1.45)	0.83
	rs4771436	T	G	202	168	101	79	0.95 (0.68, 1.33)	0.78
	rs1047768	C	T	114	112	189	135	1.12 (0.81, 1.54)	0.49
	rs2020915	G	A	203	140	100	107	0.80 (0.58, 1.10)	0.16
	rs4150355	C	T	217	173	86	74	1.02 (0.72, 1.44)	0.92
	rs4150360	T	C	18	17	285	230	0.95 (0.64, 1.42)	0.80
	rs4150383	G	A	240	196	63	51	0.95 (0.67, 1.35)	0.78
	rs17655	C	G	88	68	215	179	0.98 (0.70, 1.37)	0.91
	rs873601	A	G	29	30	274	217	1.13 (0.77, 1.67)	0.52
	rs1051677	T	C	232	181	71	66	0.89 (0.65, 1.23)	0.48
	rs1051685	A	G	136	117	167	130	0.99 (0.73, 1.33)	0.93
ERCC4 (XPF)	rs3136038	C	T	92	84	213	167	1.12 (0.82, 1.54)	0.46
	rs744154	C	G	221	174	84	77	0.97 (0.68, 1.40)	0.88
	rs3136085	G	C	173	146	132	105	1.08 (0.78, 1.49)	0.65
	rs3136091	C	G	255	199	50	52	0.86 (0.59, 1.24)	0.41
	rs3136130	G	T	75	65	230	186	0.99 (0.71, 1.37)	0.93
	rs3136172	A	G	216	171	89	80	1.01 (0.70, 1.44)	0.97
	rs2020955	T	C	193	165	112	86	1.03 (0.75, 1.42)	0.86
RAD23A	rs2974752	A	G	77	62	216	170	1.06 (0.75, 1.50)	0.73
	rs11558955	A	G	245	197	48	35	1.13 (0.76, 1.68)	0.54
ERCC2 (XPD)	rs13181	T	G	171	139	131	108	1.01 (0.75, 1.37)	0.93

		Coded Allele		Cases/Controls N					
Gene	**SNP**	**Referent (A)**	**Variant (B)**	**AA**		**AB + BB**		**OR (95% I)[a]**	**p-value[b]**
	rs238418	C	A	8	9	294	238	1.09 (0.70, 1.69)	0.72
	rs1799787	C	T	232	189	70	58	0.98 (0.71, 1.37)	0.92
	rs3916874	G	C	265	223	37	24	1.09 (0.74, 1.59)	0.67
	rs238416	G	A	241	206	61	41	1.15 (0.80, 1.64)	0.45
	rs50872	C	T	220	156	82	91	0.78 (0.58, 1.05)	0.10
	rs50871	T	G	226	193	76	54	1.10 (0.80, 1.52)	0.57
	rs238407	A	T	223	189	79	58	0.99 (0.69, 1.42)	0.97
	rs3810366	C	G	209	179	93	68	1.06 (0.75, 1.49)	0.74
ERCC1	rs735482	A	C	156	120	147	128	0.96 (0.71, 1.30)	0.79
	rs3212964	G	A	207	142	96	106	0.78 (0.57, 1.07)	0.13
	rs3212955	A	G	157	139	146	109	1.09 (0.80, 1.50)	0.58
	rs3212948	C	G	9	6	294	242	0.94 (0.60, 1.48)	0.79
	rs3212935	A	G	142	124	161	124	1.10 (0.81, 1.50)	0.54
	rs3212930	T	C	248	202	55	46	0.94 (0.66, 1.34)	0.74
LIG1	rs156641	G	A	233	192	71	59	1.02 (0.72, 1.45)	0.91
	rs20580	C	A	62	57	242	194	1.09 (0.77, 1.54)	0.62
	rs20579	C	T	150	128	154	123	0.99 (0.72, 1.36)	0.96
	rs439132	A	G	172	136	132	115	0.93 (0.67,1.30)	0.68

OR odds ratio, I interval estimates

[a]Odds ratios adjusted for matching factors (age and sex including pairwise interactions) and proportion African ancestry.

[b]Significant associations using a dominant genetic model (p<0.05) highlighted in gray.

Table 5

Odds Ratios and Relative Excess Risk Due to Interaction Estimates for Joint Effects of Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Ever Cigarette Smoking on Head and Neck Cancer Risk Using Conventional Logistic Regression, the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, Whites

