SINGLE NUCLEOTIDE POLYMORPHISMS IN NUCLEOTIDE EXCISION REPAIR GENES AND HEAD AND NECK CANCER RISK AND OUTCOMES

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A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology.

Chapel Hill
2013

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ABSTRACT

ANNAH B. WYSS: Single Nucleotide Polymorphisms in Nucleotide Excision Repair Genes and Head and Neck Cancer Risk and Outcomes
(Under the direction of Dr. Andrew Olshan)

An estimated 52,140 incident head and neck cancers (HNC), with 11,460 associated deaths occurred in the US during 2011. Cigarette smoke contributes to HNC risk by causing bulky DNA adducts. Such adducts are removed by nucleotide excision repair (NER) processes. Previous studies have suggested that polymorphisms in NER genes are independent risk factors for HNC, as well as modifiers of smoking-HNC associations. Treatment of HNC with radiation and platinum-based chemotherapies also produce bulky DNA adducts, and previous studies suggest independent NER SNP and joint SNP-treatment associations with HNC survival.

Race-specific (white and African American) odds ratios (ORs) and 95% intervals (Is) for the individual and joint effects of 84 single nucleotide polymorphisms (SNPs) in 15 NER genes and cigarette smoking on HNC risk were estimated from unconditional and hierarchical logistic regression models using data from the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study (1,227 cases and 1,325 controls). Race-specific hazard ratios (HRs) and 95% confidence intervals (CIs) for the individual and joint effects of the same SNPs in NER genes and treatment (surgery, radiation, and chemotherapy) on survival among cases were estimated using Cox proportional hazards models, with Bonferroni corrected p-values to account for multiple comparisons.

Among whites, rs4150403 on *ERCC3 (XPB)* was associated with increased HNC risk (OR=1.28, 95% I=1.01, 1.61). Among African Americans, rs4253132 on *ERCC6* was associated with decreased

HNC risk (OR=0.62, 95% I=0.45, 0.86). For HNC survival, no associations were significant at a Bonferroni-corrected alpha of 0.0006. However, rs3136038 and rs3136130 of *ERCC4* and rs50871 of *ERCC2 (XPD)* were suggestively associated with similarly improved survival among whites at an uncorrected 0.05 alpha (overall survival HRs≈0.80 and disease-specific survival HRs≈0.70). Likewise, rs2607755 of *XPC* was suggestively associated with improved survival among African Americans (overall survival HR=0.62 and disease-specific survival HR=0.51). A few SNP-cigarette smoking and SNP-treatment interactions suggested possible additive effects.

We conducted one of the largest and most comprehensive evaluations of SNPs in multiple NER genes, identifying only a few SNPs from biologically plausible genes associated with HNC risk or survival, and possibly interacting with cigarette smoking or treatment.

DEDICATION

To my husband, Richie, for your love and support

and

To my parents, Bruce and Cathie, for your example and encouragement

ACKNOWLEDGEMENTS

I would first like to thank my dissertation committee: Drs. Andrew Olshan, Christy Avery, Jeannette Bensen, Amy Herring, and Mark Weissler. Thank you for the many hours you invested in my dissertation. Thank you for offering both your expertise and encouragement. I also wish to honor my late committee member Dr. Robert Millikan, whom I thank for his guidance in my coursework and on this dissertation. Bob, you are missed.

I express deep gratitude to my adviser, Dr. Olshan, for his years of exceptional mentoring. Thank you for always making time to advise me despite your busy schedule. Thank you for facilitating many valuable research opportunities. Under your mentoring, I have expanded my understanding and appreciation for cancer epidemiology in countless ways. I am grateful for the opportunity to work with you on several CHANCE and INHANCE projects. Thank you for going above and beyond the call of duty as my adviser.

I thank my classmates for all their help along the way. In particular, I'd like to thank Dr. Anne Hakenewerth, Katie O'Brien, Nikhil Khankari, Jessica Petrick, Jeanette Stingone, and Anne Butler. I could not have accomplished this research without their insight and support. I also thank the Department of Epidemiology and CHANCE staff. Nancy Colvin and Carmen Woody, you are the glue that holds the epidemiology students together. Kathy Wisniewski and Kim Ludgwig, thank you for your exceptional programming support. I am also grateful to the funding agencies who support the CHANCE study, and in particular my dissertation research. The Cancer Epidemiology Training Grant (T32CA09330) and Environmental Epidemiology Training Grant (P30ES01012) have afforded me invaluable educational and career development experiences.

To the CHANCE participants and their families, I offer sincere gratitude for their participation. I hope our research continues to move the field forward to better serve you.

Last, but certainly not least, I would like to thank my family. UNC will always hold a special place in my heart not only because it is my alma mater, but because it is where I meet my husband. Richie Wyss, thank you for patiently answering all my statistics questions, encouraging me to press forward, and enriching my life with laughter and love. I am so grateful to have you as my companion in this journey. I thank my parents, Bruce and Cathie Layman, and my siblings, Julia and Alex Baker, Christina Layman, and Christian Layman, for their unfailing love and support. Thank you also to my in-laws and other extended family for their encouragement.

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LIST OF ABBREVIATIONS

AFT	Accelerated failure time
AIM	Ancestral informative marker
ACC	American Cancer Society
AJCC	American Joint Committee on Cancer
ARCAGE	Alcohol Related Cancers and Genetic Susceptibility in Europe
ASW	African ancestry in Southwest United States
BER	Base excision repair
CCNH	Cyclin H (non-italicized for enzyme, italicized for gene)
CDK7	Cyclin-dependent kinase 7 (non-italicized for enzyme, italicized for gene)
CEU	Utah Residents with Northern and Western European Ancestry
CHANCE	Carolina Head and Neck Cancer Epidemiology
CI	Confidence interval
CSA	Cockayne syndrome A (non-italicized for enzyme, italicized for gene); also known as ERCC8
CSB	Cockayne syndrome B (non-italicized for enzyme, italicized for gene); also known as ERCC6
DDB2	Damage-specific DNA binding 2 (non-italicized for enzyme, italicized for gene); also known as XPE
DNA	Deoxyribonucleic acid
DS	Disease-specific survival
ERCC1	Excision repair cross-complementing 1 (non-italicized for enzyme, italicized for gene)
ERCC2	Excision repair cross-complementing 2 (non-italicized for enzyme, italicized for gene); also known as XPD
ERCC3	Excision repair cross-complementing 3 (non-italicized for enzyme, italicized for gene); also known as XPB

ERCC4	Excision repair cross-complementing 4 (non-italicized for enzyme, italicized for gene); also known as XPF
ERCC5	Excision repair cross-complementing 5 (non-italicized for enzyme, italicized for gene); also known as XPG
ERCC6	Excision repair cross-complementing 6 (non-italicized for enzyme, italicized for gene); also known as CSB
ERCC8	Excision repair cross-complementing 8 (non-italicized for enzyme, italicized for gene); also known as CSA
GWA	Genome wide association
HNC	Head and neck cancer
HPV	Human papillomavirus
HR	Hazard ratio
INHANCE	International Head and Neck Cancer Epidemiology
IARC	International Agency for Research on Cancer
ICR	Interaction contrast ratio
LD	Linkage disequilibrium
LIG1	Ligase 1 (non-italicized for enzyme, italicized for gene)
MAF	Minor allele frequency
NCI	National Cancer Institute
NDI	National Death Index
NER	Nucleotide excision repair
NOS	Not otherwise specified
OPL	Oral premalignant lesions
OR	Odds ratio
OS	Overall survival
PCNA	Proliferating cell nuclear antigen
PFS	Progression free survival

RAD23A	RAD23 homolog A (non-italicized for enzyme, italicized for gene)
RAD23B	RAD23 homolog B (non-italicized for enzyme, italicized for gene)
RFC	Replication factor C
RPA	Replication protein A
RERI	Relative excess risk due to interaction
SEER	Surveillance, Epidemiology and End Results
SNP	Single nucleotide polymorphism
TFIIH	Transcription factor II H
UADT	Upper aerodigestive tract
XPA	Xeroderma pigmentosum A (non-italicized for enzyme, italicized for gene)
XPB	Xeroderma pigmentosum B (non-italicized for enzyme, italicized for gene); also known as ERCC3
XPC	Xeroderma pigmentosum C (non-italicized for enzyme, italicized for gene)
XPD	Xeroderma pigmentosum D (non-italicized for enzyme, italicized for gene); also known as ERCC2
XPF	Xeroderma pigmentosum F (non-italicized for enzyme, italicized for gene ; also known as ERCC4
XPE	Xeroderma pigmentosum E (non-italicized for enzyme, italicized for gene); also known as DDB2
XPG	Xeroderma pigmentosum G (non-italicized for enzyme, italicized for gene); also known as ERCC5
YRI	Yoruba in Ibadan, Nigeria

CHAPTER 1

BACKGROUND AND LITERATURE REVIEW

1.1 SPECIFIC AIMS

In the United States an estimated 52,140 incident cases of oral cavity, pharyngeal and laryngeal cancers, with 11,460 associated deaths occured in 2011 (1). Tobacco is a well-established risk factor for head and neck cancer (HNC) incidence, with well over 20 cohort and case-control studies demonstrating strong associations (2). Nucleotide excision repair (NER) genes remove bulky DNA adducts caused by cigarettes smoking (3) and are therefore considered independent predictors for HNC, as well as important modifiers of associations between tobacco and HNC (4,5). With regard to HNC mortality, treatment is a strong prognostic factor and NER genes are believed to also modify the association between treatment and HNC survival through increased/decreased DNA repair activities (6,7).

Previous research indicates significant associations between polymorphisms in NER genes and HNC risk, but vary with regard to which particular genes are predictive of HNC, as well as the magnitude of associations (4,5,8-46). Studies regarding the joint effects of cigarette smoking and NER genes on HNC risk are more limited, but some indicate stronger effects among smokers with polymorphisms in NER genes (4,8-10,13,15,16,22,24,26-28,30,31,33,35-38,40,44). Studies on HNC survival have also demonstrated important effects of polymorphism in NER genes and treatment, especially with regard to radiation and platinum-based chemotherapy (7,47-55).

The impact of cigarette smoking and variation in NER genes on HNC incidence, as well as treatment and polymorphisms on survival, may be further modified by race. African Americans

experience higher smoking rates compared to whites in the US (56) and a previous study using data from the Carolina Head and Neck Cancer (CHANCE) study reported higher magnitude odds ratios for cigarette smoking and HNC associations among African Americans compared to whites (57). In addition, HNC incidence and mortality rates vary by race in the US, and HNC survival is particularly low among African Americans men (58-62). Yet studies generally do not consider such associations stratified by race; only one study to date has reported NER variant-HNC estimates specific to African Americans (15).

The CHANCE study contains previously collected demographic, lifestyle and survival data, as well as DNA samples, for a large and racially diverse population (959 white and 330 African American cases and 1100 white and 261 African American controls) (57,63,64). DNA samples were recently genotyped for 1235 single nucleotide polymorphisms (SNPs) in 208 genes (64). Therefore, the CHANCE study is suitable to investigate the associations between polymorphisms in NER genes, cigarette smoking, and treatment and HNC outcomes by addressing the following dissertation aims:

Aim 1: Assess the individual and joint effects of polymorphisms in NER genes (15 genes, 84 SNPs) and cigarette smoking (ever, frequency, and duration) on HNC risk. *Hypothesis*. Polymorphisms in NER genes will be associated with HNC incidence, with larger effects among smokers compared to never smokers. *Methods.* Unconditional logistic regression will be used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for cigarette smoking, SNPs, and joint effects. Gene-environment interactions will be assessed for synergistic effects on the additive scale. Adjustment variables will be determined through a directed acyclic graph (DAG), as well as previous literature. Possible adjustment variables include: age, sex, education, family history of cancer, alcohol drinking, cigar and pipe smoking, smokeless tobacco use, marijuana smoking, nutrition, and oral health. Models will also be adjusted for ancestral informative markers (AIMS) and stratified by race (African American and white). P-values will be corrected for multiple testing using an alpha

adjustment method(s) such as the Bonferroni method. In addition, hierarchical regression will be employed to address correlation of exposures (i.e. SNPs in in linkage disequilibrium, LD).

Aim 2: Assess the individual and joint effects of polymorphisms in NER genes (15 genes, 84 SNPs) and treatment (various types of chemotherapy, radiation therapy, and surgery) on risk of mortality among HNC cases. *Hypothesis.* Polymorphisms in NER genes will be associated with overall survival and disease-specific survival, with varying prognosis across treatment types. *Methods.* To assess survival, CHANCE data was linked with the National Death Index (NDI) to ascertain deaths through 2009. Cox proportional hazards models will be used to estimate hazard ratios (HRs) and 95% CIs to compare hazards of mortality among cases based on SNPs in NER, treatment (various types of chemotherapy, radiation therapy, and surgery), and their joint effects. Interactions will be assessed similar to aim 1. Adjustment variables will be determined using the methods described in aim 1, and will include clinical variables, such as tumor stage and site, in addition to demographic and behavioral covariates. Models will also be adjusted for ancestral informative markers (AIMS) and stratified by race (African American and white). The Bonferroni method will be used to account for multiple comparisons. Absolute differences in months of survival will also be assessed via Kaplan-Meier plots.

1.2 HEAD AND NECK CANCER: OVERVIEW

1.2.1 Definition

Head and neck cancer (HNC) is defined as cancers of the oral cavity (lips, gums, tongue, and floor and roof of the mouth, also known as the hard palate), pharynx (nasopharnynx, oropharynx, including tonsils and base of tongue, and hypopharynx), and larynx (65-67). Nasopharyngeal cancers are generally considered separate from HNC given the different risk factor profile and global distribution of the cancer (68). In addition, most studies of HNC exclude lip cancers since the primary

risk factor for these cancers is sun exposure and not smoking and alcohol drinking (69). More than 90% of HNC are squamous cell carcinomas (70).

1.2.2 Natural progression

Although many HNCs arise without detectable premalignant conditions, the presence of leukoplakia and erythroplakia may indicate developing disease (71). Leukopakia is characterized by white lesions, while erythroplakia is characterized by red lesions (71). Several factors affect the likelihood and rate of progression of pre-malignant lesions to cancer, such as anatomic site, demographic profile of the individual (e.g., age) and behavioral risk factors (e.g., types of tobacco used)(71). For example, it has been suggested that premalignant lesions on the floor of the mouth are more likely to progress to cancer than other sites within the oral cavity (71). Likewise, some studies have reported higher rates of regression among pipe smokers or tobacco chewers compared to cigarette smokers, and smoking cessation has also been associated with a greater likelihood of tumor regression (71). Genetic susceptibility is also an important factor in tumor progression (71). Alterations of tumor suppressor genes, including p53, are strongly associated with tumor progression (71) A complete description of molecular and clinical progression from hyperplasia to cancer can be found in Forastiere et al., 2001 (72).

1.2.3 Global and US Burden

Head and neck cancer is among the most common cancers worldwide with nearly 600,000 incident cases and 300,000 deaths occurring globally each year (73). High incidence regions include India and other parts of Southeast Asia, Brazil, Russia, Australia (which is mostly due to lip cancers attributed to sun exposure), parts of Europe (mainly Spain and France), and the United States(72,74). In the United States, there were an estimated 52,140 new cases of oral cavity, pharyngeal and laryngeal cancers, with 11,460 associated deaths in 2011 (1). The age-adjusted incidence rate for oral cavity and pharyngeal cancers in the US is 10.6 per 100,000 people per year

and the mortality rate is 2.5 per 100,000 people per year (59) (tables 1 and 2). For laryngeal cancers, the US incidence and mortality rates are 3.4 per 100,000 and 1.2 per 100,000, respectively (60) (tables 1 and 2). HNC is a relatively fatal disease with poor survival. Within three years of diagnosis, approximately a third of patients have died; among African Americans more than 40-50% have died (61,62) (table 3 and 4). By five years, 40% of patients have died; among African Americans nearly 50-60% (61,62) (table 3 and 4). As of January 1, 2008, the prevalence of HNC in the US was approximately 341,656 men and women (59,60). It is estimated that 1 in 98 people in the US will be diagnosed with oral cavity or pharyngeal cancer, and 1 in 277 with laryngeal cancer, during their lifetime (59,60).

1.3 HEAD AND NECK CANCER: DEMOGRAPHIC RISK FACTORS

1.3.1 Age

The median age of diagnosis among oral cavity and pharyngeal cancer cases in the US is 62 years, with "approximately 0.6% diagnosed under age 20; 2.3% between 20 and 34 years; 6.3% between 35 and 44 years; 20.5% between 45 and 54 years; 27.5% between 55 and 64 years; 21.2% between 65 and 74 years; 15.6% between 75 and 84 years; and 6.0% 85+ years" (59). The median age at death among oral cavity and pharyngeal cancer cases in the US is 67 years, with "approximately 0.2% [dying] under age 20; 0.8% between 20 and 34 years; 3.3% between 35 and 44 years; 14.6% between 45 and 54 years; 24.0% between 55 and 64 years; 23.8% between 65 and 74 years; 22.1% between 75 and 84 years; and 11.3% 85+ years" (59). The median age at diagnosis and death among laryngeal cancer cases is 65 and 68, respectively, with age distributions similar to oral cavity and pharyngeal cancers (60).Survival decreases with increasing age (61) (table 3 and 4).

1.3.2 Sex

Incidence and mortality of HNC is much higher in men compared to women in the US (59,60). As summarized in table 1, the age-adjusted incidence rates for oral cavity and pharyngeal

and laryngeal cancers in men were 2.5 and 4.6 times, respectively, the incidence rates in women (15.7 versus 6.2 and 6.0 versus 1.3 per 100,000, respectively) (59,60). With respect to mortality, the age-adjusted mortality rates for oral cavity and pharyngeal and laryngeal cancers in men were 2.8 and 4.4 times, respectively, the mortality rates in women (3.9 versus 1.4 and 2.2 versus 0.5 per 100,00 people, respectively, table 2) (59,60).

1.3.3 Race

The incidence of oral cavity and pharyngeal cancers has historically been higher among African Americans compared to whites in the US; however, starting in 2005 incidence rates began to be higher among whites due to more rapid decline in incidence among African American men (58,75). In 2008, the age-adjusted incidence rates of oral cavity and pharyngeal cancers were 9.1 per 100,000 among African Americans and 11.0 per 100,000 among whites (58). In contrast, age-adjusted mortality rates continue to be higher among African Americans compared to whites for all HNC subsites (59,60). Incidence and mortality rates based on the 2004-2008 Surveillance, Epidemiology and End Results (SEER) data are presented in tables 1 and 2 according to HNC subsite, race, and gender. For African Americans, 5-year survival rates are 30.7% for males and 50.6% for females (61,62,76) (tables 3 and 4). For whites, corresponding rates are 58.9% and 61.2%, respectively (tables 3 and 4) (61,62,76).

1.3.4 Socioeconomic Status

As with many diseases, social determinants, such as income and education, are associated with HNC outcomes. Socioeconomic status is believed to influence a number of other risk factors for HNC, such as smoking and drinking habits, diet, human papillomavirus (HPV) infection, and exposure to harmful chemicals in the workplace and housing, but may also act through other mechanisms such as access to health information and health care, as well as levels of stress (77). A recent meta-analysis of 41 case-control studies (15,344 oral cancer cases and 33,852 controls) considered

associations between various measures of SES and oral cavity cancer (77,78). Since the individual studies varied greatly with regard to measurement scale of income, occupation and education, Conway et al. (77) selected the lowest and highest categories for each variable as reported by the original authors and then collapsed across the heterogeneous definitions to form 'high' and 'low' categories for the meta-analysis. Of the 41 studies considered, five studies reported information on household income resulting in a summary OR (95% CI) for low income compared to high income of 2.41 (1.59, 3.65) (77). Fourteen studies reported on occupation resulting in a summary OR (95% CI) of 1.84 (95%CI 1.47, 2.31) for low occupation social class compared to high occupation social class (77). Thirty-seven studies reported on education resulting in a summary OR (95% CI) of 1.85 (1.60, 2.15) for low educational attainment compared to high educational attainment (77).

1.3.5 Family History

Family history is often considered as a marker of inherited genetic susceptibility, which can play a strong role in cancer incidence and mortality (79). In 2004, International Head and Neck Cancer Epidemiology (INHANCE) Consortium began pooling HNC case-control studies throughout the world to better characterize risk factors (80). In an INHANCE study on family history, having a relative diagnosed with HNC was associated with increased risk; OR (95% CI) was 1.62 (1.32, 1.98) for 1 affected relative and 2.65 (1.13, 6.22) for 2 or more affected relatives (79). Specifically, having a parent with HNC was associated with a 45% increase in risk [OR (95% CI0 = 1.45 (1.14, 1.84)] and having a sibling with HNC was associated with a 123% increase in risk [OR (95% CI) = 2.23 (1.61, 3.08)] (79).

1.3.6 Genetic Variation

In addition to variants in nucleotide excision repair (NER) genes (as will be discussed in detail in later sections), associations between variants in a number of other genes and HNC have been investigated. For example, the INHANCE consortium, in collaboration with the Central Europe study

and the Alcohol Related Cancers and Genetic susceptibility in Europe (ARCAGE) study, recently published a genome-wide analysis (GWA) detailing the association between 294,620 variants and upper-aerodigestive tract (UADT) cancers, including HNC (81). In the first phase of this study, associations between all 294,620 single nucleotide polymorphisms (SNPs) and UADT cancers were examined in the Central Europe and ARCAGE study populations (2,091 cases and 3,513 controls from the studies, plus an additional 4,821 genomic controls) (81). In the second phase, the top nineteen SNPs associated with UADT cancer, as identified in phase 1, were then examined for association with only HNC in the INHANCE population (6,514 cases and 7,892 controls) (81). From this paper it is unclear which NER variants were tested, but based on a Bonferroni corrected alpha level of ($p \leq 5x10^{-7}$), five SNPs were found to be significantly associated with UADT cancers: rs4767364 in *ALDH2;* rs1494961in *HEL208* (related to the *ADH* genes); and rs1573496, rs1229984 and rs698 in *ADH7, AHD1B,* and *ADH1C,* respectively (81). All of these genes are known to function in alcohol metabolism, and the individual and joint effects of variants in *ALDH2* and *ADH* genes and alcohol on HNC incidence and survival in CHANCE were recently analyzed by Dr. Anne Hakenewerth as part of her dissertation (64,82).

1.4 HEAD AND NECK CANCER: ENVIRONMENTAL AND BEHAVIORAL RISK FACTORS

1.4.1 Cigarette Smoking

Although the cigarette smoking is on the decline in the US, an estimated 17.2% of individuals in the US smoke cigarettes (56). With regard to prevalence of smoking by race in the US, 17.4% of whites and 19.1% of African Americans smoked in the US in 2010 (56). Cigarettes contain many IARC classified probable and known carcinogens, including tar, nicotine, nickel, arsenic, lead, benzene and a host of nitrosamines (2). The effects of tobacco use on the incidence and mortality of HNC is well established (2). For example, the *IARC Monograph on Tobacco Smoke* (2) concluded that there is sufficient evidence for a casual association between cigarette smoking and head and neck

cancer based on biologic and epidemiologic evidence. The monograph summarizes the findings of 3 cohort studies on cigarette smoking and HNC with risk ratios (RR) from 1.5 to 3.4 and over 15 case-control studies with odds ratios (OR) ranging from approximately 2.0 to 10.0. Strong dose-response trends in frequency and duration were also noted across studies (2).

In one of the first studies published by INHANCE, which included data from 15 case-control studies at the time, investigators estimated the individual effects of cigarette smoking on HNC by focusing analyses on never alcohol drinkers to better understand the independent effects of cigarette smoking separate from other major risk factors (83). Among never alcohol drinkers, the summary OR (95% CI) for cigarette smoking and HNC was found to be 2.13 (1.52, 2.98), with individual study estimates ranging from 0.36 (0.07, 1.91) for Seattle to 11.53 (4.69, 28.31) for Milan (83). Given the heterogeneity of studies, which may reflect regional differences in smoking habits and products among other reasons, the authors considered the impact of removing the four most influential studies (including Seattle and Milan) which resulted in a summary OR of 2.02 (1.61, 2.53) for cigarette smoking and HNC (83). The effect estimate also did not change substantially when only large studies (i.e. more than 500 cases) were considered (83). The authors also noted strong dose-response trends ($p<0.001$) across frequency (cigs/day), duration (years), and cumulative packyears of cigarette smoking, with ORs over 4.0 for the highest levels of frequency and packyears (83). With regard to subsite, INHANCE reported the strongest association for cigarette smoking and laryngeal cancer. Among never alcohol drinkers, ORs (95% CIs) associated with cigarette smoking were 1.35 (0.90, 2.01) for oral cavity cancer, 2.02 (1.34, 3.05) for oropharyngeal and hypopharyngeal cancer, and 6.84 (4.25 to 11.01) for laryngeal cancer (83). The estimated population attributable fraction of cigarette smokers among never drinkers was near 25%, and 75% of HNC were attributed to cigarette smoking and alcohol drinking combined (83,84).

A recently published analysis from the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study reported an adjusted OR (95% CI) for current cigarette smoking compared to never cigarette smoking was 3.92 (3.00, 5.13) which agreed with estimates from similarly powered studies included INHANCE (57). Likewise, risk appeared to increase with increasing frequency, duration, and packyears of use, with ORs over 3.0 for the highest levels of frequency and duration in CHANCE (57). CHANCE also provided an opportunity to consider race-stratified estimates. The adjusted ORs (95% CIs) for current cigarette smoking were 15.1 (7.11, 32.0) among African Americans and 3.14 (2.36, 4.20) among whites (57). Increasing trends in frequency, duration, and packyears of use were noted for each race (57).

Cigarette smoking has also been linked to decreases in survival. In the National Institutes of Health – American Association of Retired Persons (NIH-AARP) cohort study, investigators from the National Cancer Institute (NCI) found adjusted hazard ratios (HRs) for former and current smokers, compared to never smokers, of 3.47 (2.06, 5.87) and 12.96 (7.81, 21.52), respectively (85). Elevated risk of death among HNC cases who currently smoke compared to non-smokers was also noted in a Japanese study (86).

1.4.2 Use of Other Tobacco Products

Cigars and pipes contain carcinogens similar to cigarettes and delivered dosages of some carcinogens may even be higher in cigars than in cigarettes (2). Elevated risk of head and neck cancer among pipe and cigar smokers has been consistently reported in literature (2,87). For example, in an unpublished analysis of the INHANCE pooled case-control data, the adjusted ORs (95% CIs) among never-cigarette smokers were (2.54, 95% CI=1.93, 3.34) for ever cigar smoking and (2.08, 95% CI=1.55, 2.81) for ever pipe smoking (87). Risk of head and neck cancer also increased with increasing frequency and duration of cigar and pipe smoking (87) .

Heavy daily use of smokeless tobacco products directly exposes the oral cavity to carcinogens and can result in exposure to nicotine comparable to that of heavy smokers (88). Previous estimates on the risk of HNC among smokeless tobacco users in the US are varied and often hard to interpret due to low frequencies of users and indistinct definitions of exposure (89). A review by Boffetta on smokeless tobacco and risk of head and neck cancer in the US (90), considered nine studies with risk estimates ranging from 0.9 (0.1, 6.7) to 11.2 (4.1, 30.7). The pooled relative risk (RR) and 95% CI for the nine studies was 2.6 (1.3, 5.2 (90). Likewise, studies summarized in the *IARC Monograph on Smokeless Tobacco* (88) varied between null and elevated ORs for ever tobacco chewers and ever snuff users. In an unpublished INHANCE study, the adjusted ORs (95% CIs) among never cigarette smokers were 1.40 (0.71, 2.09) for ever tobacco chewing and 1.56 (0.68, 2.44) for ever snuff use in the US (91). Internationally, betel quid and other regional forms of smokeless tobacco products have been more strongly associated with HNC (88).

1.4.3 Environmental Tobacco Smoke

Environmental tobacco smoke (ETS), also known as involuntary, passive or secondhand smoke, occurs from sidestream and exhaled mainstream cigarette smoke (2,92). Although the composition and concentration of ETS varies based on the setting, experimental and observational studies have consistently demonstrated elevated levels of many tobacco-related carcinogens in the ambient air (2). Although IARC has classified ETS as a causal agent for lung cancer, relatively few studies have considered the effects of ETS on HNC risk (2,92). As of April 2012, only six studies were found to report on the association between ETS and HNC risk (92-97). Results have been somewhat mixed with smaller studies tending to find larger magnitude ORs for the association between ETS and HNC and larger studies more likely to report attenuated ORs (92-97). However, the conclusion of potentially modest increased risk of HNC associated with ETS was relatively uniform across studies. The two largest studies, both by Lee et al, reported ORs (95% CIs) for ever ETS exposure in

home or at work of 1.07 (0.85, 1.34) in the International Head and Neck Cancer Epidemiology (INHANCE) consortium (92) and 1.87 (1.08, 3.23) and 1.98 (0.77, 5.07) with respect to oral/oropharyngeal and laryngeal/hypopharngyeal cancer in the ARCAGE study (96). Both of these studies also found evidence for increasing HNC risk with increasing intensity of ETS exposure (92,96).

1.4.4 Alcohol Consumption

Next to cigarette smoking, alcohol drinking is the second most established risk factor for HNC. Alcohol contains several possible, probable and known carcinogens, including nitrosamines (98). Further, genetic variants that help regulate the metabolism of alcohol can impact the levels of acetaldehyde which may cause DNA damage through several pathways, including the formation of DNA adducts (98). The *IARC Monograph on Alcohol Consumption* (98) concluded that there is sufficient evidence to classify alcohol as a carcinogen for HNC. Nearly 20 cohort and case-control studies have reported positive associations between alcohol and HNC, including dose-response relationships with highest risk among heaviest consumption (98).

In the first INHANCE study on alcohol drinking, investigators found the OR (95% CI) between ever drinking alcohol and HNC to be 1.18 (0.93 to 1.50) among never tobacco users, with the association being significantly elevated after 'influential' studies were dropped from the analysis (83). In addition, risk of HNC increased with increasing frequency of alcohol drinking (p_{trend}<0.0001), with elevated risk among individuals who consumed 3 or more drinks a day (83). In a subsequent INHANCE publication on the joint effects of alcohol and tobacco, the authors reported a greater than multiplicative effect with an interaction parameter [Ψ = OR11 / (OR01 * OR10)] and 95% CI of 2.15 (1.53-3.04) (84). Approximately 7% of HNC are attributed to alcohol drinking alone, and 75% to alcohol drinking and cigarette smoking combined (83,84).

Recently, a series of meta-analyses on the association between alcohol consumption and risk of HNC have been published. Including 40 studies on the association between alcohol and

laryngeal cancer, the summary estimate was found to be RR (95% CI) = 1.90 (1.59, 2.28), with null associations among light drinkers and increased risk among heavy drinkers (99). For oral cavity and pharyngeal cancers, both light drinkers (1 drink or less per day) and heavy drinkers (4 or more drinks per day) had increased risk; summary RRs (95% CIs) for 45 studies were 1.21 (1.10, 1.33) and 5.24 (4.36, 6.30), respectively (100). Neither meta-analysis appeared to consider the effects of alcohol on HNC risk among non-smokers, however.

1.4.5 Human Papillomavirus

Human papillomavirus (HPV) up-regulates oncoproteins, namely E6 and E7, which disrupt p53 and pRb tumor suppression pathways (101). An estimated 20-25% of HNC are attributed to oral infection with HPV (101). Increases in HPV infection have been implicated in recent increases in oropharyngeal cancer incidence, especially as alcohol and tobacco consumption appear to remain stable or decline in the US (78,101). The *IARC Monograph on HPV* summarizes several case series which report the prevalence of HPV in HNC ranging from 0% to 100%. A review of case-control studies showed mixed results, but most demonstrated elevated ORs for HNC, especially for oropharyngeal cancer, among HPV-positive individuals (102). With regard to survival, a meta-analysis reported a decrease in the 5-year risk of dying among HNSCC cases who were HPV-positive compared to HPV-negative, with hazard ratios (HR) ranging from 0.20 to 0.75 (103).

1.4.6 Diet and Body Mass Index

Nutrition and body mass index (BMI) have also been hypothesized as risk factors for HNC (78). Although studies on specific micro- and macronutrients and HNC are limited, carotene, vitamin C, vitamin A, calcium, flavonoids, and fiber have all been implicated as beneficial due to antioxidant and other properties (104). Most studies on diet and HNC have focused on fruit and vegetable intake (78). In a meta-analysis by Pavia et al. (105), 16 studies of oral cavity cancer resulted in summary ORs (95% CIs) of 0.51 (0.40, 0.65) for fruit consumption and 0.50 (0.38, 0.65) for vegetable

consumption. In a separate meta-analysis by Riboli (106), 12 studies on oral/pharyngeal cancer (9 studies and 7 studies included for fruits and vegetables, respectively) and 8 studies on laryngeal cancer (5 studies and 7 studies included for fruits and vegetables), produced summary ORs (95% CIs) of 0.53 (0.37, 0.76) for fruits and oral/pharyngeal cancer, 0.84 (0.67, 1.07) for vegetables and oral/pharyngeal cancer, 0.73 (0.64, 0.84) for fruits and laryngeal cancer, and 0.93 (0.83, 1.02) for vegetables and laryngeal cancer. In addition to fruits and vegetables, other diets and foods have been associated with lower or higher risk of HNC (78,104).

With regard to BMI, a recent INHANCE study showed increased risk of HNC among low BMI individuals and decreased risk among high BMI individuals at reference (diagnosis for cases and enrollment for controls) (107). Specifically, the study reported adjusted ORs (95% CIs) of 2.13 (1.75, 2.58) for BMI ≤18.5 kg/m, 0.52 (0.44, 0.60) for BMI >25-30 kg/m, and 0.43 (0.33, 0.57) for BMI ≥30 kg/m (BMI >18.5-25 was used as the referent).

1.4.7 Oral Health

Poor oral health is believed to contribute to HNC risk due to chronic bacterial infection (78). Studies investigating oral health and HNC risk have reported mixed results, but most suggest a modest increased risk associated with 'poor' oral health (63,78,108,109). Individual evaluations of two multicenter studies included in IHANCE found a positive association between poor general oral health and HNC in Central Europe [OR (95% CI) = 2.89 (1.74, 4.81)] and Latin America [OR (95% CI) = 1.91 (1.49, 2.45)], where general oral health was scored by a trained dentist as good, average, or poor based on the presence of tartar, gingival bleeding, mucosal irritation, and decaying teeth (108). Tooth loss was also assessed and was not associated with HNC in Central Europe [OR (95% CI) =1.09 (0.73, 1.62) for 6-15 teeth lost and 0.70 (0.44, 1.11) for greater than 15 teeth lost], but was associated with an increased risk in Latin America [OR (95% CI) =1.28 (0.99, 1.65) for 6-15 teeth lost and 1.31 (1.00, 1.72) for greater than 15 teeth lost](108). Self-reported indicators of oral health,

namely frequency of tooth brushing, were also assessed but no strong (i.e. significant) associations were found in either the Central European or Latin American populations (108).

In a recent CHANCE study, tooth loss and use of mouth wash were not strongly associated HNC; adjusted ORs (95% CIs) were 1.07 (0.81, 1.42) for 6-15 teeth lost, 1.21 (0.94, 1.56) for 16-28 teeth lost, and 0.95 (0.78, 1.15) for mouthwash use (63). In contrast, tooth mobility was associated with an increased risk of HNC [OR (95% CI) = 1.33 (1.07, 1.65)] and routine dental visits was associated with a decreased risk of HNC [OR (95% CI) = 0.68 (0.53, 0.87)] (63).

1.4.8 Marijuana Use

Since marijuana contains combustion-related carcinogens similar to cigarettes, associations between marijuana use and HNC have been suggested (110). However, results of several case-control studies have been mixed. While one study reported elevated risk (111) and another study reported decreased risk among ever marijuana smokers (112), the majority of studies report near null ORs (110,113-117). The INHANCE pooled analysis of 5 case-control studies on marijuana use reported a summary adjusted OR (95% CI) of 0.88 (0.67, 1.16) for ever use (110).

1.5 HEAD AND NECK CANCER: SURVIVAL SPECIFIC FACTORS

1.5.1 Stage

Cancer stage is a measure of tumor progression or metastasis (59,60). SEER classifies stage into four general categories: localized (confined to primary site), regional (spread to lymohnodes), distant (cancer has metastasized), and unknown (unstagged) (59,60). Approximately half of oral cavity and pharyngeal cancers are diagnosed at a regional stage (59). An additional one-third of oral cavity and pharyngeal cancers are diagnosed at a localized stage, while 15% at a distant stage (59). For laryngeal cancers, the bulk of tumors are diagnosed at a localized stage (57%) (60). Approximately 20% of laryngeal cancers are diagnosed at a regional stage and another 20% at a distant stage (60). For oral cavity, pharyngeal, and laryngeal cancers, the 5-year relative survival

ranges from approximately 80% for localized tumors to around 33% for distant cancers based on the SEER estimates from 2001-2007 (59,60).

Survival based on TNM staging display similar survival distributions. TNM staging, as instituted by the American Joint Committee on Cancer (AJCC) and utilized by the American Cancer Society (ACS), classifies tumors based on the size of the tumor (T), the spread of the tumor (N), and metastasis to other locations (M) into 7 standard stages: 0 (in situ) I, II, III, IVA, IVB, and IVC (118). Based on this system, five- year survival rates range from 70-80% for stage 1 to 30-40% for stage IV among oral cavity cancers and from 60-90% for stage 1 to 35-45% for stage IV among laryngeal cancers (119). Survival among oropharyngeal and hypopharyngeal cancers is somewhat lower and more consistent across TNM stages (119).

1.5.2 Grade

Tumor grade is used to classify cancer cells with respect to appearance (also known as histologic grade or differentiation) and progression as measured by nucleus size and shape and cell division (also known as nuclear grade) (120). SEER classifies grade into 4 general categories: well-differentiated (low grade, G1), moderately differentiated (intermediate grade, G2), poorly differentiated (high grade, G3), and undifferentiated (high grade, G4) (120). Among oral cavity cancers, approximately 18% of tumors are grade 1, 43% grade 2, 21% stage 3 or 4, and 18% are of unknown stage at diagnosis (121). Among oropharyngeal and hypopharyngeal cancers, approximately 6% of tumors are grade 1, 39% grade 2, 40% stage 3 or 4, and 15% are of unknown stage (121). In general, survival improves with increasing level of differentiation (decreasing grade number) for HNC (120,121). Among cancer sites in the oral cavity, 5-year survival ranges from 63-70% for grade 1 to 40-48% for grade 3 or 4 (121). For cancer of the pharynx, 5-year survival ranged from 50% (oropharynx) to 26% (hypopharynx) for grade 1 and 55% (oropharynx) to 29% (hypopharynx) for grade 3 and 4 (121).

1.5.3 Treatment

Treatment for HNC usually involves one or more of the following medical procedures: surgery, radiation therapy, or chemotherapy (122). Choice of treatment is determined based on a variety of factors such as tumor location, tumor size, and tumor stage, as well as the patients' age, health, and preference (122). Historically, HNC was treated by surgery, radiation therapy, or both, with patients with stage 3 and 4 tumors received higher doses of radiation (65,72). Chemotherapy was reserved for treating recurrent tumors (65,72). However, in the 1990's a series of clinical trials demonstrated improved survival among advanced primary HNC by adding chemotherapy to existing treatment regimens (72). Radiation and chemotherapy can be administered using an induction (chemotherapy before surgery or radiation), concurrent (chemotherapy and radiotherapy at the same time), or adjuvant (chemotherapy after surgery or radiation) approach (72). Patients with stage 1 and 2 tumors are still typically treated with surgery and/or radiation therapy (possibly chemotherapy), but the majority of advanced tumors (stage 3 and 4), especially those that have metastasized to be inoperable, are now treated with concurrent or induction chemotherapy (65,72). It should also be noted that given the potential for voice loss with surgery, laryngeal and hypopharyngeal cancers are usually treated with radiotherapy and/or chemotherapy; though advances in surgical techniques which preserve the voice are making surgery more feasible (65,72).

1.6 NUCLEOTIDE EXCISION REPAIR

1.6.1 DNA Damage and Repair

DNA damage includes base substitutions, strand breaks, and bulky adducts which bind to DNA (123). DNA damage is caused by a host of endogenous and exogenous factors (123). Endogenous causes include spontaneous alterations and oxidative damage by reactive oxygen species (123). Exogenous causes include externally induced damage catalyzed by physical and chemical agents such as ionizing radiation, UV radiation, and tobacco-related nitrosamines

(123,124). To resolve DNA damage, endogenous systems detect and repair alterations (123). Specifically, DNA repair comprises several biologic processes or pathways which include direct reversal, mismatch repair (MMR), nucleotide excision repair (NER), base excision repair (BER), homologous recombination, and non-homologous end joining (125,126).

Direct reversal repairs methylation damage and unlike other DNA repair pathways it is a single step process that does not involve excision of bases (123,125). Mismatch repair (MMR) corrects single base insertions and deletions (125). MMR plays a crucial role in a number of cancers including colorectal cancer, skin cancer, and lymphomas (125). Nucleotide excision repair (NER) removes bulky adducts (around 30 nucleotides) and base excision repair (BER) removes smaller adducts (typically 1-13 nucleotides) (123-125). Homologous recombination and non-homologous end joining genes are responsible for repairing double strand breaks in the DNA in conjunction with cell cycle genes (125). Non-homologous end joining repairs 90% of double strand breaks in mammals (125).

This dissertation focused on the function of genes in the NER pathway. In addition to a number of studies linking SNPs in NER genes directly to HNC (as will be detailed in later sections), genes within the NER pathway were chosen as the focus of this dissertation for two reasons. First, NER is the pathway primarily responsible for removing bulky DNA adducts produced from tobacco smoke (3,126). Second, NER genes also repair bulky DNA adducts produced from ionizing radiation and platinum containing agents such as several chemotherapies used in treating HNC (6). Therefore, NER has been shown to have the potential to impact both HNC incidence and survival.

1.6.2 DNA Adducts

DNA adducts are defined by La et al. (127) as "a covalent interaction between an electrophile and a nucleophilic site in DNA." A number of carcinogenic compounds can act as electrophiles and form such complexes with DNA. Chemicals contained in tobacco smoke, such as

benzo[a]pyrene, have been shown to form bulky DNA adducts (3,4). In addition, radiotherapy and platinum-based chemotherapy have been associated with DNA adduct formation (6,7,48). If left unrepaired, DNA adducts can contribute to cancer initiation and progression (127).

1.6.3 Nucleotide Excision Repair Mechanism

Nucleotide excision repair involves four general phases: recognition, pre-incision, incision, polymerization and ligation (also known as repair synthesis) (123,124,128). Table 5 and figure 1 (adapted from Friedberg 2001 (124)) provide an overview of the proteins involved in each phase of NER. During the recognition phase, XPC, HHRAD23A, and HHRAD23B proteins (encoded by *XPC*, *RADA*, and *RADB* genes, respectively) bind with a DNA adduct, followed by XPA (encoded by the *XPA* gene) and the RPA complex which begin to distort the damaged nucleotide region, marking it for incision (123,124,128) (figure1, panel b). The transition from the recognition phase to the incision phase continues with the binding of the TFIIH complex (123,124,128) (figure 1, panel c). This complex is composed of several subunits, including proteins ERCC3 (XPB), ERCC2 (XPD), CDK7, and CCNH which are encoded by genes of the same name, and has the primary function to unwind the DNA strands surrounding the damaged nucleotides (123,124,128). Following the denaturing of the double helix, incisions on either side of the damaged site, known as a dual incision, occur via ERCC1 and ERCC4 (XPF) at the 5' end and ERCC5 (XPG) at the 3' end (proteins encoded by genes of the same name) (123,124,128) (figure1, panel d). Once the DNA adduct (approximately 27-30 nucleotides) is removed, the gap is filled with functional nucleotides which are mobilized by DNA polymerase, in connection with RPA, RFC, and PCNA (123,124,128) (figure1, panel e). Finally, the functional nucleotides are covalently bound by DNA ligase which is encoded by *LIG1* (123,124,128) (figure1, panel e). DDB2 (XPE) also contributes to NER, but its exact function remains to be elucidated (124). *ERCC6* and *ERCC8* encode proteins of the same name, also known as CSB and CSA, which function in transcription-coupled NER (123,124). While the general steps of transcription-

coupled NER have been outlined, the exact mechanisms of transcription-coupled NER, namely during the recognition phase, is not known as well as the NER mechanisms previously discussed (123,124).

1.6.4 Health Consequences of Variants in Nucleotide Excision Repair Genes

Germline mutations in NER genes can result in a number of diseases and conditions including Xeroderma pigmentosum (XP), Cockayne syndrome (CS), Cerebo-oculo-facio-skeletoal syndrome, and UV-sensitive syndrome (123). Most of these conditions are neurological and/or skin-related and arise when mutations in NER genes prevent repair of nucleotides damaged by UV-radiation (123). In addition, mutations in NER genes have been linked to a number of cancers, including skin cancer, lung cancer, bladder cancer and head and neck cancer (3). As described in detail in the *Nature Reviews Cancer* article titled *How Nucleotide Excision Repair Protects Against Cancer* by Friedberg (124), SNPs in NER genes can contribute to carcinogenesis if left unrepaired. Although Friedman's article is in specific reference to skin cancer (124), the principle holds for HNC; when SNPs render NER genes inoperative, DNA damage persists and HNC can arise.

In the context of HNC incidence, SNPs in NER genes may influence the efficiency of excision of bulky DNA adducts caused by tobacco smoking (3,4). Therefore, the odds of HNC may vary based on the population distribution of variants in NER genes, especially among smokers. With regard to survival, radiotherapy and chemotherapy target damaged DNA sites to produce bulky DNA adducts, among other alterations, in order to initiate apoptosis of cancerous cells (6,7). Therefore, functional NER genes can actually counteract this effect by repairing damage and reducing the impact of treatment (6). As noted in a *New England Journal of Medicine* article by Gazdar (6), "it has been known for about a decade that nucleotide excision repair is involved in the resistance of several types of tumors to certain drugs, including platinum compounds." While some HNC studies support

the hypothesis of improved survival associated with polymorphisms in NER genes, some studies suggest no association or a counter effect with respect to mortality (7,47-55).

The following sections summarize previous epidemiologic studies on the effects of SNPs in NER genes, as well as interactions between NER genes and tobacco, on HNC incidence. Previous epidemiologic studies on the associations between SNPs in NER genes, as well as interactions between NER genes and treatment, and HNC mortality will also be discussed.

1.7 SINGLE NUCLEOTIDE POLYMORPHISMS IN NUCLEOTIDE EXCISION REPAIR GENES, CIGARETTE SMOKING, AND HNC INCIDENCE

1.7.1 ERCC3 (XPB)

XPB, previously known as ERCC3, is one of many components in the TFIIH subunit which is responsible for unwinding the double helix surrounding the DNA adduct (123). The gene which encodes this protein is located at 2q21 (129,130). Only one study has reported on the association between variants in *XPB* and HNC incidence (table 7) (31). Michiels et al. (31) investigated the role of rs423358 among former and current smokers in France. Age, tobacco, and alcohol adjusted ORs (95% CIs) of 0.37 (0.15, 0.90) and 0.62 (0.39, 0.97) for AA and AC, respectively, compared to CC were reported (31).