		Coded Allele		Cases/Controls N[a]								OR (95% I)[b]			
Gene	SNP	Referent (A)	Variant (B)	Never Cigarette, Referent SNP		Never Cigarette, Variant SNP		Ever Cigarette, Referent SNP		Ever Cigarette, Variant SNP		Never Cigarette, Variant SNP	Ever Cigarette, Referent SNP	Ever Cigarette, Variant SNP	RERI (95% CI)[c]
ERCC3 (XPB)	rs4150496	G	A	70	154	79	255	331	238	441	427	0.66 (0.44, 0.98)	1.83 (1.27, 2.64)	1.40 (0.99, 1.98)	-0.08 (-0.63, 0.46)
	rs1011019	C	T	66	201	84	208	396	347	376	318	1.26 (0.85, 1.87)	2.18 (1.54, 3.08)	2.28 (1.61, 3.23)	-0.16 (-0.86, 0.54)
	rs4150434	G	A	89	264	61	145	459	406	313	259	1.20 (0.80, 1.80)	2.13 (1.56, 2.89)	2.09 (1.51, 2.90)	-0.24 (-0.94, 0.45)
	rs4150416	T	G	56	176	93	233	354	305	416	360	1.27 (0.84, 1.90)	2.27 (1.57, 3.30)	2.27 (1.57, 3.27)	-0.27 (-1.01, 0.46)
	rs4150407	A	G	55	129	95	280	263	182	509	483	0.77 (0.51, 1.16)	2.00 (1.33, 3.00)	1.53 (1.05, 2.21)	-0.24 (-0.90, 0.41)
	rs4150403	G	A	118	338	32	71	618	566	154	99	1.26 (0.77, 2.06)	1.95 (1.49, 2.56)	2.60 (1.80, 3.74)	0.39 (-0.57, 1.34)
	rs4150402	G	A	66	201	84	208	396	347	376	317	1.26 (0.85, 1.87)	2.19 (1.55, 3.09)	2.29 (1.62, 3.26)	-0.15 (-0.85, 0.55)
XPC	rs2228001	A	C	56	135	94	274	281	240	490	425	0.86 (0.57, 1.29)	1.91 (1.29, 2.83)	1.70 (1.17, 2.48)	-0.06 (-0.66, 0.54)
	rs3731143	T	C	135	361	15	48	683	596	89	69	0.90 (0.48, 1.70)	1.88 (1.45, 2.44)	2.51 (1.66, 3.82)	0.73 (-0.33, 1.80)
	rs2228000	C	T	91	222	59	187	433	376	337	288	0.77 (0.51, 1.14)	1.74 (1.27, 2.39)	1.78 (1.28, 2.47)	0.27 (-0.23, 0.78)
	rs3731124	A	C	81	228	69	181	440	371	332	294	1.10 (0.74, 1.64)	2.11 (1.53, 2.90)	1.98 (1.42, 2.76)	-0.23 (-0.89, 0.43)
	rs13099160	A	G	127	366	23	43	687	596	85	69	1.60 (0.90, 2.83)	2.07 (1.59, 2.69)	2.24 (1.47, 3.43)	-0.43 (-1.65, 0.80)
	rs3731093	T	C	120	350	27	56	656	569	111	90	1.52 (0.89, 2.58)	2.10 (1.60, 2.75)	2.47 (1.68, 3.64)	-0.15 (-1.26, 0.96)
	rs3731089	G	A	121	350	29	59	657	569	115	96	1.53 (0.92, 2.57)	2.07 (1.58, 2.71)	2.35 (1.61, 3.44)	-0.25 (-1.32, 0.82)
	rs2733537	A	G	70	175	80	234	346	305	426	360	0.88 (0.59, 1.31)	1.75 (1.23, 2.50)	1.91 (1.35, 2.70)	0.28 (-0.25, 0.81)
	rs3731068	C	A	99	275	51	134	525	457	247	208	1.03 (0.68, 1.56)	1.97 (1.47, 2.65)	2.01 (1.44, 2.79)	0.01 (-0.65, 0.66)
	rs2607755	T	C	39	110	111	299	203	174	569	491	1.11 (0.71, 1.73)	2.12 (1.35, 3.34)	2.12 (1.39, 3.22)	-0.11 (-0.86, 0.63)
	rs1902658	G	A	37	107	113	302	198	173	573	492	1.12 (0.71, 1.76)	2.10 (1.32, 3.33)	2.15 (1.40, 3.29)	-0.07 (-0.81, 0.67)
ERCC8	rs3117	T	C	60	144	90	265	277	253	495	412	0.81 (0.54, 1.22)	1.70 (1.16, 2.49)	1.75 (1.22, 2.51)	0.23 (-0.28, 0.75)
CDK7	rs2972388	A	G	42	122	108	287	224	213	548	452	1.06 (0.69, 1.63)	1.81 (1.17, 2.79)	2.16 (1.45, 3.23)	0.29 (-0.31, 0.89)
XPA	rs3176757	C	T	98	268	52	141	511	442	261	223	1.03 (0.68, 1.56)	1.94 (1.44, 2.62)	2.08 (1.50, 2.89)	0.11 (-0.53, 0.75)
	rs3176748	A	G	74	185	76	224	366	325	406	340	0.84 (0.57, 1.25)	1.76 (1.25, 2.48)	1.82 (1.30, 2.57)	0.22 (-0.30, 0.74)
	rs2808667	C	T	133	352	17	57	681	598	89	67	0.87 (0.47, 1.60)	1.86 (1.43, 2.42)	2.44 (1.61, 3.71)	0.71 (-0.31, 1.73)
	rs2805835	G	C	119	328	31	81	608	520	164	145	1.12 (0.69, 1.82)	2.03 (1.54, 2.68)	1.95 (1.38, 2.76)	-0.20 (-0.98, 0.58)

		Coded Allele		Cases/Controls N[a]								OR (95% I)[b]			
Gene	SNP	Referent (A)	Variant (B)	Never Cigarette, Referent SNP		Never Cigarette, Variant SNP		Ever Cigarette, Referent SNP		Ever Cigarette, Variant SNP		Never Cigarette, Variant SNP	Ever Cigarette, Referent SNP	Ever Cigarette, Variant SNP	RERI (95% CI)[c]
	rs3176689	A	T	94	279	56	130	528	449	244	216	1.14 (0.76, 1.72)	2.15 (1.60, 2.90)	1.88 (1.34, 2.63)	-0.41 (-1.12, 0.29)
	rs3176683	T	C	134	353	16	56	684	591	88	74	0.76 (0.41, 1.40)	1.88 (1.45, 2.45)	2.05 (1.35, 3.10)	0.41 (-0.46, 1.28)
	rs3176658	C	T	114	297	36	112	585	495	187	170	0.85 (0.54, 1.35)	1.91 (1.44, 2.52)	1.86 (1.32, 2.60)	0.10 (-0.54, 0.73)
	rs1800975	G	A	72	180	75	215	348	293	390	348	0.90 (0.61, 1.35)	1.83 (1.29, 2.60)	1.86 (1.32, 2.63)	0.13 (-0.43, 0.69)
RAD23B	rs1805330	C	T	125	321	25	88	639	549	133	116	0.68 (0.41, 1.13)	1.85 (1.41, 2.43)	1.68 (1.16, 2.43)	0.15 (-0.49, 0.79)
	rs1805329	C	T	101	277	49	132	489	434	283	231	1.13 (0.74, 1.72)	2.01 (1.50, 2.70)	2.12 (1.53, 2.93)	-0.02 (-0.70, 0.66)
ERCC6	rs2228529	A	G	96	258	52	146	501	403	261	250	1.08 (0.71, 1.63)	2.13 (1.57, 2.89)	1.85 (1.33, 2.56)	-0.37 (-1.05, 0.32)
	rs2228527	A	G	97	260	53	149	501	405	271	260	1.07 (0.71, 1.61)	2.13 (1.57, 2.87)	1.84 (1.33, 2.55)	-0.35 (-1.03, 0.32)
	rs4253132	T	C	126	303	24	106	597	526	175	139	0.50 (0.30, 0.84)	1.65 (1.26, 2.18)	1.86 (1.32, 2.62)	0.70 (0.14, 1.26)
	rs2228528	G	A	104	287	46	122	533	459	238	206	1.05 (0.69, 1.62)	2.01 (1.50, 2.68)	1.97 (1.42, 2.74)	-0.09 (-0.76, 0.58)
DDB2 (XPE)	rs2029298	A	G	69	195	81	214	356	283	416	382	1.22 (0.82, 1.81)	2.39 (1.69, 3.38)	2.03 (1.44, 2.86)	-0.58 (-1.34, 0.18)
	rs4647709	C	T	123	342	27	67	643	560	129	105	1.17 (0.70, 1.96)	2.01 (1.53, 2.63)	2.12 (1.46, 3.07)	-0.06 (-0.94, 0.82)
	rs2291120	T	C	123	296	27	113	562	516	210	149	0.59 (0.36, 0.96)	1.68 (1.28, 2.22)	1.95 (1.39, 2.74)	0.68 (0.11, 1.26)
	rs1685404	G	C	72	180	78	229	346	322	426	343	0.88 (0.59, 1.30)	1.66 (1.17, 2.35)	2.01 (1.43, 2.83)	0.47 (-0.03, 0.98)
	rs2957873	A	G	101	275	49	134	542	436	230	229	1.16 (0.76, 1.75)	2.22 (1.65, 2.98)	1.77 (1.28, 2.46)	-0.60 (-1.33, 0.13)
	rs326224	G	A	105	288	45	121	578	473	194	192	1.18 (0.77, 1.80)	2.14 (1.61, 2.86)	1.87 (1.33, 2.62)	-0.45 (-1.19, 0.29)
	rs2306353	G	A	109	292	41	117	587	470	185	195	1.12 (0.72, 1.74)	2.18 (1.64, 2.90)	1.66 (1.19, 2.33)	-0.64 (-1.38, 0.10)
	rs326222	C	T	76	209	74	200	408	317	364	348	1.17 (0.79, 1.73)	2.39 (1.71, 3.34)	1.88 (1.34, 2.63)	-0.68 (-1.43, 0.08)
	rs901746	A	G	76	210	74	199	409	318	363	347	1.19 (0.80, 1.77)	2.41 (1.73, 3.37)	1.89 (1.35, 2.65)	-0.71 (-1.48, 0.05)
ERCC5 (XPG)	rs2296147	T	C	41	114	109	291	239	189	528	474	1.00 (0.64, 1.55)	2.14 (1.38, 3.33)	1.88 (1.24, 2.83)	-0.27 (-1.01, 0.48)
	rs4771436	T	G	97	259	53	150	466	400	306	265	0.98 (0.65, 1.48)	1.98 (1.46, 2.68)	1.92 (1.39, 2.65)	-0.05 (-0.66, 0.57)
	rs1047768	C	T	57	142	93	267	262	235	510	429	0.84 (0.56, 1.26)	1.71 (1.16, 2.52)	1.79 (1.24, 2.59)	0.25 (-0.28, 0.78)
	rs3818356	C	T	97	259	53	149	466	400	304	264	0.99 (0.66, 1.5)	1.97 (1.46, 2.67)	1.91 (1.38, 2.64)	-0.06 (-0.67, 0.56)
	rs4150351	A	C	97	258	53	151	498	434	274	231	0.94 (0.63, 1.42)	1.92 (1.42, 2.60)	1.94 (1.40, 2.69)	0.07 (-0.53, 0.68)
	rs4150355	C	T	57	159	93	250	345	269	427	396	1.06 (0.70, 1.58)	2.28 (1.57, 3.32)	1.87 (1.29, 2.69)	-0.47 (-1.20, 0.26)
	rs4150360	T	C	50	119	100	290	225	197	547	468	0.81 (0.53, 1.24)	1.70 (1.12, 2.58)	1.71 (1.16, 2.51)	0.19 (-0.36, 0.74)
	rs4150383	G	A	106	296	44	113	524	453	248	212	1.08 (0.70, 1.67)	2.02 (1.51, 2.70)	2.00 (1.44, 2.78)	-0.10 (-0.78, 0.58)
	rs4150386	A	C	113	317	37	92	611	519	161	145	1.03 (0.65, 1.63)	2.03 (1.53, 2.68)	1.84 (1.29, 2.61)	-0.22 (-0.95, 0.51)

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2014 August 01.