1.7.2 XPC

XPC acts first in the NER pathway to bind the DNA adduct in a complex (123). The *XPC* gene is located at 3p25 (129,130). Three SNPs in *XPC* have been considered for HNC incidence: PAT, rs2228001, and rs2228000 (table 7). The PAT SNP, an insertion/deletion polymorphism, has been associated with increased odds of HNC in two studies, but not in a third (24,35,40). Contrasting the ++ versus - - genotypes, Kietthubthew et al. (24) reported an adjusted OR (95% CI) of 1.60 (0.55, 2.36) for oral cancer among a Thai population, and the more powered study by Shen et al. (35) (287 HNC cases and 311 controls) reported an OR (95% CI) of 1.85 (1.12, 3.05) for HNC among a predominantly Caucasian population in Texas. In contrast, a study conducted in a Japanese

population by Sugimura et al. (40) reported an OR (95% CI) of 0.83 (0.51, 1.34) for PAT and oral cancer using a dominant genetic model. A meta-analysis by Flores-Obando et al. of these three studies (131), plus a South Korean study which focused on expression of XPC but reported frequency of PAT (42), resulted in crude ORs (95% CIs) of 1.09 (0.86-1.37) for +- versus ++, 1.39 (0.99-1.97) for -- versus ++, and 1.14 (0.92-1.43) for +- and -- versus ++. These results therefore suggest elevated risk may be associated with the absence of the PAT SNP. Another meta-analysis which considered the studies on *XPC* and oral cancer separate from the studies on HNC found similar results (132).

Three studies have investigated the association between rs2228001, which is a Lys939Gln substitution, and HNC incidence (4,5,24). The largest case-control study (829 HNC cases and 854 controls) in the US reported a near null association, with an adjusted OR (95% CI) of 1.08 (0.81, 1.43) under a recessive model (Gln/Gln vs. Lys/Gln + Lys/Lys) (5). A dominant model of this SNP (Gln/Gln + Lys/Gln vs. Lys/Lys) was also explored in a large study (248 laryngeal cases and 647 controls) in Germany, and also resulted in near null results; OR (95% CI) = 0.98 (0.68, 1.40) (4). A Thai study on oral cancer reported an OR (95% CI) of 1.35 (0.50, 3.92) for CC versus AA genotypes, but as evidenced by the wide confidence interval for the estimated effect estimate, this study was much smaller (106 oral cancer cases and 164 controls) (24). A meta-analysis of these three studies by Flores-Obando (2010) (131) suggested modest increased risk from rs2228001 with crude ORs (95% CIs) of 0.94 (0.80-1.12) for Lys/Gln versus Lys/Lys, 1.17 (0.92-1.49) for Gln/Gln versus Lys/Lys, and 0.99 (0.85-1.16) for Lys/Gln and Gln/Gln versus Lys/Lys. The large US-based study by An et al. (5) also reported an elevated association for the genotype associated with Val/Val of rs2228000. Even after adjustment for age, gender, tobacco, and alcohol, the OR (95% CI) was 1.65 (1.16, 2.36) (5).

For the PAT SNP in *XPC*, Shen et al. (35) investigated the joint role of tobacco, but found no substantial differences between smoking groups (table 8). Across never smokers, former smokers, and current smokers, the OR (95% CI) associated with the risk genotype appeared similarly elevated;

ORs (95% CIs) were 1.87 (0.72, 4.86), 1.83 (0.85, 3.94), and 1.69 (0.66, 4.35), respectively (35). A Japanese study by Sugimura et al. (40) also reported on the interaction between XPC-PAT and tobacco finding the OR (95% CI) for HNC to be 0.48 (0.13, 1.87).

1.7.3 XPA

XPA is located at 9q22.3 (129,130). The XPA protein, along with the RPA complex, acts early in the NER pathway to bind DNA and proteins in a pre-incision complex (123). One SNP in *XPA* has been studied extensively in relation to HNC incidence; a nucleotide substitution of A23G (rs1800975) (table 7). Across five studies mixed results have been observed, with a dominant model suggesting some elevated risk (OR = 1.20; 95% CI = 0.86, 1.70 for AG + AA versus GG) (4), a recessive model also suggesting an effect (OR = 2.04; 95% CI =1.18, 3.55 for AG + GG versus AA) (40) and other recessive and general models suggesting no or weak associations (5,9,18). A recent meta-analysis of these five studies found a summary crude ORs (95% CIs) of 1.15 (0.96, 1.36) for GG vs. AA (general model) and 1.12 (0.95-1.32) for AG + GG vs. AA (dominant model)(131).

One of the studies which considered the SNP rs1800975 reported on the interaction with tobacco, concluding a synergistic effect of the SNP and cigarette smoking (9). Specifically, this Taiwanese study (154 cases and 105 controls) reported ORs with wide confidence intervals of 3.52 (1.26, 9.84) for nonsmokers with the risk genotype and 47.7 (15.48, 147.01) for smokers with the risk genotype compared to nonsmokers with the reference genotype (table 8) (9). Another study which considered this SNP found an interaction OR (95% CI) of 0.48 (0.11, 2.16) for smokers with the risk genotype AG or GG in a Japanese population (122 cases and 241 controls) (40).

1.7.4 RAD23B

RAD23B, along with XPC and RAD23A, binds the distorted DNA adduct in a pre-incision complex (123). The *RAD23B* gene is located at 9q31.2 (129,130). One study has investigated the association between one SNP in *RAD23B* and HNC (table 7) (4). Abbasi et al. (4), a case-control study

of 248 laryngeal cancer cases and 647 controls in Germany, reported a borderline elevated OR (95% CI) of 1.30 (0.92, 1.90) for rs1805239 (Ala/Val + Val/Val versus Ala/Ala) after adjusting for age, gender, education, tobacco, and alcohol. Unfortunately, this study did not consider joint effects of this SNP with tobacco.

1.7.5 ERCC6

ERCC6 operates in transcription-coupled NER (123). The gene which encodes this protein is located at 10q11.23 (129,130). Five different SNPs in *ERCC6* have been investigated in the context of HNC incidence (table 7) (4,13). Abbasi et al. (4) reported on two SNPs, finding a protective effect of an arginine substitution of proline in a dominant model of rs4253211 (OR = 0.52; 95% CI = 0.34, 0.85) and no apparent effect for an arginine substitution of glycine in a similar model of rs2228527 (OR=0.87; 95% CI = 0.61, 1.20) on laryngeal cancer among 248 cases and 647 controls in Germany. Chiu et al. (13) investigated 3 additional SNPs among 292 oral cancer cases and 290 controls in Taiwan using unadjusted logistic regression. Elevated odds were found in a dominant model of rs2228528 (OR = 1.43, 95% CI = 1.02, 2.01 for GA + AA vs. GG) (13). For the other two SNPs, rs2228526 and rs228529, no strong associations were noted (13).

Abbasi et al. (4) and Chiu et al. (13) both examined the joint effects of selected SNPs and tobacco on HNC incidence (table 8). For rs4253211, the ORs (95% CIs) were similar between light (≤ 20 packyears) and heavy (>20 packyears) smokers; 0.52 (0.18, 1.50) and 0.56 (0.34, 0.93), respectively (4). For rs2228528, the OR (95% CI) among ever smokers was 0.99 (0.64, 1.55) using never smokers as the referent (13).

1.7.6 ERCC5 (XPG)

XPG, previously named *ERCC5*, encodes a 3' incision nuclease which functions with XPF to remove DNA adduct complexes (123). The *XPG* gene is located at 13q33 (129,130). The most commonly studied SNP in *XPG* in relation to HNC is rs17655. Seven studies have considered this

Asp1104His substitution (table 7) (4,5,15,28,40,41,45). The study with the most power (1059 cases and 1066 controls) was conducted in Texas and reported a null association for rs17655 and HNC (OR=0.99, 95% CI=0.83, 1.19) using a dominant genetic model (CG + GG vs. CC) (28). Another large study from Texas (829 HNC cases and 854 controls) found an adjusted OR (95% CI) for rs17655 and HNC of 0.80 (0.51, 1.28) based on a recessive model (Asp/Asp versus His/Asp + His/His) (5). Likewise, a study in Los Angeles by Cui (2005) (15) used a recessive model (Asp/Asp vs. His/Asp + His/His) and found a similar adjusted OR (95% CI) of 0.67 (0.42, 1.10). Stratifying by race, this study was also the only study on polymorphisms in NER genes and HNC to date to report the effects in African Americans only, finding an OR (95% CI) of 0.51 (0.15, 1.80) among 119 African Americans (15). A study conducted among 397 cases and 900 controls in China reported an OR (95% CI) of 0.97 (0.82, 1.15) using an additive model (CC vs. CG vs. GG) (45). Finally, two other studies reported on rs17655, with one using a dominant genetic model (His/Asp + His/His versus Asp/Asp) in a German population (4) and the other contrasting the heterozygote genotype with the wild-type genotype (Asp/His versus Asp/Asp) in a Chinese population (41). Both studies reported elevated ORs (95% CIs) of 1.30 (0.93, 1.90) [OR = 0.77 if referent group assigned to be His/Asp + His/His as in other studies] and 1.88 (1.05, 3.40), respectively (4,41).

The largest study, conducted by Ma et al. (28), also reported on associations between 11 other *ERCC4 (XPF)* SNPs and HNC risk. Of these SNPs, only 1 appeared to be associated with HNC risk (28). Specifically, rs4150351 was associated with reduced HNC risk using a dominant model (AC+CC vs AA, OR=0.81, 95% CI=0.67,0.98) (28). Both Ma et al. (28)and Abbasi et al. (4) investigated the SNP rs1047768, finding adjusted ORs (95% CIs) of 1.00 (0.84, 1.21) and 1.20 (0.80, 1.70), respectively, for the genotypes CT and TT versus CC which results in no amino acid change. Finally, a study by Zavras et al. (46) found an association between another SNP, rs751402, and HNC using the general model; OR (95% CI) were 1.71 (1.04, 2.79) for CT vs TT and 2.2 (0.93, 4.75) for TT vs CC.

The most comprehensive exploration of interaction between *XPG* and tobacco HNC was conducted by Cui et al. (15) (table 8). Using never smokers with the referent genotype for rs17655 (Asp/Asp) as the referent, the adjusted ORs (95% CIs) were 3.60 (1.20, 11.00) for never smokers with the risk genotype, 2.20 (0.51, 9.60) for individuals who smoked 1-20 packyears with the referent genotype, and 3.20 (1.10, 9.50) for individuals who smoked 1-20 packyears with the risk genotype (15). Although the risk genotype resulted in larger magnitude ORs in both nonsmokers and smokers, interaction between this SNP and smoking did not appear to be additive. Abbasi et al. (4) also considered joint effects by stratifying the adjusted ORs (95% CIs) for rs1047768 by cigarette smoking, finding that the odds among heavy smokers (>20 packyears, OR = 1.40, 95% CI = 0.97, 2.20) appeared larger than among light smokers (≤20 packyears, OR = 0.85, 95% CI = 0.43, 1.70). In addition, Ma et al. (28) stratified the adjusted ORs (95% CIs) for rs4150351 by cigarette smoking and found similar odds among never (OR = 0.84, 0.63, 1.34) and ever (OR=0.79, 95% CI=0.62, 1.00) cigarette smokers.

1.7.7 ERCC4 (XPF)

ERCC4, also commonly known as *XPF*, is located at 16p13.12 (129,130). The XPF protein acts along with XPG as an incision nuclease on the 5' end of the DNA adduct (123). Five studies have explored the relationship between *XPF* and HNC (table 7) (4,11,40,44). *XPF* SNP rs1800067 is marked by an amino acid substitution of Arg415Gln (4,11,40,44). Canova et al. (11), the largest study to date with 1511 cases of HNC and esophageal cancer and 1457 controls from the ARCAGE study, considered a general model of this SNP, reporting an adjusted OR (95% CI) of 1.13 (0.46, 2.78) for individuals homozygote for the risk allele (A) compared to individuals homozygote for the reference allele (G). Yu et al. (44), which considered a recessive model (AA vs. GG + AG), reported an OR (95% CI) of 1.40 (0.51, 3.85) after adjustment for age, gender, tobacco, and alcohol. In comparison, Abbasi et al. (4), which considered a dominant model (Arg/Gln + Gln/Gln) vs Arg/Arg), reported a

borderline elevated OR (95% CI) of 1.40 (0.89, 2.20) after adjustment for age, gender, education, tobacco, and alcohol. Canova et al. (11) also reported on SNP rs1799801, finding a near null OR (95% CI) of 1.06 (0.80, 1.41) for CC versus TT and Yu et al. (44) also reported on SNPs rs2776466, rs1799798, and rs3136038 finding near null OR 95% CIs based on recessive models. In addition, Sugimura et al. (40) explored a nucleotide replacement of A for T at position 2063 on *XPF* in a small Japanese case-control study (122 oral cancer cases and 241 controls), resulting in an OR (95% CI) of 0.84 (0.53, 1.32) for a dominant model.

Yu et al. (44) assessed the effects of rs2276466 and rs3136038 within strata of nonsmokers and smokers, finding both SNPs were associated with reduced HNC risk among nonsmokers (OR=0.57, 95% CI=0.33, 1.00 and OR=0.55, 95% CI=0.34, 0.88, respectively) but not smokers (OR= 0.78, 95% CI=0.52, 1.17 and OR=0.96, 95% CI=0.66, 1.39, respectively] (table 8). For a 5' UTR SNP on *ERCC4 (XPF),* Sugimura et al. (40) reported an interaction OR (95% CI) of 0.60 (0.17, 2.12) for smokers with a risk genotype (TA or AA). Krupa et al. (26), which used a dominant genetic model (Arg/Gln + Gln/Gln) vs Arg/Arg) in a study population of 253 laryngeal cancer cases and 253 controls in Poland, found similar near null odds associated with the risk genotype of rs1800067 among 4 smoking levels. The ORs (p-values) were 1.13 (p=0.69) among never smokers, 1.07 (p=0.80) among ever smokers, 1.06 (p=0.85) among moderate smokers, and 0.98 (p=0.95) among heavy smokers (26).

1.7.8 ERCC2 (XPD)

ERCC2, also commonly known as *XPD*, is located at 19q13.3 and encodes a protein which functions as a component of the TFIIH subunit to denature the double helix in preparation for incision (123,129,130). With respect to HNC incidence, *XPD* is the most studied NER gene. In particular, three SNPs, rs13181, rs17991793, and rs238406, have been studied extensively (table 7).

rs13181 is known as a nucleotide substitution as A35931C and as an amino acid substitution as Lys751Gln (4,5,8-10,14,16,17,19-22,24,25,29,30,32-34,36,37,45,133). Over 20 case-control studies have studied the impact of rs13181 on HNC (4,5,8-10,14,16,17,19-22,24,25,29,30,32-34,36,37,45,133). Chuang et al. (14) investigated the effect of rs13181 on HNC risk in the INHANCE study, the largest study to date to explore this association, finding a null association based on a general model (OR=0.97, 95% CI=0.87, 1.07 for Lys/Gln vs. Lys/Lys and OR=1.03, 95% CI=0.88, 1.21 for Gln/Gln vs. Lys/Lys). An et al. (5), the study with the next largest sample size (829 HNC cases and 854 controls), reported an OR (95% CI) of 1.06 (0.79, 1.43) for a recessive model (Gln/Gln vs. Lys/Gln + Lys/Lys). Another study from Texas which considered a recessive model (CC vs. AA + AC) noted an even stronger positive association with an OR (95% CI) of 1.55 (0.96, 2.52) (37). Seven studies with similar sample sizes (250 to 550 cases) used a dominant model ((Lys/Gln + Gln/Gln vs. Lys/Lys or AC + CC vs. AA) and reported OR (95% CIs) ranging from 0.83 (0.41, 1.69) to 1.5 (1.3, 2.0) (4,8,10,19,20,25,32). Eight other studies considered general genetic models, with two overlapping analyses suggesting protective effects (17), one study suggesting harmful effects (33), and the majority showing no association with HNC for Gln/Gln compared to Lys/Lys (or CC compared to AA) (22,24,29,30,34,36).The odds ratios (95% CIs) for homozygous variant versus homozygous referent allele from general models ranged from 0.51 (0.27, 0.95) to 2.72 (1.07, 6.91)(9,21,21,24,29,36) (17,22,24,29,30,33,34,36). Besides the INHANCE study (14), the next most powered study for a general model (310 oral cancer cases and 389 controls from India) reported an age, sex, and tobacco adjusted effect estimate of 1.0 (0.9, 2.3) for Gln/Gln versus Lys/Lys and 1.0 (0.9, 2.3) for Gln/Lys versus Lys/Lys (29). A meta-analysis of rs13181 and HNC incidence, which included the majority of studies listed in table 7, found summary crude ORs (95% CIs) of 1.01 (0.91-1.12) for AC versus AA and 0.96 (0.82, 1.11) for CC versus AA suggesting no association between the variant allele and HNC incidence (131).

rs17991793 results from a nucleotide substitution of G23591A and an amino acid substitution of Asp312Asn (4,5,8,10,17,19,21,22,29,30,38). Eleven different case controls studies have investigated rs17991793 and HNC incidence (4,5,8,10,17,19,21,22,29,30,38). The study with the most power was An et al. (5) which used a recessive model (Asn/Asn vs. Asp/Asn + Asp/Asp). This study reported a borderline elevated OR (95% CI) of 1.15 (0.85, 1.57) (5). Four studies used a dominant genetic model (Asp/Asn + Asn/Asn vs. Asp/Asp or GA + AA vs. GG). The two studies with the largest number of cases (approximately 275 to 300 cases) were both conducted in the US (Texas and Pennsylvania) and reported nearly identical elevated adjusted odds (OR= 1.3; 95% CI = 1.0, 1.8 and OR=1.28; 95% CI = 0.93, 1.76, respectively) (10,39), while the other two studies reported near null results (OR =0.97; 95% CI=0.68, 1.40 and OR=0.86; 95% CI=0.57, 1.30, respectively) (4,19). It is important to note that the Pennsylvania study included both HNC and lung cancer cases (10). Four studies considered general genetic models, but none of the studies reported any significant findings (17,22,29,30). A meta-analysis of rs17991793 and HNC incidence, which included the majority of studies listed in table 7, found a summary crude ORs (95% CIs) of 1.14 (1.01, 1.29) for GA versus AA (general model) and 1.11 (0.99, 1.25) for GA and AA versus GG (dominant model) suggesting a weakly increased risk with the variant allele (131).

The nucleotide substitution C22541A results in no amino acid substitution (Arg156Arg) and is known as rs238406 (4,16,19,24,29,34,37). Seven studies, one using a recessive model) AA vs. CA + CC) (37), three using a dominant model (AA + CA vs. CC) (4,16,19), and three using a general genetic model (24,29,34), have explored the role of rs238406 on HNC. All of these studies, except one (16), found near null results. A meta-analysis of rs17991793 and HNC incidence, which included the majority of studies listed in table 7, found a summary crude OR (95% CI) of 0.84 (0.68, 1.04) for AA versus CC supporting the hypothesis of no association (131).

Nine studies reported joint effects for rs13181 and tobacco smoking (table 8) (8-10,16,22,30,33,36,37). The study with the largest population (655 cases and 805 controls) reported an adjusted additive OR (95% CI) for rs13181 among never tobacco users as 0.55 (0.28, 1.08), among exclusive users of chewing tobacco as 0.76 (0.59, 0.97), among exclusive smokers as 0.78 (0.59, 1.03), and among individuals with mixed tobacco habits as 0.78 (0.59, 1.03) (8). A study by Buch et al. (10)conducted among 273 cases and 269 controls in the US found that compared to nonsmokers with the reference genotype, the adjusted ORs (95% CIs) were 1.26 (0.73, 2.18) among nonsmokers with the risk genotype, 0.79 (0.45, 1.36) among smokers with the referent genotype, and 3.99 (2.30, 6.92) among smokers with the risk genotype suggesting a possible additive effect. Likewise, a smaller study in Taiwan by Bau et al. (9) concluded a synergistic effect of rs13181and cigarette smoking. However, this conclusion was based on imprecise ORs (95% CIs) of 28.48 (13.93, 58.23) for nonsmokers with the risk genotype and 26.33 (7.87, 88.04) for smokers with the risk genotype compared to nonsmokers with the reference genotype (9). In addition, a study conducted in India by Ramachandran et al. (33) noted a stronger association between the variant of allele of rs13181 and HNC among ever smokers (OR=3.37, 95% CI=1.51, 7.51) than among never smokers (OR=1.48, 95% CI = 0.80, 2.74). Other studies which stratified by the effect of rs13181 by smoking status did not note substantial differences in effect across smoking groups (22,30,36,37).

For rs1799793, the study by Anantharaman et al. (8) was again the largest and reported adjusted additive OR (95% CI) for this SNP among never tobacco users as 1.50 (0.69, 3.12), among exclusive users of chewing tobacco as 0.92 (0.0.69, 1.22), among exclusive smokers as 0.89 (0.37, 2.13), and among individuals with mixed tobacco habits as 1.15 (0.83, 1.58). Among never or former smokers, Mautllo et al. (30) reported an OR (95% CI) of 0.34 (0.09, 1.24) for AA vs. GG genotypes using data from the European Prospective Investigation into Cancer and Nutrition (EPIC) study.

Among light and heavy smokers, Ji et al. (22) reported ORs (95% CIs) for GA vs. AA of 2.4 (0.78, 7.35) and 0.94 (0.47, 7.35), respectively.

Two other studies considered the joint effects between rs238406 and tobacco. Using a recessive genetic model (AA vs. CA +CC), Sturgis et al. (37) reported ORs (95% CIs) of 1.15 (0.57, 2.32) among never smokers, 0.72 (0.41, 1.58) among former smokers, and 1.48 (0.64, 2.44) among current smokers suggesting little modification by cigarette smoking. In a separate study of only current smokers, or at least controls who smoked, Gajecka et al. (16) reported an OR (95% CI) of 0.81 (0.49, 1.31).

1.7.9 ERCC1

ERCC1 encodes a 5' incision nuclease subunit and is located at 19q13.32 (123,129,130). Several SNPs within this gene have been considered in the etiology of HNC (table 7). The most studied SNP is an adenine replacement of cysteine at 8092 (rs3212986) (4,5,38,40,43). Five studies have investigated the effects of this SNP on HNC incidence, with three resulting in comparable near null ORs for various dominant (CA + AA vs. CC) and recessive models (AA vs. CA + CC and CC vs. CA +AA) (4,5,38), one reporting little difference in the frequency of genotypes between cases and controls (43), and one suggesting increased risk (i.e. an elevated OR) in a Japanese population using a recessive model (AA vs. CC + CA) (40). In 2010, Flores-Obando et al. (131) meta-analyzed the four studies which investigated rs3212986 in *ERCC1*. The summary ORs (95% CIs) were 1.07 (0.80-1.43) for A/A versus C/C (general model) and 1.00 (0.87-1.14) for C/A + A/A versus C/C (dominant model) (131).

A study by Jones et al. (23), conducted among 175 cases and 790 controls in Florida, studied four additional SNPs in *ERCC1*: rs1319052, rs3212948, rs3212955, rs735482. No strong associations between these SNPs, nor haplotypes of these SNPS, and HNC incidence were found, though some excess risk may exist for rs3212955 (OR = 1.36; 95% CI = 0.67, 2.75 for GG versus AA) (23). Estimates

were adjusted for demographic factors (age, sex, and race), but not behavioral factors (tobacco and alcohol). Other SNPs which have been studied by Abbasi et al. (4), Canova et al. (11), and Matullo et al. (30) in relation to HNC incidence are summarized in table 7 and include rs3212961, rs11615, and rs3177700.

Evidence regarding the joint effects of *ERCC1* SNPs and tobacco on HNC is more limited, but seems to suggest interactions may exist (table 8). For rs3212986, Sugimura et al. (40) reported a highly elevated, but imprecise, interaction OR (95% CI) for smokers with the risk genotype (AA) as 8.49 (1.22, 59.31). Among a study population of only never and former smokers from the EPIC study, the OR (95% CI) was 1.79 (0.80, 4.01) for rs3177700 and HNC incidence (30). In a study by Sturgis et al. (38) at MD Anderson in Texas, the adjusted OR (95% CI) for risk genotypes in both ERCC1 and XPD among nonsmokers was 1.24 (0.61, 2.51) and among smokers was 1.46 (0.95, 2.25). Given the low sample sizes of these studies, especially when restricted or stratified by smoking groups, further replication in larger studies is needed.

1.7.10 LIG1

LIG1 operates in the final step of NER and BER by encoding DNA ligase which binds function DNA strands after excision of DNA adducts (123). *LIG1* is located at 19q13.2-q13.3 (129,130). Two studies have considered the effect of multiple SNPs in *LIG1* on HNC incidence (table 7) (27,31). Lee et al. (27), a large study conducted among 489 oral, pharyngeal, laryngeal, and esophageal cancer cases and 948 controls in Los Angeles, considered four SNPs: rs20581, rs20580, rs20579, and rs439132. rs20581 demonstrated the strongest, positive association with HNC; age, sex, education, ethnicity, and tobacco adjusted ORs (95% CIs) were 1.20 (0.85, 1.80) for CT versus TT and 1.5 (1.0, 2.3) for CC versus TT(27). ORs (95% CIs) for rs20580, rs20579, and rs439132 also suggested possible positive associations with HNC. For example, the adjusted ORs (95% CIs) for rs20579 were 1.30 (1.00, 1.80) for CT versus CC and 2.00 (0.69, 5.80) for TT versus CC (27). Lee et al. (27) also estimated

haplotype effects across these 4 *LIG1* SNPs. With regard to interaction with tobacco, modification appeared strongest for rs20581 (table 8). The adjusted ORs (95% CIs) for the risk genotype compared to the referent genotype were 0.83 (0.42, 1.60) among never smokers (0 packyears), 2.30 (0.95, 5.40) among individuals who smoked 0.1 to 20 packyears, and 2.20 (1.00, 4.70) among individuals who smoked more than 20 packyears (27). The effect of rs20580 also appeared to be stronger in smokers compared to nonsmokers (27). There was less evidence for differences in ORs across smoking groups for rs20579 and rs439132, but strata were sparse for these analyses (27).

Michiels et al. (31) identified 251 cases and 172 controls among a cohort of smokers in France. This study investigated 10 *LIG1* SNPs, of which 9 were found to have a positive relationship with HNC (31). The strongest associations were observed for rs13436/rs3182008 (OR = 1.94; 95% CI 1.06, 2.75, GG vs. CC); rs153023 (OR = 2.13; 95% CI = 1.13, 2.90, TT vs. CC); rs156640 (OR = 1.94; 95% CI=1.06, 3.56, CC vs. GG); and rs274892 (OR = 2.05; 95% CI = 1.12, 3.78, AA vs. CC) (31).

1.7.11 ERCC8, CDK7, CCNH, DDB2 (XPE), RAD23A

There is no previous literature regarding the associations between *ERCC8, DDB2, RAD23A, CDK7*, and *CCNH* and HNC. Therefore, this dissertation was the first study to consider the effects of SNPs in these 5 NER genes on HNC. *ERCC8*, located at 15q2.1, encodes a protein which functions with ERCC6 in Cockayne syndrome and transcription coupled NER (123,129,130). CDK7 and CCNH are subunits of the TFIIH complex and assist in the unwinding of DNA surround DNA adducts prior to incision (123). Both *CDK7* and *CCNH* genes are located at 5q12.1 and 5q13.3-q14, respectively (129,130). *DDB2*, also known as *XPE*, is located at 11p12-p11 and functions in NER, but its mechanism is not well understood (123,129,130). *RAD23A*, located at 19p13.2, encodes a protein which functions with XPC and RAD23B to bind the distorted DNA adduct as a complex (123,129,130).

1.7.12 Nucleotide Excision Repair Genes and Oral Premalignant Lesions Incidence

In addition to the studies on NER genes and HNC listed in table 7, a study by Wang et al. (2007) (134) considered the effects of polymorphisms in NER genes on oral premalignant lesions (OPL; leukoplakia and erythroplakia) among 144 OPL cases and 288 controls. In addition to considering SNPs in the core NER genes, namely *XPA, XPC, ERCC2 (XPD), ERCC4 (XPF),* and *ERCC5 (XPG)*, this study estimated the effects of SNPs in *ERCC6, RAD23B* and *CCNH* (134). Among the core NER genes, the strongest association was found between a SNP in *XPA* (rs1800975) and OPL; OR (95% CI) was 1.97 (1.27, 3.06) under a recessive genetic model (134). Elevated risk was also noted for SNPs in *XPD* (rs13181 and rs1799793) under a dominant model (134). Among SNPs in the less studied NER genes, *ERCC6, RAD23B* and *CCNH,* there was little evidence for an association with OPL, except for a suggested protective effect among RAD23B (rs1805239); OR (95% CI) was 0.67 (0.41, 1.07) under a dominant model (134). When stratified by smoking, the joint effects of smoking with rs1800975 in *XPA* appeared have an above additive or synergistic effect on OPL incidence, while rs1805239 in *RAD23B* and rs13181 in *XPD* appeared to have below additive or antagonistic effect (134). In addition, studies by Majumder et al. (29), Ramachandran et al. (33), and Anantharaman et al. (8) reported mixed results on the association between polymorphisms in *ERCC2 (XPD)* and leukoplakia, with studies reporting null results for rs13181, rs1799793, and rs238406 (8,29,33), except one study reporting a highly elevated OR for rs13181 (OR = 4.2, 95% CI = 1.2, 15.0 for Gln/Gln/ vs. Lys/Lys) (29).

1.7.13 Summary of NER Genes, Tobacco, and HNC Incidence

Approximately 40 previous studies have collectively investigated the role of 10 NER genes and nearly 60 associated SNPs (4,5,8-46). The most studied SNPs and genes were rs13181 (Lys751Gln), rs1799793 (Asp312Asn), and rs238406 (Arg156Arg) in *XPD (ERCC1*) and rs3212986 in *ERCC1*. Studies on the effects of rs13181 and rs1799793 reported mixed results (4,5,9,10,16,17,19-

21,24,29,30,32-34,36-38), while studies on rs238406 and rs3212986 reported mostly null associations with HNC (4,5,16,19,24,29,34,37,38,40,43). Other commonly studied genes included *ERCC6* and *LIG1*. SNPs in *ERCC6* seemed to be associated with reduced risk of HNC (4,13), while SNPs in *LIG1* seemed to be associated with increased risk (27,31). Joint effects of SNPs and cigarette smoking were reported in approximately 20 studies. Again the most studied SNP was rs13181 (Lys751Gln) in XPD. Two studies on the effect of rs13181 on HNC reported stronger positive associations among smokers with risk genotype (9,10), while two studies observed similar effects across smokers and non-smokers (36,37). Results for joint effects between cigarette smoking and other SNPs in NER genes were mixed for other studies, but some suggested stronger effects in smokers compared to non-smokers for most SNPs (4,8-10,13,15,16,22,24,26-28,30,31,33,35-38,40,44).

1.8 SINGLE NUCLEOTIDE POLYMORPHISMS IN NUCLEOTIDE EXCISION REPAIR GENES, TREATMENT, AND HEAD AND NECK CANCER MORTALITY

1.8.1 XPA and XPC

Evidence linking SNPs in *XPA* and *XPC* to HNC survival are limited (table 10). Only two studies have considered SNPs in *XPA* and *XPC* (47,48). Azad et al. (47) found no association between rs1800975, a 5' UTR SNP on *XPA,* and overall survival (OS HR=0.96, 95% CI=0.78, 1.18) nor disease free survival (DFS HR=1.10, 95% CI 0.88, 1.36) among 531 HNC cases from Canada treated with radiation therapy based on an additive genetic model (A>G). Likewise, Carles et al. (48) found no difference in progression free survival (p=0.23) nor overall survival (p=0.64) across genotypes (TT, CT, CC) using the log-rank test among 107 HNC and 1 esophageal cancer patients receiving radiotherapy in Spain. Carles et al. (48) also noted no difference in progression free survival (p=0.74) nor overall survival (p=0.96) across genotypes of for rs2228001 in *XPC* (CC, CA, AA).

1.8.2 ERCC5 (XPG)

The studies by Azad et al. (47) and Carles et al. (48) also studied two SNPs in *ERCC5* (*XPG)* (table 10). Azad et al. (47) found near null associations between rs17655 (G>C, OS HR=0.89, 95% CI=0.70, 1.13 and DFS HR=0.85, 95% CI=0.66, 1.09) and rs1047768 (T>C, OS HR=1.03, 95% CI=0.85, 1.25 and DFS HR=1.06, 95% CI=0.86, 1.30) and survival using an additive model. Carles et al. (48) also found little difference in progression free or overall survival was reported across genotypes (AA, AG, and GG) for rs17655. In contrast, Carles et al. (48) did find significant differences in progression free (p=0.049) and overall (p=0.0066) survival for rs1047768, with individuals with the genotype TC and CC experiencing better survival compared to individuals with TT.

1.8.3 ERCC4 (XPF)

In addition to the study by Azad et al. (47) which reported near null HRs for rs1799801 and survival using an additive model (T>C, OS HR = 1.02, 95% CI= 0.83, 1.27 and DFS HR= 0.96, 95% CI= 0.77,1.21), a study by Vaezi et al. (55) considered the impact of 9 SNPs in *ERCC4* (*XPF)*, as well as expression of *XPF*, on 1 year progression free survival following initiation of treatment (table 10). The study included 80 HNC cases in Pennsylvania, of whom 70 received X-ray therapy and platinum-based chemotherapy and 10 received only radiotherapy (55). Forty-two of the 72 patients also received surgery (55). Although all SNPs were found to have elevated HRs for the variant allele versus the common allele, only four SNPs demonstrated borderline significance using a recessive or additive model (55). The age, gender, stage, site, and treatment adjusted HRs (p-values) for these four SNPs were 1.94 (p=0.065) for rs1799799 (T>C), 2.00 (p=0.053) for rs3136155 (C>T), 1.94 (p=0.065) for rs3136166 (T>G), and 1.95 (p=0.065) for rs3136202 (G>A) (55).

1.8.4 ERCC2 (XPD)

ERCC2 (XPD) is another commonly studied NER gene in relation to HNC mortality (table 10). Six studies have investigated the role of rs13181 on HNC mortality (7,47,48,50,53,54). In addition,

three studies have considered rs1799793 (47,53,54). Zhong et al. (7) provides the most comprehensive analysis of rs13181 with 485 HNC from Pennsylvania, and is the only study to stratify any relationship between NER genes and HNC survival by different treatment types. Among 275 patients receiving radiotherapy and 210 not receiving radiotherapy, the effect of rs13181 varied by treatment regime (7). Among cases with stage 3 and 4 tumors, the genotype AA (wild-type genotype) was associated with poorer overall survival among those treated with radiation (HR = 1.66, 95% CI = 1.15, 2.40, Kaplan Meier p-value < 0.01), but better survival among those not receiving radiation (HR = 0.26, 95% CI = 0.11, 0.62, Kaplan Meier p-value <0.01) (7). Distinct differences in disease free survival and progression free survival were also noted (7). Among cases with stage 1 and 2 tumors who did not receive radiation, overall, disease free, and progression free survival did not vary across genotypes (p=0.78, 0.98, 0.79, respectively) (7). Carles et al. (48) also considered the impact of rs13181 on survival among HNC cases treated with radiotherapy, but found no differences in progression free or overall survival across genotypes (Kaplan Meier p-value = 0.78 and 0.87, respectively). In contrast, Azad et al. (47)and Mahimakr et al. (53) found that rs13181 was associated with improved disease/relapse free survival (HR=0.80, 95% CI=0.64, 1.00 and HR=0.52, 95% CI=0.20, 0.91 respectively) using an additive (A>C) and dominant model (Lys/Gln + Gln/Gln vs. Lys/Lys)respectively. Likewise, these studies reported improved disease/relapse free survival associated with rs1799793 (G>A, HR=0.89, 95% CI=0.72, 1.11 in Azad et al. study and Asp/Asn + Asn/Asn vs. Asp/Asp, HR=0.43, 95% CI=0.22, 0.84 for Mahimakr et al. study) (47,53). Among those treated with chemotherapy, Quintela-Fandino et al. (54) found significantly improved overall survival among individuals with the common allele (p=0.0012) for both rs13181 and rs1799793. In contrast, Gal et al. (50) found no association between rs13181 and survival outcomes using a dominant model (Lys/Gln + Gln/Gln vs. Lys/Lys).

1.8.5 ERCC1

ERCC1 is one of the most commonly studied NER genes in relation to HNC mortality (table 10). In particular, three SNPs have been investigated: rs735482, rs3212986, and rs11615. rs735482 is marked by a Thr substitution of Lys resulting from a cysteine replacement of adenine (47,48,51). Three studies have explored the association between this SNP and HNC survival (47,48,51). The largest study conducted by Azad et al. (47) found that rs735482 was not associated with overall survival (HR=0.92, 95% CI=0.68, 1.24), but was associated with disease free survival (HR=0.78, 95% CI=0.44, 0.95) using an additive model (A>C) among a population receiving radiation therapy. The study by Carles et al. (48), also among patients receiving radiation treatment, reported significant differences in progression free survival (p=0.0005) and overall survival (p=0.0089) were found across all three genotypes, with individuals homozygous for the risk allele (Thr259Thr) experiencing much worse survival than individuals with Lys259Lys or Lys259Thr (48). Grau et al. (51) also noted increased, although nonsignificant, risk associated with the variant allele of this SNP. Specifically, this study found unadjusted ORs (95% CIs) of 1.54 (0.71, 3.32) for AC versus AA and 1.57 (0.63, 3.91) for CC versus AA (51). Two studies reported on the association between rs3212986 and survival. Azad et al. (47) reported HRs (95% CIs) for this SNP and overall and disease free survival as 0.85 (0.67, 1.09) and 0.96 (0.75, 1.23), respectively, using an additive model (C>A) among HNC patients treated with radiation. In addition, Quintela-Fandino reported a Kaplan Meier p-value of 0.8 for comparing the common and polymorphic allele of this SNP among HNC patients receiving chemotherapy (54). Finally, two low powered studies considered rs11615 (cysteine substitution of tyrosine), with one study concluding that there was no association among 59 HNC patients receiving surgery and chemotherapy in Brazil (49) and the other suggesting poorer survival associated with the variant genotype (OS HR =3.4, 95% CI=0.9, 12.0 for CC + CT vs. TT) (52).

1.8.6 ERCC3 (XPB), ERCC8, CDK7, CCNH, RAD23B, ERCC6, DDB2 (XPE), RAD23A, LIG1

To date, no studies have considered the impact of SNPs in *ERCC3 (XPB), ERCC8, CDK7, CCNH, RAD23B, ERCC6, DDB2 (XPE), RAD23A,* and *LIG1* and HNC survival. Therefore, this dissertation was the first to assess the associations between these genes and overall and disease-specific survival in a large, racially diverse population of HNC cases.

1.8.7 Summary of NER Genes, Treatment, and HNC Mortality

Approximately 10 studies investigated the role of variants in NER genes and treatment on HNC survival (7,47-55). Five studies considered populations of patients who received radiation (with or without surgery or chemotherapy) (7,47,48,50,53), while the other five studies considered patients receiving chemotherapy (2 studies induction chemotherapy, 1 study concurrent chemotherapy, 1 study adjuvant chemotherapy, and 1 study with various combinations of chemotherapy and radiation) (49,51,52,54,55). Only 1 study compared 2 separate treatment regimens: radiation versus no radiation (7). Most studies (N=8) considered overall survival as an endpoint (7,47-52,54). In addition, 3 studies reported disease-specific survival (50,52,53)and 7 studies progression/relapse/recurrence/disease free survival (7,47,48,51-53,55). These studies collectively investigated a total of 6 NER genes and nearly 20 associated SNPs (7,47-55). The most studied SNP was rs13181 (Lys751Gln) in XPD (47,48,50,53,54). For this SNP, 2 studies among patients receiving radiation showed no difference in OS, PFS, of DS across genotypes (48,50). In contrast, 2 other studies suggested the variant genotype using an additive and dominant model, respectively, may be associated with improved survival (47,53). Another study found the common allele was associated with worse survival among a radiation treatment group but better survival among a no treatment group (7). Other studied NER genes with regard to treatment and HNC survival were *XPF (ERCC4)* and *ERCC1* (47-49,51,54,55). For *ERCC4*, most SNPs displayed worse survival associated with the variant allele (55). For *ERCC1*, evidence for rs735482 was mixed

(47,48,51), and no difference in OS or PFS was noted across genotypes for rs3212986 and rs11615 (49,54).

1.9 SUMMARY OF LITERATURE REVIEW

Head and neck cancers, principally squamous cell carcinomas, comprise tumors of the oral cavity, pharynx, and larynx (65,66,70). Numerous demographic and behavioral factors are associated with HNC incidence, with 75% of cancers attributed to cigarette smoking and alcohol drinking (84). With regard to mortality, several clinical factors, including treatment, as well as demographic and behavioral factors are associated with survival. Historically, HNC were treated with surgery and/or radiotherapy, but over the last few decades individuals treated with chemotherapy in addition to surgery and radiotherapy have demonstrated improved survival (72).

Tobacco contains a number of chemicals, including nitrosamines and benzenes, known to produce bulky DNA adducts (2,3). Nucleotide excision repair is the primary pathway responsible for removing such adducts (3,4). Single nucleotide polymorphisms in NER genes, however, can alter this pathway, allowing DNA damage to persist and initiation of carcinogenesis (3,124). Studies regarding the individual effects of polymorphisms in NER genes, as well as joint effects with cigarette smoking, on HNC risk have reported mixed results (tables 7 and 8) (4,5,8-46).

Radiotherapy and platinum-based chemotherapies also produce bulky DNA adducts (6,7,48). However, since these DNA adducts can function to initiate apoptosis in cancer cells, SNPs in NER genes may actually confer a survival advantage (6). Studies regarding the individual effects of polymorphisms in NER genes, as well as joint effects with treatment, on HNC risk have reported mixed results, but some support this hypothesis (table 10) (7,47-55).

As discussed in detail in the methods chapter, this dissertation builds upon the existing literature by 1) including one of the largest study population to date (1,227 cases and 1,325 controls); 2) estimating effects among African Americans (305 cases and 251 controls); 3) evaluating

more NER genes, including more SNPs, than previous studies (84 SNPs in 15 NER genes); and 4) formally assessing gene-environment interactions, namely the joint effects of polymorphisms in NER genes and cigarette smoking with respect to HNC incidence and polymorphisms in NER genes and treatment with respect to HNC mortality, which few studies have done.

Table 1. Head and Neck Cancer Incidence in the United States from SEER, 2004-2008 (59,60)

	Oral Cavity and Pharyngeal Cancer Cases (per 100,000 persons)		Laryngeal Cancer Cases (per Deaths persons)	
Race/Ethnicity	Male	Female	Male	Female
All Races	15.7	6.2	6.0	1.3
White	16.1	6.2	6.0	1.3
Black	15.6	5.6	9.8	1.9

Table 2. Head and Neck Cancer Mortality in the United States from SEER, 2004-2008 (59,60)

	Oral Cavity and Pharyngeal Cancer Deaths (per 100,000 persons)		Laryngeal Cancer Deaths (per 100,000 persons)	
Race/Ethnicity	Male	Female	Male	Female
All Races	3.9	1.4	2.2	0.5
White	3.7	1.4	2.0	0.4
Black	6.3	1.5	4.6	0.7

Table 3. Oral and Pharyngeal Cancer Survival in the United States from SEER 9, 1988-2007 (61)

	Ages <65 (% dead)			Ages 65+ (% dead)		
Survival (years since diagnosis)	All Races	White	Black	All Races	White	Black
0	100.0	100.0	100.0	100.0	100.0	100.0
1	87.2	88.8	74.30	77.7	78.7	64.7
2	76.2	78.7	56.9	65.9	67.1	50.3
3	70.1	73.0	48.4	59.8	61.2	42.2
4	66.2	69.2	44.0	55.6	57.1	37.8
5	63.4	66.6	40.7	52.5	54.0	34.3
6	61.3	64.6	37.5	49.5	51.1	31.5
7	59.3	62.7	35.6	46.8	48.3	29.5
8	57.5	60.9	33.9	44.2	45.6	27.7
9	55.8	59.1	32.3	41.8	43.1	26.3
10	53.9	57.2	30.8	40.0	41.1	25.6

Table 4. Laryngeal Cancer Survival in the United States from SEER 9, 1988-2007 (62)

	Ages <65 (% dead)			Ages 65+ (% dead)		
Survival (years since diagnosis)	All Races	White	Black	All Races	White	Black
0	100.0	100.0	100.0	100.0	100.0	100.0
1	89.5	90.8	83.0	85.0	85.7	79.4
2	79.1	81.4	68.4	75.5	76.4	68.3
3	73.2	75.9	60.6	69.8	70.7	61.6
4	69.0	71.9	55.7	65.7	66.6	57.8
5	65.9	68.8	52.7	62.1	63.2	51.9
6	62.7	65.7	49.1	59.1	60.4	46.2
7	60.3	63.3	46.7	56.1	57.2	44.0
8	57.7	60.7	44.0	53.2	54.6	39.2
9	55.6	58.5	42.3	49.8	51.4	35.5
10	53.4	56.2	40.3	47.3	48.7	34.6

Table 5. Nucleotide Excision Repair Genes Locations (HapMap (129)) and Function (Friedberg et al., 2006 (123))

Gene	Chromosome and Position (HapMap)		Protein Function (Friedberg, 2006)
ERCC3 (XPB)	2	127,731,336 to 127,768,222	Subunit of transcription factor II H (TFIIH) which unwinds double helix
XPC	3	14,161,651 to 14,195,143	Binds to DNA adduct
ERCC8	5	60,205,415 to 60,276,648	Transcription-coupled NER
CDK7	5	68,566,471 to 68,609,004	Subunit of transcription factor II H (TFIIH) which unwinds double helix
CCNH	5	86,725,839 to 86,744,592	Subunit of transcription factor II H (TFIIH) which unwinds double helix
XPA	9	99,477,013 to 99,499,460	Binds to DNA adduct
RAD23B	9	109,085,365 to 109,134,290	Binds to DNA adduct
ERCC6	10	50,336,715 to 50,417,078	Transcription-coupled NER
DDB2 (XPE)	11	47,193,089 to 47,217,339	
ERCC5 (XPG)	13	102,296,175 to 102,326,346	3' incision nuclease (dual incision to remove adduct)
ERCC4 (XPF)	16	13,921,524 to 13,949,704	5' incision nuclease (dual incision to remove adduct)
RAD23A	19	12,917,654 to 12,925,455	Binds to DNA adduct
ERCC2 (XPD)	19	50,546,686 to 50,565,669	Subunit of transcription factor II H (TFIIH) which unwinds double helix
ERCC1	19	50,604,712 to 50,619,017	5' incision nuclease (dual incision to remove adduct)
LIG1	19	53,310,515 to 53,365,372	DNA ligase

Table 6. Characteristics of case-control studies on the association between polymorphisms in nucleotide excision repair genes and head and neck cancer incidence (4,5,8-46)

Author	Year	Country	N Cases / Controls	Recruitment of Cases / Controls	Matching	HN Site(s)	Genes	Genetic Model	Adjustment Variables	Interaction with Smoking
Abbasi	2009	Germany	248 / 647	population / population	age and gender	larynx	ERCC1, ERCC2 (XPD), ERCC4 (XPF),ERCC5 (XPG), ERCC6, XPA, XPC, RAD23B	dominant (general also available)	age, gender, education, smoking, alcohol	X
An	2007	US (TX)	829 / 854	hospital /visitors	age and gender	oral, pharynx, larynx	ERCC1, ERCC2 (XPD), ERCC5 (XPG), XPA, XPC	recessive (general also available)	age, gender, smoking, alcohol	X (1-3 or 4-6 risk genotypes by smoking)
Anantharaman	2012	India	655/ 802	hospital / hospital	age, sex, tobacco	oral	ERCC2	additive	age, sex, education	X
Bau	2007	Taiwan	154 / 105	hospital / hospital	age	oral	ERCC2 (XPD), XPA	dominant (general also available)		X
Buch	2005	US (PA)	273 / 269	hospital / hospital		larynx, tongue, oral, lung	ERCC2 (XPD)	dominant (general also available)	age, smoking	X
Canova	2009	Europe	1511 / 1457	hospital / hospital and population	sex, age, center, ethnicity, referal/ residence area	oral, pharynx, larynx, esophagus	ERCC1, ERCC4 (XPF)	general	age, sex, smoking, alcohol, country	
Chiu	2008	Taiwan	292 / 290	hospital / hospital	age, sex	oral	ERCC6	dominant (general also available)		X
Chuang	2011	International (CHANCE)	5,915/ 10,644	hospital and population/ hospital and population	age, sex, race, location	oral, pharynx, larynx	ERCC2	general	age, sex, country, race	
Cui	2005	US (CA)	443 / 912	population / neighborhood	age, sex	oral, pharynx, larynx, esophagus	ERCC5 (XPG)	recessive (general also available)	age, sex, ethnicity, education, smoking, alcohol	X
Gajecka	2005	Poland	293 / 322	hospital / smokers from blood bank		larynx	ERCC2 (XPD)	recessive (general also available)		X
Gugatschka	2011	Austria	169 / 463	hospital / another study		oral, pharynx, larynx	ERCC2 (XPD)	general		
Gugatschka replication	2011	Austria	294 / 463	hospital / another study		oral, pharynx, larynx	ERCC2 (XPD)	general		
Hall	2007	Central & Eastern Europe	811 / 1083	hospitals and clinics / hospitals and clinics	age, sex, referal/ residence area	oral, pharynx, larynx, esophagus	XPA	general	age, sex, country, smoking, alcohol	
Harth	2008	Germany	312 / 300	hospital / clinic		oral, pharynx, larynx	ERCC2 (XPD)	dominant (general also available)	age (simple and quadratic), sex	X (2 genotypes by smoking)
Huang	2005	US (WA & NC) & Puerto Rico	555 / 792	hospital / hospital (population / population for Puerto Rico)	age, sex	oral, pharynx, larynx	ERCC2 (XPD)	dominant (general also available)	age, sex, smoking, alcohol, center	
Jelonek	2010	Poland	105 / 507	hospital / blood donors at cancer institute	age, sex	oral, pharynx, larynx	ERCC2 (XPD), XPA	general (X^2 p-value)		
Ji	2010	South Korea	290/ 358	hospital / hospital		oral, pharynx, larynx	ERCC2 (XPD)	general	age, sex	X
Jones	2011	US (FL)	175 / 790	hospital / community (cancer sreening program)		oral, pharynx, larynx	ERCC1	general	age, sex, smoking	
Kietthubthew	2006	Thailand	106 / 164	hospital / community	age, sex, smoking, alcohol	oral	ERCC2 (XPD), XPC	general	age, sex, smoking, alcohol, betel quid chewing	X
Kostrzewska-Poczekaj	2013	Poland	295 160	population / population	age	oral, larynx, other	ERCC2 (XPD)	dominant (general also available)	crude	

Table 6 cont. Characteristics of case-control studies on the association between polymorphisms in nucleotide excision repair genes and head and neck cancer incidence

Author	Year	Country	N Cases / Controls	Recruitment of Cases / Controls	Matching	HN Site(s)	Genes	Genetic Model	Adjustment Variables	Interaction with Smoking
Krupa	2011	Poland	253 / 253	hospital / hospital	age, sex	larynx	ERCC4 (XPF)	dominant	age, sex	X (only)
Lee	2008	US (CA)	489 / 948	hospital / neighborhood	age, sex, neighborhood	oral, pharynx, larynx, esophagus	LIG1	general	age, sex, education, ethnicity, smoking	X
Ma	2012	US (TX)	1059/ 1066	hospital / hospital	age, sex	oral, pharynx, larynx	ERCC5 (XPG)	dominant (general also available)	age, sex, smoking, alcohol	X
Majumder	2007	India	310 / 389	hospital / hospital (dental patients)		oral	ERCC2 (XPD)	general	age, sex, tobacco	
Matullo	2006	Western Europe (Epic)	88 / 1094	nested case-control (population); never or former smokers only		oral, pharynx, larynx	ERCC1, ERCC2 (XPD)	general		X
Michiels	2007	France	251 / 172	nested case-control (hospital); regular smokers only	age, sex , hospital	oral, pharynx, larynx	ERCC3 (XPB), LIG1	general	age, smoking, alcohol	X
Mitra	2009	India	285 / 400	hospital / blood donors in province	ethnicity	oral, pharynx, larynx	ERCC2 (XPD)	dominant (general also available)	age, smoking, tobacco chewing, pan masala	
Ramachandran	2005	India	110 / 110	hospital / relatives and visitors	age, sex, smoking, betel quid chewing, alcohol	oral	ERCC2 (XPD)	general	age, sex, smoking, betel quid chewing, alcohol	X
Rydzanicz	2005	Poland	182 / 143	hospital / smokers from blood bank		tonsil, tongue, hypopharynx and paranasal sinus	ERCC2 (XPD)	general		
Shen	2001	US (TX)	287 / 311	hospital / MCO	age, sex, ethnicity, smoking	oral, pharynx, larynx	XPC	general	age, sex, smoking, alcohol	X
Sliwinski	2010	Poland	265 / 280	hospital / hospital		oral, pharynx, larynx	ERCC2 (XPD)	general		X
Sturgis	2002	US (TX)	180 / 400	hospital / MCO	age, sex, smoking, alcohol	oral, pharynx, larynx	ERCC2 (XPD)	dominant (X^2 p-value) (general also available)		
Sturgis	2002	US (TX)	313 / 313	hospital / MCO	age, sex, smoking, alcohol	oral, pharynx, larynx	ERCC1, ERCC2 (XPD)	ERCC1 recessive ERCC2 (XPD) dominant	age, sex, smoking, alcohol	X
Sturgis	2000	US (TX)	189 / 496	hospital / MCO	age, sex, smoking, alcohol	oral, pharynx, larynx	ERCC2 (XPD)	recessive (general also available)	age,sex, smoking, alcohol	X
Sugimura	2005	Japan	122 / 241	hospital / hospital		oral	ERCC1, ERCC4 (XPF), ERCC5 (XPG), XPA, XPC	XPA, XPC and XPF dominant XPG and ERCC1 recessive (general also available)	age, sex, smoking, alcohol	X
Wen	2006	China	175 / 525			larynx, hypopharynx	ERCC5 (XPG)	dominant		
Yang	2005	South Korea	73 / 85	hospital / hospital		oral, pharynx, larynx	XPC	general (X^2 p-value)	age, sex, smoking, alcohol	
Yang	2006	South Korea	67 / 73	hospital / hospital		oral, pharynx, larynx	ERCC1	general (X^2 p-value)	age, sex, smoking, alcohol	
Yu	2012	US (TX)	1040 / 1046	hospital / hospital	age, sex	oral, pharynx, larynx	ERCC4 (XPF)	recessive (general also available)	age, sex, smoking, alcohol	X
Yuan	2012	China	397 / 900	hospital / hospital		oral, pharynx, larynx	ERCC2 (XPD), ERCC5 (XPG)	additive	age, sex, smoking, alcohol	
Zavras	2012	Taiwan	239 / 336	hospital / population	race	oral	ERCC5 (XPG)	general	age, smoking, alcohol, and areca nut	

Table 7. Effect estimates among case-control studies on the association between polymorphisms in nucleotide excision repair genes and head and neck cancer incidence (4,5,8-46)

Gene	SNP variant	Study	OR (95% CI)	Genetic Contrast (risk vs ref)
ERCC3 (XPB)	rs4233583	Michiels 2007 (smokers)	0.37 (0.15, 0.90)	AA vs CC
XPC	rs2228001	Abbasi 2009	0.98 (0.68, 1.40)	(Lys/Gln + Gln/Gln) vs Lys/Lys
		An 2007	1.08 (0.81, 1.43)	Gln/Gln vs (Lys/Gln + Lys/Lys)
		Kietthubthew 2006	1.35 (0.50, 3.92)	CC vs AA
	rs2228000	An 2007	1.65 (1.16, 2.36)	Val/Val vs (Ala/Val + Ala/Ala)
	PAT	Kietthubthew 2006	1.60 (0.55, 4.66)	++ vs --
		Shen 2001	1.85 (1.12, 3.05)	++ vs --
		Sugimura 2005	0.83 (0.51, 1.34)	(-+ '+' ++) vs --
		Yang 2005	p=0.96	X^2 for freq in cases vs controls
ERCC8	none			
CDK7	none			
CCNH	none			
XPA	rs1800975	Abbasi 2009	1.20 (0.86, 1.70)	(AG + AA) vs GG
		Bau 2007	1.17 (0.66, 2.05)	(AG + GG) vs AA
		Sugimura 2005	2.04 (1.18, 3.55)	(AG + GG) vs AA
		An 2007	0.87 (0.65, 1.16)	AA vs (AG + GG)
		Hall 2007	0.74 (0.53, 1.03)	AA vs GG
	unspecfied	Jelonek 2010	p=0.1881	X^2 for freq of AA in cases vs controls
RAD23B	rs1805239	Abbasi 2009	1.30 (0.92, 1.90)	(Ala/Val + Val/Val) vs Ala/Ala
ERCC6	rs4253211	Abbasi 2009	0.53 (0.34, 0.85)	(Arg/Pro + Pro/Pro) vs Arg/Arg
	rs2228527	Abbasi 2009	0.87 (0.61, 1.20)	(Arg/Gly + Gly/ Gly) vs Arg/Arg
	rs2228526	Chiu 2008	0.82 (0.50, 1.34)	(AG + GG) vs AA
	rs2228528	Chiu 2008	1.43 (1.02, 2.01)	(GA + AA) vs GG
	rs2228529	Chiu 2008	0.79 (0.49, 1.26)	(AG + GG) vs AA
DDB2 (XPE)	none			
ERCC5 (XPG)	rs2094258	Ma 2012	0.99 (0.82, 1.20)	(CT + TT) vs CC
	rs2296147	Ma 2012	1.06 (0.87, 1.28)	(CT + CC) vs TT
	rs4771436	Ma 2012	1.01 (0.85, 1.20)	(GT + TT) vs GG
	rs1047768	Abbasi 2009	1.20 (0.80, 1.70)	(CT + TT) vs CC
		Ma 2012	1.00 (0.84, 1.21)	(CT + TT) vs CC
	rs2227869	Ma 2012	0.73 (0.52, 1.01)	(CC+CG) vs GG
	rs4150351	Ma 2012	0.81 (0.67, 0.98)	(AC + CC) vs AA
	rs4150355	Ma 2012	1.10 (0.92, 1.31)	(CT + TT) vs CC
	rs4150383	Ma 2012	1.02 (0.85, 1.24)	(AG + GG) vs AA
	rs4150386	Ma 2012	0.97 (0.79, 1.20)	(AC + CC) vs AA
	rs17655	Abbasi 2009	1.30 (0.93, 1.90)	(His/Asp + His/His) vs Asp/Asp
		Wen 2006	1.88 (1.05, 3.40)	Asp/His vs Asp/Asp
		An 2007	0.80 (0.51, 1.28)	Asp/Asp vs (His/Asp + His/His)
		Cui 2005	0.67 (0.42, 1.10)	Asp/Asp vs (His/Asp + His/His)
		Ma 2012	0.99 (0.83, 1.19)	(CG + GG) vs CC
		Sugimura 2005	0.79 (0.44, 1.42)	GG vs (CC + CG)
		Yuan 2012	0.97 (0.82, 1.15)	CC vs CG vs GG
	rs873601	Ma 2012	1.04 (0.87, 1.24)	(AG + GG) vs AA
	rs4150393	Ma 2012	0.93 (0.76, 1.15)	(AG + GG) vs AA
	rs751402	Zavras 2012	2.20 (0.93-4.57)	TT vs CC
ERCC4 (XPF)	rs2276466	Yu 2012	0.69 (0.50, 0.96)	GG vs (CC + CG)
	rs1800067	Abbasi 2009	1.40 (0.89, 2.20)	(Arg/Gln + Gln/Gln) vs Arg/Arg
		Yu 2012	1.40 (0.51, 3.85)	AA vs (GG + AG)
		Canova 2009	1.13 (0.46, 2.78)	AA vs GG
	rs1799801	Canova 2009	1.06 (0.80, 1.41)	CC vs TT
	rs1799798	Yu 2012	0.90 (0.33, 2.52)	AA vs (GG + AG)
	rs3136038	Yu 2012	0.76 (0.58, 1.01)	TT vs (CC+ CT)
	5' UTR, T2063A	Sugimura 2005	0.84 (0.53, 1.32)	(TA + AA) vs TT
RAD23A	none			

Table 7 cont. Effect estimates among case-control studies on the association between polymorphisms in nucleotide excision repair genes and head and neck cancer incidence

Gene	SNP variant	Study	OR (95% CI)	Genetic Contrast (risk vs ref)
ERCC2 (XPD)	rs13181	Abbasi 2009	0.89 (0.63, 1.30)	(Lys/Gln + Gln/Gln) vs Lys/Lys
		Buch 2005	1.5 (1.3, 2.0)	(Lys/Gln + Gln/Gln) vs Lys/Lys
		Huang 2005	1.04 (0.81, 1.34)	(Lys/Gln + Gln/Gln) vs Lys/Lys
		Bau 2007	0.83 (0.41, 1.69)	(Lys/Gln + Gln/Gln) vs Lys/Lys
		Harth 2008	0.86 (0.58, 1.28)	(AC + CC) vs AA
		Kostrzewska-Poczekaj 2013	0.74 (0.42, 1.29)	(AC + CC) vs AA, young adults
		Kostrzewska-Poczekaj 2013	1.05 (0.62, 1.79)	(AC + CC) vs AA, older adults
		Mitra 2009	1.33 (0.75, 2.35)	(AC + CC) vs AA
		Anantharaman 2012	0.75 (0.63-0.89)	Gln/Gln vs Lys/Gln vs Lys/Lys
		An 2007	1.06 (0.79, 1.43)	Gln/Gln vs (Lys/Gln + Lys/Lys)
		Gajecka 2005 (controls smokers)	1.13 (0.74, 1.72)	CC vs (AC+ AA)
		Sturgis 2000	1.55 (0.96, 2.52)	CC vs (AA + AC)
		Chuang 2011	1.03 (0.88, 1.21)	Gln/Gln vs Lys/Lys
		Gugatschka 2011	0.51 (0.27, 0.95)	Gln/Gln vs Lys/Lys
		Gugatschka 2011 rep	0.54 (0.32, 0.92)	Gln/Gln vs Lys/Lys
		Majumder 2007	1.0 (0.9, 2.3)	Gln/Gln vs Lys/Lys
		Ramachandran 2005	2.72 (1.07, 6.91)	Gln/Gln vs Lys/Lys
		Sliwinski 2010	0.84 (0.42, 1.67)	Gln/Gln vs Lys/Lys
		Ji 2010	2.68 (0.71, 10.10)	CC vs AA
		Kietthubthew 2006	2.04 (0.19, 21.66)	CC vs AA
		Rydzanicz 2005	0.93 (0.49, 1.78)	CC vs AA
		Matullo 2006 (nonsmokers)	0.62 (0.25, 1.53)	CC vs AA
		Jelonek 2010	p=0.3802	X^2 for freq of CC in cases vs. controls
		Yuan 2012	1.00 (0.73, 1.36)	GG vs TG vs TT
	rs1799793	Abbasi 2009	0.97 (0.68, 1.40)	(Asp/Asn + Asn/Asn) vs. Asp/Asp
		Buch 2005	1.3 (1.0, 1.8)	(Asp/Asn + Asn/Asn) vs. Asp/Asp
		Harth 2008	0.86 (0.57, 1.30)	(GA + AA) vs GG
		Sturgis 2002	1.28 (0.93, 1.76)	(GA + AA) vs GG
		Anantharaman 2012	1.05 (0.86, 1.27)	Asn/Asn vs Asp/Asn vs Asp/Asp
		An 2007	1.15 (0.85, 1.57)	Asn/Asn vs (Asp/Asn + Asp/Asp)
		Gugatschka 2011	0.70 (0.38, 1.28)	Asn/Asn vs Asp/Asp
		Gugatschka 2011 rep	0.73 (0.44, 1.21)	Asn/Asn vs Asp/Asp
		Majumder 2007	1.0 (0.9, 1.0)	Asn/Asn vs Asp/Asp
		Ji 2010	1.94 (0.92, 4.08)	GA vs GG
		Matullo 2006 (nonsmokers)	0.34 (0.09–1.24)	AA vs GG
		Jelonek 2010	p=0.3209	X^2 for freq of AA in cases vs. controls
	rs1799792	Sturgis 2002	p=0.682	X^2 for freq of CT + TT in cases vs. controls
	rs1799791	Sturgis 2002	p=0.832	X^2 for freq of CG + GG in cases vs. controls
	rs238406	Abbasi 2009	0.98 (0.68, 2.40)	(CA + AA) vs CC
		Harth 2008	0.98 (0.66, 1.47)	(CA + AA) vs CC
		Gajecka 2005 (controls smokers)	0.81 (0.49, 1.31)	AA vs (CA + CC)
		Sturgis 2000	0.92 (0.98, 1.32)	AA vs (CA + CC)
		Majumder 2007	1.0 (0.9, 1.0)	AA vs CC
		Kietthubthew 2006	0.85 (0.30, 2.37)	AA vs CC
		Rydzanicz 2005	0.96 (0.48, 0.90)	AA vs CC
ERCC1	rs735482	Jones 2011	0.32 (0.04, 2.49)	CC vs AA
	rs3212986	Abbasi 2009	0.90 (0.64, 1.30)	(CA + AA) vs CC
		An 2007	0.89 (0.59, 1.35)	AA vs (CA+CC)
		Strugis 2002	1.15 (0.84, 1.59)	CC vs (AA + AC)
		Sugimura 2005	1.95 (0.93, 4.09)	AA vs (CC + CA)
		Yang 2006	p=0.82	X^2 for freq in cases vs controls
	rs3212961	Abbasi 2009	0.77 (0.51, 1.20)	(CA + AA) vs CC
		Canova 2009	0.45 (0.23, 0.90)	CC vs AA
	rs3212955	Jones 2011	1.36 (0.67, 2.75)	GG vs AA
	rs11615	Abbasi 2009	0.83 (0.58, 1.20)	(TC + CC) vs TT
	rs3212948	Jones 2011	0.82 (0.46, 1.45)	GG vs CC
		Canova 2009	1.02 (0.79, 1.31)	GG vs CC
	rs1319052	Jones 2011	0.90 (0.51, 1.59)	AA vs GG
	rs3177700	Mautllo 2006 (nonsmokers)	1.79 (0.80, 4.01)	CC vs TT
	rs11615, rs3177700	Canova 2009	1.02 (0.80, 1.30)	

Table 7 cont. Effect estimates among case-control studies on the association between polymorphisms in nucleotide excision repair genes and head and neck cancer incidence

Gene	SNP variant	Study	OR (95% CI)	Genetic Contrast (risk vs ref)
LIG1	rs13436, rs3182008	Michiels 2007 (smokers)	1.94 (1.06, 2.75)	GG vs CC
	rs153023	Michiels 2007 (smokers)	2.13 (1.13, 2.90)	TT vs CC
	rs156640	Michiels 2007 (smokers)	1.94 (1.06, 3.56)	CC vs GG
	rs156641	Michiels 2007 (smokers)	1.75 (0.92, 3.31)	TT vs CC
	rs2241721	Michiels 2007 (smokers)	1.69 (0.89, 3.21)	CC vs TT
	rs274892	Michiels 2007 (smokers)	2.05 (1.12, 3.78)	AA vs CC
	rs3730912	Michiels 2007 (smokers)	0.86 (0.53, 1.40)	GT vs GG
	rs20581	Lee 2007	1.50 (1.00, 2.30)	CC vs TT
	rs20580	Lee 2007	1.20 (0.83, 1.70)	AA vs CC
	rs20579	Lee 2007	2.00 (0.69, 2.30)	TT vs CC
	rs439132	Lee 2007	5.90 (1.10, 31.00)	GG vs AA
	rs288882	Michiels 2007 (smokers)	1.83 (0.96, 3.50)	AA vs GG
	rs228883	Michiels 2007 (smokers)	1.78 (0.94, 3.40)	GG vs TT

Table 8. Effect estimates by cigarette smoking among case-control studies on the association between polymorphisms in nucleotide excision repair genes and head and neck cancer incidence (4,8-10,13,15,16,22,24,26-28,30,31,33,35-38,40,44)

			Nonsmokers		Smokers		
Gene	**SNP variant**	**Study**	**Definition**	**OR (95% CI)**	**Definition**	**OR (95% CI)**	**Genetic Contrast (risk vs ref)**
ERCC3 (XPB)	rs4233583	Michiels 2007			regular smokers (5 cigarettes/day for 5+ years)	0.37 (0.15, 0.90)	AA vs CC
XPC	PAT	Shen 2001	never smoker	1.87 (0.72, 4.86)	former smoker	1.83 (0.85, 3.94)	++ vs --
					current smoker	1.69 (0.66, 4.35)	
		Sugimura 2005			smoker, risk genotype	0.48 (0.13, 1.87)	(-+ '+' ++) vs --
ERCC8	none						
CDK7	none						
CCNH	none						
XPA	rs1800975	Bau 2007	nonsmoker, ref genotype	1.00 (ref)	smoker, ref genotype	--	(AG + GG) vs AA
			nonsmoker, risk genotype	3.52 (1.26, 9.84)	smoker, risk genotype	47.7 (15.48, 147.01)	
		Sugimura 2005			smoker, risk genotype	0.48 (0.11, 2.16)	(AG + GG) vs AA
RAD23B	rs1805239	Abbasi 2009	light smoker (≤20 packyears)	0.95 (0.47, 1.90)	heavy smoker (>20 packyears)	1.60 (1.10, 2.50)	(Ala/Val + Val/Val) vs Ala/Ala
ERCC6	rs4253211	Abbasi 2009	light smoker (≤20 packyears)	0.52 (0.18, 1.50)	heavy smoker (>20 packyears)	0.56 (0.34, 0.93)	(Arg/Pro + Pro/Pro) vs Arg/Arg
	rs2228528	Chiu 2007	never smoker	0.99 (0.64, 1.55)	ever smoker	2.36 (1.36, 4.10)	(GA + AA) vs GG
DDB2 (XPE)	none						
ERCC5 (XPG)	rs1047768	Abbasi 2009	light smoker (≤20 packyears)	0.85 (0.43, 1.70)	heavy smoker (>20 packyears)	1.40 (0.97, 2.20)	(His/Asp + His/His) vs Asp/Asp
	rs17655	Cui 2005	never smoker, ref genotype	1.00 (ref)	1-20 packyears, ref genotype	2.20 (0.51, 9.60)	(His/Asp + His/His) vs Asp/Asp
			never smoker, risk genotype	3.60 (1.20, 11.0)	1-20 packyears, risk genotype	3.20 (1.10, 9.50)	
					>20 packyears, ref genotype	3.80 (1.00, 1.40)	
					>20 packyears, risk genotype	8.00 (2.70, 24.0)	
		Sugimura 2005			smoker, risk genotype	0.33 (0.06, 1.74)	GG vs (CC + CG)
	rs4150351	Ma 2012	never smoker	0.84 (0.63, 1.34)	ever smoker	0.79 (0.62, 1.00)	(AC + CC) vs AA
ERCC4 (XPF)	rs2276466	Yu 2012	nonsmoker	0.57 (0.33, 1.00)	smoker	0.78 (0.52, 1.17)	GG vs (CC + CG)
	rs1800067	Krupa 2011	never smoker	1.13 (p=0.69)	ever smoker	1.07 (p=0.80)	(Arg/Gln + Gln/Gln) vs Arg/Arg
					moderate smoking	1.06 (p=0.85)	
					heavy smoking	0.98 (p=0.95)	
	rs3136038	Yu 2012	nonsmoker	0.55 (0.34, 0.88)	smoker	0.96 (0.66, 1.39)	TT vs (CC + CT)
	5' UTR, T2063A	Sugimura 2005			smoker, risk genotype	0.60 (0.17, 2.12)	(TA + AA) vs TT
RAD23A	none						
ERCC2 (XPD)	rs13181	Anantharaman 2012	no tobacco habit	0.55 (0.28, 1.08)	exlusive chewer	0.76 (0.59, 0.97)	Gln/Gln vs Lys/Gln vs Lys/Lys
					exlusive smoker	0.69 (0.33, 1.43)	
					mixed habits	0.78 (0.59, 1.03)	
		Bau 2007	nonsmoker, ref genotype	1.00 (ref)	smoker, ref genotype	--	(AG + GG) vs AA
			nonsmoker, risk genotype	28.48 (13.93, 58.23)	smoker, risk genotype	26.33 (7.87, 88.04)	
		Buch 2005	nonsmoker, ref genotype	1.00 (ref)	smoker, ref genotype	0.79 (0.45, 1.36)	(Lys/Gln + Gln/Gln) vs Lys/Lys
			nonsmoker, risk genotype	1.26 (0.73, 2.18)	smoker, risk genotype	3.99 (2.30, 6.92)	
		Gajecka 2005			control current smoker	1.13 (0.74, 1.72)	CC vs (AC+ AA)
		Ji 2010	nonsmoker	7.2 (0.39, 34.22)	light smoker	1.27 (0.40, 4.08)	AC vs AA
					heavy smoker	0.73 (0.39, 1.36)	
		Mautllo 2006	never or former smoker	0.62 (0.25, 1.53)			CC vs AA
		Ramachandran 2005	never smoker	1.48 (0.80, 2.74)	ever smoker	3.37 (1.51, 7.51)	(Lys/Gln + Gln/Gln) vs Lys/Lys
		Sliwinski 2010	nonsmoker	1.07 (0.36, 3.21)	smoker	0.72 (0.29, 1.76)	Gln/Gln vs Lys/Lys
		Sturgis 2000	never smoker	1.44 (0.54, 3.81)	former smoker	1.40 (0.65, 3.00)	CC vs (AA + AC)
					current smoker	1.83 (0.79, 4.27)	

Table 8 cont. Effect estimates by cigarette smoking among case-control studies on the association between polymorphisms in nucleotide excision repair genes and head and neck cancer incidence

			Nonsmokers		Smokers		
Gene	**SNP variant**	**Study**	**Definition**	**OR (95% CI)**	**Definition**	**OR (95% CI)**	**Genetic Contrast (risk vs ref)**
ERCC2 (XPD)	rs1799793	Mautllo 2006	never or former smoker	0.34 (0.09, 1.24)			AA vs GG
		Anantharaman 2012	no tobacco habit	1.50 (0.69, 3.12)	exlusive chewer	0.92 (0.69, 1.22)	Asn/Asn vs Asp/Asn vs Asp/Asp
					exlusive smoker	0.89 (0.37, 2.13)	
					mixed habits	1.15 (0.83, 1.58)	
		Ji 2010			light smoker	2.4 (0.78, 7.35)	
					heavy smoker	0.94 (0.47, 7.35)	GA vs AA
	rs238406	Sturgis 2000	never smoker	1.15 (0.57, 2.32)	former smoker	0.72 (0.41, 1.58)	AA vs (CA + CC)
					current smoker	1.04 (0.54, 2.01)	
		Gajecka 2005			control current smoker	0.81 (0.49, 1.31)	AA vs (CA + CC)
	exon 6	Kietthubthew	nonsmoker and nondrinker	4.10 (1.20, 14.0)	smoker and drinker	1.48 (0.64, 3.44)	AA vs CC
ERCC1 and ERCC2 (XPD)	rs3212986/rs1799793	Sturgis 2002	nonsmoker	1.24 (0.61, 2.51)	smoker	1.46 (0.95, 2.25)	CC vs (AA + AC) and (GA + AA) vs GG
ERCC1	rs3212986	Sugimura 2005			smoker, risk genotype	8.49 (1.22, 59.31)	AA vs (CC + CA)
	rs3177700	Mautllo 2006	never or former smoker	1.79 (0.80, 4.01)			CC vs TT
LIG1	rs13436/rs3182008	Michiels 2007			regular smokers (ie 5 cigarettes/day for 5+ years)	1.94 (1.06, 2.75)	GG vs CC
	rs153023	Michiels 2007			regular smokers	2.13 (1.13, 2.90)	TT vs CC
	rs156640	Michiels 2007			regular smokers	1.94 (1.06, 3.56)	CC vs GG
	rs156641	Michiels 2007			regular smokers	1.75 (0.92, 3.31)	TT vs CC
	rs2241721	Michiels 2007			regular smokers	1.69 (0.89, 3.21)	CC vs TT
	rs274892	Michiels 2007			regular smokers	2.05 (1.12, 3.78)	AA vs CC
	rs3730912	Michiels 2007			regular smokers	0.86 (0.53, 1.40)	TT vs GG
	rs20581	Lee 2007	0 packyears	0.83 (0.42, 1.60)	>0 to 20 packyears	2.30 (0.95, 5.40)	CC vs TT
					>20 packyears	2.20 (1.00, 4.70)	
	rs20580	Lee 2007	0 packyears	0.86 (0.47, 1.60)	>0 to 20 packyears	1.50 (0.74, 3.20)	AA vs CC
					>20 packyears	1.60 (0.84, 3.10)	
	rs20579	Lee 2007	0 packyears (heterozygote presented)	1.50 (0.91, 2.30)	>0 to 20 packyears	1.20 (0.21, 6.90)	TT vs CC
					>20 packyears	0.95 (0.18, 5.00)	
	rs439132	Lee 2007	0 packyears	2.70 (0.16, 45.0)	>0 to 20 packyears	3.30 (0.18, 60.0)	GG vs AA
					>20 packyears (heterozygote presented)	2.00 (0.74, 5.70)	
	rs288882	Michiels 2007			regular smokers	1.83 (0.96, 3.50)	AA vs GG
	rs228883	Michiels 2007			regular smokers	1.78 (0.94, 3.40)	GG vs TT

Table 9. Characteristics of case-only studies on the association between polymorphisms in nucleotide excision repair genes and head and neck cancer mortality (7,47-55)

Author	Year	Country	N Cases	HN Site(s)	Treatment	Genes	Genetic Model	Kaplan Meier Curve	Cox Proptional Model	Cox Proportinoal Model Adjustment Variables
Azad	2012	Canada	531	oral, pharybx, larynx	radiation	ERCC1, ERCC4, ERCC5, XPA, ERCC2	additive (general also available)		X	age, smoking, alcohol, BMI, comorbidity, performance status, tumor site, stage
Carles	2006	Spain	108	oral, pharynx, larynx, nasopharynx	radiation	ERCC1, XPA, XPC, XPD, XPG	general (dominant also available for time to progression)	X		
De Castro	2011	Brazil	59	oral, pharynx, larynx	ajuvant chemotherapy (cisplatin)	ERCC1	general	X		multivariate model
								X	X	
								X	X	
Gal	2005	US (WA)	328	oral	radiation or surgery	XPD	dominant (general also available)		X	age, smoking, alcohol, tumor site
Grau	2009	Spain	47	oral, pharynx, larynx	induction chemotherapy (paclitaxel)	ERCC1	general		X	unadjusted
Hao	2012	Canada	55	oral, pharynx, larynx	concurrent chemotherapy (cisplatin)	ERCC1	dominant		X	unadjusted
Mahimkar	2012	India	458	oral	surgery and radiation	XPD	dominant (general also available)		X	age, sex, tobacco, grade, stage
Quintela-Fandino	2006	Spain	103	oral, pharynx, larynx	induction chemotherapy CDDP + radiotherapy (N=26), CDDP + fluoropyrimidine (N=31), CDDP + fluoropyrimidine + taxane (N=42), and cisplatin + cetuximab (N=4)	ERCC1, XPD	general	X		
Vaezi	2011	US (PA)	80	oral, pharynx, larynx	radiation and chemotherapy (platinum-based) (N=70), radiation only (N=10), primary chemotherapy or radiation (N=38), or surgery + chemotherapy + radiotherapy (N=42)	XPF	additive or recessive? (homozygous variant versus referent allele)		X	age, sex, tumor stage, tumor site, treatment
Zhong	2011	US (PA)	485	oral, pharynx, larynx	radiation (with/without chemotherapy) N=275 no treatment N=210	XPD	dominant (inverted)	X	X	age, sex, tumor site, stage, treatment, CCND1 G870A genotype

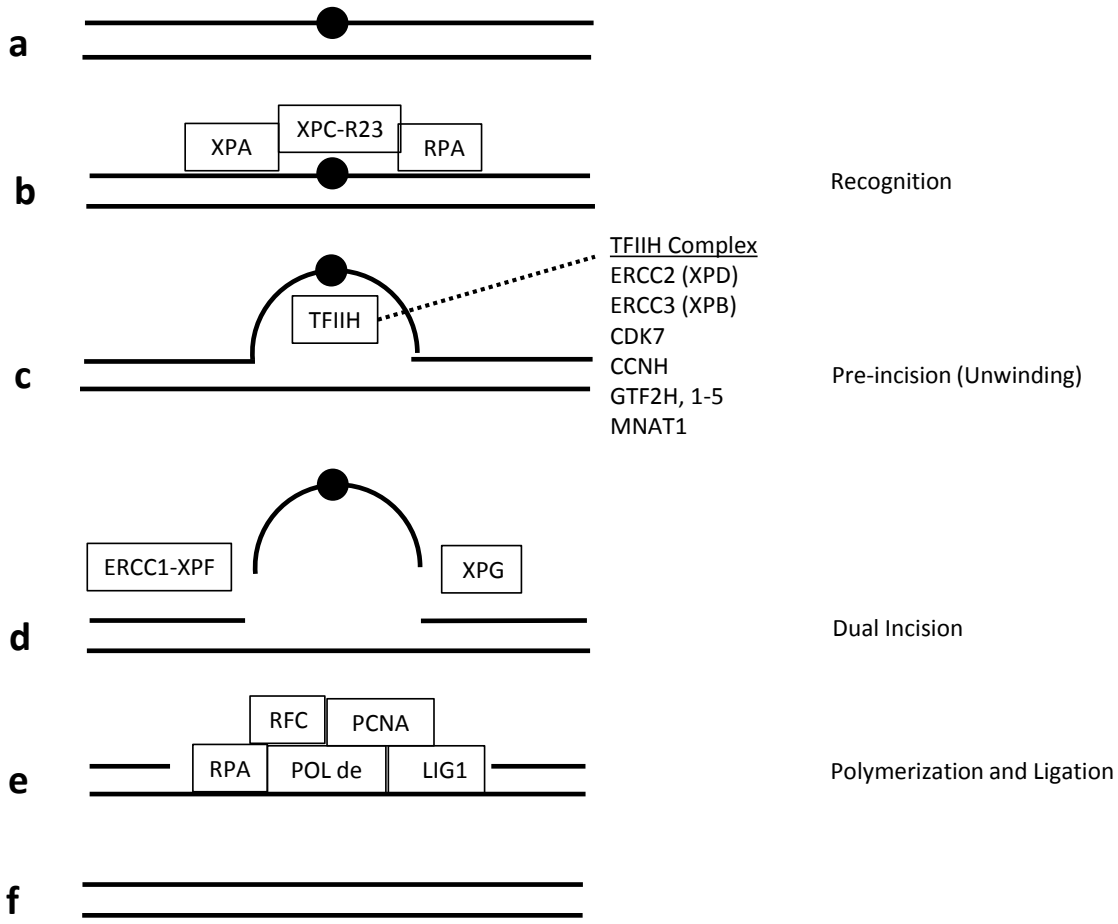
Table 10. Effect estimates of case-only studies on the association between polymorphisms in nucleotide excision repair genes and head and neck cancer mortality (7,47-55)

Gene	SNP variant	Study	Treatment	Outcome	Cox Proportional HR (95% CI)	Kaplan Meier Curve p-value	Genetic Contrast
ERCC3 (XPB)	none						
XPC	rs2228001	Carles 2006	radiation	progression free survival		0.74	general (C>A)
				overall survival		0.96	
ERCC8	none						
CDK7	none						
CCNH	none						
XPA	rs1800975	Azad 2012	radiation	overall survival	0.96 (0.78, 1.18)		additive (A>G)
				disease free survival	1.10 (0.88, 1.36)		
		Carles 2006	radiation	progression free survival		0.23	general (T>C)
				overall survival		0.64	
RAD23B	none						
ERCC6	none						
DDB2	none						
ERCC5 (XPG)	rs1047768	Azad 2012	radiation	overall survival	1.03 (0.85, 1.25)		additive (T>C)
				disease free survival	1.06 (0.86, 1.30)		
		Carles 2006	radiation	progression free survival		0.049	general (T>C)
				overall survival		0.0066	
	rs17655	Azad 2012	radiation	overall survival	0.89 (0.70, 1.13)		additive (G>C)
				disease free survival	0.85 (0.66, 1.09)		
		Carles 2006	radiation	progression free survival		0.22	general (G>C)
				overall survival		0.44	
ERCC4 (XPF)	rs3136105	Vaezi 2011	X-ray therapy, chemotherapy, surgery	1-year progression free survival	1.41 (p=0.415)		T>C
	rs3136146	Vaezi 2011	X-ray therapy, chemotherapy, surgery	1-year progression free survival	1.69 (p=0.191)		G>A
	rs3136152	Vaezi 2011	X-ray therapy, chemotherapy, surgery	1-year progression free survival	2.30 (p=0.240)		G>A
	rs3136155	Vaezi 2011	X-ray therapy, chemotherapy, surgery	1-year progression free survival	2.00 (p=0.053)		C>T
	rs3136166	Vaezi 2011	X-ray therapy, chemotherapy, surgery	1-year progression free survival	1.94 (p=0.065)		T>G
	rs3136189	Vaezi 2011	X-ray therapy, chemotherapy, surgery	1-year progression free survival	1.44 (p=0.285)		T>C
	rs3136202	Vaezi 2011	X-ray therapy, chemotherapy, surgery	1-year progression free survival	1.95 (p=0.065)		G>A
	rs1799799	Vaezi 2011	X-ray therapy, chemotherapy, surgery	1-year progression free survival	1.94 (p=0.065)		T>C
	rs1799801	Azad 2012	radiation	overall survival	1.02 (0.83, 1.27)		additive (T>C)
				disease free survival	0.96 (0.77, 1.21)		
		Vaezi 2011	X-ray therapy, chemotherapy, surgery	1-year progression free survival	1.46 (p=0.265)		T>C
RAD23A	none						
ERCC2 (XPD)	rs13181	Azad 2012	radiation	overall survival	0.86 (0.71, 1.06)		additive (A>C)
				disease free survival	0.80 (0.64, 1.00)		
		Carles 2006	radiation	progression free survival		0.78	general (A>C)
				overall survival		0.87	
		Gal 2005	radiation or surgery	overall survival	1.06 (0.74, 1.51)		(Lys/Gln + Gln/Gln) vs Lys/Lys
				disease-specific survival	0.80 (0.41, 1.56)		
		Mahimkar 2012	sugery and radiation	disease-specific survival	0.72 (0.41, 1.24)		(Lys/Gln + Gln/Gln) vs Lys/Lys
				relapse free survival	0.52 (0.20, 0.91)		
		Quintela-Fandino 2006	induction chemotherapy	overall survival		0.0012	common vs polymorphic allele

Table 10 cont. Effect estimates of case-only studies on the association between polymorphisms in nucleotide excision repair genes and head and neck cancer mortality

Gene	SNP variant	Study	Treatment	Outcome	Cox Proportional HR (95% CI)	Kaplan Meier Curve p-value	Genetic Contrast
ERCC2 (XPD)	rs13181 cont	Zhong 2011	stage 3-4, radiation	overall survival	1.66 (1.15,2.40)	<0.01	AA vs (AC + CC)
				disease free survival		0.02	
				progression free survival		0.03	
			stage 3-4, no radiation	overall survival	0.26 (0.11,0.62)	<0.01	
				disease free survival		0.05	
				progression free survival		0.02	
			stage I-II, no radiation	overall survival		0.78	
				disease free survival		0.98	
				progression free survival		0.79	
	rs1799793	Azad 2012	radiation	overall survival	0.89 (0.73, 1.10)		additive (G>A)
				disease free survival	0.89 (0.72, 1.11)		
		Mahimkar 2012	sugery and radiation	disease-specific survival	0.51 (0.28, 0.92)		(Asp/Asn + Asn/Asn) vs Asp/Asp
				relapse free survival	0.43 (0.22, 0.84)		
		Quintela-Fandino 2006	induction chemotherapy	overall survival		0.0012	common vs polymorphic allele
ERCC1	rs735482	Azad 2012	radiation	overall survival	0.92 (0.68, 1.24)		additive (A>C)
				disease free survival	0.78 (0.44, 0.95)		
		Carles 2006	radiation	progression free survival		0.0005	general (A>C)
				overall survival		0.0089	
		Grau 2009	induction chemotherapy	overall survival	1.54 (0.71, 3.32)		AC vs AA
				overall survival	1.57 (0.63, 3.91)		CC vs AA
				progression free survival	"No statistically significant differences in time to progression….between wild-type and SNP patients"		
	rs3212986	Azad 2012	radiation	overall survival	0.85 (0.67, 1.09)		additive (C>A)
				disease free survival	0.96 (0.75, 1.23)		
		Quintela-Fandino 2006	induction chemotherapy	overall survival		0.80	common vs polymorphic allele
	rs11615	Hao 2012	concurrent chemotherapy	overall survival	3.4 (0.9, 12.0)		CC + CT vs TT
				disease-specific survival	6.8 (0.8, 54.8)		
				recurrence	3.6 (0.8 ,16.6)		
		De Castro 2011	adjuvant chemotherapy	5-year overall survival	p=0.808		general (C>T)
LIG1	none						

Figure 1. Overview of Nucleotide Excision Repair Pathway (adapted from Friedberg (124); other sources consulted include: (123,128))



CHAPTER 2

METHODS

2.1 STUDY POPULATION

2.1.1 Carolina Head and Neck Cancer Epidemiology (CHANCE) Study

The Carolina Head and Neck Cancer Epidemiology (CHANCE) study is a population-based case-control study of 2,785 individuals (1,389 cases and 1,396 controls) from 46 of 100 counties in North Carolina (57,63,64). To be eligible, cases and controls were between 20 to 80 years of age at diagnosis (57,63,64). Cases were identified from the North Carolina Central Cancer Registry between January 1, 2002 and February 28, 2006 (57,63,64). To ensure quick recruitment of cases, rapid case ascertainment was employed (57,63,64). Cancers were classified according to ICD-03 codes; cancers 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; C32.9), 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 cancers of the salivary glands (C07.9, C08.0 to C08.9), nasopharynx (C11 .0 to C11.9), nasal cavity (C30.0), and nasal sinuses (C31.0 to C31 .9) were excluded (57,63,64). With regard to histology, only invasive squamous cell carcinomas (basaloid, keratinizing, large and small cell nonkeratinizing, spindle cell, microinvasive, verrucous, not otherwise specified, and epithelial neoplasms not otherwise specified) were included, while benign and in situ carcinomas, including papillary carcinomas and adenoid squamous cell carcinomas, were excluded (82,135). Medical records and tumor samples for cases were reviewed by the CHANCE study pathologist, Dr. William K. Funkhouser to verify

diagnoses (82,135). Controls, defined as never being diagnosed with HNC, were randomly sampled from the Department of Motor Vehicle records and were frequency matched to cases based on strata of age (20-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-80 years of age), race (white, African American, other race), and sex (male, female) (57,63,64).

2.1.2 Recruitment Methods

Physicians of HNC cases who were eligible for CHANCE were provided with information regarding the study and a request for permission for investigators to contact the patient(s) under their care (82,135). If physicians did not refuse or did not respond, eligible cases were then approached about participation via mail (82,135). Likewise, eligible controls were initially contacted via mail (82,135). Mailed materials explained the purpose of the study, study components (administration of interview and collection of biologic samples), and compensation ($50) (82,135). Following mailings, trained nurses followed-up with individuals by phone to inquire about their willingness to participate, verify eligibility, and schedule an interview (82,135). Consenting participants were then given in-person interviews by a trained nurse (57,63,64). In circumstances where the selected case was deceased at the time of interview, the interview was administered to a proxy who was usually a close relative, which is considered a reliable substitute for some items (82,135,136). Interviews consisted of questions on demographic (age, gender, race, education level, etc.) and behavioral (tobacco use, alcohol use, diet, oral health, etc.), as well as collection of biologic specimens (57,63,64). Details of the CHANCE questionnaire and collection of biologic samples will discussed in the exposure and covariate assessment sections.

2.1.3 Study Population

A total of 2,135 cases of HNC were identified within the study time and location (figure 2) (82,135). Of these, physicians refused permission for investigators to contact 39 (1.8%) cases, 269 (12.6%) cases were determined to be ineligible (e.g., outside the age range), 50 (2.3%) cases were

unlocatable, and 77 (3.6%) cases were deceased and had no proxy (82,135). Of the remaining 1700 eligible cases, 311 (18.3%) refused to participate in the study (82,135). In-person and proxy interviews were completed by 1337 (78.6%) and 52 (3.1%) individuals, respectively (82,135). Therefore, the response for cases was approximately 81.7% (1389 completed interviews / 1700 eligible cases).