		Coded Allele		Cases/Controls N[a]								OR (95% I)[b]			
Gene	SNP	Referent (A)	Variant (B)	Never Cigarette, Referent SNP		Never Cigarette, Variant SNP		Ever Cigarette, Referent SNP		Ever Cigarette, Variant SNP		Never Cigarette, Variant SNP	Ever Cigarette, Referent SNP	Ever Cigarette, Variant SNP	RERI (95% CI)[c]
	rs17655	C	G	89	238	61	171	466	420	306	245	0.88 (0.59, 1.32)	1.78 (1.30, 2.42)	2.04 (1.46, 2.84)	0.38 (-0.18, 0.94)
	rs873601	A	G	73	190	77	219	391	349	381	316	0.82 (0.55, 1.21)	1.72 (1.22, 2.41)	1.83 (1.30, 2.58)	0.30 (-0.21, 0.80)
	rs4150393	A	G	114	317	36	92	588	527	184	138	1.14 (0.72, 1.81)	1.94 (1.47, 2.57)	2.35 (1.67, 3.32)	0.27 (-0.53, 1.06)
	rs876430	C	T	73	190	77	219	392	350	380	315	0.82 (0.55, 1.21)	1.72 (1.22, 2.41)	1.83 (1.30, 2.58)	0.30 (-0.21, 0.80)
	rs1051677	T	C	126	331	23	78	609	527	163	138	0.80 (0.47, 1.36)	1.88 (1.43, 2.46)	2.01 (1.42, 2.85)	0.34 (-0.36, 1.03)
	rs1051685	A	G	117	323	33	86	619	509	152	156	1.12 (0.70, 1.80)	2.10 (1.59, 2.76)	1.67 (1.17, 2.38)	-0.55 (-1.31, 0.22)
ERCC4 (XPF)	rs3136038	C	T	51	195	99	214	351	295	421	370	1.77 (1.17, 2.66)	2.88 (1.97, 4.21)	2.67 (1.84, 3.87)	-0.97 (-1.99, 0.04)
	rs1799798	G	A	126	331	24	78	631	570	141	95	0.80 (0.47, 1.34)	1.82 (1.39, 2.39)	2.32 (1.59, 3.40)	0.70 (-0.11, 1.52)
	rs744154	C	G	59	224	91	185	421	358	351	307	1.85 (1.24, 2.76)	2.81 (1.98, 3.99)	2.63 (1.84, 3.77)	-1.02 (-2.02, -0.02)
	rs3136085	G	C	59	220	91	189	416	356	356	309	1.80 (1.21, 2.69)	2.75 (1.93, 3.92)	2.63 (1.84, 3.77)	-0.92 (-1.89, 0.05)
	rs3136130	G	T	51	193	99	216	349	292	423	373	1.73 (1.15, 2.61)	2.85 (1.95, 4.16)	2.65 (1.83, 3.83)	-0.93 (-1.93, 0.06)
	rs1800067	G	A	125	355	25	54	653	565	119	100	1.26 (0.73, 2.17)	2.03 (1.55, 2.64)	2.11 (1.45, 3.07)	-0.18 (-1.13, 0.77)
	rs3136172	A	G	59	216	91	193	399	350	373	315	1.71 (1.14, 2.55)	2.63 (1.85, 3.76)	2.63 (1.84, 3.76)	-0.71 (-1.63, 0.20)
RAD23A	rs2974752	A	G	56	180	92	216	277	244	469	401	1.43 (0.95, 2.16)	2.38 (1.63, 3.46)	2.41 (1.68, 3.44)	-0.40 (-1.22, 0.42)
ERCC2 (XPD)	rs13181	T	G	55	155	95	252	326	282	439	381	1.06 (0.71, 1.60)	2.08 (1.42, 3.05)	1.97 (1.36, 2.85)	-0.18 (-0.84, 0.49)
	rs238418	C	A	54	155	96	254	328	271	444	394	1.10 (0.73, 1.65)	2.21 (1.50, 3.24)	2.01 (1.38, 2.91)	-0.30 (-1.00, 0.41)
	rs1799787	C	T	68	203	82	206	404	342	368	323	1.17 (0.79, 1.74)	2.19 (1.56, 3.09)	2.08 (1.47, 2.94)	-0.29 (-0.98, 0.40)
	rs3916874	G	C	81	201	69	208	396	344	376	321	0.75 (0.50, 1.11)	1.69 (1.21, 2.35)	1.72 (1.23, 2.40)	0.28 (-0.20, 0.77)
	rs238416	G	A	62	193	88	216	307	275	464	388	1.34 (0.90, 1.99)	2.17 (1.51, 3.12)	2.40 (1.69, 3.41)	-0.11 (-0.83, 0.61)
	rs50872	C	T	80	221	70	187	451	363	319	301	1.06 (0.71, 1.57)	2.15 (1.55, 2.97)	1.85 (1.32, 2.59)	-0.36 (-1.02, 0.31)
	rs50871	T	G	43	89	107	320	199	169	573	495	0.66 (0.42, 1.03)	1.37 (0.86, 2.16)	1.47 (0.96, 2.23)	0.44 (-0.01, 0.89)
	rs238407	A	T	43	136	107	273	220	202	551	463	1.40 (0.91, 2.16)	2.36 (1.54, 3.62)	2.53 (1.71, 3.76)	-0.23 (-1.05, 0.59)
	rs3810366	C	G	32	95	118	314	146	137	625	528	1.29 (0.80, 2.09)	2.29 (1.38, 3.77)	2.42 (1.54, 3.80)	-0.16 (-1.03, 0.72)
ERCC1	rs735482	A	C	117	302	33	107	571	495	201	170	0.81 (0.51, 1.30)	1.87 (1.41, 2.47)	1.90 (1.36, 2.65)	0.22 (-0.40, 0.84)
	rs2336219	G	A	117	302	33	107	571	495	201	170	0.81 (0.51, 1.30)	1.87 (1.41, 2.47)	1.90 (1.36, 2.65)	0.22 (-0.40, 0.84)
	rs3212964	G	A	118	302	32	107	574	492	198	173	0.78 (0.49, 1.24)	1.86 (1.41, 2.46)	1.84 (1.32, 2.56)	0.20 (-0.40, 0.80)
	rs3212955	A	G	82	229	68	180	446	378	326	286	1.10 (0.74, 1.63)	2.08 (1.51, 2.86)	2.02 (1.45, 2.81)	-0.16 (-0.81, 0.49)
	rs3212948	C	G	60	171	90	238	322	287	450	378	1.10 (0.74, 1.64)	2.01 (1.39, 2.90)	2.14 (1.50, 3.05)	0.03 (-0.60, 0.66)

Gene	SNP	Coded Allele		Cases/Controls N[a]								OR (95% I)[b]			
		Referent (A)	Variant (B)	Never Cigarette, Referent SNP		Never Cigarette, Variant SNP		Ever Cigarette, Referent SNP		Ever Cigarette, Variant SNP		Never Cigarette, Variant SNP	Ever Cigarette, Referent SNP	Ever Cigarette, Variant SNP	RERI (95% CI)[c]
	rs3212930	T	C	92	248	58	161	484	409	288	256	0.99 (0.66, 1.48)	1.95 (1.43, 2.65)	1.98 (1.43, 2.75)	0.04 (-0.57, 0.65)
LIG1	rs156641	G	A	56	166	94	243	314	274	458	391	1.22 (0.81, 1.82)	2.14 (1.46, 3.13)	2.27 (1.58, 3.27)	-0.09 (-0.77, 0.60)
	rs20580	C	A	30	109	120	300	207	184	565	481	1.54 (0.95, 2.48)	2.52 (1.55, 4.12)	2.83 (1.79, 4.47)	-0.23 (-1.15, 0.69)
	rs20579	C	T	105	305	45	104	586	521	186	144	1.34 (0.87, 2.08)	2.06 (1.55, 2.73)	2.43 (1.71, 3.45)	0.03 (-0.81, 0.87)

OR odds ratio, RERI relative excess risk due to interaction, I interval estimates

[a]Referent SNP defined as heterozygote for referent (major) allele (denoted AA) and variant SNP defined as heterozygote or homozygote for the variant (minor) allele (denoted as AB and BB).

[b]Odds ratios adjusted for matching factors (age and sex including pairwise interactions), education, alcohol drinking, and proportion African ancestry. 122 individuals missing alcohol drinking, and therefore dropped from models.

[c]Significant associations using a dominant genetic model ($p<0.05$) highlighted in gray. No associations significant at Bonferroni corrected level ($p<0.0006$).

Interval estimates presented not corrected for multiple comparisons.

Table 6

Odds Ratios and Relative Excess Risk Due to Interaction Estimates for Joint Effects of Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Ever Cigarette Smoking on Head and Neck Cancer Risk Using Hierarchical Logistic Regression, the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, Whites