A total of 4,049 controls were sampled to match cases within the study time and location (figure 3) (82,135). Of these, 780 (19.3%) controls were not contacted, 234 (5.8%) controls were determined to be ineligible (e.g., outside the age range), 655 (16.2%) controls were unlocatable, and 109 (2.7%) controls were deceased and had no proxy (82,135). Of the remaining 2271 eligible controls, 875 (38.5%) refused to participate in the study (82,135). In-person and proxy interviews were completed by 1379 (60.7%) and 17 (0.7%) individuals, respectively (82,135). Therefore, the response for controls was approximately 61.5% (1396 completed interviews / 2271 eligible controls).

Of the 1,389 cases and 1,379 controls who completed interviews, 1329 (95.7%) cases and 1376 controls (99.8%) provided blood and/or buccal cell samples (82,135). Of these, 1313 (98.8%) cases and 1368 (99.4%) controls had sufficient quantity and quality of DNA for genotyping (82,135). DNA samples from 1274 (97.0%) cases and 1343 (98.2%) controls were successfully genotyped (82,135).

To address the dissertation aims only cases and controls with successfully genotyped DNA were included. Individuals who self-reported race as white or African American were included; other races and minorities (26 cases and 18 controls) were not considered in this dissertation due to sparse data. In addition, lip cancers (21 cases) were excluded. The study population therefore comprised 1,227 cases and 1,325 controls. Table 11 summarizes the distribution of demographic characteristics for cases and controls in the overall CHANCE study and those eligible for this

dissertation. No material differences between the overall and dissertation study populations were noted.

2.2 EXPOSURE ASSESSMENT: GENETIC FACTORS

2.2.1 Biologic Specimen Collection

At the time of interview, trained nurses collected three 10 ml blood samples from participants (82,135). As described in the CHANCE Protocol and Dr. Anne Hakenewerth's dissertation (82,135):

> [One] tube was used for plasma and collection of mononuclear cells for subsequent DNA extraction… [, one] tube was used for plasma, buffy coat and packed red blood cell separation (the buffy coat was stored frozen for subsequent DNA extraction)…[, and one] tube was used to collect serum that was stored for potential use in future assays (82,135).

If individuals refused to provide a blood sample, they were asked to provide buccal cell samples instead (82,135). Buccal cell samples were collected using 1.5 ounces of mouthwash or saline for 30 seconds and repeating (82,135). All blood and buccal samples were packed on ice and returned to the lab within 12 hours for processing (82,135). DNA extraction was usually completed within 12-72 hours of sample receipt (82,135). Among cases, 1217 provided blood samples and 112 provided buccal cell samples. Among controls, 1280 provided blood samples and 96 provided buccal samples (82,135). As described in the CHANCE Protocol and Dr. Anne Hakenewerth's dissertation (82,135):

> DNA was extracted from [fresh blood samples or buccal cell pellets] frozen at -80°C using a modified salt procedure with Puregene chemistries. DNA samples were quantified in multi-spectral optical density spectrophotometers. The 260/280 ratio was used to assess sample quality. Ratios of >1.7 for DNA extracted from blood or >1.6 for buccal rinse samples were considered to be quality samples. In addition, each DNA sample was subjected to 0.4% agarose gel electrophoresis to assess the size of the DNA. Greater than 96% of the blood samples' genomic DNA was of high quality as demonstrated by a single large band of DNA with a size greater than 25kb. DNA from [some] buccal samples was of insufficient quantity for genotyping. DNA was aliquotted into multiple vials which were stored at -80°C for long-term storage (82,135).

2.2.2 Genotyping Methods

Genotyping was conducted at the University of North Carolina at Chapel Hill, Mammalian Genotyping Core Facility (64). Illumina GoldenGate assay with Sentrix Array Matrix and 96-well standard microtiter plates were used to genotype 1,536 different SNPs from CHANCE, including the 129 SNPs proposed in this dissertation (82,135). In addition to the large number of SNPs processed simultaneously, the Illumina GoldenGate technology is a commonly used due to the relatively small amount of DNA required for the assay (approximately 160 pg of DNA for each SNP) and efficiency of the process (3 days) (137). As described in the manufacturer's online materials, the Illumina GoldenGate assay comprises nine general steps: 1) activation of DNA; 2) addition of DNA to oligonucleotides followed by hybridization, 3) extension, ligation, and clean-up, 4) universal PCR cycles, 5) binding PCR product, elution of dye-labeled strand, preparation for hybridization; 6) hybridization to the Sentrix Array Matrix; 7) washing and drying of array matrix; 8)imaging of array matrix; 9) auto-calling genotypes and generating report (137).

To improve the integrity of genotyping results, several laboratory and analytic quality control measures were implemented. First, laboratory technicians were blinded to which samples were from cases and which were from controls (82,135). Second, samples from cases and controls, as well as DNA controls, were included on each plate (82,135). Third, 109 samples were randomly selected for duplicated or blinded genotyping (82,135). Among the repeated or blinded SNPs, five out 145,568 pairs (0.003%) were discrepant (82). Only one SNP for one participant included in this dissertation was discrepant, and only that single SNP was dropped for that single individual (138). Fourth, genetic data were checked for illogical values (82,135). For example, inconsistencies between self-reported and genetically determined sex were checked using an algorithm in SAS (Cary, NC), and six samples were found to be inconsistent (138). Gender discrepancies were resolved for five of these samples, but not for one sample which was excluded from analyses (138). Finally,

commonalities among samples which failed genotyping were explored (e.g, plate location or DNA volume and concentration) and resolved by re-testing, or in circumstances where re-testing failed set to missing (82,135).

2.2.3 Single Nucleotide Polymorphisms Selection

The majority of the 129 SNPs for NER genes were chosen based on two previous studies: the MD Anderson Head and Neck Cancer Study and the Carolina Breast Cancer Study (CBCS). In addition, a few SNPs were chosen by the CHANCE PI, Dr. Andrew Olshan. Tables 12 and 13 summarize the selection methods for each SNP.

2.2.3.1 MD Anderson Head and Neck Cancer Study

Dr. Qingyi Wei and colleagues at MD Anderson Hospital in Dallas, Texas conducted a case-control study on HNC (28,44,139). As part of this study, investigators considered the effects of 8 NER genes: *ERCC3 (XPB), XPC, XPA, DDB2 (XPE), ERCC5 (XPG), ERCC4 (XPF), ERCC2 (XPD),* and *ERCC1* (28,44,139). To select tag SNPs for these genes, investigators queried the NIEHS-EGP (140) and HapMap (129) databases using a selection criteria of $r^2 \geq 0.80$, minor allele frequency (MAF) ≥ 0.05, 1-2Kb flanking region (139). The NIEHS-EGP database is based on a heterogeneous population which includes whites, African Americans, and Asians (140). However, since the MD Anderson study contained over 80% Caucasians, only the CEU (Utah residents with ancestry from northern and western Europe) population was ultimately considered (139). From this database, 67 tag SNPs were selected to capture the variation in NER genes among whites (139). Using the CEU population in HapMap, an additional 58 tag SNPs (63 including flanking regions) were identified (139). Taking into account duplicates between the databases, 85 tag SNPs were chosen to represent the variation in the 8 NER genes: 6 SNPs in ERCC1, 9 SNPs in XPA, 8 SNPs in XPB, 15 SNPs in XPC, 13 SNPs in XPD, 7 SNPs in XPF, 13 SNPS in XPG, and 14 SNPS in DDB2 (139). The majority of these SNPs were targeted for genotyping in CHANCE as summarized in table 12. Some tag SNPs chosen by Wei were not

included in CHANCE: rs229881 in ERCC1; rs238405, rs1799793, rs1799788 in ERCC2; rs1047768, rs2094258 in ERCC5, rs3176633 in XPA, rs1124303, rs2470353, rs1126547, rs2470352 in XPC; rs2276466 in XPF; rs3758667, rs10742797, rs11039138 in DDB2.

2.2.3.2 Carolina Breast Cancer Study (CBCS)

Dr. Robert Millikan and colleagues at UNC-Chapel Hill conducted a case-control study on breast cancer (141). As part of this study, investigators considered the effects of 13 NER genes: *XPC, ERCC8, CDK7, CCNH, XPA, RAD23B, ERCC6, ERCC5 (XPG), XPF (ERCC4), RAD23A, ERCC2 (XPD), ERCC1, and LIG1* (142). Candidate SNPs for these genes were selected based on previous studies and/or potential function, such as amino acid changes, 3'UTR, and 5'UTR (table 12) (142).

2.2.3.3 Carolina Head and Neck Cancer Epidemiology Study

In addition to SNPs identified from the MD Anderson HNC and CBCS studies, Dr. Andrew Olshan and colleagues at UNC-Chapel Hill selected several additional candidate SNPs included in CHANCE based on previous studies and/or potential functions (135). Two additional SNPs were included for *ERCC1*, 3 for *ERCC5* (*XPG),* and 4 for *LIG1* (table 12).

2.2.3.4 Variation Captured by CHANCE SNPs

Since a mixture of tag and candidate SNPs are included in this dissertation, the variation within each gene captured by SNPs in CHANCE was calculated as the percentage of SNPs on each gene which were in linkage disequilibrium (LD; i.e. correlated) with SNPs in CHANCE. A "complete" list of SNPs for each gene was identified using HapMap for the CEU and YRI (Yoruba in Ibadan, Nigeria) populations separately (129). Using Tagger in Haploview, SNPs with a MAF above 0.05 and an $r^2 \geq 0.8$ were considered for tagging (143). Using the force include and exclude options, only SNPs which were genotyped in CHANCE were ultimately chosen as tag SNPs. The proportion of HapMap SNPs with a MAF above 0.05 which were tagged by CHANCE SNPs are summarized in table 12 by gene and ancestral population. Variation captured by CHANCE SNPs varied by gene. The most

complete coverage was achieved for ERCC1; 76% and 53% among the CEU and YRI populations, respectively. While comparable coverage was achieved for several other genes, some genes had relatively low proportions of SNPs captured in CHANCE. Therefore, haplotype estimation was not considered in this dissertation.

2.2.3.5 SNP Exclusion Criteria

Of the 129 NER SNPs, variants with weak signal intensity or indistinguishable genotype clusters (14 SNPs) or a MAF less than 0.05 (30 SNPs among whites and 36 SNPs among African Americans) were excluded (table 13). Nearly all excluded SNPs were candidate SNPs selected based on previous literature (i.e. only 5 tag SNPs were excluded for failing genotyping and only 1 tag SNP among whites was excluded for having a MAF < 0.05). Therefore, the analysis included 84 SNPs in 15 NER genes among whites and 79 SNPs in 14 NER genes among African Americans. A summary of inclusion and exclusion criteria for each SNP is provided in table 13.

2.2.4 Assessment of Hardy-Weinberg Equilibrium

As outlined in the US National Institutes of Health online glossary, Hardy-Weinberg equilibrium (HWE) is based on the principle that genotype frequencies are expected to be constant across generations of a population given that the population is 1) sufficiently large, 2) randomly mating, 3) devoid of selection, migration, and mutation (144). If p represents the frequency of one allele in a population and q the frequency of the other allele, as is commonly notated, then one would expect the frequency of genotypes to be described by the following equation: $p^2 + 2pq + q^2 = 1$ (145,146). To assess HWE for each SNP in this dissertation, the predicted frequency of genotypes in the controls was calculated using the preceding equation (145). The predicted frequencies were then compared to the frequency of genotypes observed in the study population using a Pearson's chi-square test (145). It is important to note that HWE was assessed only in controls as they represent the target population. Further, assessment of HWE was conducted separately among

African Americans and whites. Frequencies for 7 SNPs in white controls and 7 SNPs in African American controls were inconsistent with Hardy-Weinberg equilibrium ($p<0.05$); however, since genotype scatter plots showed reasonable clustering none of these SNPs were excluded from analyses (147).

2.2.5 Genetic Model

Previous studies on the association between polymorphisms in NER genes and HNC risk and survival have utilized a variety of genetic models (tables 6) (4,5,8-46). Although no single model has emerged as the standard, the general model appeared to be the most frequently used and was therefore originally considered in this dissertation. The general (or codominant) model considers three exposure categories to estimate two ORs: the odds of HNC for heterozygous individuals and the odds of HNC for individuals homozygous for the variant allele compared to individuals homozygous for the referent allele (146). It was further intended to assess the additive effects of each copy of the variant allele (146). However, a large portion of SNPs had fewer than 5 cases or controls homozygous for the variant allele (~7% among whites and ~33% among African Americans). Therefore, SNPs were ultimately defined using a dominant genetic model, as it was more commonly used in the literature than the recessive model. For the dominant model, the effect of having any copy of the variant allele was assessed. In other words, heterozygous individuals and individuals homozygous for the variant allele were combined and compared to individuals homozygous for the referent allele to produce a single OR (146). The referent allele for both whites and African Americans was assigned to be the major (i.e. more frequent) 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 SNP in African Americans).

2.3 EXPOSURE ASSESSMENT: ENVIRONMENTAL AND BEHAVIORAL FACTORS

2.3.1 Cigarette Smoking

To ascertain self-reported information on cigarette smoking, the CHANCE interview asked several questions on duration and frequency of use. Self-reported cigarette-smoking is generally considered a valid and accurate measure of actual cigarette smoking. A systematic review of studies which compared self-reported cigarette smoking with measured cotinine levels found that the majority of studies reported measurements that differed by less than 10%; specifically, the median difference between reported and measured cigarette smoking was −4.8% for studies based on saliva measurements, −6.2% for studies based on serum, blood, or plasma measurements, and −9.4% for studies based on urine measurements (148). Questions used in CHANCE to ascertain cigarette smoking were based on questionnaires from previous studies of HNC and other cancers (82,135). Exact questions from the CHANCE questionnaire are provided in table 14. Ever cigarette users were defined as smoking at least 100 cigarettes or 5 packs during one's lifetime (149). Frequency was measured in number of cigarettes smoked per day (149). Duration of use was measured in years from initiation to cessation (149). For analysis, frequency, and duration of cigarette smoking were categorized based on previous CHANCE publications (57) and quantity of observations in each strata.

In addition to active cigarette smoking, information on environmental tobacco smoke (ETS) was also ascertained during interviews. Such information included ever/never and duration (years) of exposure in the home or at a workplace, separately (135). For analysis, duration of ETS exposure was categorized similar to active cigarette smoking.

2.3.2 Treatment

First-course treatment information was abstracted from patients' medical records which were obtained from health care providers if patients provided informed consent at the time of the

interview (medical records were obtained for all cases in this dissertation) (82,135). Information included whether the patient received surgery, radiation therapy, and chemotherapy, including types of chemotherapy drugs. Chemotherapy drugs included: carboplatin, paraplatin, cisplatin, 5 FU, taxol, taxotere, docetaxel, paclitaxel, ifosfamide, and other. Information on concurrent treatment and duration of treatment, including start and stop dates, was also abstracted, but were not considered complete (138). Since treatment dates were most frequently missing due to a missing value in the day field (138), individuals having month and year recorded but no day were assigned a day of '15' based on the approximate midpoint of the month (138). However, even after this correction was applied, a sizeable portion of individuals were still missing treatment dates (138). In particular, chemotherapy end dates (e.g., month and/or year) were missing for approximately a quarter of patients treated with chemotherapy (138). Therefore, combinations of treatment were generated from dichotomous variables for surgery, radiation, chemotherapy regardless of timing.

Specifically, treatment was categorized into six mutually exclusive levels: surgery only; radiation only; surgery and radiation; radiation and chemotherapy; surgery, radiation, and chemotherapy; and other (no treatment, chemotherapy only, or surgery and chemotherapy without radiation). Surgery only was used as the referent category because few individuals received no treatment (9 cases, 0.7%). Because even fewer individuals received chemotherapy only or chemotherapy with surgery without radiation (4 cases, 0.3%), these individuals were combined with individuals receiving no treatment into a single category labeled "other treatment." In a separate model, treatment was also defined as ever receiving platinum-based chemotherapy drugs (carboplatin, paraplatin, or cisplatin, N=464) versus never receiving platinum-based chemotherapy drugs (i.e. never receiving chemotherapy, N=754, or only receiving non-platinum based chemotherapy drugs, including 5 FU, taxol, taxotere, docetaxel, paclitaxel, or ifosfamide, N=9).

2.4 OUTCOME ASSESSMENT

2.4.1 Incidence

As previously discussed, incident cases with invasive cancers of the oral cavity, pharynx, and larynx were identified from the North Carolina Central Cancer Registry between January 1, 2002 and February 28, 2006 using rapid identification techniques (57,63,64). Medical records and tumor samples for cases were reviewed by the CHANCE study pathologist, William K. Funkhouser (UNC-Chapel Hill) to verify diagnoses (82,135). Controls were identified through the North Carolina Department of Motor Vehicles records and trained nurses verified with the controls during the interview that he/she had never been diagnosed with HNC (57,63,64)

2.4.2 Mortality

To assess survival, CHANCE was recently linked to the National Death Index (NDI) based on name, social security number, and date of birth to identify deaths through 2009, including date of death, location of death, and cause of death. Recent research indicates that linkage to the NDI with proper information (e.g., social security number, name, and birth date) accurately identifies up to 95% of deceased individuals (150). Analyses primarily considered overall survival (i.e. risk of dying from any cause), but also considered disease-specific survival (i.e. risk of dying from HNC). Disease-specific deaths were defined as those having HNC listed as the primary or secondary cause of death. While misclassification of cause of death may occur in the NDI, it is estimated to be below 7% for all causes of death and below 3% for cancer related deaths (151).

2.5 COVARIATE ASSESSMENT

2.5.1 Interview Variables

2.5.1.1 Demographics

Demographics were self-reported and included: sex (male, female); age (continuous based on date of birth); and race (white, African American, American Indian, Alaskan Native,

Asian/Pacific Islander); education (less than high school, some college, college or more) (57,63,64). Controls were matched to cases based on age, sex, and race (57,63,64). Age was matched and analyzed within categorizes (20-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-80 years of age) (57). For race, only white and African American cases were considered in this analysis due to low frequencies of other minorities in CHANCE. For analysis, education was collapsed into three levels (less than a high school education, a high school education, or a college education).

2.5.1.2 Alcohol Drinking

Alcohol use was self-reported and assessed separately for beer, wine, and hard liquor (57,64). Ever beer drinkers were defined as drinking at least 50 beers or two cases during one's lifetime, ever wine drinkers as drinking wine 20 or more times in one's lifetime, and ever hard liquor drinkers as drinking hard liquor 20 or more times in one's lifetime (57,64). Frequency of each alcohol product was measured in ounces per day and duration of each alcohol product was measured in years from initiation to cessation (57,64). For consideration as a covariate in models, total frequency of alcohol drinking frequency summed across type of alcohol (i.e. ml ethanol per week) was used.

2.5.1.3 Other Tobacco Use

Use of tobacco products were self-reported and assessed separately for cigars, pipes, chewing tobacco, and snuff (57). Ever use for each tobacco product was defined as engaging in the behavior 20 or more times during one's lifetime (57). Frequency of each tobacco product was measured in number of cigars smoked, pipe fulls smoked, times tobacco chewed or times snuff used per day, respectively (57). Duration of use for each product was measured in years from initiation to cessation. For adjustment, a single dichotomous variable for ever using any tobacco product other than cigarettes was assessed.

2.5.1.4 Family History of Cancer

Information on cancer diagnoses among family members (mother, father, siblings, children, and spouse) was self-reported by participants (135,152). This information was condensed into a single variable capturing the total number of first-degree blood relatives with a cancer diagnosis (135,152). Given the limited number of CHANCE participants with a family member who was diagnosed with HNC, a dichotomous variable (yes/no) which enumerates any cancer diagnoses among first degree relatives was considered in models (135,152).

2.5.1.5 Oral Health

Behaviors related to oral health were self-reported and included oral medical conditions (leukoplakia, erythroplakia, ulcers, and sores), dental exams, cavities and tooth loss, brushing and flossing, and mouthwash (63). Based on a previous analysis of oral health variables in CHANCE, which showed no association between tooth loss nor mouthwash use and HNC but strong associations between routine dental visits and tooth mobility and HNC, frequency of dental exams (categorized) was considered as a covariate in models (63).

2.5.2 Tumor Characteristics

Information on stage, grade and location of tumors were abstracted from cases' medical records (135,153). Stage was classified according to TNM measures where T characterizes the size of the tumor, N the spread of the tumor, and M metastasis to other locations (118). These three measures were then collapsed into a single categorized variable, which was included in models, with 4 stages: I, II, III, and IV (note: stage 0 indicates in situ cancers and were therefore not be included in this study) (118). Information on grade was found to be incomplete for many cases and was therefore not considered (135,138). For primary site, HNC was classified according to ICD-03 codes into five categories as has been done in previous studies: oral cavity (N=172; 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 (N=333; C01.9; C02.4; C05.1-

C05.2; C09.0-C09.1; C09.8-C10.4; C10.8-C10.9), hypopharynx (N=55; C12.9-C13.2;C13.8-C13.9); larynx (N= 443; C32.0-C32.3;C32.9), and not otherwise specified (N=224; C02.8-C02.9;C05.8-C05.9;C14.0;C14.2;C14.8) (57,64).

2.5.3 Ancestral Informative Markers (AIMs)

Ancestral informative markers (AIMS) are SNPs which display ancestry-specific genotype frequencies that allow for the estimation of an individual's admixture (154-156). In recent years, AIMS have become widely accepted as a cost-effective way to control for ancestry (154,155). Several validation studies have shown the efficiency of AIMS in predicting and controlling for admixture in logistic regression (154-156). For example, these studies demonstrate that approximately 100 to 200 AIMS accurately estimate the proportion of European ancestry in African American populations, yet suggest that as few as 30 AIMs can sufficiently estimate admixture (154-156).

Since CHANCE is comprised primarily of African Americans and whites, 157 AIMS (table 15) were selected to estimate the proportions of African and European ancestry of each participant (64,157). A total of 12 AIMS failed genotyping procedures and were therefore excluded (table 15) (138). The AIMS were selected and the proportions of African and European ancestry calculated by Dr. Jill Barnholtz-Sloan at Case-Western Reserve University using an algorithm based on differences in allele frequencies between HapMap populations and Fisher's information criterion (FIC) (82,157,158). Since only two ancestral populations were considered, the proportions of European and African ancestry for each individual sum to one and analyses need only include one or the other ancestral variables as a covariate. In this dissertation, analyses were adjusted for proportion African ancestry. In addition, since self-reported race is important when considering the distribution of socially related exposures and confounders, population stratification (i.e. stratification by self-reported race) was also employed.

2.5.4 Assessment of Confounding and Effect Measure Modification

Since this dissertation included 84 different SNPs (i.e., different exposures), it would have been logistically difficult to use empirical methods, such as change in estimate approaches or likelihood ratio tests (159), to determine adjustment sets because one covariate may significantly contribute to the model for one SNP but not another. Therefore, a priori covariate selection was based primarily on directed acyclic graphs (figures 4-7) (160). In addition, the following covariate selection criteria were considered. First, variables used in matching cases and controls, namely age and sex, were included because failure to account for matching variables in models can bias results (159). Although self-reported race was also a matching variable, it was not included in the final model because it is highly correlated with ancestry. Rather, models were stratified by self-reported race and adjusted for ancestry. Second, variables were examined for completeness. Since a large proportion of cases and controls are missing certain diet variables, these variables were not included in models (82,135,153). Third, strength of associations based on previous literature were considered. Since marijuana smoking is weakly associated with HNC in previous studies it was not included in models (110).

Because genetic exposures were based on germline DNA, which would not reflect the influences of behavioral factors such as smoking and drinking, SNP-HNC risk were only adjusted for matching factors (sex and age, including pairwise interactions) and ancestry (continuous percent African ancestry) based on the DAG (figure 4). Cigarette smoking-HNC and ETS-HNC models were adjusted for matching factors (sex and age, including pairwise interactions), education (categorical indicator for less than a high school education, a high school education, or a college education), and frequency of alcohol use (categorical indicator for never drinking alcohol and quartiles of lifetime alcohol consumption in ml/day) (figure 5). ETS ORs were additionally adjusted for duration of cigarette smoking (continuous years), as well as stratified

by ever/never cigarette smoking. Models were not adjusted for use of other tobacco products (cigars, pipes, chewing tobacco, and snuff), family history of cancer, and oral health variables because estimates did not change substantially when these variables were included in models. SNP-cigarette smoking joint effects models were adjusted for age, sex, education, frequency of alcohol use, and ancestry since both behavioral and genetic exposures were being modeled.

For HNC survival, SNP models were again adjusted for matching factors (sex and age, including pairwise interactions) and ancestry (continuous percent African ancestry) based on the DAG (figure 6). Behavioral factors, namely cigarette smoking and alcohol drinking, are not believed to impact germline SNPs. SNP models were not adjusted for tumor characteristics, such as stage, because they were determined to be causal intermediates (e.g., SNPs may impact stage, but stage would not impact SNPs). However, SNP-HNC survival models stratified by stage and tumor location were considered. All treatment models were adjusted for sex, age (5 year categories), race, stage (categorical stage I, II, III, IV), anatomic subsite (oral cavity, oropharynx, hypopharynx, larynx, HNC NOS), education (less than a high school education, a high school education, or a college education), duration of cigarette smoking (years), and frequency of alcohol use (categorical indicator for lifetime alcohol consumption in ml/day) (figure 7). Likewise, SNP-treatment joint effects models were adjusted for sex, age, stage, anatomic site, education, cigarette smoking, alcohol drinking, and ancestry.

2.6 STATISTICAL ANALYSIS

2.6.1 Aim 1: Incidence Models

Unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for SNP and cigarette smoking and HNC risk. As previously described, SNPs were defined using a dominant genetic model and cigarette smoking were considered as ever, frequency and duration. Models of ETS exposure (ever, duration) were also considered as

a supplemental analysis. All models were adjusted for confounders as determined by the DAG and other criteria as described in the covariate assessment section. In addition, since allele frequencies, cigarette consumption and HNC incidence differs by race in the US, models were stratified by self-reported race (white and African American) (56,59,60,129).

Logistic regression is considered the standard for analyzing case-control data as it allows the estimation of risk for a binary outcome while controlling for possible confounders (160). Traditionally conditional logistic regression is used for matched case-control and sparse strata data (159). However, when sample size is large compared to the number of matching strata, such as in CHANCE, unconditional logistic regression provides accurate estimates (159). As discussed previously, though, matching variables should still be included as covariates in unconditional logistic regression to avoid bias (159). Therefore, unconditional logistic regression including matching covariates (represented as indicator variables for the cross-products of the matching factors) was utilized in this dissertation to estimate odds of HNC incidence.

Odds ratios for the joint effects of SNPs in NER genes and cigarette smoking were also estimated using unconditional logistic regression. Interaction between SNPs in NER genes and cigarette smoking were assessed on the additive scale using the interaction contrast ratio (ICR), also known as the relative excess risk due to interaction (RERI), as follows: OR11 - OR01 - OR10 + OR00, where OR11 is the odds ratio among smokers with the variant genotype, OR01 is among smokers with the referent genotype, OR10 is among never smokers with the variant genotype, and OR00 is among never smokers with the referent genotype (which equals 1.0 as it is the referent) (160,161). An ICR of zero indicates no interaction beyond what is expected on the additive scale (160,161). An ICR above zero should be interpreted as a superadditive (or synergistic) effect, while an ICR below zero as a less than subadditive (or antagonistic) effect (160,161). A 95% CI for the ICR was also calculated using the Hosmer and Lemeshow method (161). Although interaction may also be

assessed on the multiplicative scale, the additive scale was used to enhance power as suggested by Weinberg (162). Joint effects were primarily assessed among whites, because low cell counts precluded precise estimation among African Americans. Estimation of joint effects among African Americans was performed for exploratory purposes only. Analyses for aim 1 were completed using the statistical software package SAS (Cary, NC) (163).

2.6.2 Aim 1: Multiple Testing

Multiple testing, also referred to as multiple comparisons, is a concern when conventional statistical significance testing methods are applied to studies which investigate multiple exposure-disease associations (e.g., exploring associations between 84 SNPs and HNC risk) because this may amplify the number of false positive results (160,164-166). As described by Rothman in *Modern Epidemiology*, in a study of 10 exposures and 10 disease outcomes (i.e. 100 associations) one would expect 5 confidence intervals (5%) to not contain the null value by chance alone using the conventional 0.05 alpha level (160). To account for this, this dissertation employed the conservative Bonferroni approach which is widely used. In addition, an innovative hierarchical approach which incorporates dependence of associations (i.e. correlation of SNPs) was also used. For reasons described below, preference was given to results from hierarchical modeling.

2.6.2.1 Bonferroni Method

Bonferroni is the most commonly used method to account for multiple testing. It is employed by dividing the chosen alpha level, customarily 0.05, by the number of associations being tested (160). For this dissertation, the Bonferroni corrected alpha level was set at 0.0006 based on the conventional 0.05 alpha level divided by 84 tests (i.e. one for each SNP) among whites and 79 tests among African Americans. The major advantage of the Bonferroni correction is its accessibility, both in terms of ease and uptake (166). The major disadvantages of Bonferroni is that it ignores

correlation of tests, which occurs among SNPs, and produces overly conservative confidence intervals for individual estimates which may fail to highlight true associations (160,164-166).

2.6.2.2 Hierarchical Regression

Hierarchical regression incorporates multiple levels or stages of data into a single model (164,165,167,168). For this reason, it is also commonly referred to as multilevel regression. One level of data is often defined by individual observations, while a higher level represents natural aggregates or clusters of observations (164,165,167,168). In the context of genetics, SNPs on the same gene are more likely to be inherited (e.g., if in linkage disequilibrium) and share function than SNPs on different genes (166). Likewise, genes within the same pathway are related with regard to function (164,165,168). Therefore models which incorporate this clustering of data within a hierarchical structure provide more accurate and plausible estimates (164). Since this dissertation is concerned with only one pathway, NER, hierarchical logistic regression was used to model the effects of individual SNPs while incorporating a SNP-gene matrix to account for clustering of SNP data by gene. The model is described as follows (164,165,167):

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

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 (164,165).

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

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 (164,165).

To create the SNP-gene matrix (i.e. Z_j) required for this model, SNPs are assigned a 'one' for the gene on which they are located and a 'zero' for all other genes (164,165). Since SNPs are located on only one gene, each SNP (i.e. each row) only contained one 'one.' However, since genes contain

many SNPs, each gene (i.e. each column) may contain several 'ones.' See table 16 for an example of part of this matrix. To avoid over-parameterization by modeling one large SNP-gene matrix (ie 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. Since SNPs on the same gene were included in the same model, one SNP from pairs of extremely correlated SNPs was excluded (rho>0.98; 11 SNPs in whites and 5 SNPs in African Americans).

Using first level and second level (i.e. SNP-gene matrix; Z_j) data, hierarchal modeling addresses non-independence of tests. In addition, hierarchical regression allows shrinking the error term towards a prior through controlling its variance (τ^2) (164,165,167). In other words, using a Bayesian approach, the posterior distribution of the error becomes the average of the prior distribution and the maximum likelihood distribution (167). Therefore, stronger priors for the variance (i.e. smaller values of τ^2) will invoke a greater influence on the posterior estimate of the error (167). In this dissertation, a semi-Bayesian approach was used to set τ^2 to 0.05 as this corresponded with the most plausible range of expected ORs for the association between SNPs in NER genes and HNC based on previous literature (i.e. 0.6 to 1.6) (165).

Cigarette-SNP joint effects were modeled using three disjoint indicator variables for 1) individuals who smoked but did not have the variant genotype, 2) individuals who did not smoke but had the variant genotype, and 3) individuals who smoked and had the variant genotype (165). As described in Hung et al. (165), hierarchical models included a 3x2 gene-environment matrix to account for clustering of the disjoint indicator variables by single SNP and cigarette effects (see table 17 for an example). Models with a larger gene-environment matrix to account for all SNPs on the same gene were explored, but found to be over-parameterized. A τ^2 of 0.35 was used for joint effect models since this corresponded to expected ORs between approximately 0.3 and 3.0 for each

indicator variable (165). The GLIMMIX procedure in SAS (Cary, NC) was used for all hierarchical models (163,164,169).

Use of hierarchical modeling is becoming more common in the epidemiologic literature. Witte, Carmichael, and colleagues have championed its use in exploring the effect of nutritional exposures on neural tube defects and breast cancer (164,170). Likewise, Hung and colleagues has published several studies using hierarchical modeling to estimate the effect of genetic exposures on bladder cancer and lung cancer (165,168). Of particular interest, a recent paper by Hung et al. (2007) utilized hierarchical regression via the GLIMMIX macro to estimate the effects of various DNA repair genes (which were defined by one or two SNPs in the gene) on lung cancer incidence in a large case-control study (168). In this analysis, first level data were based on genes and second level data on a gene-pathway matrix (168). Comparing hierarchical and conventional logistic regression models, Hung et al. (168) found 5 genes associated with lung cancer using conventional logistic regression with a single gene in each regression, 4 genes associated with lung cancer using conventional logistic regression with all genes in a single regression, and 3 genes associated with lung cancer using hierarchical logistic regression (whether using empirical or semi-Bayes, with or without a covariate for sequence conservation of the variants) based on a 0.05 alpha level. As concluded by Hung et al in this study, compared to the conventional models, the hierarchical models improved the precision of estimates (i.e. narrower intervals), mitigated false positives by shrinking estimates toward a prior mean, and allowed for pathway estimation (168). Therefore, it is believed that hierarchical modeling was a valuable tool to account for multiple comparisons and more accurately estimate SNP effects on HNC incidence in this dissertation.

2.6.3 Aim 2: Survival Models

Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% CIs for SNP and cigarette smoking and HNC risk. As previously described, SNPs were defined using a

dominant genetic model and treatment was defined as combinations of dichotomous variables for surgery, radiation, and chemotherapy (irrespective of timing). Models of platinum-based chemotherapy (yes/no) were also considered. All models were adjusted for confounders as determined by the DAG and other criteria as described in the covariate assessment section. In addition, since allele frequencies and survival rates differ by race in the US, models were stratified by self-reported race (white and African American) (59-61,129).

Joint effects of SNPs and treatment (combinations of surgery, chemotherapy, and surgery) were also estimated using Cox proportional hazard models. In addition, joint effects of SNPs and platinum-based chemotherapy (yes/no) were assessed in a separate model. Like aim 1, interactions were assessed on the additive scale, only calculating the RERI using HRs instead of ORs, and considered primarily among whites because low cell counts precluded reliable precise estimation among African Americans.

Cox proportional hazards modeling have been frequently used in previous literature on SNPs in NER genes, treatment, and HNC survival (table 9) (7,47-55). Although other survival models are available and can be useful in analyzing survival data, these parametric models often have stringent assumptions regarding the distribution and function of the hazard rate (171,172). As examples, consider the following accelerated failure time models: under the exponential distribution it is assumed that the hazard rates are constant, under the Weibull distribution it is assumed that the hazard rates smoothly increase or decrease, and under the log-normal, generalized gamma, and log-logistic distributions, proportional hazards modeling cannot be utilized (171,172). In contrast, Cox proportional hazards models are semi-parametric in that no assumptions about the distribution of the baseline hazard is required, but it is assumed that the hazard is expressed as a function of covariates (171,172). Further, Cox proportional models fit non-constant hazards (171). However, it is assumed that the hazard functions for each group

(e.g., the hazard function for each genotype) are proportional (171). This assumption was checked by examining adjusted log negative log plots by treatment/genotype and assessing the significance of including an interaction term for treatment/genotype and time in models (171,172). Evidence of non-proportional hazards (i.e. log plots indicated a violation of the proportional hazards assumption and interaction terms with time were significant, $p<0.05$) was noted for 4 SNPs in whites (rs3731068, rs744154, rs3136085, rs3136172) and 3 SNPs in African Americans (rs4150360, rs2020955, rs13181). However, because p-values for the AFT models were similar to those obtained from Cox models (i.e. the same set of significant SNP-HNC survival associations resulted from both approaches), results from the Cox models without an interaction term between SNPs and time are presented for simplicity.

Absolute differences in HNC survival by genotype and treatment were also assessed via Kaplan-Meier plots (171). Kaplan-Meier curves were constructed by graphing time on the x-axis and the cumulative survival on the y-axis (171). In this dissertation, time was measured in days and cumulative survival was calculated as the percent of cases alive at each time point (171). Log rank tests were used to assess differences in survival (171).

For overall survival models, follow-up started at date of diagnosis for all cases and ended at date of death for individuals who died or censoring on December 31, 2009 for individuals who were still alive. For HNC disease-specific survival models, follow-up started at date of diagnosis for all cases and ended at date of death for individuals who died of HNC or censoring at date of death for individuals who died from other causes or December 31, 2009 for individuals who were still alive.

For survival analyses, a Bonferroni corrected 0.0006 alpha level of significance (based on a 0.05 alpha divided by 84 SNPs among whites and 79 SNPs among African Americans) was used to account for multiple comparisons. The GLIMMIX procedure for hierarchical modeling is not designed

for survival analyses on a continuous time scale so hierarchal models were not considered for aim 2 (173). Analyses for aim 2 were completed using the statistical software SAS (Cary, NC) (163).

2.7 POWER

2.7.1 Aim 1: Incidence Models

2.7.1.1 Power Calculations

To calculate the power in CHANCE to detect associations between SNPs in NER genes and HNC incidence, as well as the joint effects of SNPs and cigarette smoking, I used the National Cancer Institute's Power program (174,175). For these calculations alpha was set at 0.05 and the incidence of HNC in the general population was assumed to be 0.0001 based on NCI and ACS estimates (1,59,60). The overall sample size was 2552 with a case-control ratio of 1.08 (1,325 controls to 1,227 cases) for reasons summarized in figures 2 and 3. For race-specific power calculations, the overall sample sizes and case-control ratios were 1996 and 1.16 for whites and 556 and 0.82 for African Americans. The prevalence of exposure (i.e. frequency of the risk genotype) was varied between 0.10 and 0.50 based on the minor allele frequencies for SNPs in NER genes as determined by HapMap (table 12) (129). The effect estimate (i.e. OR) was also varied between 1.05 and 2.00 based on previous literature which indicated weakly to moderately elevated risks (or conversely weakly to moderately reduced risks with ORs between 0.50 to 0.95) (4,5,8-46). For joint effects, the prevalence and effect estimate (i.e. OR) for cigarette smoking among the overall study population was set at 0.62 and 2.13, respectively, based on a preliminary analysis by Stingone et al. prior to publication (57,176). For race-specific joint effect power calculations, preliminary estimates of prevalence and ORs for cigarette smoking were 0.61 and 1.83, respectively, for whites and 0.62 and 4.00 (which is a dampened estimate of the preliminary OR of 13.5 for African Americans in CHANCE), respectively, for African Americans (57,176). Joint effects were considered on the

additive scale as suggested by Weinberg (162) and gamma (excess OR for interaction) was set at the default value of 2.0 (174,175).

2.7.1.2 Power Results

Figure 8a displays the resulting trends in power to detect associations between SNPs and HNC incidence. If the frequency of the risk genotype is 10%, then CHANCE achieves 80% power to detect an OR of approximately 1.40 or higher. If the frequency of the risk genotype is 50%, then CHANCE achieves 80% power to detect an OR of approximately 1.20 or higher. Figures 8b,c display the power to detect various ORs for SNPs among whites and African Americans separately. Among whites, CHANCE achieves 80% power to detect an OR of approximately 1.50 or higher if the frequency of the risk genotype is 10% and an OR of approximately 1.30 or higher if the frequency is 50%. Among African Americans, the study has 80% power to detect an OR of approximately 1.65 or higher if the frequency is 50%.

Figures 9a shows the power to detect joint effects of SNPs and cigarette smoking on HNC incidence on the additive scale among the overall study population. If the frequency of the risk genotype is 20% and the OR for the risk genotype is approximately 1.45 or higher, then CHANCE achieves approximately 80% power to detect an excess OR for interaction of 2.0. If the frequency of the risk genotype is 50% and OR for the risk genotype is approximately 1.25 or higher, then CHANCE achieves approximately 80% power to detect an excess OR for interaction of 2.0. Figure 9b,c show the power to detect joint effects on the additive scale among whites and African Americans separately. For whites, CHANCE achieves 80% power when the prevalence of the risk genotype is at minimum 0.30 and the OR for the risk genotype is at minimum 1.75. For African Americans, CHANCE achieves only 62.4% power under the same conditions.

CHANCE is one of the largest case-control studies to date to estimate the effects of SNPs in NER genes, including joint effects with cigarette smoking, on HNC risk. Based on the power calculations and results just described, it is believed that this dissertation has sufficient power to achieve aim 1. Although power is lower among African Americans, CHANCE will only be the second study to date to provide an African American specific estimate for the effects of SNPs in NER genes on HNC incidence, and will include more African Americans than the previous study. Therefore race-specific analyses are warranted for main effect analyses. For analysis of gene environment interactions, CHANCE has sufficient power in the overall study populations, but questionable power in the race-stratified populations. Therefore, analyses of joint effects stratified by race were primarily considered in whites, and for exploratory purposes only in African Americans.

2.7.2 Aim 2: Survival Models

2.7.2.1 Power Calculations

To calculate the power of log rank tests to detect statistically significant differences in HNC survival by genotype and treatment status (i.e. significant hazard ratios), the Lakatos normal approximation methods in SAS 9.2 (Cary, NC) were used (163,177). For these calculations alpha was specified as 0.05. The overall sample size was 1,227 cases, including 922 white cases and 305 African American cases. Since follow-up begins at the date of diagnosis for cases, accrual time was set to zero. Survival estimates were based on National Cancer Institute (NCI) Surveillance and Epidemiology and End Results (SEER) survival rates from 1988-2007 for cancers of the oral cavity and pharynx (table 3) respectively (61,62). Overall 3- and 5-year survival rates were approximately 65% and 58%, respectively (61,62). Among whites, 3- and 5-year survival rates were approximately 67% and 60% , respectively, and among African Americans 3- and 5-year survival rates were approximately 45% and 38%, respectively (61,62). For disease-specific

survival rates, it was assumed that survival rates would be slightly higher than overall survival rates; 75% for 3-year 70% for 5-year survival. For all analyses, loss to follow-up was assumed to be 5% based on research indicating that the NDI accurately identifies up to 95% of deceased individuals (150). The prevalence of exposure (i.e. frequency of the risk genotype) was varied between 0.10 and 0.50 based on the minor allele frequencies for SNPs in NER genes as determined by HapMap (table 12) (129). The effect estimate (i.e. HR) was also varied between 1.05 and 2.00 based on previous literature which indicated weakly to moderately elevated hazards (or conversely weakly to moderately reduced hazards with HRs between 0.50 and 0.95) (table 10) (7,47-55). To estimate the power to detect joint effects of NER genes and treatment on HNC, power calculations for overall survival were stratified by treatment type. Therefore, all parameters (i.e. accrual time, survival rates, and loss to follow-up) remained the same, while only sample size varied. In CHANCE, 690 cases received surgery, 945 cases received radiation, and 473 cases received chemotherapy.

2.7.2.2 Power Results

Figure 10a,b display the resulting trends in power to detect overall HRs for SNPs and HNC survival during various follow-up periods in CHANCE. For all cases, CHANCE achieves approximately 80% power to detect a HR of approximately 1.55 or greater for a risk genotype prevalence of 0.10 and 1.25 or greater for a risk genotype prevalence of 0.50 during 3-year and 5-year follow-up. For disease-specific survival (data not shown), CHANCE achieves 80% power to detect a HR of 1.70 for a risk genotype prevalence of 0.10 and 1.35 for a risk genotype prevalence of 0.50 during 3-year and 5-year follow-up. Figure10c,d display the achieved power to detect HRs for polymorphisms in NER genes and HNSCC survival among whites and African Americans separately. For white cases, CHANCE achieves 80% power to detect a HR of 1.70 for a risk genotype prevalence of 0.10 and 1.35 for a risk genotype prevalence of 0.50 during 3-year

and 5-year follow-up (only 3-year shown). For African American cases, CHANCE achieves 80% power to detect a HR of approximately 2.10 for a risk genotype prevalence of 0.10 and 1.50 for a risk genotype prevalence of 0.50 during 3-year and 5-year follow-up (only 3-year shown).

Figure 11 displays the power achieved in each treatment group in CHANCE. Among cases who underwent surgery, CHANCE achieves 80% power to detect a HR of approximately 1.85 or greater for a risk genotype prevalence of 0.10 and 1.45 or greater for a risk genotype prevalence of 0.50 during 3-year and 5-year follow-up. Among cases who received radiation treatment, CHANCE achieves 80% power to detect a HR of approximately 1.65 or greater for a risk genotype prevalence of 0.10 and 1.35 or greater for a risk genotype prevalence of 0.50 during 3-year and 5-year follow-up. Among cases who received chemotherapy, CHANCE achieves 80% power to detect a HR of approximately 2.10 or greater for a risk genotype prevalence of 0.10 and 1.55 or greater for a risk genotype prevalence of 0.50 during 3-year and 5-year follow-up.

CHANCE is the largest study to date to estimate the effects of SNPs in NER genes, including joint effects with treatment, on HNC survival. As demonstrated in figure 10 this dissertation has adequate power to detect an association over a range of HRs among all cases, as well as among white and African American cases separately (aim 2). Although power to detect associations is lower among African Americans and among cases treated with chemotherapy, it still appears sufficient. Further, this analysis is the first to estimate HRs for SNPs in NER genes and HNC survival among African Americans only. Power to detect joint effects of NER genes and treatment stratified by race were not conducted, but are believed to have questionable power. Therefore, analyses of joint effects stratified by race were primarily considered in whites, and for exploratory purposes only in African Americans.

2.8 SUMMARY OF METHODS

2.8.1 Limitations

As with any research, some analyses and interpretations proposed in this disstertion were limited. First, it should be noted that not all genes in the NER pathway were included in this dissertation. Although some accessory NER genes which code for protein subunits of the TFIIH complex were not included, namely *GTF2H1, GTF2H2, GTF2H3, GTF2H4, GTF2H5 (TTDA),* and *MNAT1 (MAT1)*, several SNPs in all of the core NER genes were analyzed (123). Second, a combination of candidate and tag SNPs were selected for this dissertation. Candidate SNPs include polymorphisms which have been reported in previous studies or have presumed functional impact. Tag SNPs were based on a previous HNC case-control study conducted at MD Anderson which utlized only the CEU population in NIEHS-EGP and HapMap databases (129,139,140). Therefore, the amount of variation captured across some genes was limited, especially among African Americans. The percentage of SNPs on each gene which were in LD with SNPs in CHANCE is reported in table 12. As a result of low coverage across some genes and ancestral populations, haplotype estimation was not conducted in this dissertation.

With regard to treatment information, information on yes/no receiving surgery, radiation therapy, and chemotherapy are considered complete for this dissertation. Information on start and stop dates for treatments were more frequently missing and therefore not considered. With regard to potential covariates, several studies have shown strong associations between human pappilomavirus (HPV) and HNC incidence and survival (78,103). However, HPV status of cases and controls in CHANCE has not yet been assayed and was therefore not considered as a covariate in analyses for this dissertation. Also with regard to covariates, survival analyses were adjusted for behaviors (e.g. cigarette smoking) prior to diagnosies rather than post-diagnsosis. Although post-diagnosis behaviors among cases in CHANCE were collected

through a follow-up study, such information was often incomplete (135,153). Further, despite our large sample size, exploration of gene-environment interactions among African Americans was limited. Some HNC tumor site-specific estimates were also limited by sparse numbers. Finally, I did not have access to information on tumor recurrent disease and were therefore unable to consider disease-free or relapse-free survival.