		Coded Allele		Cases/Controls N[a]								OR (95% I)[b]			
Gene	SNP	Referent (A)	Variant (B)	Never Cigarette, Referent SNP		Never Cigarette, Variant SNP		Ever Cigarette, Referent SNP		Ever Cigarette, Variant SNP		Never Cigarette, Variant SNP	Ever Cigarette, Referent SNP	Ever Cigarette, Variant SNP	RERI
ERCC3 (XPB)	rs4150496	G	A	70	154	79	255	331	238	441	427	0.66 (0.45, 0.98)	1.84 (1.28, 2.64)	1.41 (1.00, 1.99)	-0.09
	rs1011019	C	T	66	201	84	208	396	347	376	318	1.25 (0.85, 1.85)	2.17 (1.54, 3.05)	2.27 (1.60, 3.22)	-0.15
	rs4150434	G	A	89	264	61	145	459	406	313	259	1.19 (0.80, 1.77)	2.12 (1.56, 2.87)	2.09 (1.50, 2.90)	-0.23
	rs4150416	T	G	56	176	93	233	354	305	416	360	1.25 (0.84, 1.87)	2.26 (1.57, 3.26)	2.26 (1.57, 3.25)	-0.26
	rs4150407	A	G	55	129	95	280	263	182	509	483	0.77 (0.51, 1.15)	2.00 (1.34, 2.98)	1.53 (1.05, 2.21)	-0.24
	rs4150403	G	A	118	338	32	71	618	566	154	99	1.26 (0.78, 2.04)	1.96 (1.49, 2.56)	2.60 (1.80, 3.74)	0.38
	rs4150402	G	A	66	201	84	208	396	347	376	317	1.25 (0.85, 1.85)	2.18 (1.54, 3.06)	2.29 (1.61, 3.24)	-0.14
XPC	rs2228001	A	C	56	135	94	274	281	240	490	425	0.86 (0.57, 1.28)	1.91 (1.30, 2.82)	1.70 (1.17, 2.48)	-0.06
	rs3731143	T	C	135	361	15	48	683	596	89	69	0.93 (0.51, 1.70)	1.89 (1.46, 2.45)	2.50 (1.65, 3.78)	0.67
	rs2228000	C	T	91	222	59	187	433	376	337	288	0.77 (0.52, 1.15)	1.75 (1.28, 2.39)	1.78 (1.29, 2.48)	0.26
	rs3731124	A	C	81	228	69	181	440	371	332	294	1.10 (0.74, 1.62)	2.10 (1.53, 2.88)	1.98 (1.42, 2.75)	-0.22
	rs13099160	A	G	127	366	23	43	687	596	85	69	1.56 (0.90, 2.70)	2.06 (1.59, 2.68)	2.26 (1.48, 3.45)	-0.36
	rs3731093	T	C	120	350	27	56	656	569	111	90	1.50 (0.89, 2.50)	2.09 (1.60, 2.74)	2.48 (1.68, 3.65)	-0.11
	rs3731089	G	A	121	350	29	59	657	569	115	96	1.51 (0.91, 2.49)	2.06 (1.58, 2.69)	2.36 (1.61, 3.45)	-0.21
	rs2733537	A	G	70	175	80	234	346	305	426	360	0.89 (0.60, 1.31)	1.76 (1.24, 2.50)	1.92 (1.36, 2.71)	0.26
	rs3731068	C	A	99	275	51	134	525	457	247	208	1.02 (0.68, 1.54)	1.97 (1.48, 2.64)	2.01 (1.44, 2.79)	0.01
	rs2607755	T	C	39	110	111	299	203	174	569	491	1.10 (0.71, 1.71)	2.11 (1.36, 3.29)	2.11 (1.40, 3.19)	-0.10
	rs1902658	G	A	37	107	113	302	198	173	573	492	1.11 (0.71, 1.74)	2.09 (1.33, 3.29)	2.14 (1.40, 3.27)	-0.06
ERCC8	rs3117	T	C	60	144	90	265	277	253	495	412	0.82 (0.55, 1.22)	1.71 (1.18, 2.50)	1.76 (1.23, 2.52)	0.22
CDK7	rs2972388	A	G	42	122	108	287	224	213	548	452	1.06 (0.70, 1.63)	1.82 (1.19, 2.78)	2.17 (1.46, 3.23)	0.29
XPA	rs3176757	C	T	98	268	52	141	511	442	261	223	1.03 (0.69, 1.55)	1.94 (1.44, 2.61)	2.09 (1.50, 2.89)	0.11
	rs3176748	A	G	74	185	76	224	366	325	406	340	0.85 (0.57, 1.25)	1.77 (1.26, 2.49)	1.83 (1.30, 2.57)	0.21
	rs2808667	C	T	133	352	17	57	681	598	89	67	0.90 (0.50, 1.61)	1.87 (1.44, 2.43)	2.42 (1.60, 3.68)	0.65
	rs2805835	G	C	119	328	31	81	608	520	164	145	1.11 (0.69, 1.78)	2.03 (1.54, 2.67)	1.95 (1.38, 2.76)	-0.19

		Coded Allele		Cases/Controls N[a]								OR (95% I)[b]			
Gene	SNP	Referent (A)	Variant (B)	Never Cigarette, Referent SNP		Never Cigarette, Variant SNP		Ever Cigarette, Referent SNP		Ever Cigarette, Variant SNP		Never Cigarette, Variant SNP	Ever Cigarette, Referent SNP	Ever Cigarette, Variant SNP	RERI
	rs3176689	A	T	94	279	56	130	528	449	244	216	1.13 (0.75, 1.69)	2.14 (1.59, 2.88)	1.87 (1.34, 2.62)	-0.39
	rs3176683	T	C	134	353	16	56	684	591	88	74	0.78 (0.43, 1.40)	1.89 (1.46, 2.45)	2.04 (1.35, 3.08)	0.37
	rs3176658	C	T	114	297	36	112	585	495	187	170	0.86 (0.55, 1.34)	1.91 (1.45, 2.52)	1.86 (1.32, 2.60)	0.09
	rs1800975	G	A	72	180	75	215	348	293	390	348	0.91 (0.61, 1.34)	1.84 (1.30, 2.60)	1.87 (1.32, 2.63)	0.12
RAD23B	rs1805330	C	T	125	321	25	88	639	549	133	116	0.69 (0.42, 1.14)	1.86 (1.42, 2.43)	1.68 (1.16, 2.43)	0.13
	rs1805329	C	T	101	277	49	132	489	434	283	231	1.13 (0.75, 1.70)	2.01 (1.50, 2.69)	2.12 (1.53, 2.93)	-0.02
ERCC6	rs2228529	A	G	96	258	52	146	501	403	261	250	1.07 (0.71, 1.61)	2.12 (1.57, 2.87)	1.84 (1.33, 2.56)	-0.35
	rs2228527	A	G	97	260	53	149	501	405	271	260	1.06 (0.71, 1.58)	2.12 (1.57, 2.86)	1.84 (1.33, 2.54)	-0.34
	rs4253132	T	C	126	303	24	106	597	526	175	139	0.53 (0.32, 0.86)	1.67 (1.27, 2.20)	1.86 (1.32, 2.62)	0.65
	rs2228528	G	A	104	287	46	122	533	459	238	206	1.05 (0.69, 1.60)	2.01 (1.51, 2.68)	1.97 (1.42, 2.74)	-0.08
DDB2 (XPE)	rs2029298	A	G	69	195	81	214	356	283	416	382	1.20 (0.82, 1.77)	2.37 (1.68, 3.34)	2.02 (1.44, 2.84)	-0.55
	rs4647709	C	T	123	342	27	67	643	560	129	105	1.16 (0.71, 1.92)	2.00 (1.53, 2.62)	2.12 (1.46, 3.07)	-0.05
	rs2291120	T	C	123	296	27	113	562	516	210	149	0.61 (0.38, 0.98)	1.70 (1.29, 2.24)	1.95 (1.39, 2.74)	0.64
	rs1685404	G	C	72	180	78	229	346	322	426	343	0.89 (0.60, 1.31)	1.67 (1.19, 2.36)	2.02 (1.43, 2.84)	0.46
	rs2957873	A	G	101	275	49	134	542	436	230	229	1.14 (0.76, 1.71)	2.20 (1.64, 2.95)	1.77 (1.27, 2.46)	-0.57
	rs326224	G	A	105	288	45	121	578	473	194	192	1.16 (0.76, 1.77)	2.13 (1.60, 2.84)	1.87 (1.33, 2.62)	-0.43
	rs2306353	G	A	109	292	41	117	587	470	185	195	1.10 (0.72, 1.69)	2.17 (1.64, 2.87)	1.66 (1.19, 2.33)	-0.61
	rs326222	C	T	76	209	74	200	408	317	364	348	1.15 (0.78, 1.70)	2.37 (1.70, 3.29)	1.87 (1.34, 2.62)	-0.65
	rs901746	A	G	76	210	74	199	409	318	363	347	1.17 (0.80, 1.73)	2.39 (1.72, 3.32)	1.88 (1.35, 2.63)	-0.68
ERCC5 (XPG)	rs2296147	T	C	41	114	109	291	239	189	528	474	0.99 (0.65, 1.53)	2.13 (1.38, 3.28)	1.87 (1.24, 2.81)	-0.26
	rs4771436	T	G	97	259	53	150	466	400	306	265	0.98 (0.66, 1.47)	1.98 (1.47, 2.68)	1.92 (1.39, 2.65)	-0.05
	rs1047768	C	T	57	142	93	267	262	235	510	429	0.85 (0.57, 1.26)	1.72 (1.17, 2.52)	1.80 (1.25, 2.60)	0.24
	rs3818356	C	T	97	259	53	149	466	400	304	264	0.99 (0.66, 1.48)	1.97 (1.46, 2.66)	1.91 (1.38, 2.64)	-0.06
	rs4150351	A	C	97	258	53	151	498	434	274	231	0.95 (0.63, 1.42)	1.92 (1.43, 2.59)	1.94 (1.40, 2.69)	0.07
	rs4150355	C	T	57	159	93	250	345	269	427	396	1.05 (0.70, 1.56)	2.26 (1.56, 3.27)	1.86 (1.29, 2.67)	-0.45
	rs4150360	T	C	50	119	100	290	225	197	547	468	0.82 (0.54, 1.24)	1.71 (1.14, 2.59)	1.71 (1.17, 2.52)	0.18
	rs4150383	G	A	106	296	44	113	524	453	248	212	1.08 (0.70, 1.65)	2.02 (1.51, 2.69)	2.00 (1.44, 2.78)	-0.09
	rs4150386	A	C	113	317	37	92	611	519	161	145	1.02 (0.65, 1.60)	2.02 (1.53, 2.67)	1.84 (1.29, 2.61)	-0.21