2.8.2 Strengths

This dissertation offers several advantages to previous studies. Strengths include a large, racially diverse population-based study; assessment of numerous SNPs across core NER genes; correction for multiple comparisons and correlated exposures using traditional and hierarchical approaches; and consideration of interactions with genetic and environmental (e.g., behavioral and treatment) factors.

This dissertation has the third largest study population to date (1,227 cases and 1,325 controls). However, the two larger studies included esophageal cancer cases and considered only 5 polymorphisms in ERCC1 and ERCC4 among an all Caucasian study population (11,14). With 305 African American cases and 251 African American controls, this dissertation encompasses a racially diverse population. No previous studies have estimated effects of polymorphisms in NER genes on HNC survival among African Americans, and only one smaller study (N=119 African Americans) has reported effects with regard to HNC and esophageal cancer incidence (15). As demonstrated in the statistical power section, this study has adequate power to detect main effect associations in the overall and race-stratified populations.

In addition to being one of the largest study, this dissertation considered 84 SNPs in 15 NER genes which, despite shortcomings to completely tag variation, was the most comprehensive evaluation of NER genes and HNC incidence and survival to date. Further, to my knowledge, this was the first study on NER genes and HNC incidence to use both Bonferroni

corrections and hierarchical regression methods to account not only for multiple testing, but correlated exposures. Most previous studies have not corrected for multiple or correlated comparisons when testing associations between various polymorphisms in NER genes and HNC outcomes. Of those that have, one study utilized the Bonferroni method (4), two studies employed the false discovery rate (31,55), and four used an assortment of other methods, mainly the false positive report probability (18,23,24,30). One other study used a full Bayesian approach to weight variables based on known function (i.e. higher weights for variables with stronger associations with HNC) (19); however, this approach does not appear to utilize a matrix of SNP-gene relationships. Therefore, it is believed that the approach used in this dissertation will improve the accuracy of estimates and better inform conclusions regarding the effect of polymorphisms in NER genes, including joint effects with tobacco and treatment, on HNC incidence and survival.

Finally, given the prior knowledge linking tobacco, ionizing radiation, and platinum-containing chemotherapies to the formation of bulky DNA adducts, estimation of interactions between polymorphisms in NER genes and tobacco and treatment is an imperative contribution of this dissertation. Characterizing such gene-environment interactions clarifies the etiology of HNC and can identify avenues for more tailored and effective interventions.

Table 11. Characteristics of the Overall CHANCE Study Population and Participants with Genotype Data Included in Dissertation

	Overall CHANCE Study Population*				Dissertation Study Population**			
							Controls	
Characterisitc	Cases N	%	Controls N	%	Cases N	%	N	%
Total	1289		1361		1227		1325	
Sex								
Male	984	76.3	945	69.4	938	76.4	924	69.7
Female	305	23.7	416	30.6	289	23.6	401	30.3
Race/Ethnicity								
White	959	74.4	1100	80.8	922	75.1	1074	81.1
African American	330	25.6	261	19.2	305	24.9	251	18.9
Age								
20-49	253	19.6	156	11.5	239	19.5	151	11.4
50-54	200	15.5	160	11.8	189	15.4	156	11.8
55-59	216	16.8	206	15.1	207	16.9	199	15.0
60-64	217	16.8	205	15.1	205	16.7	202	15.2
65-69	174	13.5	241	17.7	168	13.7	237	17.9
70-74	141	10.9	227	16.7	135	11.0	216	16.3
75-80	88	6.8	166	12.2	84	6.8	164	12.4
Education								
High school or less	798	61.9	540	39.7	754	61.5	520	39.2
Some college	307	23.8	406	29.8	294	24.0	395	29.8
College or more	184	14.3	415	30.5	179	14.6	410	30.9

*The overall CHANCE study population represents interviewed participants (N=1389 cases and 1396 controls)without proxy interviews (N=52 cases and 17 controls), individuals of other race (N=26 cases and 18 controls), or lip cancer (N=21 cases), or gender discrepancies (N=1 case)

**The dissertation study population represents participants with successfully genotyped samples (N=1274 cases and 1343 controls) without individuals of other race (N=26 cases and 18 controls) or lip cancer (N=21 cases)

Table 12. Single nucleotide polymorphisms in nucleotide excision repair genes included in the Carolina Head and Neck Cancer Study (4,5,9,18,28,40,129,178-198)

						Minor Allele Frequency (MAF)			Selection Method			Variation Captured by CHANCE SNPs*			
Gene	SNP	Chromosome and Position		Major Allele	Minor Allele	CEU	YRI	ASW	Investigator (Study)	Reason for Selection	Articles for Candidate SNPs		CEU		YRI
ERCC3 (XPB)	rs4150496	2	127,745,973	C	T	0.336	0.163	0.307	Wei (MD Anderson HNC)	Tag		X	60% (23/38)	X	26% (13/49)
	rs4150459	2	127,753,948	C	T	0.062	0.218	0.158	Wei (MD Anderson HNC)	Tag		X		X	
	rs1011019	2	127,754,030	G	A	0.270	0.272	0.237	Wei (MD Anderson HNC)	Tag		X		X	
	rs4150434	2	127,758,570	C	T	0.300	0.087	--	Wei (MD Anderson HNC)	Tag		X		X	
	rs4150416	2	127,763,018	T	G	0.283	0.542	--	Wei (MD Anderson HNC)	Tag					
	rs4150407	2	127,766,101	T	C	0.429	0.432	0.491	Wei (MD Anderson HNC)	Tag		X		X	
	rs4150403	2	127,766,538	C	T	0.120	0.000	0.009	Wei (MD Anderson HNC)	Tag		X			
	rs4150402	2	127,766,604	C	T	0.270	0.272	0.237	Wei (MD Anderson HNC)	Tag		X		X	
XPC	rs2228001	3	14,162,450	T	G	0.407	0.276	0.316	Wei (MD Anderson HNC), Millikan (CBCS)	Tag		X	72% (32/44)	X	24% (14/58)
	rs2279017†	3	14,165,238	G	T	0.403	0.306	0.333	Millikan (CBCS)		Joshi, 2009	X		X	
	rs3731143	3	14,172,547	A	G	0.071	0.000	0.009	Wei (MD Anderson HNC)	Tag		X			
	rs2228000	3	14,174,889	G	A	0.288	0.031	0.175	Wei (MD Anderson HNC), Millikan (CBCS)	Tag		X		X	
	rs3731124	3	14,176,404	T	G	0.203	0.097	0.061	Wei (MD Anderson HNC), Millikan (CBCS)	Tag		X		X	
	rs13099160	3	14,177,803	A	G	0.062	0.000	--	Wei (MD Anderson HNC)	Tag		X			
	rs35629274	3	14,181,357	--	--	--	--	--	Millikan (CBCS)	Function, F287C					
	rs3731093	3	14,185,043	A	G	0.080	0.065	0.061	Wei (MD Anderson HNC)	Tag		X		X	
	rs3731089	3	14,185,666	G	A	0.085	0.067	--	Wei (MD Anderson HNC)	Tag					
	rs2733537	3	14,186,105	A	G	0.367	0.105	0.246	Wei (MD Anderson HNC)	Tag		X		X	
	rs3731068	3	14,188,760	G	T	0.164	0.000	0.018	Wei (MD Anderson HNC)	Tag		X			
	rs2607755	3	14,189,037	T	C	0.492	0.358	--	Wei (MD Anderson HNC)	Tag		X		X	
	rs3731062	3	14,189,528	G	A	0.022	0.000	0.018	Millikan (CBCS)	Function, L48F					
	rs1902658	3	14,190,161	A	G	0.417	0.467	--	Wei (MD Anderson HNC)	Tag					
	rs3731055	3	14,195,443	C	T	0.004	0.003	--	Millikan (CBCS)	Candidate	Bai, 2007				
ERCC8	rs4647153	5	60,205,962	A	G	0.000	0.016	0.016	Millikan (CBCS)	Function, 3'UTR			18% (12/65)	X	19% (12/61)
	rs3117	5	60,206,094	A	G	0.447	0.315	0.315	Millikan (CBCS)	Function, 3'UTR		X		X	
	rs158922†	5	60,276,743	C	T	0.392	0.305	--	Millikan (CBCS)	Function, upstream					
CDK7	rs2972388	5	68,567,009	A	G	0.392	0.175	--	Millikan (CBCS)	Candidate	Jeon, 2010		0%(0/13)		0%(0/14)
	rs34584424	5	68,604,614	C	T	--	--	--	Millikan (CBCS)	Function, T28 M					
CCNH	rs2266690†	5	86,731,030	A	G	0.195	0.048	--	Millikan (CBCS)	Function, V270A		X	55% (10/18)	X	14% (4/27)
	rs2266691	5	86,739,661	T	C	0.000	0.095	0.088	Millikan (CBCS)	Function, K138R				X	
	rs2266692	5	86,744,396	C	A	0.013	0.105	0.105	Millikan (CBCS)	Function, 5' UTR		X		X	
	rs1807895	5	86,744,593	A	C	0.008	0.000	--	Millikan (CBCS)	Fucntional change, upstream		X			

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†SNPs which failed genotyping (i.e. weak signal intensity or in distinguishable genotype clusters)

Table 12 cont. Single nucleotide polymorphisms in nucleotide excision repair genes included in the Carolina Head and Neck Cancer Study

						Minor Allele Frequency (MAF)			Selection Method			Variation Captured by CHANCE SNPs*			
Gene	SNP	Chromosome and Position		Major Allele	Minor Allele	CEU	YRI	ASW	Investigator (Study)	Reason for Selection	Reason for Selection		CEU		YRI
XPA	rs3176757	9	99,476,879	G	A	0.252	0.109	0.167	Wei (MD Anderson HNC)	Tag		X	55% (10/18)	X	18% (11/59)
	rs3176753	9	99,477,264	A	G	0.004	0.160	0.149	Millikan (CBCS)	Function, 3'UTR				X	
	rs3176750	9	99,477,610	G	C	0.000	0.041	0.018	Millikan (CBCS)	Function L252V				X	
	rs3176748	9	99,478,165	T	C	0.354	0.032	--	Wei (MD Anderson HNC)	Tag		X		X	
	rs2808667	9	99,482,627	C	T	0.081	0.007	--	Wei (MD Anderson HNC)	Tag		X			
	rs2805835	9	99,484,772	C	G	0.100	0.008	--	Wei (MD Anderson HNC)	Tag		X		X	
	rs3176689	9	99,487,617	T	A	0.092	0.000	--	Wei (MD Anderson HNC)	Tag		X			
	rs3176683	9	99,488,438	A	G	0.106	0.000	0.018	Wei (MD Anderson HNC)	Tag		X			
	rs2808668†	9	99,492,256	T	C	0.423	0.325	--	Wei (MD Anderson HNC)	Tag		X		X	
	rs3176658	9	99,493,684	G	A	0.115	0.143	--	Wei (MD Anderson HNC)	Tag		X		X	
	rs1800975	9	99,499,399	C	T	0.381	0.245	0.259	Millikan (CBCS)	Function, upstream	Abassi, 2009; An, 2007; Hall, 2007; Bau, 2007; Sugimara, 2005; Han, 2010; Qian, 2011; Pan, 2009; Joshi, 2009; Hung, 2008; Wu, 2008; Lin, 2008; Wu, 2006	X		X	
RAD23B	rs1805330	9	109,124,082	C	T	0.098	0.197	0.149	Millikan (CBCS)	Funcation, splice		X	10% (9/82)	X	10% (11/101)
	rs1805329	9	109,124,149	C	T	0.154	0.000	--	Millikan (CBCS)	Function, Ala249Val	McKean, 2009; Pan, 2009; Wu, 2008; Lin, 2008; Change, 2008; Zhang, 2008; Mechanic, 2006; Hill, 2006; Wu, 2006	X			
ERCC6	rs4253230	10	50,337,027	G	A	0.000	0.099	0.035	Millikan (CBCS)	Function, !1441I		X	34% (34/99)	X	27% (38/136)
	rs2228529	10	50,337,111	T	C	0.204	0.122	0.096	Millikan (CBCS)	Function Q1413R	Han, 2009	X		X	
	rs2229761	10	50,339,465	C	G	0.000	0.024	--	Millikan (CBCS)	Function, V1308L				X	
	rs2228527	10	50,348,375	T	C	0.204	0.153	0.114	Millikan (CBCS)	Function Arg1213Gly	Abassi, 2009; Mechanic, 2006	X		X	
	rs2228526†	10	50,348,723	T	C	0.204	0.136	0.107	Millikan (CBCS)	Function, M1097V	Rajaraman, 2008; Ma, 2009; Pan, 2009; Wu, 2008; Lin, 2008; Wu, 2006; Han, 2009	X		X	
	rs4253132	10	50,371,162	A	G	0.133	0.329	0.316	Millikan (CBCS)	Function, splice		X		X	
	rs4253072	10	50,394,022	T	C	0.016	0.038	0.009	Millikan (CBCS)	Function, R382K				X	
	rs4253047†	10	50,402,145	C	T	0.027	0.000	--	Millikan (CBCS)	Function, 5' UTR		X		X	
	rs2228528	10	50,402,286	C	T	0.161	0.177	0.211	Millikan (CBCS)	Function, G399D		X		X	
DDB2 (XPE)	rs2029298	11	47,191,294	T	C	0.327	0.378	0.535	Wei (MD Anderson HNC)	Tag			70% (17/24)		36% (12/33)
	rs4647709	11	47,193,935	C	T	0.085	0.000	0.080	Wei (MD Anderson HNC)	Tag		X			
	rs2291120	11	47,194,256	T	C	0.128	0.003	0.018	Wei (MD Anderson HNC)	Tag		X			
	rs1685404	11	47,200,241	G	C	0.323	0.221	--	Wei (MD Anderson HNC)	Tag		X		X	
	rs2957873	11	47,205,870	A	G	0.181	0.510	0.386	Wei (MD Anderson HNC)	Tag		X		X	
	rs326224	11	47,212,174	G	A	0.083	0.525	--	Wei (MD Anderson HNC)	Tag					
	rs2306353	11	47,213,284	C	T	0.092	--	--	Wei (MD Anderson HNC)	Tag		X			
	rs326222	11	47,216,244	C	T	0.301	0.646	0.623	Wei (MD Anderson HNC)	Tag		X			
	rs901746	11	47,216,895	A	G	0.301	0.605	0.588	Wei (MD Anderson HNC)	Tag		X		X	
	rs11988†	11	47,217,836	G	A	0.372	0.054	0.158	Wei (MD Anderson HNC)	Tag		X		X	

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Table 12 cont. Single nucleotide polymorphisms in nucleotide excision repair genes included in the Carolina Head and Neck Cancer Study

						Minor Allele Frequency (MAF)			Selection Method			Variation Captured by CHANCE SNPs*			
Gene	SNP	Chromosome and Position		Major Allele	Minor Allele	CEU	YRI	ASW	Investigator (Study)	Reason for Selection	Reason for Selection	CEU		YRI	
ERCC5 (XPG)	rs2296147	13	102,296,376	T	C	0.442	0.156	0.254	Wei (MD Anderson HNC), Millikan (CBCS)	Tag		X	70% (40/57)	X	31% (33/104)
	rs2296148	13	102,296,546	C	T	0.046	--	--	Millikan (CBCS)		Hussain, 2009	X			
	rs4771436	13	102,300,021	T	G	0.214	0.249	0.158	Wei (MD Anderson HNC)	Tag		X		X	
	rs1047768	13	102,302,518	C	T	0.425	0.274	0.333	Olshan (CHANCE)	Candidate	Abassi, 2009; Hussain, 2009; Kiyohara, 2007	X		X	
	rs2020915	13	102,302,651	G	A	0.000	0.323	--	Millikan (CBCS)	Function, splice				X	
	rs4987063†	13	102,304,691	G	A	0	0.067	--	Millikan (CBCS)	Function, V148I					
	rs4150313	13	102,311,952	A	G	0.000	0.122	0.116	Millikan (CBCS)	Function, Q259R				X	
	rs2227869	13	102,313,086	G	C	0.053	0.044	0.035	Wei (MD Anderson HNC), Millikan (CBCS)	Tag		X		X	
	rs3818356	13	102,317,471	C	T	0.225	0.142	--	Wei (MD Anderson HNC)	Tag					
	rs4150351	13	102,320,968	A	C	0.177	0.000	0.009	Wei (MD Anderson HNC)	Tag		X			
	rs4150355	13	102,321,313	C	T	0.345	0.139	0.196	Wei (MD Anderson HNC)	Tag		X		X	
	rs4150360	13	102,322,763	T	C	0.478	0.789	0.254	Millikan (CBCS)	Function, L968F	Chang, 2006			X	
	rs4150383	13	102,325,231	G	A	0.168	0.087	0.061	Wei (MD Anderson HNC)	Tag		X		X	
	rs4150386	13	102,325,529	A	C	0.123	0.000	--	Wei (MD Anderson HNC)	Tag		X			
	rs17655	13	102,326,003	G	C	0.277	0.460	--	Wei (MD Anderson HNC), Millikan (CBCS)	Tag		X		X	
	rs873601	13	102,326,338	A	G	0.308	0.714	0.357	Wei (MD Anderson HNC)	Tag		X		X	
	rs4150393	13	102,326,659	A	G	0.102	0.016	--	Wei (MD Anderson HNC)	Tag		X		X	
	rs876430	13	102,327,285	G	A	0.310	0.687	0.377	Wei (MD Anderson HNC)	Tag		X		X	
	rs1051677	13	216,778,493	T	C	0.106	0.163	0.105	Olshan (CHANCE)	Candidate					
	rs1051685	13	216778621,	A	G	0.111	0.364	0.333	Olshan (CHANCE)	Candidate	Hayden, 2007; Cibeira, 2011; Wu, 2006				
ERCC4 (XPF)	rs3136038	16	13,920,880	C	T	0.296	0.418	0.482	Wei (MD Anderson HNC)	Tag		X	51% (28/54)	X	34% (24/70)
	rs1799798	16	13,921,779	G	A	0.083	0	--	Wei (MD Anderson HNC)	Tag					
	rs744154	16	13,922,582	G	C	0.227	0.095	--	Millikan (CBCS)	Candidate	Osorio, 2009; Gaudet, 2009; Milne, 2006	X		X	
	rs3136085	16	13,927,082	G	C	0.246	0.297	--	Wei (MD Anderson HNC)	Tag					
	rs3136091	16	13,927,883	C	G	0.000	0.075	0.044	Millikan (CBCS)	Function, intron				X	
	rs254942	16	13,933,508	A	G	0.035	0.000	--	Millikan (CBCS)	Function, splice		X			
	rs3136130	16	13,934,452	G	T	0.258	0.443	--	Wei (MD Anderson HNC)	Tag		X		X	
	rs1799802	16	13,935,582	C	T	0.018	0.000	0.018	Millikan (CBCS)	Candidate		X			
	rs1800067	16	13,936,534	G	A	0.049	0.000	0.018	Wei (MD Anderson HNC), Millikan (CBCS)	Tag		X			
	rs3136172	16	13,940,377	A	G	0.250	0.108	--	Wei (MD Anderson HNC)	Tag					
	rs1799800†	16	13,946,053	G	A	0.230	0.088	0.132	Wei (MD Anderson HNC)	Tag		X		X	
	rs2020955	16	13,946,160	T	C	0.000	0.272	0.196	Millikan (CBCS)	Function, Ser662Pro				X	
	rs4986933	16	13,949,533	C	A	0.004	0.007	--	Millikan (CBCS)	Function, A863D		X		X	
RAD23A	rs2974752	19	12,917,557	A	G	0.379	0.490	0.544	Millikan (CBCS)	Function, upstream		X	60% (3/5)	X	50% (2/4)
	rs11558955	19	12,920,147	A	G	--	--	--	Millikan (CBCS)	Function, T131A					
	rs4987202	19	12,920,626	C	T	0.008	0.000	--	Millikan (CBCS)	Function, T200M		X			

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Table 12 cont. Single nucleotide polymorphisms in nucleotide excision repair genes included in the Carolina Head and Neck Cancer Study

						Minor Allele Frequency (MAF)			Selection Method			Variation Captured by CHANCE SNPs*			
Gene	SNP	Chromosome and Position		Major Allele	Minor Allele	CEU	YRI	ASW	Investigator (Study)	Reason for Selection	Reason for Selection	CEU		YRI	
ERCC2 (XPD)	rs13181	19	50,546,759	T	G	0.332	0.177	0.263	Wei (MD Anderson HNC), Millikan (CBCS)	Tag		X	55% (16/29)	X	43% (14/32)
	rs238418	19	50,547,102	C	A	0.339	0.025	--	Wei (MD Anderson HNC)	Tag					
	rs1799787	19	50,547,984	G	A	0.270	0.071	0.096	Wei (MD Anderson HNC)	Tag		X		X	
	rs3916874	19	50,548,766	C	G	0.329	0.000	0.061	Wei (MD Anderson HNC)	Tag		X			
	rs238416	19	50,548,889	C	T	0.350	0.027	0.088	Wei (MD Anderson HNC)	Tag		X		X	
	rs238414†	19	50,549,660	C	T	0.325	0.728	--	Wei (MD Anderson HNC)	Tag					
	rs50872	19	50,554,289	G	A	0.305	0.139	0.842	Wei (MD Anderson HNC)	Tag		X		X	
	rs50871	19	50,554,355	C	A	0.465	0.973	0.886	Wei (MD Anderson HNC)	Tag		X		X	
	rs238407	19	50,560,318	A	T	0.500	0.016	--	Wei (MD Anderson HNC)	Tag		X		X	
	rs3810366	19	50,565,782	G	C	0.425	0.976	--	Wei (MD Anderson HNC)	Tag		X		X	
ERCC1	rs735482	19	50,603,842	A	C	0.133	0.259	0.289	Olshan (CHANCE)	Candidate	Jones, 2011; Cibeira, 2011; Ricceri, 2010	X	76% (10/13)	X	53% (7/13)
	rs762562†	19	50,604,183	A	G	0.133	0.257	0.300	Wei (MD Anderson HNC)	Tag		X		X	
	rs2336219	19	50,604,246	G	A	0.133	0.248	0.281	Wei (MD Anderson HNC)	Tag		X		X	
	rs3212986†	19	50,604,576	C	A	0.232	0.330	0.298	Olshan (CHANCE)	Candidate	Abassi, 2009; An, 2007; Sturgis, 2002; Sugimara, 2005; etc.	X		X	
	rs3212964	19	50,612,636	C	T	0.129	0.178	0.231	Wei (MD Anderson HNC)	Tag		X		X	
	rs3212955	19	50,615,336	T	C	0.238	0.294	--	Wei (MD Anderson HNC)	Tag		X			
	rs3212948	19	50,616,202	G	C	0.325	0.976	--	Wei (MD Anderson HNC)	Tag		X			
	rs3212935	19	50,618,615	T	C	--	0.394	0.325	Millikan (CBCS)	Function, intron				X	
	rs3212930	19	50,619,450	T	C	0.208	0.051	--	Millikan (CBCS)	Candidate					
LIG1	rs13436†	19	53,312,848	G	C	0.388	0.520	--	Millikan (CBCS)	Function, splice	Michiels, 2007		37% (27/72)		20% (20/97)
	rs3729512†	19	53,314,187	G	A	0.117	0.288	--	Olshan (CHANCE)	Candidate					
	rs3731003	19	53,323,070	G	A	0.000	0.027	0.018	Millikan (CBCS)	Function, T614I				X	
	rs156641	19	53,323,220	C	T	0.381	0.058	--	Olshan (CHANCE)	Candidate	Chang,2008; Michiels, 2007	X		X	
	rs3730980	19	53,330,834	T	C	0.000	0.040	--	Millikan (CBCS)	Function, M480V				X	
	rs3730933	19	53,339,009	T	C	0.000	0.041	0.009	Millikan (CBCS)	Function, N267S				X	
	rs20580	19	53,346,365	G	T	0.487	0.566	0.554	Olshan (CHANCE)	Candidate	Liu, 2009; Lee, 2007	X		X	
	rs4987070	19	53,356,469	T	C	0.000	0.000	--	Millikan (CBCS)	Function, D72G					
	rs20579	19	53,360,642	G	A	0.119	0.323	--	Millikan (CBCS)	Function, 5' UTR	Liu, 2009; Chang, 2008; Lee, 2007	X		X	
	rs439132	19	53,360,726	T	C	0.004	0.364	--	Olshan (CHANCE)	Candidate	Chang,2008; Lee, 2007			X	

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†SNPs which failed genotyping (i.e. weak signal intensity or in distinguishable genotype clusters)

Table 13. Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes Inclusion and Exclusion Criteria, Carolina Head and Neck Cancer Epidemiology (CHANCE) Study

						MAF < 0.05		HWE P-value < 0.05	
Gene	**SNP**	**Major Allele**	**Minor Allele**	**Selection Method**	**Failed Genotyping**	**Whites**	**African Americans**	**Whites**	**African Americans**
ERCC3 (XPB)	rs4150496	G	A	Tag					
	rs4150459	G	A	Tag		X			
	rs1011019	C	T	Tag					
	rs4150434	G	A	Tag					
	rs4150416	T	G	Tag					
	rs4150407	A	G	Tag					
	rs4150403	G	A	Tag			X		
	rs4150402	G	A	Tag					
XPC	rs2228001	A	C	Literature/Function					
	rs3731143	T	C	Tag			X		
	rs2228000	C	T	Function					
	rs3731124	A	C	Literature/Function					
	rs13099160	A	G	Tag			X		
	rs35629274	A	C	Literature /Function		X	X		
	rs3731093	T	C	Tag					
	rs3731089	G	A	Tag					
	rs2733537	A	G	Tag				X	
	rs3731068	C	A	Tag			X		
	rs2607755	T	C	Tag					
	rs3731062	C	T	Literature/Function		X	X		
	rs1902658	G	A	Tag					X
	rs3731055	G	A	Literature/Function		X	X		
	rs2279017	--	--	Literature/Function	X				
ERCC8	rs4647153	T	C	Literature/Function		X	X		
	rs3117	T	C	Literature/Function					
	rs58922	--	--	Literature/Function	X				
CDK7	rs2972388	A	G	Literature/Function				X	
	rs34584424	C	T	Literature/Function		X	X		
CCNH	rs2266691	A	G	Literature/Function		X			
	rs2266692	G	T	Literature/Function		X			
	rs1807895	T	--	Literature/Function		X	X		
	rs2266690	--	--	Literature/Function	X				
XPA	rs3176757	C	T	Tag					
	rs3176753	T	C	Literature/Function		X			
	rs3176750	C	G	Literature/Function		X	X		
	rs3176748	A	G	Tag					
	rs2808667	C	T	Tag			X		
	rs2805835	G	C	Tag			X		
	rs3176689	A	T	Tag			X		
	rs3176683	T	C	Tag			X		
	rs3176658	C	T	Tag					X
	rs1800975	G	A	Literature/Function					
	rs2808668	--	--	Tag	X				

MAF Minor Allele Frequency, HWE Hardy-Weinberg Equilibrium

Table 13 cont. Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes Inclusion and Exclusion Criteria, Carolina Head and Neck Cancer Epidemiology (CHANCE) Study

						MAF < 0.05		HWE P-value < 0.05	
Gene	**SNP**	**Major Allele**	**Minor Allele**	**Selection Method**	**Failed Genotyping**	**Whites**	**African Americans**	**Whites**	**African Americans**
RAD23B	rs1805330	C	T	Literature/Function					
	rs1805329	C	T	Literature/Function			X		
ERCC6	rs4253230	C	--	Literature/Function		X	X		
	rs2228529	A	G	Literature/Function					
	rs2229761	G	C	Literature/Function		X	X		
	rs2228527	A	G	Literature/Function					
	rs4253132	T	C	Literature/Function				X	
	rs4253072	A	G	Literature/Function		X	X		
	rs2228528	G	A	Literature/Function					
	rs4253047	--	--	Literature/Function	X				
	rs2228526	--	--	Literature/Function	X				
DDB2 (XPE)	rs2029298	A	G	Tag					
	rs4647709	C	T	Tag			X		
	rs2291120	T	C	Tag			X		
	rs1685404	G	C	Tag					
	rs2957873	A	G	Tag					
	rs326224	G	A	Tag					
	rs2306353	G	A	Tag					
	rs326222	C	T	Tag					
	rs901746	A	G	Tag					
	rs11988	--	--	Tag	X				
ERCC5 (XPG)	rs2296147	T	C	Tag					
	rs2296148	C	T	Literature/Function		X			X
	rs4771436	T	G	Tag					
	rs1047768	C	T	Literature/Function					
	rs2020915	G	A	Literature/Function		X			
	rs4150313	A	--	Literature/Function		X	X		
	rs2227869	G	C	Tag		X	X		
	rs3818356	C	T	Tag					
	rs4150351	A	C	Tag			X		
	rs4150355	C	T	Tag					
	rs4150360	T	C	Literature/Function				X	
	rs4150383	G	A	Tag					
	rs4150386	A	C	Tag			X		
	rs17655	C	G	Tag					
	rs873601	A	G	Tag					
	rs4150393	A	G	Tag			X		
	rs876430	C	T	Tag					
	rs1051677	T	C	Literature/Function					
	rs1051685	A	G	Literature/Function					
	rs4987063	--	--	Literature/Function	X				

MAF Minor Allele Frequency, HWE Hardy-Weinberg Equilibrium

Table 13 cont. Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes Inclusion and Exclusion Criteria, Carolina Head and Neck Cancer Epidemiology (CHANCE) Study

						MAF < 0.05		HWE P-value < 0.05	
Gene	**SNP**	**Major Allele**	**Minor Allele**	**Selection Method**	**Failed Genotyping**	**Whites**	**African Americans**	**Whites**	**African Americans**
ERCC4 (XPF)	rs3136038	C	T	Tag					X
	rs1799798	G	A	Tag			X		
	rs744154	C	G	Literature/Function					
	rs3136085	G	C	Tag					
	rs3136091	C	G	Literature/Function		X			
	rs254942	T	C	Literature/Function		X	X		
	rs3136130	G	T	Tag					
	rs1799802	C	T	Literature/Function		X	X		
	rs1800067	G	A	Literature/Function			X		
	rs3136172	A	G	Tag					
	rs2020955	T	C	Literature/Function		X			X
	rs4986933	C	A	Literature/Function		X	X		
	rs1799800	--	--	Tag	X				
RAD23A	rs2974752	A	G	Literature/Function				X	
	rs11558955	A	G	Literature/Function		X			
	rs4987202	C	T	Literature/Function		X	X		
ERCC2 (XPD)	rs13181	T	G	Tag					
	rs238418	C	A	Tag					
	rs1799787	C	T	Tag					
	rs3916874	G	C	Tag					
	rs238416	G	A	Tag					
	rs50872	C	T	Tag					
	rs50871	T	G	Tag					
	rs238407	A	T	Tag					
	rs3810366	C	G	Tag					
	rs238414	--	--	Tag	X				
ERCC1	rs735482	A	C	Literature/Function					
	rs2336219	G	A	Tag					
	rs3212964	G	A	Tag					
	rs3212955	A	G	Tag					
	rs3212948	C	G	Tag					
	rs3212935	A	G	Literature/Function		X		X	
	rs3212930	T	C	Literature/Function					
	rs3212986	--	--	Literature/Function	X				
	rs762562	--	--	Tag	X				
LIG1	rs3731003	C	T	Literature/Function		X	X		
	rs156641	G	A	Literature/Function					X
	rs3730980	A	G	Literature/Function		X	X		
	rs3730933	A	G	Literature/Function		X	X		
	rs20580	C	A	Literature/Function					
	rs4987070	A	--	Literature/Function		X	X		
	rs20579	C	T	Literature/Function					
	rs439132	A	G	Literature/Function		X		X	X
	rs13436	--	--	Literature/Function	X				
	rs3729512	--	--	Literature/Function	X				

MAF Minor Allele Frequency, HWE Hardy-Weinberg Equilibrium

Table 14. Questions Related to Cigarette Smoking from the CHANCE Questionnaire (149)

Variable	**Question**
Ever Cigarette Smoking	Have you smoked 100 cigarettes or 5 packs in your entire life?
Current Cigarette Smoking	Do you still smoke cigarettes?
Duration of Cigarette Smoking	At what age did you start smoking cigarettes?
	At What age did you stop?
	For how many years did you not smoke cigarettes during this period?
Frequency of Cigarette Smoking	How many cigarettes did you usually smoke?...per day, week, month, year?
Types of Cigarettes Smoked	Did you usually smoke?...filtered, non-filtered, both filtered and non-filtered, menthol, non-menthol, both menthol and non-menthol?

Table 15. Ancestral Informative Markers used in CHANCE

rs12094678	rs11264110	rs10908312*	rs7161*	rs6666101	rs7512316	rs4659762	rs12129648	rs798443	rs12612040	rs1508061	rs7575147*
rs3755446	rs10195705	rs1257010	rs4149436	rs17049450	rs17261772	rs1117382	rs1372115	rs12692701	rs1982235	rs7424137	rs12997060
rs10202705	rs3791896	rs11901793	rs155409*	rs1303629	rs13318432	rs2660769	rs1462309	rs6414248	rs1256197	rs13080353*	rs6765491
rs9849733	rs833282	rs4859147	rs6820509	rs2687427	rs9306906	rs4619931	rs12640848	rs7689609	rs10028057*	rs6535244	rs385194
rs1372894	rs316598	rs13169284	rs16891982	rs10056388	rs13173738	rs10041728	rs33957	rs1917028	rs1380014	rs13178470	rs6556352
rs857440	rs2451563	rs10806263	rs6937164	rs4896780*	rs10952147	rs7810554	rs7788641	rs17520733	rs10254729	rs10255169	rs344454
rs4602918	rs4143633	rs1870571	rs12676654	rs13261248	rs9297712	rs7021690	rs10124991	rs1415723	rs3861709	rs10962612*	rs1885167*
rs2777804	rs1412521	rs870272	rs2488465	rs1335826	rs9416972	rs1733731	rs2184033	rs4529792	rs503677	rs9416026	rs11000419
rs1911999	rs1125217*	rs7107482	rs11607932	rs7111814	rs11223503	rs2416791	rs1490728	rs10842753	rs7134682	rs328744	rs3759171
rs2596793	rs645510	rs9525462	rs9543532	rs4885162	rs9530646	rs6491743	rs1477921	rs222674	rs2246695	rs710052	rs12900552
rs1470608	rs12900262	rs4489979	rs7086	rs4923940	rs12594483	rs567357	rs735480	rs1426654*	rs17269594	rs6494466	rs9806307
rs4506877	rs4350528	rs9923864	rs7187359	rs12926237	rs11150219	rs7189172	rs1862819	rs4792105	rs12945601	rs1043809	rs2593595
rs4793237	rs228768	rs11652805	rs4789070	rs897351	rs8113143	rs1991818	rs1011643	rs2426515	rs6023376	rs4811651*	rs2075902
rs4823460											

*SNPs which failed genotyping (i.e. weak signal intensity or in distinguishable genotype clusters)

Table 16. Example of SNP-gene matrix (Z_j) using select single nucleotide polymorphisms and genes included in the Carolina Head and Neck Cancer Study

	ERCC3	XPC	ERCC8	CDK7	CCNH	XPA	RAD23B	…
rs41509496	1	0	0	0	0	0	0	0
Rs4150459	1	0	0	0	0	0	0	0
…								
rs2228001	0	1	0	0	0	0	0	0
rs2279017	0	1	0	0	0	0	0	0
…								
rs4647153	0	0	1	0	0	0	0	0
rs3117	0	0	1	0	0	0	0	0

Table 17. Example of SNP-environment matrix

	SNP	Cigarette Smoking
Never cigarette smoking, variant genotype	1	0
Ever cigarette smoking, referent genotype	0	1
Ever cigarette smoking, variant genotype	1	1

Referent: Never cigarette smoking, referent genotype (i.e. SNP=0, Cigarette Smoking=0)

Figure 2. Flowchart of CHANCE Cases Included in Dissertation (adapted from Hakenewerth dissertation (82,135))

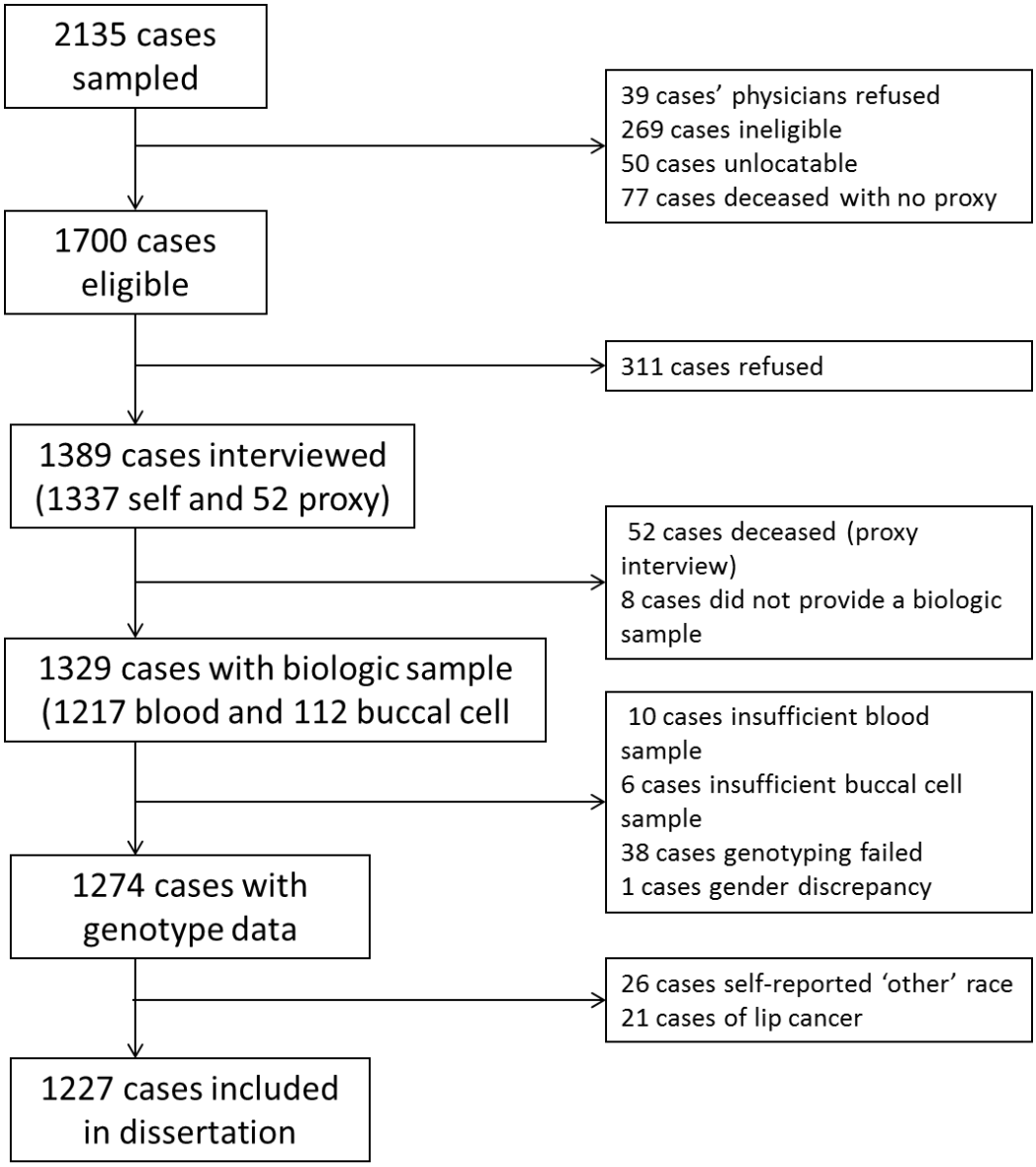


Figure 3. Flowchart of CHANCE Controls Included in Dissertation (adapted from Hakenewerth dissertation (82,135))

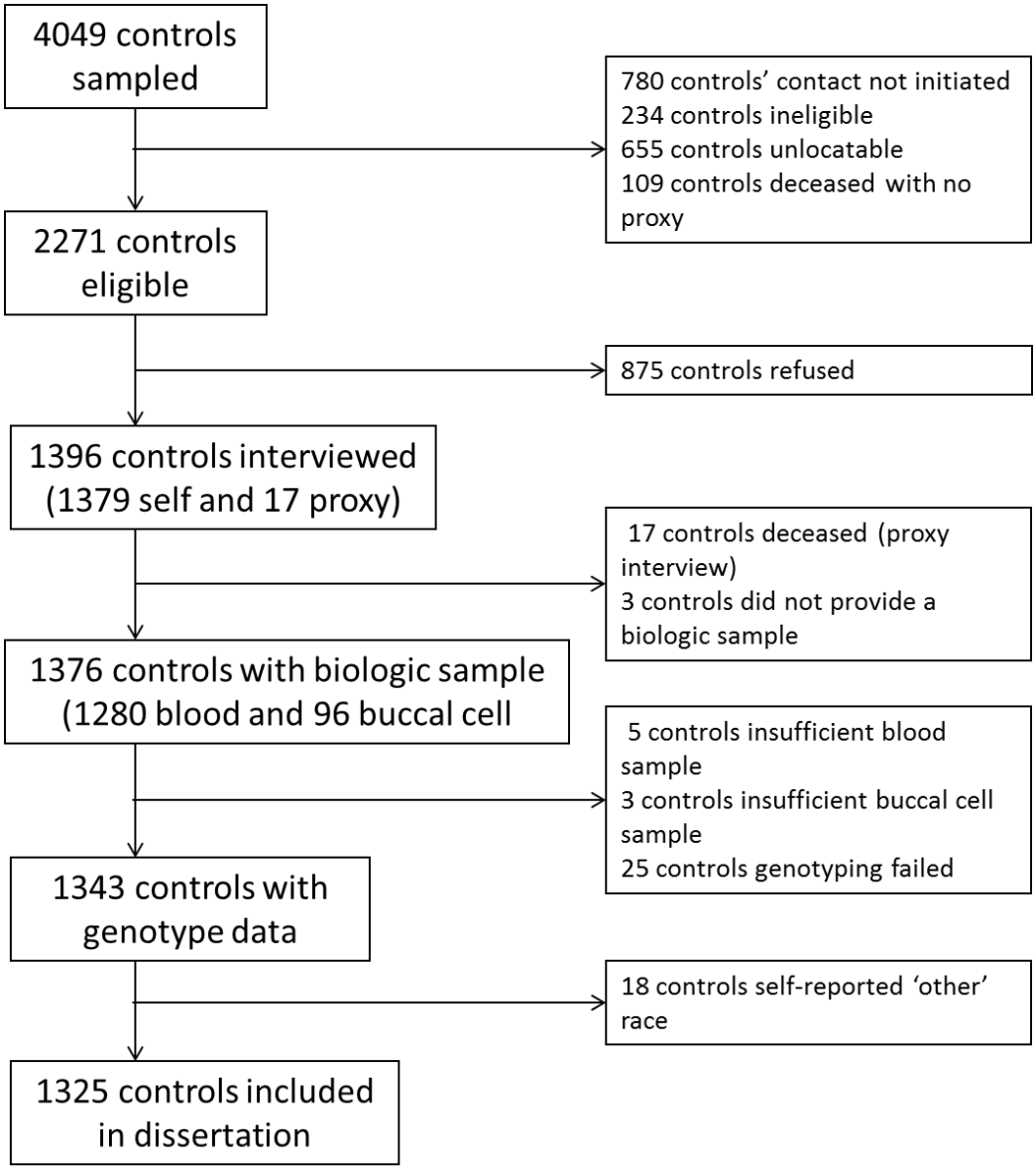


Figure 4. Direct Acyclic Graph for Nucleotide Excision Repair Genes (SNPs) and Head and Neck Cancer Incidence

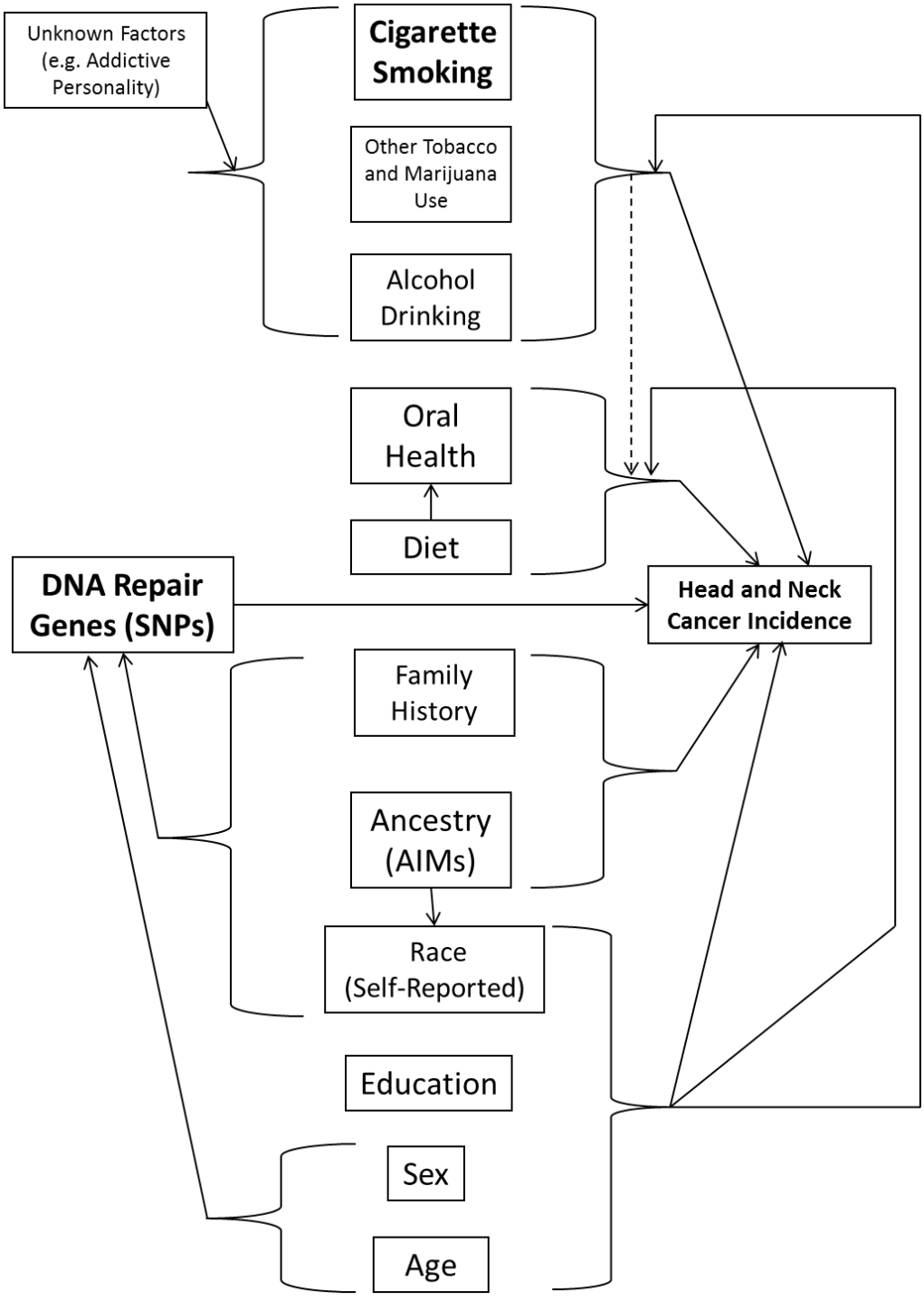


Figure 5. Direct Acyclic Graph for Cigarette Smoking and Head and Neck Cancer Incidence