		Coded Allele		Cases/Controls N[a]								OR (95% I)[b]			
Gene	SNP	Referent (A)	Variant (B)	Never Cigarette, Referent SNP		Never Cigarette, Variant SNP		Ever Cigarette, Referent SNP		Ever Cigarette, Variant SNP		Never Cigarette, Variant SNP	Ever Cigarette, Referent SNP	Ever Cigarette, Variant SNP	RERI
	rs17655	C	G	89	238	61	171	466	420	306	245	0.89 (0.60, 1.32)	1.78 (1.31, 2.43)	2.04 (1.46, 2.84)	0.36
	rs873601	A	G	73	190	77	219	391	349	381	316	0.83 (0.56, 1.21)	1.73 (1.24, 2.42)	1.84 (1.31, 2.58)	0.28
	rs4150393	A	G	114	317	36	92	588	527	184	138	1.15 (0.73, 1.80)	1.94 (1.47, 2.56)	2.35 (1.67, 3.32)	0.26
	rs876430	C	T	73	190	77	219	392	350	380	315	0.83 (0.56, 1.21)	1.73 (1.24, 2.41)	1.84 (1.31, 2.59)	0.29
	rs1051677	T	C	126	331	23	78	609	527	163	138	0.81 (0.49, 1.36)	1.89 (1.44, 2.47)	2.01 (1.42, 2.85)	0.31
	rs1051685	A	G	117	323	33	86	619	509	152	156	1.10 (0.70, 1.75)	2.09 (1.59, 2.74)	1.67 (1.18, 2.38)	-0.52
ERCC4 (XPF)	rs3136038	C	T	51	195	99	214	351	295	421	370	1.72 (1.16, 2.57)	2.82 (1.94, 4.10)	2.64 (1.83, 3.81)	-0.91
	rs1799798	G	A	126	331	24	78	631	570	141	95	0.82 (0.50, 1.36)	1.83 (1.40, 2.40)	2.32 (1.58, 3.39)	0.66
	rs744154	C	G	59	224	91	185	421	358	351	307	1.80 (1.22, 2.66)	2.76 (1.95, 3.90)	2.61 (1.82, 3.73)	-0.95
	rs3136085	G	C	59	220	91	189	416	356	356	309	1.76 (1.19, 2.60)	2.71 (1.91, 3.83)	2.61 (1.82, 3.73)	-0.86
	rs3136130	G	T	51	193	99	216	349	292	423	373	1.69 (1.13, 2.52)	2.79 (1.92, 4.05)	2.61 (1.81, 3.78)	-0.87
	rs1800067	G	A	125	355	25	54	653	565	119	100	1.24 (0.73, 2.11)	2.02 (1.55, 2.63)	2.11 (1.45, 3.07)	-0.15
	rs3136172	A	G	59	216	91	193	399	350	373	315	1.67 (1.13, 2.48)	2.60 (1.83, 3.68)	2.61 (1.82, 3.73)	-0.66
RAD23A	rs2974752	A	G	56	180	92	216	277	244	469	401	1.42 (0.95, 2.11)	2.35 (1.62, 3.41)	2.39 (1.67, 3.42)	-0.37
ERCC2 (XPD)	rs13181	T	G	55	155	95	252	326	282	439	381	1.06 (0.71, 1.58)	2.08 (1.43, 3.02)	1.96 (1.36, 2.84)	-0.17
	rs238418	C	A	54	155	96	254	328	271	444	394	1.09 (0.73, 1.63)	2.19 (1.50, 3.20)	2.00 (1.38, 2.89)	-0.28
	rs1799787	C	T	68	203	82	206	404	342	368	323	1.16 (0.79, 1.71)	2.18 (1.56, 3.06)	2.07 (1.47, 2.93)	-0.27
	rs3916874	G	C	81	201	69	208	396	344	376	321	0.76 (0.51, 1.11)	1.70 (1.22, 2.36)	1.73 (1.24, 2.41)	0.27
	rs238416	G	A	62	193	88	216	307	275	464	388	1.33 (0.90, 1.96)	2.16 (1.51, 3.09)	2.40 (1.69, 3.39)	-0.09
	rs50872	C	T	80	221	70	187	451	363	319	301	1.05 (0.71, 1.55)	2.14 (1.55, 2.95)	1.85 (1.32, 2.58)	-0.34
	rs50871	T	G	43	89	107	320	199	169	573	495	0.67 (0.44, 1.05)	1.40 (0.89, 2.19)	1.49 (0.98, 2.25)	0.41
	rs238407	A	T	43	136	107	273	220	202	551	463	1.39 (0.91, 2.11)	2.33 (1.53, 3.55)	2.51 (1.70, 3.72)	-0.21
	rs3810366	C	G	32	95	118	314	146	137	625	528	1.28 (0.81, 2.04)	2.26 (1.39, 3.68)	2.41 (1.54, 3.75)	-0.14
ERCC1	rs735482	A	C	117	302	33	107	571	495	201	170	0.82 (0.52, 1.30)	1.87 (1.42, 2.47)	1.90 (1.36, 2.65)	0.20
	rs2336219	G	A	117	302	33	107	571	495	201	170	0.82 (0.52, 1.30)	1.87 (1.42, 2.47)	1.90 (1.36, 2.65)	0.20
	rs3212964	G	A	118	302	32	107	574	492	198	173	0.79 (0.50, 1.24)	1.87 (1.42, 2.46)	1.84 (1.32, 2.56)	0.18
	rs3212955	A	G	82	229	68	180	446	378	326	286	1.09 (0.74, 1.61)	2.08 (1.51, 2.85)	2.02 (1.45, 2.81)	-0.15
	rs3212948	C	G	60	171	90	238	322	287	450	378	1.10 (0.74, 1.63)	2.01 (1.40, 2.88)	2.14 (1.50, 3.05)	0.03

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2014 August 01.

Gene	SNP	Coded Allele: Referent (A)	Coded Allele: Variant (B)	Cases/Controls N[a]: Never Cigarette, Referent SNP		Never Cigarette, Variant SNP		Ever Cigarette, Referent SNP		Ever Cigarette, Variant SNP		OR (95% I)[b]: Never Cigarette, Variant SNP	Ever Cigarette, Referent SNP	Ever Cigarette, Variant SNP	RERI
	rs3212930	T	C	92	248	58	161	484	409	288	256	0.99 (0.67, 1.47)	1.95 (1.44, 2.64)	1.98 (1.43, 2.75)	0.04
LIG1	rs156641	G	A	56	166	94	243	314	274	458	391	1.21 (0.81, 1.80)	2.13 (1.47, 3.10)	2.26 (1.57, 3.26)	-0.08
	rs20580	C	A	30	109	120	300	207	184	565	481	1.51 (0.95, 2.41)	2.48 (1.54, 4.00)	2.80 (1.78, 4.38)	-0.20
	rs20579	C	T	105	305	45	104	586	521	186	144	1.34 (0.87, 2.05)	2.05 (1.55, 2.72)	2.43 (1.71, 3.45)	0.04

OR odds ratio, RERI relative excess risk due to interaction, I interval estimates

[a]Referent SNP defined as heterozygote for referent (major) allele (denoted AA) and variant SNP defined as heterozygote or homozygote for the variant (minor) allele (denoted as AB and BB).

[b]Odds ratios adjusted for matching factors (age and sex including pairwise interactions), education, alcohol drinking, and proportion African ancestry. 122 individuals missing alcohol drinking, and therefore dropped from models.

Interval estimates presented not corrected for multiple comparisons.