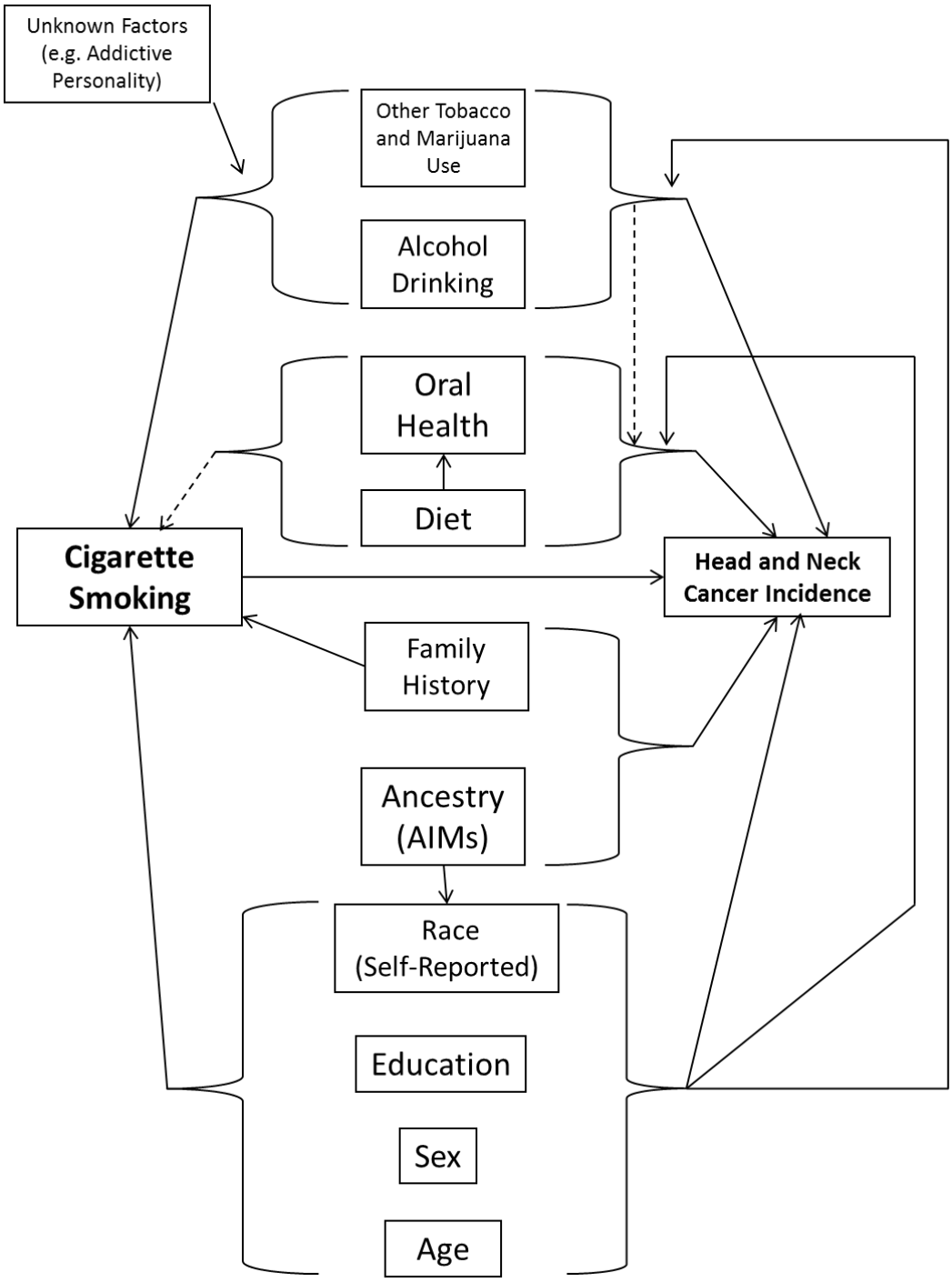


Figure 6. Direct Acyclic Graph for Nucleotide Excision Repair Genes (SNPs) and Head and Neck Cancer Mortality

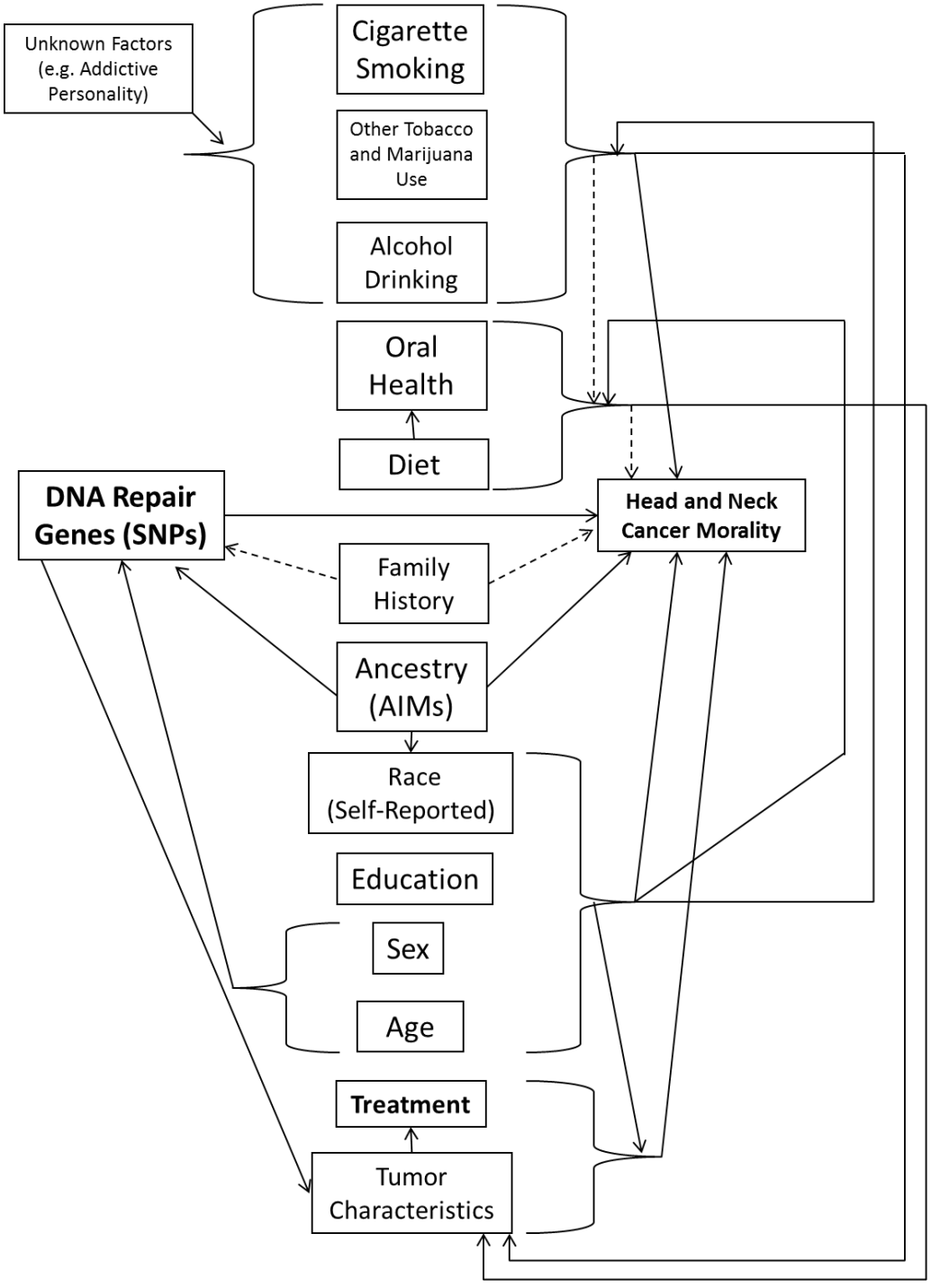


Figure 7. Direct Acyclic Graph for Treatment and Head and Neck Cancer Mortality

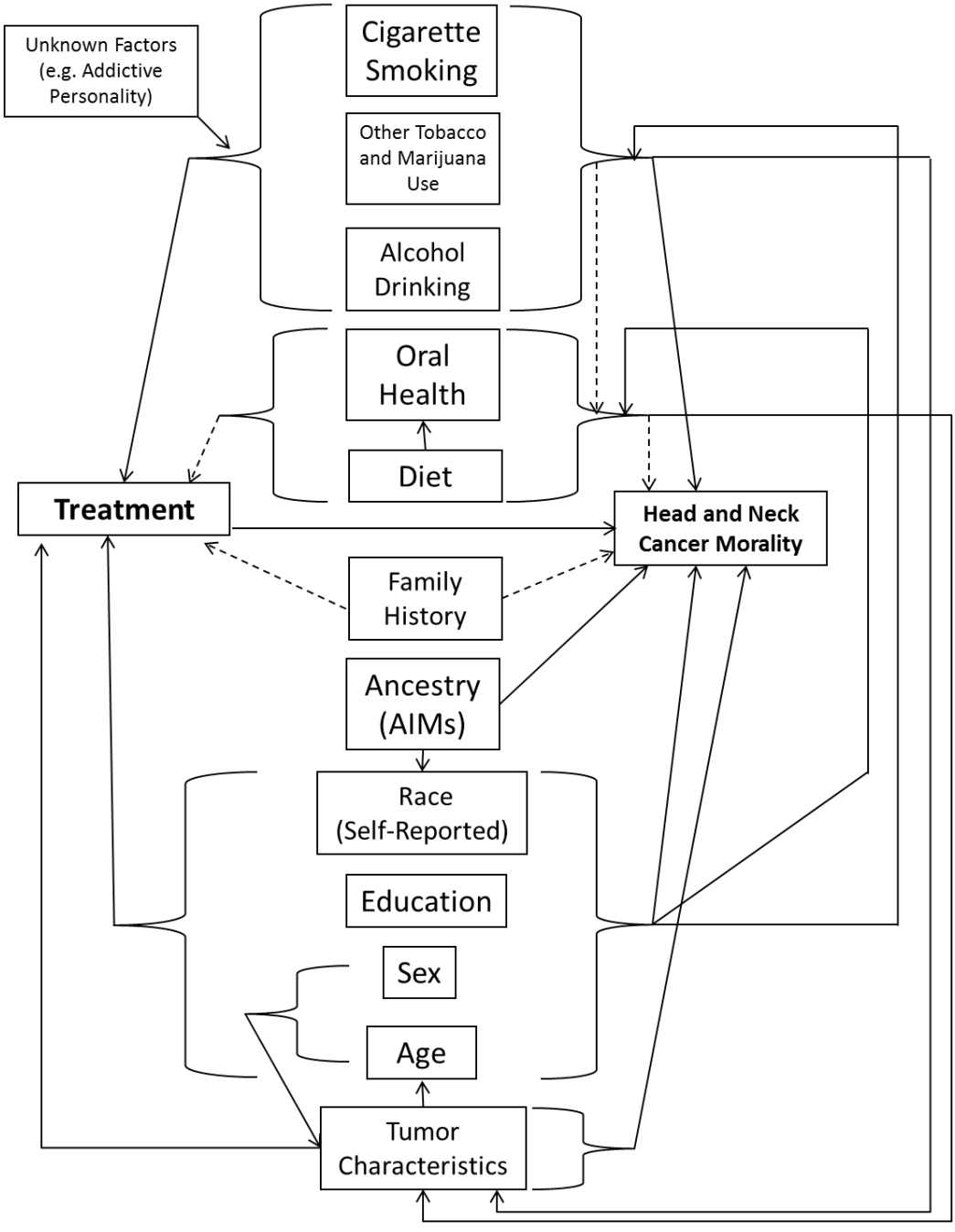


Figure 8. Power to detect main effects of single nucleotide polymorphisms in nucleotide excision repair genes on head and neck cancer incidence, CHANCE

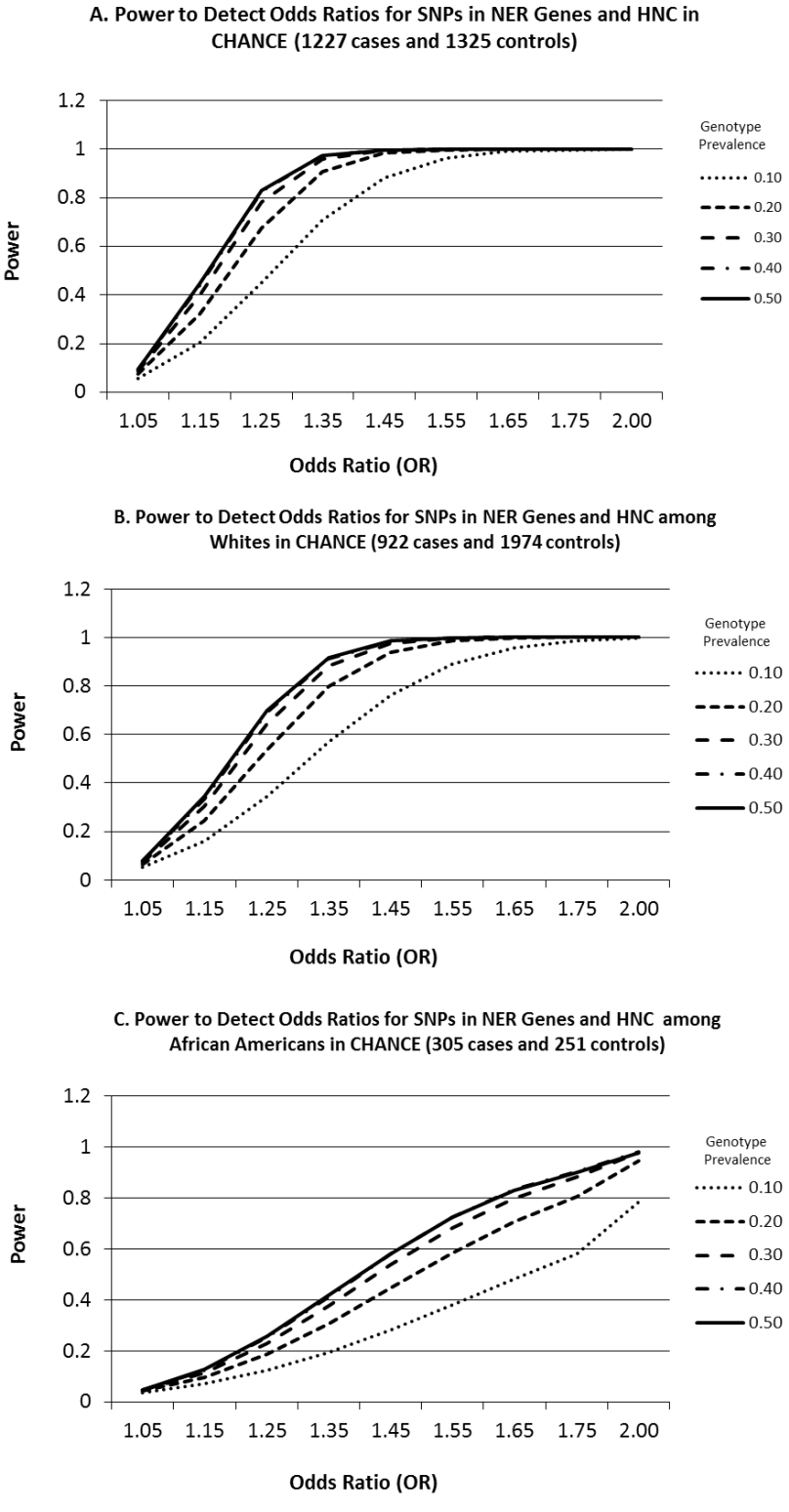
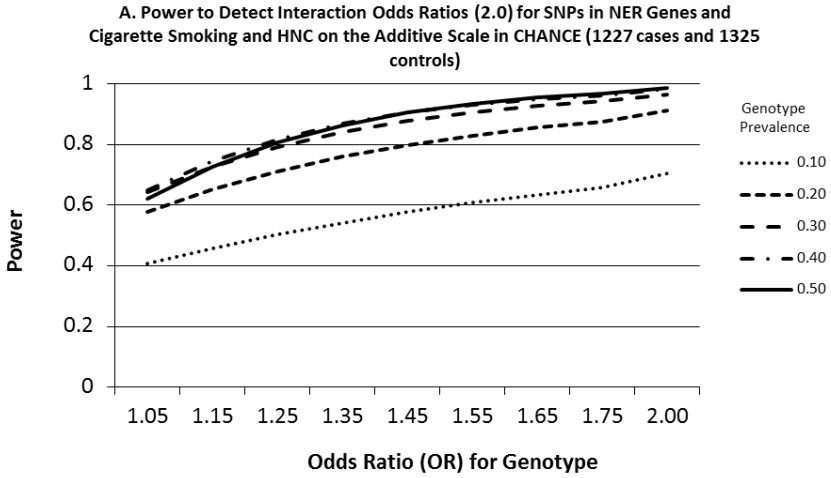
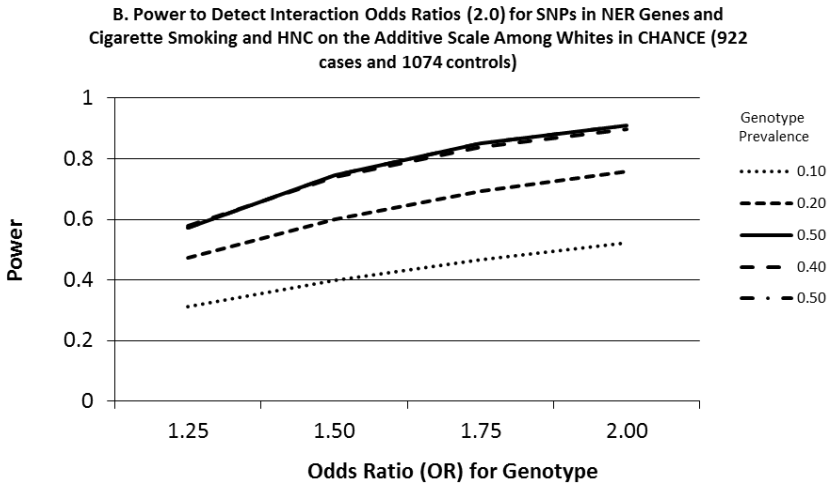


Figure 9. Power to detect joint effects of single nucleotide polymorphisms in nucleotide excision repair genes and cigarette smoking on head and neck cancer incidence, CHANCE





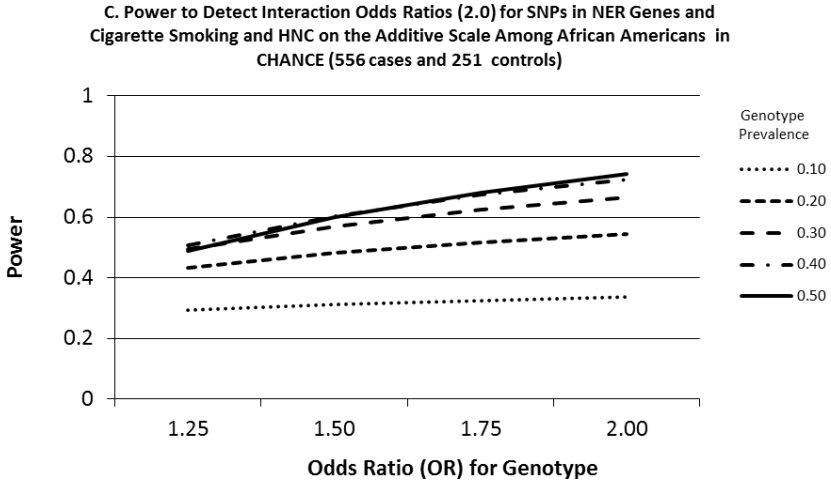
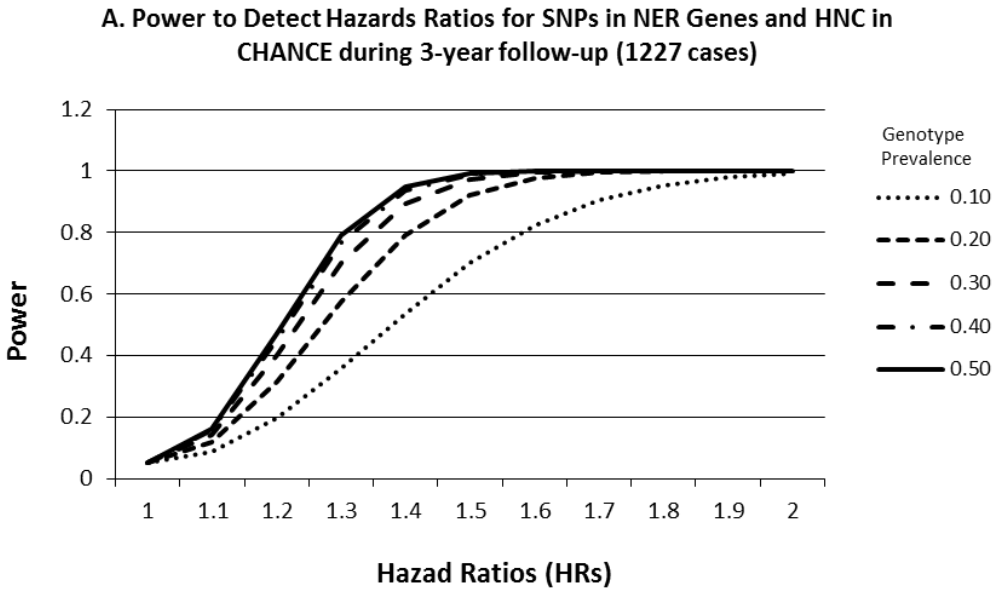


Figure 10. Power to detect main effects of single nucleotide polymorphisms in nucleotide excision repair genes on head and neck cancer mortality, CHANCE



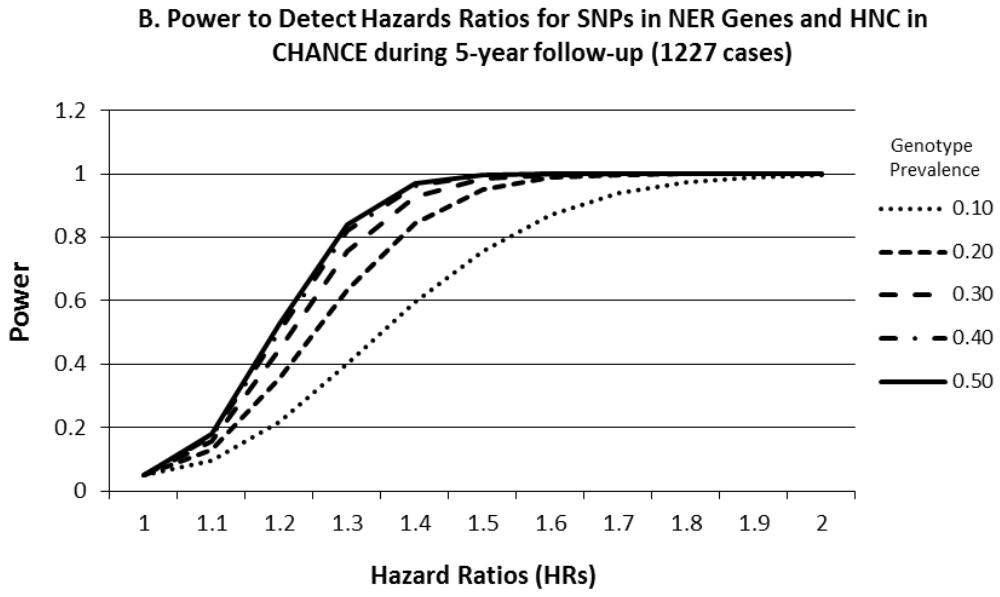
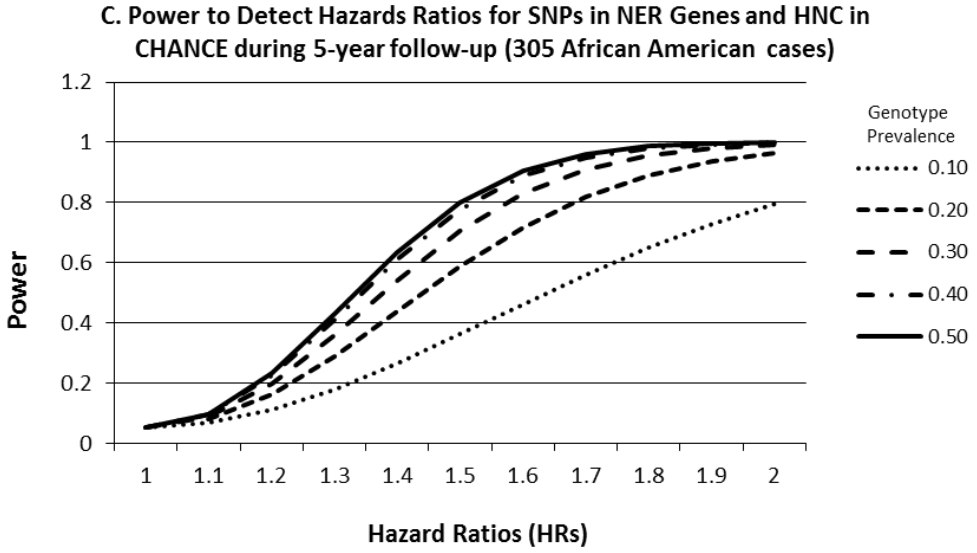


Figure 10 cont. Power to detect main effects of single nucleotide polymorphisms in nucleotide excision repair genes on head and neck cancer mortality, CHANCE



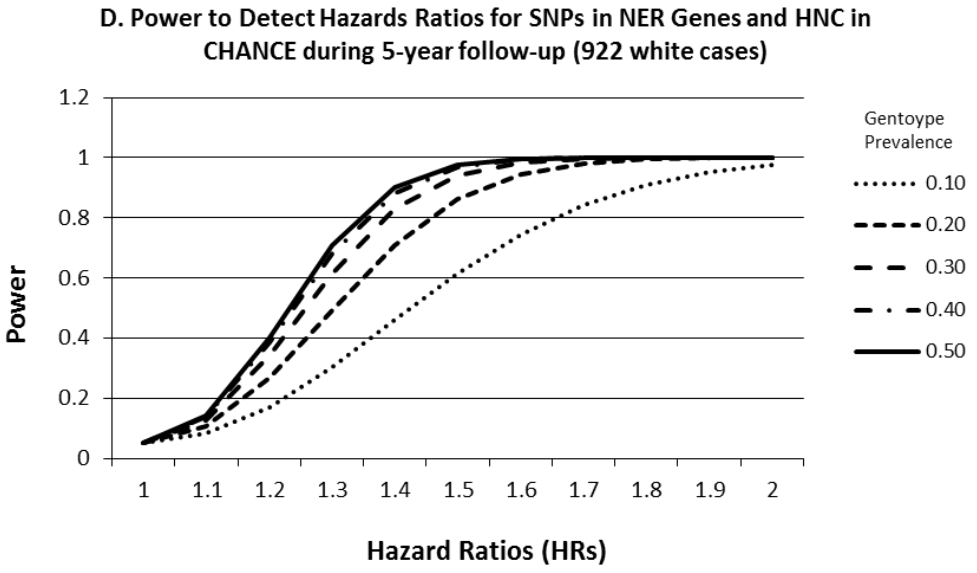
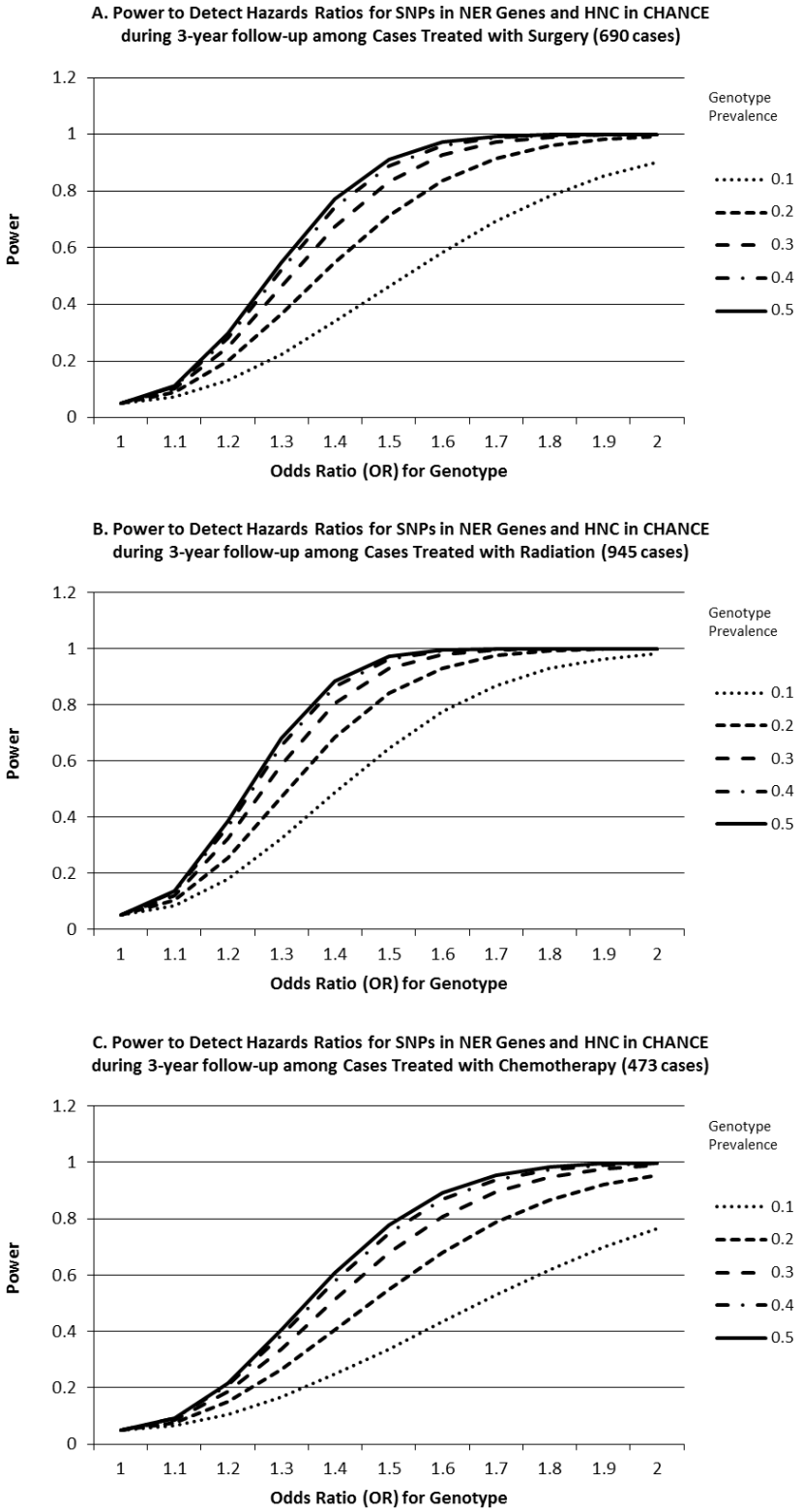


Figure 11. Power to detect joint effects of single nucleotide polymorphisms in nucleotide excision repair genes and treatment on head and neck cancer mortality, CHANCE



Chapter 3

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

3.1 OVERVIEW

Cigarette smoking is strongly associated with increased risk of head and neck cancer (HNC). Carcinogens in cigarette smoke are known to cause bulky DNA adducts. Nucleotide excision repair (NER) genes encode enzymes that remove adducts and may be independent risk factors for HNC, as well as modifiers of the association between smoking and HNC. Using population-based case-control data from the Carolina Head and Neck Cancer Epidemiology (CHANCE) 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. The odds of HNC were elevated among ever cigarette smokers (OR=1.97, 95% I=1.54, 2.53 among whites and OR=7.75, 95% I=3.57, 16.83 among African Americans), and showed a dose-response gradient with smoking duration and frequency (p_{trend}<0.0001). 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 cigarette smoking and 3 SNPs (rs4253132 on *ERCC*6, rs2291120 on *DDB2*, and rs744154 on *ERCC4*) suggested possible departures from additivity among whites. We conducted one of the largest and most comprehensive evaluations of NER variants, identifying only a few SNPs from

biologically plausible candidate genes associated with HNC and possibly interacting with cigarette smoking.

3.2 BACKGROUND

Head and neck cancer (HNC) includes tumors, principally squamous cell carcinomas, of the oral cavity, pharynx, and larynx (199). In the United States, an estimated 52,140 incident HNC cases and 11,460 associated deaths occurred in 2011 (1). Cigarette smoking is considered 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 smoking duration and frequency (2). Among non-alcohol drinking HNC cases, 25% of cases are attributed to cigarette smoking (83).

Cigarette smoke contains numerous chemical carcinogens, such as benzo-a-pyrene, that are known to cause a host of DNA damage, including bulky DNA adducts (2,3,124,126). 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 cigarette smoking and HNC (3,124,126). 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 (4,5,8-46,131-133). In general, most previous studies have evaluated only a few SNPs on a single NER gene among a few hundred HNC cases (4,5,8-46). Few studies have examined the association of NER SNPs and HNC among African-Americans (15), a group shown to have a stronger association for smoking and HNC (57). Studies of the joint effects of cigarette smoking and variants in NER genes on HNC risk also present varying results, though some studies indicate stronger associations among smokers with polymorphisms in NER genes (4,8-10,13,15,16,22,24,26-28,30,31,33,35-38,40,44). However, many of these studies

were limited by sparse numbers of NER SNPs investigated and small sample sizes (4,8-10,13,15,16,22,24,26-28,30,31,33,35-38,40,44).

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).

3.3 METHODS

3.3.1 Study Population

The CHANCE study is a population-based case-control study of 2,785 individuals (1,389 cases and 1,396 controls) from 46 of 100 counties in North Carolina (57,63,64). Eligible participants were between 20 to 80 years of age (57,63,64). Cases were identified from the North Carolina Central Cancer Registry between January 1, 2002 and February 28, 2006 using rapid case ascertainment (57,63,64). Tumors were classified according to ICD-03 codes; cancers 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; C32.9), 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 cancers of the salivary glands (C07.9, C08.0 to C08.9), nasopharynx (C11 .0 to C11.9), nasal cavity (C30.0), and nasal sinuses (C31.0 to C31 .9) were excluded (57,63,64,200). Controls were randomly sampled from the Department of Motor Vehicle records and were frequency matched to cases based on strata of age (20-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-80 years of age), race (white, African American, other race), and sex (male, female) (57,63,64).

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

3.3.2 Cigarette Smoking

Self-reported demographic and behavioral information was ascertained through nurse-administered questionnaires (57,63,64). Information on cigarette smoking included ever/never, 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.

3.3.3 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 (64). 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 (64,137). Seventy-one tag SNPs in NER genes were selected based on a case-control study of HNC at MD Anderson, 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 (Utah residents with ancestry from northern and western Europe) (Table 13) (129,139,140). The other 58 SNPs in NER genes were selected based on several criteria including association in other cancer studies and/or potential function (Table 13). We excluded SNPs in NER genes for which genotyping resulted in weak signal intensity or indistinguishable genotype clusters (14 SNPs), as well as SNPs with a minor allele frequency less than 0.05 (31 SNPs among whites and 36 SNPs among African Americans) (Table 13). Most excluded SNPs had been selected based on

previous literature and/or function (Table 13). Among the remaining SNPs, genotype frequencies for 7 SNPs in whites and 7 SNP in African Americans were not consistent with Hardy-Weinberg equilibrium ($p<0.05$) (Table 13); however, because genotyping scatter plots showed reasonable genotype clustering, these SNPs were not excluded from analyses but interpreted with caution (147). Our final analysis included 84 SNPs in 15 NER genes among whites and 79 SNPs in 14 NER genes among African Americans.

3.3.4 Statistical Analysis

3.3.4.1 Cigarette Smoking-HNC Associations.

Unconditional logistic regression models were used to estimate OR 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 (categorical age, sex, race), education (categorical less than high school education, high school education, or college education), and frequency of alcohol use (categorical for never drinking alcohol and quartiles of lifetime alcohol consumption in ml/day). ETS ORs were additionally adjusted for duration of cigarette smoking (continuous years), as well as stratified by ever/never cigarette smoking. Cigarette smoking and ETS models were considered in the overall study population and stratified by race (white and African American).

3.3.4.2 SNPs-HNC Associations

For SNPs, race-stratified hierarchical unconditional logistic regression was used to estimate OR and 95% I for the main effects of SNPs on HNC risk by including a SNP-gene matrix to account for clustering of SNP data by gene. 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 generally not the case with

correlated exposures, we selected a hierarchical approach (164,165,167). Results from the conventional approach are provided in supplemental tables.

We used a two-stage hierarchical model:

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

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 (164,165,167).

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

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 (164,165,167). 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 collinearity (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 the most plausible range of expected ORs for the association between SNPs in NER genes and HNC based on previous literature (i.e. 0.6 to 1.6) (165). 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 behavioral factors such as smoking and drinking, SNP models were adjusted for matching factors (sex and age, including pairwise interactions) and ancestry (continuous percent African ancestry), as informed by our directed acyclic graph (DAG) analysis (160). Based on previous studies of cancer among whites and African Americans in North Carolina, 157 ancestral informative markers (AIMS) were selected based on differences in allele frequencies between European and African HapMap populations and then used to estimate the proportion of African ancestry in each participant based on Fisher's information criterion (FIC) (64,157,201). Finally, site-specific models were considered to estimate the association between SNPs and tumors of the oral cavity, pharynx (oropharynx and hypopharynx), larynx, and not otherwise specified (NOS) separately.

3.3.4.3 Joint Effects

Odds ratios and 95% Is for the joint effects of ever cigarette smoking and SNPs in NER genes were estimated using conventional and hierarchical logistic regression. Joint effects were modeled using three disjoint indicator variables for 1) individuals who smoked but did not have the variant genotype, 2) individuals who did not smoke but had the variant genotype, and 3) individuals who smoked and had the variant genotype (165). As described in Hung et al., hierarchical models included a 3x2 gene-environment matrix to account for clustering of the 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) (165). A τ^2 of 0.35 was used since this corresponded to expected ORs between 0.3 and 3.0 for each indicator variable (165). 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, including pairwise interactions), education, frequency of alcohol use, and ancestry since both behavioral and genetic exposures were being modeled. Interactions between SNPs in NER genes and cigarette smoking were assessed on the additive scale using the relative excess risk due to interaction (RERI), also known as the interaction contrast ratio (ICR), with 95% CIs calculated using the Hosmer and Lemeshow method (161). Statistical analyses were performed using SAS 9.3 (Cary, NC) (163).

3.4 RESULTS

3.4.1 Characteristics of Study Population

The study population included 922 cases and 1074 controls who self-reported race as white and 305 cases and 251 controls who self-reported African American (table 18). 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.

3.4.2 Cigarette Smoking-HNC Associations

In the overall study population, the adjusted OR was elevated for ever compared to never cigarette smokers (2.28, 95% I=1.81, 2.88; table 19). Stratified by race, the adjusted OR for ever cigarette smoking was 1.97 (1.54, 2.53) among whites and 7.75 (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 1S, Appendix A); the adjusted OR (95% I) for ever compared to never ETS exposure was 0.87 (0.63, 1.19) among whites and 0.91 (0.45, 1.82) among African Americans. Stratified by active cigarette smoking, ETS ORs were not elevated among never cigarette smokers (0.84, 95% I=0.54, 1.33) nor ever cigarette smokers (0.92, 95% I=0.62, 1.37). Duration of ETS

exposure at work or home was also not associated with HNC risk (supplementary table 1S, Appendix A).

3.4.3 SNPs-HNC Associations

Among whites, most ORs were close to the null value for associations between SNPs and HNC (table 20). 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 2S, Appendix A). For rs4150496, associations with oral cavity and orpharyngeal 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,* rs4253132, was significantly associated with reduced HNC risk (CC + CT vs. TT, OR=0.62, 95% I=0.45, 0.86; table 21). 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 3S, Appendix A).

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 on *ERCC2 (XPD)* and HNC among whites (GG + TG vs. TT, OR=1.05, 95% I=0.76, 1.45; table 20) nor among African Americans (OR=1.01, 95% I=0.75, 1.37; table 21). In sensitivity analyses, results from tables 20 and 21 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 4S and 5S, Appendix A).

3.4.4 Joint Effects

Using the conventional method (table 22), interactions between 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* (RERI=0.70, 95% I=0.14, 1.26) as well as rs2291120 on *DDB2* (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* (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 22). It should also be noted that 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 interpreted with some caution. ORs (95% Is) for joint effects from the hierarchical model (table 23) were similar to estimates from the conventional method. RERI point estimates were also similar between the two methods, but I was unable to obtain the covariance matrix using hierarchical regression and therefore could not estimate 95% intervals for RERI estimates using that method. Among African Americans, no significant interactions were noted; however, estimates were unreliable due to relatively low cell counts and are therefore not presented (Appendix B). For the joint effects of SNPs and ETS, a few possible interactions were noted among whites (supplementary table 6S, Appendix A).

3.5 DISCUSSION

Consistent with extensive literature, we found a positive association between cigarette smoking and HNC risk (2). 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 (57). Briefly, elevated HNC ORs among African American cigarette smokers were noted even when accounting for frequency and duration of smoking, cigarette product preferences (e.g., mentholated vs. non-mentholated), and tumor site (57). Racial differences in carcinogen metabolism and smoking cessation patterns may be contributing factors (57).

Our study identified associations between two tag SNPs in the same NER gene and HNC among whites. Specifically, we detected elevated HNC risk associated with rs4150403 and possibly reduced HNC risk associated with rs4150496. These SNPs are in intron 3 and 11, respectively, of *ERCC3 (XPB)* which is a component of the transcription factor II H (TFIIH) subunit which unwinds the double helix surrounding a DNA adduct (123,124,202). In the epidemiologic literature neither of these SNPs has previously been evaluated with respect to HNC risk. Only one previous study has examined the effects of any variant in *ERCC3 (XPB)*. This study by Michiels et al., conducted among a European population of smokers, found reduced HNC risk associated with rs4233583 (AA vs. CC, OR=0.37, 95% CI=0.15, 0.90), which is correlated with rs4150496 (r^2=0.96, CEU population) (31,203).

An association between rs4253132 and reduced HNC risk was detected among African Americans in our study. This candidate SNP occurs in intron 9 of *ERCC6* which operates in NER of transcriptionally active DNA (123,124,202). 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 (4,13). A study by Abbasi et al. in a European population 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) (4). Another study by Chiu et al. conducted in an Asian population found elevated HNC risk associated with rs2228528 (GA + AA vs. GG, OR=1.43, 95% CI=1.02, 1.34) and no association with rs2228526 (AG + GG vs AA, OR= 0.82, 95% CI= 0.61, 1.20) and rs2228529 (AG + GG vs. AA, OR =0.79, 95% CI=0.49, 1.26) (13). Our study also evaluated rs2228527, rs2228528, and rs2228529 finding near null associations among whites and African Americans (ORs~0.9). SNPs rs2228526, rs2228527, and rs2228529 are correlated (r^2=1.0, CEU population), but not rs4253132, rs4253211, or rs2228528 (203).

Among all previous studies of NER variants and HNC, SNPs in *ERCC2 (XPD)* have been the most commonly investigated, in particular rs13181 which results in an amino acid change of Lys751Gln. *ERCC2 (XPD)* is located on chromosome 19 and encodes a protein component of the TFIIH subunit which denatures the double helix of DNA in preparation for excision of bulky DNA adducts (123,124). Over 20 previous case-control studies have studied rs13181 and HNC risk, with the majority finding null associations (4,5,8-10,14,16,17,19-22,24,25,29,30,32-34,36,37,45,133). The largest study, based on data from the International Head and Neck Cancer Epidemiology (INHANCE) consortium, found no association between rs13181 and HNC risk (OR= 0.97, 95% CI=0.86, 1.09 for Lys/Gln vs. Lys/Lys and OR= 1.03, 95% CI=0.88, 1.21 for Gln/Gln vs. Lys/Lys) (14). 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 (8-10,16,30,33,36,37). Of particular interest, Buch et al. estimated joint effects using an approach similar to our method, reporting ORs (95% CIs) of 1.26 (0.73, 2.18) for nonsmokers with the risk genotype, 0.79 (0.45, 1.36) for smokers with the referent genotype, and 3.99 (2.30, 6.92) for smokers with the risk genotype (25). In our study, we did not find an additive effect for smoking and rs13181.

Interactions between cigarette smoking and 3 SNPs, rs4253132 (candidate SNP, intron 9 of *ERCC*6), rs2291120 (tag SNP, intron 1 of *DDB2*), and rs744154 on (candidate SNP, intron 1 of *ERCC4*), were suggestive of possible super- or sub-additive effects among whites in our study (203). 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* within strata of cigarette smoking (4,13,26,44,203). Studies of rs4253211 on *ERCC6*, rs1800067 on *ERCC4*, and rs2276466 on *ERCC4* reported similar SNP-HNC associations across strata of cigarette smokers (4,26,44), while a study of rs2228528 on *ERCC6* found the SNP 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) (13) and a study of rs3136038 on *ERCC4* found the SNP 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 likely 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 (4,8,13,24,26-28,30,31,33,35,37,38,44). Although previous studies may have found an effect for having both the variant genotype of a SNP and smoking cigarettes, it is likely that RERIs may have been insignificant if calculated given the smaller sample size of previous studies. 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 (11,14), this study was the largest 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 (4,5,8-46). Further, our study included more African Americans than any previous study. Only one previous study, which included 119 African Americans, has considered effects for HNC and esophageal cancer incidence (15). 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 linkage disequilibrium among SNPs varies by ancestry (56,59,60,129). Despite our large sample size, 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 studies have collectively examined approximately 60 SNPs in 10 NER genes and HNC risk (4,5,8-46). Our study alone included 84 SNPs across 15 NER genes. Although our study included the largest array of SNPs in NER genes 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.

Although we did not confirm some previously reported associations, we found new associations between SNPs in NER genes and HNC risk. 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 cigarette smoking- SNP interactions were 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.

Table 18. Demographic Characteristics of Study Population, Carolina Head and Neck Cancer Epidemiology (CHANCE) Study

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

Table 19. Odds Ratios for Cigarette Smoking and Head and Neck Cancer in the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study

	Overall			Whites			African Americans		
Active Cigarette Smoking	**Controls**	**Cases**	**OR (95% I)[a]**	**Controls**	**Cases**	**OR (95% I)[a]**	**Controls**	**Cases**	**OR (95% I)[a]**
Never	508	163		409	150		99	13	
Ever	817	1064	2.28 (1.81, 2.88)	665	772	1.97 (1.54, 2.53)	152	292	7.75 (3.57, 16.83)
Missing	0	0		0	0		0	0	
Duration (years)									
Never Smokers	508	163		409	150		99	13	
1-19	280	110	0.98 (0.72, 1.35)	228	92	0.88 (0.63, 1.23)	52	18	2.54 (0.94, 6.87)
20-39	320	465	2.34 (1.79, 3.07)	256	305	1.95 (1.46, 2.62)	64	160	7.62 (3.38, 17.21)
40+	214	485	5.30 (3.94, 7.13)	178	373	4.75 (3.45, 6.53)	36	112	16.28 (6.52, 40.62)
Missing	3	4		3	2		0	2	
p_{trend}[b]			<0.0001			<0.0001			<0.0001
Frequency (cigarettes/day)									
Never Smokers	508	163		409	150		99	13	
1-19	322	211	1.39 (1.05, 1.85)	230	115	1.14 (0.83, 1.57)	92	96	4.78 (2.12, 10.82)
20+	495	850	2.99 (2.33, 3.84)	435	654	2.56 (1.96, 3.33)	60	196	13.16 (5.73, 30.23)
Missing	0	3		0	3		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]P-value for linear trend obtained from modeling the continuous forms of the frequency, duration, and cumulative variables

Table 20. Odds Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Head and Neck Cancer Using Hierarchical Logistic Regression for SNPs by Gene, the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, Whites

		Coded Allele		Cases/Controls					
Gene	**SNP**	**Referent (A) / Variant (B)**		**AA**		**AB + BB**		**OR (95% I)[a]**	**p-value[b]**
ERCC3 (XPB)	rs4150496	G	A	401	392	520	682	0.80 (0.62, 1.02)	0.08
	rs1011019	C	T	462	548	460	526	0.94 (0.72, 1.24)	0.68
	rs4150434	G	A	548	670	374	404	1.00 (0.81, 1.24)	0.97
	rs4150416	T	G	410	481	509	593	0.89 (0.68, 1.17)	0.4
	rs4150407	A	G	318	311	604	763	0.94 (0.72, 1.23)	0.65
	rs4150403	G	A	736	904	186	170	1.28 (1.01, 1.61)	0.04
XPC	rs2228001	A	C	337	375	584	699	0.90 (0.72, 1.12)	0.35
	rs3731143	T	C	818	957	104	117	1.05 (0.81, 1.36)	0.72
	rs2228000	C	T	524	598	396	475	0.93 (0.70, 1.25)	0.64
	rs3731124	A	C	521	599	401	475	0.88 (0.68, 1.15)	0.35
	rs13099160	A	G	814	962	108	112	1.03 (0.75, 1.40)	0.87
	rs3731089	G	A	778	919	144	155	1.03 (0.75, 1.40)	0.86
	rs2733537	A	G	416	480	506	594	0.95 (0.72, 1.25)	0.69
	rs3731068	C	A	624	732	298	342	1.05 (0.83, 1.33)	0.70
	rs2607755	T	C	242	284	680	790	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	609	710	313	364	0.98 (0.75, 1.29)	0.90
	rs3176748	A	G	440	510	482	564	0.89 (0.71, 1.12)	0.32
	rs2808667	C	T	814	950	106	124	1.11 (0.84, 1.47)	0.46
	rs2805835	G	C	727	848	195	226	0.96 (0.76, 1.22)	0.75
	rs3176689	A	T	622	728	300	346	0.92 (0.74, 1.15)	0.48
	rs3176683	T	C	818	944	104	130	0.88 (0.68, 1.16)	0.37
	rs3176658	C	T	699	792	223	282	0.81 (0.62, 1.07)	0.14
	rs1800975	G	A	420	473	465	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
	rs1805329	C	T	590	711	332	363	1.10 (0.92, 1.33)	0.30
ERCC6	rs2228529	A	G	597	661	313	396	0.87 (0.72, 1.05)	0.15
	rs4253132	T	C	723	829	199	245	0.90 (0.73, 1.12)	0.36
	rs2228528	G	A	637	746	284	328	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

OR odds ratio, I interval estimates

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

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

Table 20 cont. Odds Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Head and Neck Cancer Using Hierarchical Logistic Regression for SNPs by Gene, the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, Whites

		Coded Allele		Cases/Controls					
Gene	**SNP**	**Referent (A) / Variant (B)**		**AA**		**AB + BB**		**OR (95% I)[a]**	**p-value[b]**
DDB2 (XPE)	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	280	303	637	765	0.96 (0.76, 1.21)	0.73
	rs4771436	T	G	563	659	359	415	0.95 (0.71, 1.26)	0.71
	rs1047768	C	T	319	377	603	696	1.01 (0.77, 1.34)	0.93
	rs4150351	A	C	595	692	327	382	0.86 (0.67, 1.11)	0.24
	rs4150355	C	T	402	428	520	646	0.85 (0.67, 1.09)	0.21
	rs4150360	T	C	275	316	647	758	0.89 (0.66, 1.19)	0.43
	rs4150383	G	A	630	749	292	325	1.09 (0.84, 1.41)	0.52
	rs4150386	A	C	724	836	198	237	1.01 (0.81, 1.25)	0.96
	rs17655	C	G	555	658	367	416	1.05 (0.79, 1.40)	0.74
	rs873601	A	G	464	539	458	535	0.97 (0.74, 1.25)	0.80
	rs4150393	A	G	702	844	220	230	1.16 (0.89, 1.52)	0.26
	rs1051677	T	C	735	858	186	216	1.02 (0.83, 1.25)	0.87
	rs1051685	A	G	736	832	185	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
RAD23A	rs2974752	A	G	333	424	561	617	1.16 (0.96, 1.40)	0.11
ERCC2 (XPD)	rs13181	T	G	381	437	534	633	1.05 (0.76, 1.45)	0.79
	rs238418	C	A	382	426	540	648	0.91 (0.66, 1.26)	0.58
	rs1799787	C	T	472	545	450	529	1.06 (0.82, 1.35)	0.67
	rs3916874	G	C	477	545	445	529	1.01 (0.83, 1.25)	0.9
	rs238416	G	A	369	468	552	604	1.10 (0.88, 1.38)	0.39
	rs50872	C	T	531	584	389	488	0.91 (0.76, 1.08)	0.27
	rs50871	T	G	242	258	680	815	0.91 (0.75, 1.11)	0.36
	rs238407	A	T	263	338	658	736	1.05 (0.82, 1.35)	0.71
	rs3810366	C	G	178	232	743	842	1.08 (0.84, 1.40)	0.54
ERCC1	rs735482	A	C	688	797	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	616	1.17 (0.91, 1.50)	0.22
	rs3212930	T	C	576	657	346	417	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 percent African ancestry

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

Table 21. Odds Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Head and Neck Cancer Using Hierarchical Logistic Regression for SNPs by Gene, the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, African Americans

		Coded Allele		Cases/Controls					
Gene	SNP	Referent (A) / Variant (B)		AA		AB + BB		OR (95% I)[a]	p-value[b]
ERCC3 (XPB)	rs4150496	G	A	178	136	125	115	0.85 (0.61, 1.20)	0.35
	rs4150459	G	A	190	164	115	87	1.04 (0.74, 1.48)	0.81
	rs1011019	C	T	183	143	122	108	0.85 (0.60, 1.20)	0.35
	rs4150434	G	A	232	186	73	65	0.94 (0.65, 1.36)	0.73
	rs4150416	T	G	85	76	219	175	1.04 (0.74, 1.47)	0.81
	rs4150407	A	G	84	68	221	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, 1.45)	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	221	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	236	193	69	58	1.00 (0.69, 1.44)	0.99
	rs3176753	T	C	225	184	80	67	1.00 (0.69, 1.44)	0.86
	rs3176748	A	G	250	208	55	43	1.05 (0.72, 1.51)	0.81
	rs3176658	C	T	260	210	45	41	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	234	189	69	60	0.85 (0.58, 1.22)	0.37
	rs2228527	A	G	218	175	87	76	0.91 (0.65, 1.29)	0.61
	rs4253132	T	C	191	125	114	126	0.62 (0.45, 0.86)	0.005
	rs2228528	G	A	212	182	92	69	0.92 (0.65, 1.30)	0.62
DDB2 (XPE)	rs2029298	A	G	90	88	215	163	1.16 (0.86, 1.56)	0.33
	rs1685404	G	C	164	140	141	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	225	188	0.87 (0.62, 1.24)	0.45
	rs2306353	G	A	106	97	199	154	1.14 (0.80, 1.61)	0.47
	rs326222	C	T	54	50	251	201	1.09 (0.75, 1.59)	0.64
	rs901746	A	G	65	58	240	193	0.97 (0.68, 1.40)	0.89
ERCC5 (XPG)	rs2296147	T	C	193	148	111	102	0.90 (0.65, 1.23)	0.51
	rs2296148	C	T	228	190	76	61	1.04 (0.74, 1.45)	0.83
	rs4771436	T	G	204	172	101	79	0.95 (0.68, 1.33)	0.78
	rs1047768	C	T	116	115	189	136	1.12 (0.81, 1.54)	0.49
	rs2020915	G	A	205	144	100	107	0.80 (0.58, 1.10)	0.16
	rs4150355	C	T	218	175	87	76	1.02 (0.72, 1.44)	0.92
	rs4150360	T	C	19	17	286	232	0.95 (0.64, 1.42)	0.80
	rs4150383	G	A	242	200	63	51	0.95 (0.67, 1.35)	0.78

OR odds ratio, I interval estimates

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

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

Table 21 cont. Odds Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Head and Neck Cancer Using Hierarchical Logistic Regression for SNPs by Gene, the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, African Americans

		Coded Allele		Cases/Controls					
Gene	SNP	Referent (A) / Variant (B)		AA		AB + BB		OR (95% I)[a]	p-value[b]
ERCC5 XPG)	rs17655	C	G	90	70	215	181	0.98 (0.70, 1.37)	0.91
	rs873601	A	G	30	30	275	221	1.13 (0.77, 1.67)	0.52
	rs1051677	T	C	232	184	73	67	0.89 (0.65, 1.23)	0.48
	rs1051685	A	G	138	117	167	133	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	256	214	49	37	1.13 (0.76, 1.68)	0.54
ERCC2 (XPD)	rs13181	T	G	173	140	131	109	1.01 (0.75, 1.37)	0.93
	rs238418	C	A	8	11	296	240	1.09 (0.70, 1.69)	0.72
	rs1799787	C	T	235	192	70	59	0.98 (0.71, 1.37)	0.92
	rs3916874	G	C	268	226	37	25	1.09 (0.74, 1.59)	0.67
	rs238416	G	A	243	208	61	41	1.15 (0.80, 1.64)	0.45
	rs50872	C	T	223	158	82	93	0.78 (0.58, 1.05)	0.10
	rs50871	T	G	229	195	76	56	1.10 (0.80, 1.52)	0.57
	rs238407	A	T	226	190	79	61	0.99 (0.69, 1.42)	0.97
	rs3810366	C	G	212	180	93	71	1.06 (0.75, 1.49)	0.74
ERCC1	rs735482	A	C	156	122	149	129	0.96 (0.71, 1.30)	0.79
	rs3212964	G	A	207	142	96	107	0.78 (0.57, 1.07)	0.13
	rs3212955	A	G	159	142	146	109	1.09 (0.80, 1.50)	0.58
	rs3212948	C	G	9	6	296	245	0.94 (0.60, 1.48)	0.79
	rs3212935	A	G	143	125	162	125	1.10 (0.81, 1.50)	0.54
	rs3212930	T	C	250	205	55	46	0.94 (0.66, 1.34)	0.74
LIG1	rs156641	G	A	234	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	155	123	0.99 (0.72, 1.36)	0.96
	rs439132	A	G	172	136	133	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 percent African ancestry

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

Table 22. Odds Ratios and Relative Excess Risk Estimates for Joint Effects of Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and 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								OR (95% I)[a]			
Gene	SNP	Referent (A) / Variant (B)		Cigarette=0, SNP=0		Cigarette=0, SNP=1		Cigarette=1, SNP=0		Cigarette=1, SNP=1		Cigarette=1, SNP=0	Cigarette=0, SNP=1	Cigarette=1, SNP=1	RERI (95% CI)
ERCC3															
(XPB)	rs4150496	G	A	70	154	79	255	331	238	441	427	1.83 (1.27, 2.64)	0.66 (0.44, 0.98)	1.40 (0.99, 1.98)	-0.08 (-0.63, 0.46)
	rs1011019	C	T	66	201	84	208	396	347	376	318	2.18 (1.54, 3.08)	1.26 (0.85, 1.87)	2.28 (1.61, 3.23)	-0.16 (-0.86, 0.54)
	rs4150434	G	A	89	264	61	145	459	406	313	259	2.13 (1.56, 2.89)	1.20 (0.80, 1.80)	2.09 (1.51, 2.90)	-0.24 (-0.94, 0.45)
	rs4150416	T	G	56	176	93	233	354	305	416	360	2.27 (1.57, 3.30)	1.27 (0.84, 1.90)	2.27 (1.57, 3.27)	-0.27 (-1.01, 0.46)
	rs4150407	A	G	55	129	95	280	263	182	509	483	2.00 (1.33, 3.00)	0.77 (0.51, 1.16)	1.53 (1.05, 2.21)	-0.24 (-0.90, 0.41)
	rs4150403	G	A	118	338	32	71	618	566	154	99	1.95 (1.49, 2.56)	1.26 (0.77, 2.06)	2.60 (1.80, 3.74)	0.39 (-0.57, 1.34)
	rs4150402	G	A	66	201	84	208	396	347	376	317	2.19 (1.55, 3.09)	1.26 (0.85, 1.87)	2.29 (1.62, 3.26)	-0.15 (-0.85, 0.55)
XPC	rs2228001	A	C	56	135	94	274	281	240	490	425	1.91 (1.29, 2.83)	0.86 (0.57, 1.29)	1.70 (1.17, 2.48)	-0.06 (-0.66, 0.54)
	rs3731143	T	C	135	361	15	48	683	596	89	69	1.88 (1.45, 2.44)	0.90 (0.48, 1.70)	2.51 (1.66, 3.82)	0.73 (-0.33, 1.80)
	rs2228000	C	T	91	222	59	187	433	376	337	288	1.74 (1.27, 2.39)	0.77 (0.51, 1.14)	1.78 (1.28, 2.47)	0.27 (-0.23, 0.78)
	rs3731124	A	C	81	228	69	181	440	371	332	294	2.11 (1.53, 2.90)	1.10 (0.74, 1.64)	1.98 (1.42, 2.76)	-0.23 (-0.89, 0.43)
	rs13099160	A	G	127	366	23	43	687	596	85	69	2.07 (1.59, 2.69)	1.60 (0.90, 2.83)	2.24 (1.47, 3.43)	-0.43 (-1.65, 0.80)
	rs3731093	T	C	120	350	27	56	656	569	111	90	2.10 (1.60, 2.75)	1.52 (0.89, 2.58)	2.47 (1.68, 3.64)	-0.15 (-1.26, 0.96)
	rs3731089	G	A	121	350	29	59	657	569	115	96	2.07 (1.58, 2.71)	1.53 (0.92, 2.57)	2.35 (1.61, 3.44)	-0.25 (-1.32, 0.82)
	rs2733537	A	G	70	175	80	234	346	305	426	360	1.75 (1.23, 2.50)	0.88 (0.59, 1.31)	1.91 (1.35, 2.70)	0.28 (-0.25, 0.81)
	rs3731068	C	A	99	275	51	134	525	457	247	208	1.97 (1.47, 2.65)	1.03 (0.68, 1.56)	2.01 (1.44, 2.79)	0.01 (-0.65, 0.66)
	rs2607755	T	C	39	110	111	299	203	174	569	491	2.12 (1.35, 3.34)	1.11 (0.71, 1.73)	2.12 (1.39, 3.22)	-0.11 (-0.86, 0.63)
	rs1902658	G	A	37	107	113	302	198	173	573	492	2.10 (1.32, 3.33)	1.12 (0.71, 1.76)	2.15 (1.40, 3.29)	-0.07 (-0.81, 0.67)
ERCC8	rs3117	T	C	60	144	90	265	277	253	495	412	1.70 (1.16, 2.49)	0.81 (0.54, 1.22)	1.75 (1.22, 2.51)	0.23 (-0.28, 0.75)
CDK7	rs2972388	A	G	42	122	108	287	224	213	548	452	1.81 (1.17, 2.79)	1.06 (0.69, 1.63)	2.16 (1.45, 3.23)	0.29 (-0.31, 0.89)
XPA	rs3176757	C	T	98	268	52	141	511	442	261	223	1.94 (1.44, 2.62)	1.03 (0.68, 1.56)	2.08 (1.50, 2.89)	0.11 (-0.53, 0.75)
	rs3176748	A	G	74	185	76	224	366	325	406	340	1.76 (1.25, 2.48)	0.84 (0.57, 1.25)	1.82 (1.30, 2.57)	0.22 (-0.30, 0.74)
	rs2808667	C	T	133	352	17	57	681	598	89	67	1.86 (1.43, 2.42)	0.87 (0.47, 1.60)	2.44 (1.61, 3.71)	0.71 (-0.31, 1.73)
	rs2805835	G	C	119	328	31	81	608	520	164	145	2.03 (1.54, 2.68)	1.12 (0.69, 1.82)	1.95 (1.38, 2.76)	-0.20 (-0.98, 0.58)
	rs3176689	A	T	94	279	56	130	528	449	244	216	2.15 (1.60, 2.90)	1.14 (0.76, 1.72)	1.88 (1.34, 2.63)	-0.41 (-1.12, 0.29)
	rs3176683	T	C	134	353	16	56	684	591	88	74	1.88 (1.45, 2.45)	0.76 (0.41, 1.40)	2.05 (1.35, 3.10)	0.41 (-0.46, 1.28)
	rs3176658	C	T	114	297	36	112	585	495	187	170	1.91 (1.44, 2.52)	0.85 (0.54, 1.35)	1.86 (1.32, 2.60)	0.10 (-0.54, 0.73)
	rs1800975	G	A	72	180	75	215	348	293	390	348	1.83 (1.29, 2.60)	0.90 (0.61, 1.35)	1.86 (1.32, 2.63)	0.13 (-0.43, 0.69)
RAD23B	rs1805330	C	T	125	321	25	88	639	549	133	116	1.85 (1.41, 2.43)	0.68 (0.41, 1.13)	1.68 (1.16, 2.43)	0.15 (-0.49, 0.79)
	rs1805329	C	T	101	277	49	132	489	434	283	231	2.01 (1.50, 2.70)	1.13 (0.74, 1.72)	2.12 (1.53, 2.93)	-0.02 (-0.70, 0.66)
ERCC6	rs2228529	A	G	96	258	52	146	501	403	261	250	2.13 (1.57, 2.89)	1.08 (0.71, 1.63)	1.85 (1.33, 2.56)	-0.37 (-1.05, 0.32)
	rs2228527	A	G	97	260	53	149	501	405	271	260	2.13 (1.57, 2.87)	1.07 (0.71, 1.61)	1.84 (1.33, 2.55)	-0.35 (-1.03, 0.32)
	rs4253132	T	C	126	303	24	106	597	526	175	139	1.65 (1.26, 2.18)	0.50 (0.30, 0.84)	1.86 (1.32, 2.62)	0.70 (0.14, 1.26)
	rs2228528	G	A	104	287	46	122	533	459	238	206	2.01 (1.50, 2.68)	1.05 (0.69, 1.62)	1.97 (1.42, 2.74)	-0.09 (-0.76, 0.58)

OR odds ratio, I interval estimates

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

[b]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 22 cont. Odds Ratios and Relative Excess Risk Estimates for Joint Effects of Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and 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								OR (95% I)[a]			
Gene	SNP	Referent (A) / Variant (B)		Cigarette=0, SNP=0		Cigarette=0, SNP=1		Cigarette=1, SNP=0		Cigarette=1, SNP=1		Cigarette=1, SNP=0	Cigarette=0, SNP=1	Cigarette=1, SNP=1	RERI (95% CI)
DDB2															
(XPE)	rs2029298	A	G	69	195	81	214	356	283	416	382	2.39 (1.69, 3.38)	1.22 (0.82, 1.81)	2.03 (1.44, 2.86)	-0.58 (-1.34, 0.18)
	rs4647709	C	T	123	342	27	67	643	560	129	105	2.01 (1.53, 2.63)	1.17 (0.70, 1.96)	2.12 (1.46, 3.07)	-0.06 (-0.94, 0.82)
	rs2291120	T	C	123	296	27	113	562	516	210	149	1.68 (1.28, 2.22)	0.59 (0.36, 0.96)	1.95 (1.39, 2.74)	0.68 (0.11, 1.26)
	rs1685404	G	C	72	180	78	229	346	322	426	343	1.66 (1.17, 2.35)	0.88 (0.59, 1.30)	2.01 (1.43, 2.83)	0.47 (-0.03, 0.98)
	rs2957873	A	G	101	275	49	134	542	436	230	229	2.22 (1.65, 2.98)	1.16 (0.76, 1.75)	1.77 (1.28, 2.46)	-0.60 (-1.33, 0.13)
	rs326224	G	A	105	288	45	121	578	473	194	192	2.14 (1.61, 2.86)	1.18 (0.77, 1.80)	1.87 (1.33, 2.62)	-0.45 (-1.19, 0.29)
	rs2306353	G	A	109	292	41	117	587	470	185	195	2.18 (1.64, 2.90)	1.12 (0.72, 1.74)	1.66 (1.19, 2.33)	-0.64 (-1.38, 0.10)
	rs326222	C	T	76	209	74	200	408	317	364	348	2.39 (1.71, 3.34)	1.17 (0.79, 1.73)	1.88 (1.34, 2.63)	-0.68 (-1.43, 0.08)
	rs901746	A	G	76	210	74	199	409	318	363	347	2.41 (1.73, 3.37)	1.19 (0.80, 1.77)	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	2.14 (1.38, 3.33)	1.00 (0.64, 1.55)	1.88 (1.24, 2.83)	-0.27 (-1.01, 0.48)
	rs4771436	T	G	97	259	53	150	466	400	306	265	1.98 (1.46, 2.68)	0.98 (0.65, 1.48)	1.92 (1.39, 2.65)	-0.05 (-0.66, 0.57)
	rs1047768	C	T	57	142	93	267	262	235	510	429	1.71 (1.16, 2.52)	0.84 (0.56, 1.26)	1.79 (1.24, 2.59)	0.25 (-0.28, 0.78)
	rs3818356	C	T	97	259	53	149	466	400	304	264	1.97 (1.46, 2.67)	0.99 (0.66, 1.5)	1.91 (1.38, 2.64)	-0.06 (-0.67, 0.56)
	rs4150351	A	C	97	258	53	151	498	434	274	231	1.92 (1.42, 2.60)	0.94 (0.63, 1.42)	1.94 (1.40, 2.69)	0.07 (-0.53, 0.68)
	rs4150355	C	T	57	159	93	250	345	269	427	396	2.28 (1.57, 3.32)	1.06 (0.70, 1.58)	1.87 (1.29, 2.69)	-0.47 (-1.20, 0.26)
	rs4150360	T	C	50	119	100	290	225	197	547	468	1.70 (1.12, 2.58)	0.81 (0.53, 1.24)	1.71 (1.16, 2.51)	0.19 (-0.36, 0.74)
	rs4150383	G	A	106	296	44	113	524	453	248	212	2.02 (1.51, 2.70)	1.08 (0.70, 1.67)	2.00 (1.44, 2.78)	-0.10 (-0.78, 0.58)
	rs4150386	A	C	113	317	37	92	611	519	161	145	2.03 (1.53, 2.68)	1.03 (0.65, 1.63)	1.84 (1.29, 2.61)	-0.22 (-0.95, 0.51)
	rs17655	C	G	89	238	61	171	466	420	306	245	1.78 (1.30, 2.42)	0.88 (0.59, 1.32)	2.04 (1.46, 2.84)	0.38 (-0.18, 0.94)
	rs873601	A	G	73	190	77	219	391	349	381	316	1.72 (1.22, 2.41)	0.82 (0.55, 1.21)	1.83 (1.30, 2.58)	0.30 (-0.21, 0.80)
	rs4150393	A	G	114	317	36	92	588	527	184	138	1.94 (1.47, 2.57)	1.14 (0.72, 1.81)	2.35 (1.67, 3.32)	0.27 (-0.53, 1.06)
	rs876430	C	T	73	190	77	219	392	350	380	315	1.72 (1.22, 2.41)	0.82 (0.55, 1.21)	1.83 (1.30, 2.58)	0.30 (-0.21, 0.80)
	rs1051677	T	C	126	331	23	78	609	527	163	138	1.88 (1.43, 2.46)	0.80 (0.47, 1.36)	2.01 (1.42, 2.85)	0.34 (-0.36, 1.03)
	rs1051685	A	G	117	323	33	86	619	509	152	156	2.10 (1.59, 2.76)	1.12 (0.70, 1.80)	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	2.88 (1.97, 4.21)	1.77 (1.17, 2.66)	2.67 (1.84, 3.87)	-0.97 (-1.99, 0.04)
	rs1799798	G	A	126	331	24	78	631	570	141	95	1.82 (1.39, 2.39)	0.80 (0.47, 1.34)	2.32 (1.59, 3.40)	0.70 (-0.11, 1.52)
	rs744154	C	G	59	224	91	185	421	358	351	307	2.81 (1.98, 3.99)	1.85 (1.24, 2.76)	2.63 (1.84, 3.77)	-1.02 (-2.02, -0.02)
	rs3136085	G	C	59	220	91	189	416	356	356	309	2.75 (1.93, 3.92)	1.80 (1.21, 2.69)	2.63 (1.84, 3.77)	-0.92 (-1.89, 0.05)
	rs3136130	G	T	51	193	99	216	349	292	423	373	2.85 (1.95, 4.16)	1.73 (1.15, 2.61)	2.65 (1.83, 3.83)	-0.93 (-1.93, 0.06)
	rs1800067	G	A	125	355	25	54	653	565	119	100	2.03 (1.55, 2.64)	1.26 (0.73, 2.17)	2.11 (1.45, 3.07)	-0.18 (-1.13, 0.77)
	rs3136172	A	G	59	216	91	193	399	350	373	315	2.63 (1.85, 3.76)	1.71 (1.14, 2.55)	2.63 (1.84, 3.76)	-0.71 (-1.63, 0.20)
RAD23A	rs2974752	A	G	56	180	92	216	277	244	469	401	2.38 (1.63, 3.46)	1.43 (0.95, 2.16)	2.41 (1.68, 3.44)	-0.40 (-1.22, 0.42)

OR odds ratio, I interval estimates

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

[b]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 22 cont. Odds Ratios and Relative Excess Risk Estimates for Joint Effects of Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and 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								OR (95% I)[a]			
Gene	SNP	Referent (A) / Variant (B)		Cigarette=0, SNP=0		Cigarette=0, SNP=1		Cigarette=1, SNP=0		Cigarette=1, SNP=1		Cigarette=1, SNP=0	Cigarette=0, SNP=1	Cigarette=1, SNP=1	RERI (95% CI)
ERCC2															
(XPD)	rs13181	T	G	55	155	95	252	326	282	439	381	2.08 (1.42, 3.05)	1.06 (0.71, 1.60)	1.97 (1.36, 2.85)	-0.18 (-0.84, 0.49)
	rs238418	C	A	54	155	96	254	328	271	444	394	2.21 (1.50, 3.24)	1.10 (0.73, 1.65)	2.01 (1.38, 2.91)	-0.30 (-1.00, 0.41)
	rs1799787	C	T	68	203	82	206	404	342	368	323	2.19 (1.56, 3.09)	1.17 (0.79, 1.74)	2.08 (1.47, 2.94)	-0.29 (-0.98, 0.40)
	rs3916874	G	C	81	201	69	208	396	344	376	321	1.69 (1.21, 2.35)	0.75 (0.50, 1.11)	1.72 (1.23, 2.40)	0.28 (-0.20, 0.77)
	rs238416	G	A	62	193	88	216	307	275	464	388	2.17 (1.51, 3.12)	1.34 (0.90, 1.99)	2.40 (1.69, 3.41)	-0.11 (-0.83, 0.61)
	rs50872	C	T	80	221	70	187	451	363	319	301	2.15 (1.55, 2.97)	1.06 (0.71, 1.57)	1.85 (1.32, 2.59)	-0.36 (-1.02, 0.31)
	rs50871	T	G	43	89	107	320	199	169	573	495	1.37 (0.86, 2.16)	0.66 (0.42, 1.03)	1.47 (0.96, 2.23)	0.44 (-0.01, 0.89)
	rs238407	A	T	43	136	107	273	220	202	551	463	2.36 (1.54, 3.62)	1.40 (0.91, 2.16)	2.53 (1.71, 3.76)	-0.23 (-1.05, 0.59)
	rs3810366	C	G	32	95	118	314	146	137	625	528	2.29 (1.38, 3.77)	1.29 (0.80, 2.09)	2.42 (1.54, 3.80)	-0.16 (-1.03, 0.72)
ERCC1	rs735482	A	C	117	302	33	107	571	495	201	170	1.87 (1.41, 2.47)	0.81 (0.51, 1.30)	1.90 (1.36, 2.65)	0.22 (-0.40, 0.84)
	rs2336219	G	A	117	302	33	107	571	495	201	170	1.87 (1.41, 2.47)	0.81 (0.51, 1.30)	1.90 (1.36, 2.65)	0.22 (-0.40, 0.84)
	rs3212964	G	A	118	302	32	107	574	492	198	173	1.86 (1.41, 2.46)	0.78 (0.49, 1.24)	1.84 (1.32, 2.56)	0.20 (-0.40, 0.80)
	rs3212955	A	G	82	229	68	180	446	378	326	286	2.08 (1.51, 2.86)	1.10 (0.74, 1.63)	2.02 (1.45, 2.81)	-0.16 (-0.81, 0.49)
	rs3212948	C	G	60	171	90	238	322	287	450	378	2.01 (1.39, 2.90)	1.10 (0.74, 1.64)	2.14 (1.50, 3.05)	0.03 (-0.60, 0.66)
	rs3212930	T	C	92	248	58	161	484	409	288	256	1.95 (1.43, 2.65)	0.99 (0.66, 1.48)	1.98 (1.43, 2.75)	0.04 (-0.57, 0.65)
LIG1	rs156641	G	A	56	166	94	243	314	274	458	391	2.14 (1.46, 3.13)	1.22 (0.81, 1.82)	2.27 (1.58, 3.27)	-0.09 (-0.77, 0.60)
	rs20580	C	A	30	109	120	300	207	184	565	481	2.52 (1.55, 4.12)	1.54 (0.95, 2.48)	2.83 (1.79, 4.47)	-0.23 (-1.15, 0.69)
	rs20579	C	T	105	305	45	104	586	521	186	144	2.06 (1.55, 2.73)	1.34 (0.87, 2.08)	2.43 (1.71, 3.45)	0.03 (-0.81, 0.87)

OR odds ratio, I interval estimates

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

[b]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 23. Odds Ratios and Relative Excess Risk Estimates for Joint Effects of Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and 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								OR (95% I)[a]			
Gene	SNP	Referent (A) / Variant (B)		Cigarette=0, SNP=0		Cigarette=0, SNP=1		Cigarette=1, SNP=0		Cigarette=1, SNP=1		Cigarette=1, SNP=0	Cigarette=0, SNP=1	Cigarette=1, SNP=1	RERI
ERCC3															
(XPB)	rs4150496	G	A	70	154	79	255	331	238	441	427	1.84 (1.28, 2.64)	0.66 (0.45, 0.98)	1.41 (1.00, 1.99)	-0.09
	rs1011019	C	T	66	201	84	208	396	347	376	318	2.17 (1.54, 3.05)	1.25 (0.85, 1.85)	2.27 (1.60, 3.22)	-0.15
	rs4150434	G	A	89	264	61	145	459	406	313	259	2.12 (1.56, 2.87)	1.19 (0.80, 1.77)	2.09 (1.50, 2.90)	-0.23
	rs4150416	T	G	56	176	93	233	354	305	416	360	2.26 (1.57, 3.26)	1.25 (0.84, 1.87)	2.26 (1.57, 3.25)	-0.26
	rs4150407	A	G	55	129	95	280	263	182	509	483	2.00 (1.34, 2.98)	0.77 (0.51, 1.15)	1.53 (1.05, 2.21)	-0.24
	rs4150403	G	A	118	338	32	71	618	566	154	99	1.96 (1.49, 2.56)	1.26 (0.78, 2.04)	2.60 (1.80, 3.74)	0.38
	rs4150402	G	A	66	201	84	208	396	347	376	317	2.18 (1.54, 3.06)	1.25 (0.85, 1.85)	2.29 (1.61, 3.24)	-0.14
XPC	rs2228001	A	C	56	135	94	274	281	240	490	425	1.91 (1.30, 2.82)	0.86 (0.57, 1.28)	1.70 (1.17, 2.48)	-0.06
	rs3731143	T	C	135	361	15	48	683	596	89	69	1.89 (1.46, 2.45)	0.93 (0.51, 1.70)	2.50 (1.65, 3.78)	0.67
	rs2228000	C	T	91	222	59	187	433	376	337	288	1.75 (1.28, 2.39)	0.77 (0.52, 1.15)	1.78 (1.29, 2.48)	0.26
	rs3731124	A	C	81	228	69	181	440	371	332	294	2.10 (1.53, 2.88)	1.10 (0.74, 1.62)	1.98 (1.42, 2.75)	-0.22
	rs13099160	A	G	127	366	23	43	687	596	85	69	2.06 (1.59, 2.68)	1.56 (0.90, 2.70)	2.26 (1.48, 3.45)	-0.36
	rs3731093	T	C	120	350	27	56	656	569	111	90	2.09 (1.60, 2.74)	1.50 (0.89, 2.50)	2.48 (1.68, 3.65)	-0.11
	rs3731089	G	A	121	350	29	59	657	569	115	96	2.06 (1.58, 2.69)	1.51 (0.91, 2.49)	2.36 (1.61, 3.45)	-0.21
	rs2733537	A	G	70	175	80	234	346	305	426	360	1.76 (1.24, 2.50)	0.89 (0.60, 1.31)	1.92 (1.36, 2.71)	0.26
	rs3731068	C	A	99	275	51	134	525	457	247	208	1.97 (1.48, 2.64)	1.02 (0.68, 1.54)	2.01 (1.44, 2.79)	0.01
	rs2607755	T	C	39	110	111	299	203	174	569	491	2.11 (1.36, 3.29)	1.10 (0.71, 1.71)	2.11 (1.40, 3.19)	-0.10
	rs1902658	G	A	37	107	113	302	198	173	573	492	2.09 (1.33, 3.29)	1.11 (0.71, 1.74)	2.14 (1.40, 3.27)	-0.06
ERCC8	rs3117	T	C	60	144	90	265	277	253	495	412	1.71 (1.18, 2.50)	0.82 (0.55, 1.22)	1.76 (1.23, 2.52)	0.22
CDK7	rs2972388	A	G	42	122	108	287	224	213	548	452	1.82 (1.19, 2.78)	1.06 (0.70, 1.63)	2.17 (1.46, 3.23)	0.29
XPA	rs3176757	C	T	98	268	52	141	511	442	261	223	1.94 (1.44, 2.61)	1.03 (0.69, 1.55)	2.09 (1.50, 2.89)	0.11
	rs3176748	A	G	74	185	76	224	366	325	406	340	1.77 (1.26, 2.49)	0.85 (0.57, 1.25)	1.83 (1.30, 2.57)	0.21
	rs2808667	C	T	133	352	17	57	681	598	89	67	1.87 (1.44, 2.43)	0.90 (0.50, 1.61)	2.42 (1.60, 3.68)	0.65
	rs2805835	G	C	119	328	31	81	608	520	164	145	2.03 (1.54, 2.67)	1.11 (0.69, 1.78)	1.95 (1.38, 2.76)	-0.19
	rs3176689	A	T	94	279	56	130	528	449	244	216	2.14 (1.59, 2.88)	1.13 (0.75, 1.69)	1.87 (1.34, 2.62)	-0.39
	rs3176683	T	C	134	353	16	56	684	591	88	74	1.89 (1.46, 2.45)	0.78 (0.43, 1.40)	2.04 (1.35, 3.08)	0.37
	rs3176658	C	T	114	297	36	112	585	495	187	170	1.91 (1.45, 2.52)	0.86 (0.55, 1.34)	1.86 (1.32, 2.60)	0.09
	rs1800975	G	A	72	180	75	215	348	293	390	348	1.84 (1.30, 2.60)	0.91 (0.61, 1.34)	1.87 (1.32, 2.63)	0.12
RAD23B	rs1805330	C	T	125	321	25	88	639	549	133	116	1.86 (1.42, 2.43)	0.69 (0.42, 1.14)	1.68 (1.16, 2.43)	0.13
	rs1805329	C	T	101	277	49	132	489	434	283	231	2.01 (1.50, 2.69)	1.13 (0.75, 1.70)	2.12 (1.53, 2.93)	-0.02
ERCC6	rs2228529	A	G	96	258	52	146	501	403	261	250	2.12 (1.57, 2.87)	1.07 (0.71, 1.61)	1.84 (1.33, 2.56)	-0.35
	rs2228527	A	G	97	260	53	149	501	405	271	260	2.12 (1.57, 2.86)	1.06 (0.71, 1.58)	1.84 (1.33, 2.54)	-0.34
	rs4253132	T	C	126	303	24	106	597	526	175	139	1.67 (1.27, 2.20)	0.53 (0.32, 0.86)	1.86 (1.32, 2.62)	0.65
	rs2228528	G	A	104	287	46	122	533	459	238	206	2.01 (1.51, 2.68)	1.05 (0.69, 1.60)	1.97 (1.42, 2.74)	-0.08

OR odds ratio, I interval estimates

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

Table 23 cont. Odds Ratios and Relative Excess Risk Estimates for Joint Effects of Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and 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								OR (95% I)[a]			
Gene	SNP	Referent (A) / Variant (B)		Cigarette=0, SNP=0		Cigarette=0, SNP=1		Cigarette=1, SNP=0		Cigarette=1, SNP=1		Cigarette=1, SNP=0	Cigarette=0, SNP=1	Cigarette=1, SNP=1	RERI
DDB2															
(XPE)	rs2029298	A	G	69	195	81	214	356	283	416	382	2.37 (1.68, 3.34)	1.20 (0.82, 1.77)	2.02 (1.44, 2.84)	-0.55
	rs4647709	C	T	123	342	27	67	643	560	129	105	2.00 (1.53, 2.62)	1.16 (0.71, 1.92)	2.12 (1.46, 3.07)	-0.05
	rs2291120	T	C	123	296	27	113	562	516	210	149	1.70 (1.29, 2.24)	0.61 (0.38, 0.98)	1.95 (1.39, 2.74)	0.64
	rs1685404	G	C	72	180	78	229	346	322	426	343	1.67 (1.19, 2.36)	0.89 (0.60, 1.31)	2.02 (1.43, 2.84)	0.46
	rs2957873	A	G	101	275	49	134	542	436	230	229	2.20 (1.64, 2.95)	1.14 (0.76, 1.71)	1.77 (1.27, 2.46)	-0.57
	rs326224	G	A	105	288	45	121	578	473	194	192	2.13 (1.60, 2.84)	1.16 (0.76, 1.77)	1.87 (1.33, 2.62)	-0.43
	rs2306353	G	A	109	292	41	117	587	470	185	195	2.17 (1.64, 2.87)	1.10 (0.72, 1.69)	1.66 (1.19, 2.33)	-0.61
	rs326222	C	T	76	209	74	200	408	317	364	348	2.37 (1.70, 3.29)	1.15 (0.78, 1.70)	1.87 (1.34, 2.62)	-0.65
	rs901746	A	G	76	210	74	199	409	318	363	347	2.39 (1.72, 3.32)	1.17 (0.80, 1.73)	1.88 (1.35, 2.63)	-0.68
ERCC5															
(XPG)	rs2296147	T	C	41	114	109	291	239	189	528	474	2.13 (1.38, 3.28)	0.99 (0.65, 1.53)	1.87 (1.24, 2.81)	-0.26
	rs4771436	T	G	97	259	53	150	466	400	306	265	1.98 (1.47, 2.68)	0.98 (0.66, 1.47)	1.92 (1.39, 2.65)	-0.05
	rs1047768	C	T	57	142	93	267	262	235	510	429	1.72 (1.17, 2.52)	0.85 (0.57, 1.26)	1.80 (1.25, 2.60)	0.24
	rs3818356	C	T	97	259	53	149	466	400	304	264	1.97 (1.46, 2.66)	0.99 (0.66, 1.48)	1.91 (1.38, 2.64)	-0.06
	rs4150351	A	C	97	258	53	151	498	434	274	231	1.92 (1.43, 2.59)	0.95 (0.63, 1.42)	1.94 (1.40, 2.69)	0.07
	rs4150355	C	T	57	159	93	250	345	269	427	396	2.26 (1.56, 3.27)	1.05 (0.70, 1.56)	1.86 (1.29, 2.67)	-0.45
	rs4150360	T	C	50	119	100	290	225	197	547	468	1.71 (1.14, 2.59)	0.82 (0.54, 1.24)	1.71 (1.17, 2.52)	0.18
	rs4150383	G	A	106	296	44	113	524	453	248	212	2.02 (1.51, 2.69)	1.08 (0.70, 1.65)	2.00 (1.44, 2.78)	-0.09
	rs4150386	A	C	113	317	37	92	611	519	161	145	2.02 (1.53, 2.67)	1.02 (0.65, 1.60)	1.84 (1.29, 2.61)	-0.21
	rs17655	C	G	89	238	61	171	466	420	306	245	1.78 (1.31, 2.43)	0.89 (0.60, 1.32)	2.04 (1.46, 2.84)	0.36
	rs873601	A	G	73	190	77	219	391	349	381	316	1.73 (1.24, 2.42)	0.83 (0.56, 1.21)	1.84 (1.31, 2.58)	0.28
	rs4150393	A	G	114	317	36	92	588	527	184	138	1.94 (1.47, 2.56)	1.15 (0.73, 1.80)	2.35 (1.67, 3.32)	0.26
	rs876430	C	T	73	190	77	219	392	350	380	315	1.73 (1.24, 2.41)	0.83 (0.56, 1.21)	1.84 (1.31, 2.59)	0.29
	rs1051677	T	C	126	331	23	78	609	527	163	138	1.89 (1.44, 2.47)	0.81 (0.49, 1.36)	2.01 (1.42, 2.85)	0.31
	rs1051685	A	G	117	323	33	86	619	509	152	156	2.09 (1.59, 2.74)	1.10 (0.70, 1.75)	1.67 (1.18, 2.38)	-0.52
ERCC4															
(XPF)	rs3136038	C	T	51	195	99	214	351	295	421	370	2.82 (1.94, 4.10)	1.72 (1.16, 2.57)	2.64 (1.83, 3.81)	-0.91
	rs1799798	G	A	126	331	24	78	631	570	141	95	1.83 (1.40, 2.40)	0.82 (0.50, 1.36)	2.32 (1.58, 3.39)	0.66
	rs744154	C	G	59	224	91	185	421	358	351	307	2.76 (1.95, 3.90)	1.80 (1.22, 2.66)	2.61 (1.82, 3.73)	-0.95
	rs3136085	G	C	59	220	91	189	416	356	356	309	2.71 (1.91, 3.83)	1.76 (1.19, 2.60)	2.61 (1.82, 3.73)	-0.86
	rs3136130	G	T	51	193	99	216	349	292	423	373	2.79 (1.92, 4.05)	1.69 (1.13, 2.52)	2.61 (1.81, 3.78)	-0.87
	rs1800067	G	A	125	355	25	54	653	565	119	100	2.02 (1.55, 2.63)	1.24 (0.73, 2.11)	2.11 (1.45, 3.07)	-0.15
	rs3136172	A	G	59	216	91	193	399	350	373	315	2.60 (1.83, 3.68)	1.67 (1.13, 2.48)	2.61 (1.82, 3.73)	-0.66
RAD23A	rs2974752	A	G	56	180	92	216	277	244	469	401	2.35 (1.62, 3.41)	1.42 (0.95, 2.11)	2.39 (1.67, 3.42)	-0.37

OR odds ratio, I interval estimates

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

Table 23 cont. Odds Ratios and Relative Excess Risk Estimates for Joint Effects of Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and 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								OR (95% I)[a]			
Gene	SNP	Referent (A) / Variant (B)		Cigarette=0, SNP=0		Cigarette=0, SNP=1		Cigarette=1, SNP=0		Cigarette=1, SNP=1		Cigarette=1, SNP=0	Cigarette=0, SNP=1	Cigarette=1, SNP=1	RERI
ERCC2															
(XPD)	rs13181	T	G	55	155	95	252	326	282	439	381	2.08 (1.43, 3.02)	1.06 (0.71, 1.58)	1.96 (1.36, 2.84)	-0.17
	rs238418	C	A	54	155	96	254	328	271	444	394	2.19 (1.50, 3.20)	1.09 (0.73, 1.63)	2.00 (1.38, 2.89)	-0.28
	rs1799787	C	T	68	203	82	206	404	342	368	323	2.18 (1.56, 3.06)	1.16 (0.79, 1.71)	2.07 (1.47, 2.93)	-0.27
	rs3916874	G	C	81	201	69	208	396	344	376	321	1.70 (1.22, 2.36)	0.76 (0.51, 1.11)	1.73 (1.24, 2.41)	0.27
	rs238416	G	A	62	193	88	216	307	275	464	388	2.16 (1.51, 3.09)	1.33 (0.90, 1.96)	2.40 (1.69, 3.39)	-0.09
	rs50872	C	T	80	221	70	187	451	363	319	301	2.14 (1.55, 2.95)	1.05 (0.71, 1.55)	1.85 (1.32, 2.58)	-0.34
	rs50871	T	G	43	89	107	320	199	169	573	495	1.40 (0.89, 2.19)	0.67 (0.44, 1.05)	1.49 (0.98, 2.25)	0.41
	rs238407	A	T	43	136	107	273	220	202	551	463	2.33 (1.53, 3.55)	1.39 (0.91, 2.11)	2.51 (1.70, 3.72)	-0.21
	rs3810366	C	G	32	95	118	314	146	137	625	528	2.26 (1.39, 3.68)	1.28 (0.81, 2.04)	2.41 (1.54, 3.75)	-0.14
ERCC1	rs735482	A	C	117	302	33	107	571	495	201	170	1.87 (1.42, 2.47)	0.82 (0.52, 1.30)	1.90 (1.36, 2.65)	0.20
	rs2336219	G	A	117	302	33	107	571	495	201	170	1.87 (1.42, 2.47)	0.82 (0.52, 1.30)	1.90 (1.36, 2.65)	0.20
	rs3212964	G	A	118	302	32	107	574	492	198	173	1.87 (1.42, 2.46)	0.79 (0.50, 1.24)	1.84 (1.32, 2.56)	0.18
	rs3212955	A	G	82	229	68	180	446	378	326	286	2.08 (1.51, 2.85)	1.09 (0.74, 1.61)	2.02 (1.45, 2.81)	-0.15
	rs3212948	C	G	60	171	90	238	322	287	450	378	2.01 (1.40, 2.88)	1.10 (0.74, 1.63)	2.14 (1.50, 3.05)	0.03
	rs3212930	T	C	92	248	58	161	484	409	288	256	1.95 (1.44, 2.64)	0.99 (0.67, 1.47)	1.98 (1.43, 2.75)	0.04
LIG1	rs156641	G	A	56	166	94	243	314	274	458	391	2.13 (1.47, 3.10)	1.21 (0.81, 1.80)	2.26 (1.57, 3.26)	-0.08
	rs20580	C	A	30	109	120	300	207	184	565	481	2.48 (1.54, 4.00)	1.51 (0.95, 2.41)	2.80 (1.78, 4.38)	-0.20
	rs20579	C	T	105	305	45	104	586	521	186	144	2.05 (1.55, 2.72)	1.34 (0.87, 2.05)	2.43 (1.71, 3.45)	0.04

OR odds ratio, I interval estimates

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

CHAPTER 4

SINGLE NUCLEOTIDE POLYMORPHISMS IN NUCLEOTIDE EXCISION REPAIR GENES, CANCER TREATMENT, AND HEAD AND NECK CANCER SURVIVAL

4.1 OVERVIEW

Head and neck cancers (HNC) are commonly treated with radiation and platinum-based chemotherapies which produce bulky DNA adducts to eradicate cancerous cells. Because nucleotide excision repair (NER) enzymes remove adducts, variants in NER genes may be associated with survival among HNC cases both independently and jointly with treatment. Cox proportional hazards models were used to estimate race-stratified (white, African American) hazard ratios (HR) and 95% confidence intervals (CI) for overall (OS) and disease-specific (DS) survival based on treatment (combinations of surgery, radiation, and chemotherapy) and 84 single nucleotide polymorphisms (SNPs) in 15 NER genes among 1,227 HNC cases from the Carolina Head and Neck Cancer Epidemiology (CHANCE) study. None of the NER variants were associated with survival at a Bonferroni-corrected alpha of 0.0006. However, rs3136038 [OS HR=0.79 (0.65, 0.97), DS HR=0.69 (0.51,0.93)] and rs3136130 [OS HR=0.78 (0.64,0.96), DS HR=0.68 (0.50,0.92)] of *ERCC4* and rs50871 [OS HR=0.80 (0.64, 1.00), DS HR=0.67 (0.48,0.92)] of *ERCC2* among whites, and rs2607755 [OS HR=0.62 (0.45, 0.86), DS HR=0.51 (0.30, 0.86)] of *XPC* among African Americans were associated with survival at 0.05 alpha before correction. Three SNP-treatment joint effects showed possible departures from additivity for overall survival among whites. Our study, the largest and most comprehensive evaluation of SNPs in NER genes to date, identified mostly null associations between SNPs in NER genes and survival among HNC cases, though a few variants were suggestively

associated with survival and potentially interacted additively with treatment.

4.2 BACKGROUND

An estimated 52,140 incident head and neck cancer (HNC) cases and 11,460 associated deaths occurred in the US during 2011 (1). HNC is a relatively fatal disease, with 5 year survival rates of 58.9% and 61.2% for white men and women, respectively, and 30.7% and 50.6% among African American men and women, respectively (61,62). HNC was historically treated with surgery and/or radiation therapy (65). However, following a series of clinical trials in the 1990s the majority of advanced tumors (stage 3 and 4) are increasingly treated with concurrent or induction radiation and chemotherapy (72). In addition to stage, other tumor characteristics (e.g., location and size) and the patients' demographics (e.g., age) can influence treatment decisions and outcomes (122).

Emerging literature suggests that genetic factors, namely, variants in nucleotide excision repair (NER) genes, may also impact treatment response and survival among HNC cases (7,47-55,204). In order to initiate cell death (apoptosis) of cancerous cells, radiation and platinum-based chemotherapy are known to cause bulky DNA adducts, among other types of DNA damage (6,7,48). Since NER is the pathway primarily responsible for removing DNA adducts, functional NER processes may lessen the efficacy of cancer treatment (6). This hypothesis has led some researchers to describe DNA repair, including NER, as a "double-edged sword" or "Janus-the two faced Roman god" since functional genes are thought to protect against cancer incidence, but may also mitigate the effectiveness of cancer treatments thus decreasing survival (6).

Previous epidemiologic studies on the effects of single nucleotide polymorphisms (SNPs) in NER genes and treatment on HNC mortality have been inconsistent (7,47-55). For example, some studies conducted among patients receiving radiation reported null associations for rs13181 in excision repair cross-complementing 2 (*ERCC2*) and survival (48,50). Other studies showed evidence for significant differences in survival across genotypes of rs13181 (47,53,54), including a study which

found the wild-type genotype was associated with worse survival among individuals treated with radiation and better survival among those receiving no treatment (7). However, previous studies have been based on small sample sizes, predominantly European-descent populations, and a limited number of variants in NER genes (7,47-55). The present study, therefore, extends the literature by estimating main and joint effects of treatment and 84 SNPs across 15 NER genes on survival among a large, racially diverse population-based study of HNC cases.

4.3 METHODS

4.3.1 Study Population

The Carolina Head and Neck Cancer Epidemiology (CHANCE) study is a population-based case-control study of 2,785 individuals (1,389 cases and 1,396 controls) from 46 of 100 counties in North Carolina (57,63,64). For the present analysis, a case-only study design was employed to compare survival among cases by treatment and genotype. All cases were aged 20 to 80 years of age and were identified from the North Carolina Central Cancer Registry between January 1, 2002 and February 28, 2006 using rapid case ascertainment (57,63,64). Self-reported demographic and behavioral information, including age, sex, race, education, alcohol drinking, and cigarette smoking, was ascertained for each case through nurse-administered questionnaires (57,63,64). Biologic samples (~90% blood and ~10% buccal cells) were also collected from cases at the time of interview (64). Individuals who self-reported race other than white or African American were excluded due to sparse data (26 cases, 1.9%) and lip cancer cases (21 cases, 1.3%) were excluded for differences in etiology compared to the more common HNC sites studied. Cases who either did not provide blood or buccal cell samples or whose sample was insufficient for genotyping (115 cases, 8.3%) were also excluded. Therefore, our analysis included 1,227 HNC cases (922 white cases and 305 African American cases).

4.3.2 SNP Selection and Genotyping

Illumina GoldenGate assay with Sentrix Array Matrix and 96-well standard microtiter plates were used for genotyping (64,137). As described for aim 1, 129 SNPs in 15 NER genes included 71 tag SNPs in 8 genes selected based on a case-control study of HNC at The University of Texas MD Anderson Cancer Center ($r^2 \geq 0.80$, a minor allele frequency (MAF) ≥ 0.05, 1 to 2 kb up- or down-stream, CEU population) (129,139,140) and 58 SNPs in 12 genes selected based on other HNC studies and/or potential function (129,139,140) (table 13). Since tagging SNPs were selected for only 8 genes among the CEU population, and other candidate SNPs were selected based on previous literature conducted primarily among European-descent populations, it should be noted that the amount of variation captured across some genes was limited, especially among African American. For this reason, haplotypes were not explored.

Of the 129 NER SNPs, variants with weak signal intensity or indistinguishable genotype clusters (14 SNPs) or a MAF less than 0.05 (30 SNPs among whites and 36 SNPs among African Americans) were excluded (table 13). Nearly all excluded SNPs were candidate SNPs selected based on previous literature (i.e. only 5 tag SNPs were excluded for failing genotyping and only 1 tag SNP among whites was excluded for having a MAF < 0.05) (table 13). As determined for aim 1, frequencies for 7 SNPs in white controls and 7 SNPs in African American controls were inconsistent with Hardy-Weinberg equilibrium ($p<0.05$); however, since genotype scatter plots showed reasonable clustering, none of these SNPs were excluded from analyses (147). Our analysis included 84 SNPs in 15 NER genes among whites and 79 SNPs in 14 NER genes among African Americans.

4.3.3 Treatment

First-course treatment information was abstracted from patients' medical records. Information included whether the patient received surgery, radiation therapy, and chemotherapy, including types of chemotherapy drugs (82,135). Chemotherapy drugs included: carboplatin,

paraplatin, cisplatin, 5 FU, taxol, taxotere, docetaxel, paclitaxel, ifosfamide, and other. Information on treatment start and end dates and whether radiation and chemotherapy were administered concurrently was not available for a large proportion of individuals (e.g., chemotherapy end dates were missing for approximately a quarter of patients treated with chemotherapy). Therefore, combinations of treatment were generated from dichotomous variables for surgery, radiation, chemotherapy regardless of timing. Finally, information on tumor histology and stage were abstracted from cases' medical records (82,135).

4.3.4 HNC Survival

CHANCE data were linked to the National Death Index (NDI) based on name, social security number, and date of birth to identify deaths through 2009, including date of death, location of death, and cause of death (205). Death records with HNC listed as the primary or secondary cause of death were considered disease-specific deaths. Individuals not present in the NDI were considered alive as of December 31, 2009.

4.3.5 Statistical Analysis

Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the independent effects of treatment, the independent effects of SNPs in NER genes, and the joint effects of treatment and SNPs on HNC survival among whites and African Americans separately. To evaluate the proportionality of hazards, we examined adjusted log negative log plots by treatment/genotype (171,172). In addition, we assessed the significance of including an interaction term for treatment/genotype and time in models (171,172). If log negative log plots indicated a violation of the proportional hazards assumption and interaction terms with time were significant ($p<0.05$), accelerated failure time (AFT) models were fit to explore robustness of results. This was the case for 4 SNPs in whites (rs3731068, rs744154, rs3136085, rs3136172) and 3 SNPs in African Americans (rs4150360, rs2020955,

rs13181). However, because p-values for the AFT models were similar to those obtained from Cox models (ie the same set of significant SNP-HNC survival associations resulted from both approaches), results from the Cox models without an interaction term between SNPs and time are presented for simplicity.

Absolute differences in HNC survival by genotype and treatment were also assessed via Kaplan-Meier plots, with cumulative survival calculated as the percent of cases alive at each time point, and log rank tests were used to assess differences in survival.

For overall survival models, follow-up started at date of diagnosis for all cases and ended at date of death for individuals who died or censoring on December 31, 2009 for individuals who were still alive. For HNC disease-specific survival models, follow-up started at date of diagnosis for all cases and ended at date of death for individuals who died of HNC or censoring at date of death for individuals who died from causes other than HNC or December 31, 2009 for individuals who were still alive.

4.3.5.1 Treatment-Survival Associations

Treatment was modeled as a categorical variable with six mutually exclusive levels: surgery only; radiation only; surgery and radiation; radiation and chemotherapy; surgery, radiation, and chemotherapy; and other (no treatment, chemotherapy only, or surgery and chemotherapy without radiation). Surgery only was used as the referent category because few individuals received no treatment (9 cases, 0.7%). Because even fewer individuals received chemotherapy only or chemotherapy with surgery without radiation (4 cases, 0.3%), these individuals were combined with individuals receiving no treatment into a single category labeled "other treatment." In a separate model, we also considered ever receiving platinum-based chemotherapy drugs (carboplatin, paraplatin, or cisplatin, N=464) versus never receiving platinum-based chemotherapy drugs (i.e. never receiving chemotherapy, N=754, or only

receiving non-platinum based chemotherapy drugs, including 5 FU, taxol, taxotere, docetaxel, paclitaxel, or ifosfamide, N=9). All treatment models were adjusted for sex, age (5 year categories), race, stage (American Joint Committee on Cancer, AJCC, stages I, II, III, IV) (118), tumor site (oral cavity, oropharynx, hypopharynx, larynx, HNC NOS), education (less than a high school education, a high school education, or a college education), duration of cigarette smoking (years), and frequency of alcohol use (categorical indicator for lifetime alcohol consumption in ml/day).

4.3.5.2 SNPs-Survival Associations

In agreement with aim 1, SNPs were defined using a dominant genetic model and the referent allele for both whites and African Americans was assigned to be the major allele based on controls from the overall CHANCE study population. Models included a single SNP at a time, with p-values adjusted using the Bonferroni method (0.05/84 =0.0006 among whites and 0.05/79=0.0006 among African Americans). SNP-survival associations with p-values below 0.05 but not significant at a Bonferroni corrected alpha level were considered as "suggestive" associations. Because NER germline SNPs are unlikely to be associated with smoking and drinking, and therefore these behaviors would not be considered confounders based on our directed acyclic graph (DAG) (160), SNP models only included sex, age, and ancestry (percent African ancestry). As described in previous studies of cancer among whites and African Americans in North Carolina, 157 ancestral informative markers (AIMS) were used to estimate the proportion of African and European ancestry of each participant based on Fisher's information criterion (FIC) (64,157,201).

4.3.5.3 Joint Effects

Joint effects models included a single SNP at a time (defined using the dominant genetic model), treatment (disjoint indicator variables for six treatment categories), and interaction

terms between the SNP and treatments. Joint effects between SNPs and platinum-based chemotherapy (yes/no) were considered in a separate model. Since both treatment and genetic exposures were assessed, joint effects models were adjusted for sex, age, stage, anatomic site, education, cigarette smoking, alcohol drinking, and ancestry. Interactions between SNPs in NER genes and treatments were assessed on the additive scale using the relative excess risk for interaction (RERI), also known as the interaction contrast ratio (ICR). Specifically, RERIs were calculated as HR11 - HR01 - HR10 + HR00, where HR11 is the hazard ratio among individuals who received the specified treatment and had a variant genotype, HR01 is among individuals who received the specified treatment and had a referent genotype, HR10 is among individuals who received surgery only and had the variant genotype, and HR00 is among individuals who received surgery only and had the referent genotype (which equals 1.0 as it is the referent) (160,161). Confidence intervals for the ICR were calculated using the Hosmer and Lemeshow method (161). Statistical analyses were performed using SAS 9.3 (Cary, NC) (163).

4.4 RESULTS

4.4.1 Characteristics of Study Population

Of the 1,227 HNC cases in CHANCE, 545 (44.4%) cases linked with the National Death Index through 2009 (table 24). The remaining 682 (55.6%) cases were assumed to be alive as of December 31, 2009. The median and mean follow-up times were 919.7 days and 764.0 days, respectively, among individuals who died and 2138.4 days and 2087.0 days, respectively, among those who were alive. Among the 545 individuals who died, just under half (227 cases, 41.7%) had head and neck cancer listed as primary or secondary cause of death. Among these disease-specific deaths, the median and mean follow-up times were 729.7 days and 594.0 days, respectively.

Very modest variation by sex and age at diagnosis was observed when comparing cases who were living and dead after study follow-up (table 24). However, a noticeably higher proportion of

individuals who died were African American (29.7% vs. 21.0%) or had a high school education or less (71.9% vs. 53.1%) compared to living cases. With respect to tumor site, similar proportions had a diagnosis of laryngeal cancer (36.1%). In contrast, 23.5% of cases who died had oropharyngeal cancer compared to 30.1% of cases who were living. As expected (59,60), the distribution of tumor stage also varied by survival status, with living individuals tending to have lower tumor stage.

4.4.2 Treatment-Survival Associations

Among whites, individuals who received radiation only tended to have worse overall survival (HR=1.59, 95% CI=1.08, 2.34) and disease-specific survival (HR=2.47, 95% CI=1.34, 4.56) compared to individuals who were treated with surgery alone (table 25). Individuals receiving no treatment or other treatment (i.e. chemotherapy only, chemotherapy and surgery, or no treatment) also appeared to have poorer overall and disease-specific survival, though estimates were imprecise. In a separate model considering the effects of platinum-based chemotherapy on HNC survival, receiving platinum-based chemotherapy appeared to be associated with better overall survival (HR=0.71, 95% CI=0.52, 0.95 among whites and HR=0.77, 95% CI=0.48, 1.20 among African Americans) and disease-specific survival (HR=0.63, 95% CI=0.41, 0.97 among whites and HR=0.44, 95% CI=0.19, 1.02 among African Americans) (table 25).

4.4.3 SNPs-Survival Associations

Among whites, 4 SNPs were modestly associated with overall survival only and 3 SNPs were modestly associated with both overall and disease-specific survival at an uncorrected 0.05 alpha level (table 26). However, after correcting the alpha level using the Bonferroni method, no SNPs were statistically significantly associated with either survival outcome. Among the SNPs associated with overall and disease-specific survival at an uncorrected 0.05 alpha level, 2 tag SNPs were in linkage disequilibrium (LD) (r^2=0.92, CEU population) on *ERCC4*, which is also known as xeroderma pigmentosum F (*XPF*) (203). Specifically, the variant genotypes of rs3136038 (TT and TC vs CC) and

rs3136130 (TT and GT vs GG) were suggestively associated with a similarly reduced hazards of overall death (HR=0.79, uncorrected 95% CI=0.65, 0.97 and HR=0.78, uncorrected 95% CI=0.64, 0.96, respectively) and disease-specific death (HR=0.69, uncorrected 95% CI=0.51, 0.93, and HR=0.68, uncorrected 95% CI=0.50, 0.92, respectively). In addition, the variant genotype of rs50871 (TT and TC vs CC), a tag SNP on *ERCC2* which is also known as *XPD*, was associated with decreased hazards of overall death (HR=0.80, uncorrected 95% CI=0.64, 1.00) and disease-specific death (HR=0.67, uncorrected 95% CI=0.48, 0.92). Stratifying by tumor stage, associations for rs3136038 or rs3136130 and survival were strongest among stage 4 cases and rs50871 among stage 3 cases (supplementary table 7S, Appendix C). Figure 12 shows the Kaplan-Meier plots for these SNPs and overall and disease-specific survival.

Among African Americans, 2 SNPs were associated with overall survival and 4 SNPs were associated disease-specific survival at a 0.05 alpha level, but again none of these SNPs were significantly associated with survival at a Bonferroni-corrected level (table 27). Only one SNP was associated with both overall and disease-specific survival at a 0.05 alpha level. Specifically, rs2607755 (CC and CT vs TT) on *XPC* was suggestively associated with reduced hazards of overall survival (HR=0.62, uncorrected 95% CI=0.45, 0.86) and disease-specific survival (HR=0.51, uncorrected 95% CI=0.30, 0.86). This association was strongest among cases with stage 4 tumors (supplementary table 7S, Appendix C). Figure 13 show the Kaplan-Meier plots for this SNP and overall and disease-specific survival.

4.4.4 Joint Effects

At an uncorrected 0.05 alpha level, 3 SNPs appeared to interact super-additively with radiation, 6 SNPs appeared to interact super-additively with radiation and chemotherapy treatment, and 1 SNP appeared to interact sub-additively with surgery, radiation, and chemotherapy, with respect to overall survival among whites (supplementary table 8S, Appendix C). Of these suggestive

interactions, 1 SNP-radiation and 2 SNP-radiation, chemotherapy interactions were significant at a Bonferroni corrected 0.0006 alpha level. Specifically, rs2972388 of *CDK7* interacted super-additively with radiation only (RERI=1.07, uncorrected 95% CI=0.55, 1.60) and radiation and chemotherapy (RERI=0.72, uncorrected 95% CI=0.33, 1.10). In addition, rs2974752 of *RAD23A* interacted super-additively with radiation and chemotherapy (RERI=0.80, uncorrected 95% CI=0.36, 1.24). However, genotype frequencies for both of these SNPs among white controls from aim 1 appeared inconsistent with HWE at a 0.05 alpha level, although the genotype clustering plots did appear reasonable. Therefore, some caution should be used in interpreting these interactions. When disease-specific survival was considered, no SNP-treatment interactions were significant at a Bonferroni-corrected level (data not shown). Examining platinum-based chemotherapy separately, 10 SNPs suggested additive interactions at an uncorrected alpha level with respect to overall survival among whites, but none were significant after correction for multiple comparisons (supplementary table 9S, Appendix C). Among African Americans, no SNP-treatment interactions appeared to be significant at a Bonferroni corrected alpha level; however, estimates were unreliable due to relatively low cell counts and are therefore not presented (data not shown, Appendix D).

4.5 DISCUSSION

We detected mostly null associations between 84 SNPs in 15 NER genes and survival among white and African American HNC cases. Identifying null associations is important for following-up early positive associations, avoiding publication bias, and informing future meta-analyses (206). It should also be noted that we used the Bonferroni approach to account for multiple comparisons, which though widely used in genetic epidemiology, assumes independence of tests (164-166). Given the correlated nature of SNPs, including a number of SNPs in our study, using the Bonferroni correction may be overly conservative potentially resulting in false negatives (164-166). Therefore

we also highlighted SNP-survival associations with the lowest p-values (i.e. p-values below 0.05) in this paper as suggestive associations warranting further investigation.

Among white HNC cases, we found that the variant genotypes of 3 tag SNPs, rs3136038 located near the 5' end of *ERCC4 (XPF)*, rs3136130 in intron 5 of *ERCC4 (XPF)*, and rs50871 in intron 11 of *ERCC2 (XPD*), were modestly associated with improved overall and disease-specific survival among white HNC cases (202,207). The ERCC4 enzyme acts in conjunction with XPG to remove DNA adducts by creating an incision at the 5' end of a damage site, while ERCC2 operates as a component of the transcription factor II H (TFIIH) subunit which denatures the double helix in preparation for this incision (123,124). Among African American HNC cases, the variant genotype of tag SNP rs2607755 of *XPC* intron 2 (202,207) was also suggestively associated with improved overall and disease-specific survival. The XPC enzyme acts first in the NER pathway to recognize and bind to DNA adducts (123,124).

Although no previous HNC studies examined rs3136038 or rs3136130 on *ERCC4 (XPF)*, two studies assessed 9 other *ERCC4 (XPF)* SNPs (rs1799799, rs1799801, rs3136105, rs3136146, rs3136152, rs3136155, rs3136166, rs3136189, rs3136202), many of which were in LD with the SNPs in our study (based on CEU population) (47,55,203). While 5 of these SNPs were not associated with progression free survival among HNC cases, 4 SNPs appeared to be potentially associated with worse progression free survival (PFS HR=1.94, p-value=0.065 for rs1799799 T>C; PFS HR= 2.00, p-value=0.053 for rs3136155 C>T; PFS HR=1.94, p-value=0.065 for rs3136166 T>G; PFS HR=1.44, p-value=0.065 for rs3136202 G>A) contrary to our study (47,55). Among esophageal cancer cases, a study by Lee et al. did assess rs3136038 reporting better overall survival associated with the genotype TT, though HRs were not statistically significant (OS HR=1.55, 95% CI=0.84, 2.86 for CT vs. TT and OS HR=1.20, 95% CI=0.66, 2.20 for CC vs TT) similar to our study. Further, ERCC4 protein expression has been found to be up regulated in HNC cell lines, and displayed cisplatin resistance

(208). With respect to *ERCC2 (XPD)*, no previous studies have considered the effects of rs50871 on HNC survival. Rather, rs13181 and rs1799793 (which are not in LD for CEU) are the most commonly studied SNPs in *ERCC2,* with the majority of studies reporting near null associations between these SNPs and survival among HNC cases (47,48,50,53,54,203). In our study, rs13181 was also not associated with survival. Finally, no previous studies have considered associations between rs2607755 of *XPC* and survival, nor have any studies considered association between any NER variants and survival among African American HNC cases. Only one previous study has investigated a single variant in *XPC,* rs2228001 (which is not in LD with rs2607755 for YRI but is for CEU), noting no association with overall survival among a cohort of Spanish HNC patients (log rank p-value=0.96 for C>A) (48,203). Likewise, we did not find an association between rs2228001 and overall or disease-specific survival.

Since radiation and platinum-based chemotherapy are known to cause DNA damage repaired by NER genes (6,7,48), we also considered associations between SNPs and survival among HNC cases in the context of treatment. Accounting for multiple comparisons using the Bonferroni method, we found interactions between the candidate SNP rs2972388 of *CDK7* and radiation only, as well as radiation and chemotherapy, were more than additive with respect to overall survival among whites. In addition, rs2974752 of *RAD23A*, also a candidate SNP, interacted super-additively with radiation and chemotherapy. However, these SNPs showed some inconsistent evidence for HWE. No previous studies have considered SNPs in *RAD23A* and *CDK7* in relation to treatment and HNC survival. Only one previous study has compared NER SNP-survival associations across strata of different treatment regimens (7). Specifically, a study by Zhong et al. analyzed the effect of rs13181 in *ERCC2* on survival among 275 HNC cases receiving radiotherapy and 210 cases not receiving radiotherapy (7). Among cases with stage 3 and 4 tumors, the genotype for those homozygous for the wild-type allele (AA) was associated with poorer overall survival among those treated with

radiation (OS HR= 1.66, 95% CI=1.15, 2.40 for AA vs. AC + CC), but better survival among those who did not receive radiation (OS HR=0.26, 95% CI=0.11, 0.62) (7). Among cases with stage 1 and 2 tumors who did not receive radiation, however, rs13181 was not associated with survival (OS log rank p-value=0.78) (7).

With a population-based study of 1,227 HNC cases, the present study included more than double the number of HNC cases of the next largest study (47). Study populations of previous publications were mostly hospital-based and ranged from 47 to 531 HNC cases (47,51). Further, the present study population included 922 white cases and 305 African Americans cases which allowed for estimation of race-specific HRs, which is an important new contribution of this study. Linkage disequilibrium is known to vary by ancestral populations and distinct differences in survival by race occur in the United States (e.g., five-year survival rates among African Americans are almost half those among whites) (61,62,129). Yet, prior to this study, no studies had considered association between NER variants and survival among African American HNC cases. Another contribution of our study was the broad evaluation of NER variants which includes a large number of SNPs that have not been previously evaluated with respect to survival among HNC cases. Previous studies have collectively examined approximately 18 SNPs in 6 NER genes and survival among HNC cases (7,47-55). This study included 84 SNPs across 15 NER genes.

Although our study included the largest study population and the largest number of SNPs in NER genes to date, a few limitations should be noted. First, information on treatment was abstracted from medical records. While information on whether patients received (yes/no) surgery, radiation, and chemotherapy (including chemotherapy drug) was available, information on duration of treatment (e.g., start and end dates) and timing of treatments combinations (e.g., induction, adjuvant, or concurrent chemotherapy) were not complete. Therefore, treatment was considered solely as the first-course combinations of dichotomous variables for surgery, radiation, and

chemotherapy. Second, tagging SNPs were not selected for all genes and SNPs were selected based on the CEU population. Therefore, the amount of variation captured across some genes was limited, especially among African Americans. Third, joint effect estimates for SNPs and treatment were generally imprecise among whites and not considered among African Americans due to small cell counts. Fourth, models were adjusted for cigarette smoking and alcohol intake information that was ascertained at baseline based on behaviors prior to diagnosis since information on behavioral risk factors following diagnosis was not uniformly available. Further, we did not have information on human papillomavirus (HPV), which is a strong predictor of survival among cases with oropharyngeal tumors. Finally, we did not have access to information on recurrent tumors and were therefore unable to consider disease-free or relapse-free survival.

Most associations between NER variants and survival among HNC cases were null. However, three SNPs in whites (rs3136038 and rs3136130 of *ERCC4* and rs50871 of *ERCC2*) and 1 SNP among African Americans (rs2607755 of *XPC*) were suggestively associated with both overall and disease-specific survival. Therefore, it is recommended that future genetic epidemiology studies of HNC survival include these SNPs for replication. With respect to SNP-treatment joint effects and overall survival, two SNPs (rs2972388 of *CDK7* and rs2974752 of *RAD23A*) appeared to possibly interact additively with treatment consisting of radiation and chemotherapy, and one SNP (rs2972388 of *CDK7*) with radiation alone among whites. While our study is the largest to date, it is only the second to consider the NER variant-treatment effects on HNC survival. Therefore, additional studies with even larger sample sizes are needed to evaluate gene-environment interactions more precisely. Further studies focusing on African American and other diverse populations are recommended.

Table 24. Demographic Characteristics of Head and Neck Cancer Cases, Carolina Head and Neck Cancer Epidemiology (CHANCE) Study

	Alive		Overall Deaths		Disease-Specific Deaths	
Characteristic	**N**	**%**	**N**	**%**	**N**	**%**
Total	682	55.6	545	44.4	227	
Sex						
Male	519	76.1	419	76.9	169	74.4
Female	163	23.9	126	23.1	58	25.6
Race/Ethnicity						
White	539	79.0	383	70.3	169	74.4
African American	143	21.0	162	29.7	58	25.6
Age at Diagnosis						
20-49	152	22.3	87	16.0	42	18.5
50-54	110	16.1	79	14.5	30	13.2
55-59	125	18.3	82	15.0	35	15.4
60-64	118	17.3	87	16.0	37	16.3
65-69	78	11.4	90	16.5	33	14.5
70-74	64	9.4	71	13.0	27	11.9
75-80	35	5.1	49	9.0	23	10.1
Education						
High school or less	362	53.1	392	71.9	157	69.2
Some college	195	28.6	99	18.2	48	21.1
College or more	125	18.3	54	9.9	22	9.7
Tumor Site						
Oral cavity	81	11.9	91	16.7	38	16.7
Oropharynx	205	30.1	128	23.5	54	23.8
Hypophaynx	16	2.3	39	7.2	15	6.6
NOS	134	19.6	90	16.5	42	18.5
Larynx	246	36.1	197	36.1	78	34.4
Stage						
I	195	28.6	84	15.4	17	7.5
II	119	17.4	101	18.5	38	16.7
III	118	17.3	93	17.1	40	17.6
IV	250	36.7	267	49.0	132	58.1
Surgery						
No	269	39.4	268	49.2	119	52.4
Yes	413	60.6	277	50.8	108	47.6
Radiation						
No	177	26.0	105	19.3	37	16.3
Yes	505	74.0	440	80.7	190	83.7
Chemotherapy						
No	428	62.8	326	59.8	130	57.3
Yes	254	37.2	219	40.2	97	42.7
Mean Follow-Up Time (Days)	2138.4		919.7		729.7	
Median Follow-Up Time (Days)	2087.0		764.0		594.0	

Table 25. Hazard Ratios for Cancer Treatment and Head and Neck Cancer Survival in the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study

	Whites					African Americans				
Cancer Treatment	**Overall Deaths**	**HNC Deaths**	**Alive**	**Overall Survival HR (95% CI)[a,b]**	**Disease-Specific Survival HR (95% CI) [a,b]**	**Overall Deaths**	**HNC Deaths**	**Alive**	**Overall Survival HR (95% CI)[a,b]**	**Disease-Specific Survival HR (95% CI)[a,b]**
Surgery only	68	21	144	1.00 (Referent)	1.00 (Referent)	26	9	31	1.00 (Referent)	1.00 (Referent)
Radiation only	77	36	83	1.59 (1.08, 2.34)	2.47 (1.34, 4.56)	24	7	31	1.00 (0.52, 1.92)	0.89 (0.26, 3.05)
Surgery and Radiation	85	35	106	1.19 (0.81, 1.73)	1.28 (0.69, 2.36)	38	16	32	1.10 (0.63, 1.94)	1.13 (0.44, 2.86)
Radiation and Chemotherapy	102	50	118	1.19 (0.78, 1.81)	1.48 (0.78, 2.81)	55	19	36	1.00 (0.56, 1.80)	0.52 (0.19, 1.39)
Surgery, Radiation, Chemotherapy	43	22	87	0.98 (0.61, 1.59)	1.26 (0.61, 2.58)	16	5	12	0.77 (0.36, 1.64)	0.36 (0.09, 1.39)
Other (No Treatment, N=9; Chemotherapy only, N=2; Chemotherapy and Surgery, N=2)	8	5	1	9.38 (3.62, 24.29)	20.39 (6.44, 64.57)	3	2	1	2.02 (0.40, 10.27)	4.13 (0.36, 47.74)
Platinum-Based Chemotherapy										
Did not receive platinum-based chemotherapy	239	98	336	1.00 (Referent)	1.00 (Referent)	93	34	95	1.00 (Referent)	1.00 (Referent)
Did receive platinum-based chemotherapy	144	71	203	0.71 (0.52, 0.95)	0.63 (0.41, 0.97)	69	24	48	0.77 (0.48, 1.22)	0.44 (0.19, 1.02)

HR hazards ratio, CI confidence interval

a) HR adjusted for matching factors (age, sex, including pairwise interactions), stage, anatomic site, education, cigarette smoking, alcohol drinking

b) Platinum-based chemotherapy HR adjusted for matching factors (age, sex, including pairwise interactions), stage, anatomic site, education, cigarette smoking, alcohol drinking, surgery, radiation

Table 26. Hazard Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Survival among Head and Neck Cancer Cases in the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, Whites

		Coded Allele		Overall Deaths / Deaths from HNC / Alive						Overall Survival		Disease-Specific Survival	
Gene	SNP	Referent (A) / Variant (B)		AA			AB + BB			HR (95% CI)[a]	p-value	HR (95% CI)[a]	p-value
ERCC3													
(XPB)	rs4150496	G	A	168	67	233	215	102	305	0.94 (0.77, 1.15)	0.55	1.10 (0.81, 1.51)	0.53
	rs1011019	C	T	191	84	271	192	85	268	1.02 (0.83, 1.24)	0.88	1.03 (0.76, 1.39)	0.87
	rs4150434	G	A	230	110	318	153	59	221	0.99 (0.80, 1.21)	0.91	0.80 (0.58, 1.10)	0.18
	rs4150416	T	G	165	69	245	217	99	292	1.10 (0.90, 1.35)	0.34	1.20 (0.88, 1.64)	0.24
	rs4150407	A	G	131	47	187	252	122	352	0.99 (0.80, 1.23)	0.94	1.32 (0.94, 1.85)	0.11
	rs4150403	G	A	303	139	433	80	30	106	1.02 (0.79, 1.31)	0.88	0.81 (0.55, 1.21)	0.31
	rs4150402	G	A	191	84	271	192	85	268	1.02 (0.83, 1.24)	0.88	1.03 (0.76, 1.39)	0.87
XPC	rs2228001	A	C	135	58	202	248	111	336	1.13 (0.92, 1.40)	0.24	1.16 (0.84, 1.60)	0.36
	rs3731143	T	C	333	147	485	50	22	54	1.18 (0.87, 1.59)	0.29	1.16 (0.73, 1.82)	0.53
	rs2228000	C	T	213	94	311	168	74	228	1.04 (0.85, 1.28)	0.68	1.04 (0.76, 1.41)	0.82
	rs3731124	A	C	215	94	306	168	75	233	1.02 (0.83, 1.26)	0.83	1.08 (0.79, 1.47)	0.63
	rs13099160	A	G	335	146	479	48	23	60	1.13 (0.83, 1.53)	0.44	1.17 (0.75, 1.82)	0.50
	rs3731093	T	C	321	141	455	59	26	79	1.03 (0.78, 1.36)	0.83	0.98 (0.64, 1.49)	0.91
	rs3731089	G	A	321	141	457	62	28	82	1.05 (0.80, 1.38)	0.74	1.02 (0.68, 1.53)	0.94
	rs2733537	A	G	167	73	249	216	96	290	1.07 (0.87, 1.31)	0.53	1.06 (0.78, 1.44)	0.71
	rs3731068	C	A	257	111	367	126	58	172	1.09 (0.88, 1.35)	0.45	1.16 (0.84, 1.60)	0.36
	rs2607755	T	C	100	46	142	283	123	397	0.99 (0.79, 1.25)	0.95	0.96 (0.68, 1.35)	0.80
	rs1902658	G	A	99	46	136	284	123	402	0.97 (0.77, 1.22)	0.78	0.92 (0.65, 1.29)	0.61
ERCC8	rs3117	T	C	126	51	211	257	118	328	1.22 (0.98, 1.51)	0.07	1.37 (0.99, 1.91)	0.06
CDK7	rs2972388	A	G	110	50	156	273	119	383	0.99 (0.79, 1.24)	0.94	0.95 (0.68, 1.33)	0.76
XPA	rs3176757	C	T	256	114	353	127	55	186	0.96 (0.77, 1.19)	0.71	0.93 (0.67, 1.29)	0.68
	rs3176753	T	C	381	169	537	1	0	2	0.47 (0.06, 3.70)	0.47		
	rs2808667	C	T	345	153	469	36	16	70	0.70 (0.50, 1.00)	0.05	0.74 (0.44, 1.25)	0.26
	rs2805835	G	C	301	133	426	82	36	113	1.00 (0.78, 1.28)	0.97	0.94 (0.65, 1.36)	0.74
	rs3176689	A	T	267	118	355	116	51	184	0.90 (0.72, 1.12)	0.34	0.91 (0.65, 1.26)	0.57
	rs3176683	T	C	342	152	476	41	17	63	0.85 (0.61, 1.18)	0.33	0.8 (0.48, 1.33)	0.40
	rs3176658	C	T	294	137	405	89	32	134	0.93 (0.73, 1.18)	0.55	0.72 (0.49, 1.07)	0.10
	rs1800975	G	A	184	87	236	185	77	280	0.88 (0.71, 1.08)	0.22	0.78 (0.57, 1.07)	0.12
RAD23B	rs1805330	C	T	306	136	458	77	33	81	1.33 (1.04, 1.72)	0.03	1.28 (0.87, 1.88)	0.21
	rs1805329	C	T	257	113	333	126	56	206	0.81 (0.65, 1.00)	0.05	0.83 (0.6, 1.14)	0.25
ERCC6	rs2228529	A	G	252	108	345	127	59	186	0.94 (0.76, 1.17)	0.58	1.03 (0.75, 1.42)	0.86
	rs2228527	A	G	251	107	347	132	62	192	0.96 (0.78, 1.19)	0.70	1.06 (0.78, 1.46)	0.70
	rs4253132	T	C	294	132	429	89	37	110	1.08 (0.85, 1.37)	0.55	1.01 (0.69, 1.46)	0.98
	rs2228528	G	A	265	115	372	117	53	167	1.05 (0.84, 1.31)	0.67	1.09 (0.78, 1.51)	0.61
DDB2													
(XPE)	rs2029298	A	G	170	68	255	213	101	284	1.05 (0.86, 1.29)	0.63	1.31 (0.96, 1.79)	0.09
	rs4647709	C	T	317	137	449	66	32	90	1.06 (0.81, 1.39)	0.68	1.21 (0.82, 1.79)	0.34
	rs2291120	T	C	283	126	402	100	43	137	1.11 (0.88, 1.39)	0.39	1.06 (0.75, 1.50)	0.73
	rs1685404	G	C	172	71	246	211	98	293	1.08 (0.88, 1.32)	0.48	1.20 (0.88, 1.64)	0.24
	rs2957873	A	G	257	109	386	126	60	153	1.11 (0.90, 1.38)	0.33	1.29 (0.94, 1.78)	0.11
	rs326224	G	A	279	119	404	104	50	135	1.05 (0.84, 1.32)	0.65	1.24 (0.89, 1.73)	0.20
	rs2306353	G	A	281	121	415	102	48	124	1.10 (0.87, 1.38)	0.43	1.25 (0.89, 1.75)	0.20
	rs326222	C	T	190	81	294	193	88	245	1.09 (0.89, 1.34)	0.39	1.21 (0.89, 1.64)	0.22
	rs901746	A	G	190	81	295	193	88	244	1.10 (0.90, 1.34)	0.37	1.22 (0.89, 1.65)	0.21
ERCC5													
(XPG)	rs2296147	T	C	130	45	150	250	123	387	0.78 (0.62, 0.97)	0.02	1.11 (0.79, 1.58)	0.54
	rs4771436	T	G	227	99	336	156	70	203	1.09 (0.89, 1.35)	0.39	1.13 (0.83, 1.55)	0.43
	rs1047768	C	T	122	62	197	261	107	342	1.20 (0.97, 1.50)	0.10	0.96 (0.70, 1.32)	0.82
	rs3818356	C	T	227	99	336	155	69	202	1.09 (0.89, 1.34)	0.41	1.12 (0.82, 1.53)	0.46
	rs4150351	A	C	254	114	341	129	55	198	0.84 (0.68, 1.04)	0.12	0.81 (0.59, 1.13)	0.22
	rs4150355	C	T	177	66	225	206	103	314	0.86 (0.70, 1.05)	0.14	1.15 (0.84, 1.57)	0.37
	rs4150360	T	C	106	55	169	277	114	370	1.18 (0.94, 1.48)	0.15	0.93 (0.67, 1.29)	0.67
	rs4150383	G	A	255	112	375	128	57	164	1.11 (0.90, 1.38)	0.34	1.13 (0.82, 1.56)	0.47
	rs4150386	A	C	304	133	420	79	36	119	1.03 (0.80, 1.33)	0.81	1.05 (0.72, 1.53)	0.80
	rs17655	C	G	223	112	332	160	57	207	1.15 (0.94, 1.41)	0.18	0.81 (0.59, 1.11)	0.19
	rs873601	A	G	190	93	274	193	76	265	1.05 (0.86, 1.28)	0.65	0.84 (0.62, 1.14)	0.25
	rs4150393	A	G	296	132	406	87	37	133	0.89 (0.70, 1.13)	0.34	0.88 (0.61, 1.26)	0.48
	rs876430	C	T	191	94	274	192	75	265	1.04 (0.85, 1.27)	0.72	0.82 (0.6, 1.11)	0.19
	rs1051677	T	C	303	129	432	80	40	106	1.06 (0.83, 1.36)	0.63	1.28 (0.89, 1.82)	0.18
	rs1051685	A	G	302	141	434	81	28	104	1.04 (0.81, 1.34)	0.74	0.79 (0.52, 1.19)	0.26
ERCC4													
(XPF)	rs3136038	C	T	184	86	218	199	83	321	0.79 (0.65, 0.97)	0.03	0.69 (0.51, 0.93)	0.02
	rs1799798	G	A	320	143	437	63	26	102	0.90 (0.69, 1.19)	0.47	0.83 (0.55, 1.27)	0.40

HR hazards ratio, CI confidence interval

a) HR for dominant genetic model (AB + BB vs AA). HRs adjusted for matching factors (age, sex, including pairwise interactions) and ancestry (% African ancestry)

Highlighting indicates significant at 0.05 level. None significant at a Bonferroni corrected level (0.05/84=0.0006)

Table 26 cont. Hazard Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Survival among Head and Neck Cancer Cases in the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, Whites

		Coded Allele		Overall Deaths / Deaths from HNC / Alive						Overall Survival		Disease-Specific Survival	
Gene	SNP	Referent (A) / Variant (B)		AA			AB + BB			HR (95% CI)[a]	p-value	HR (95% CI)[a]	p-value
ERCC4													
(XPF)	rs744154	C	G	208	96	272	175	73	267	0.88 (0.72, 1.08)	0.21	0.77 (0.57, 1.05)	0.10
	rs3136085	G	C	205	96	270	178	73	269	0.88 (0.72, 1.08)	0.23	0.75 (0.55, 1.02)	0.06
	rs3136130	G	T	184	86	216	199	83	323	0.78 (0.64, 0.96)	0.02	0.68 (0.50, 0.92)	0.01
	rs1800067	G	A	322	144	456	61	25	83	0.99 (0.75, 1.31)	0.96	0.89 (0.58, 1.37)	0.61
	rs3136172	A	G	195	91	263	188	78	276	0.92 (0.75, 1.13)	0.43	0.79 (0.58, 1.08)	0.14
RAD23A	rs2974752	A	G	135	58	198	235	106	326	1.04 (0.84, 1.29)	0.72	1.10 (0.80, 1.52)	0.57
ERCC2													
(XPD)	rs13181	T	G	154	73	227	224	94	310	1.07 (0.87, 1.31)	0.53	0.94 (0.69, 1.28)	0.69
	rs238418	C	A	156	74	226	227	95	313	1.05 (0.86, 1.29)	0.63	0.92 (0.68, 1.25)	0.59
	rs1799787	C	T	196	87	276	187	82	263	1.02 (0.83, 1.25)	0.85	1.00 (0.74, 1.35)	0.99
	rs3916874	G	C	209	96	268	174	73	271	0.85 (0.69, 1.04)	0.12	0.75 (0.55, 1.02)	0.07
	rs238416	G	A	152	68	217	231	101	321	1.00 (0.81, 1.23)	1.00	0.99 (0.73, 1.35)	0.96
	rs50872	C	T	226	91	305	157	78	232	0.95 (0.77, 1.16)	0.59	1.16 (0.86, 1.58)	0.34
	rs50871	T	G	110	55	132	273	114	407	0.80 (0.64, 1.00)	0.05	0.67 (0.48, 0.92)	0.01
	rs238407	A	T	121	54	142	262	115	396	0.81 (0.65, 1.01)	0.06	0.83 (0.60, 1.15)	0.27
	rs3810366	C	G	79	31	99	304	138	439	0.89 (0.69, 1.15)	0.36	1.09 (0.74, 1.62)	0.66
ERCC1	rs735482	A	C	278	131	410	105	38	129	1.13 (0.90, 1.42)	0.28	0.86 (0.60, 1.23)	0.40
	rs2336219	G	A	278	131	410	105	38	129	1.13 (0.90, 1.42)	0.28	0.86 (0.60, 1.23)	0.40
	rs3212964	G	A	280	132	412	103	37	127	1.13 (0.90, 1.41)	0.31	0.84 (0.58, 1.21)	0.34
	rs3212955	A	G	209	94	319	174	75	220	1.15 (0.94, 1.41)	0.18	1.10 (0.81, 1.50)	0.54
	rs3212948	C	G	154	73	228	229	96	311	1.06 (0.86, 1.30)	0.58	0.93 (0.68, 1.26)	0.64
	rs3212930	T	C	241	108	335	142	61	204	0.95 (0.77, 1.18)	0.66	0.93 (0.68, 1.27)	0.64
LIG1	rs156641	G	A	151	74	219	232	95	320	1.02 (0.83, 1.26)	0.84	0.86 (0.63, 1.17)	0.33
	rs20580	C	A	97	46	140	286	123	399	1.03 (0.82, 1.30)	0.78	0.94 (0.66, 1.32)	0.70
	rs20579	C	T	294	127	397	89	42	142	0.90 (0.71, 1.15)	0.41	1.01 (0.71, 1.44)	0.94

HR hazards ratio, CI confidence interval

a) HR for dominant genetic model (AB + BB vs AA). HRs adjusted for matching factors (age, sex, including pairwise interactions) and ancestry (% African ancestry)

Highlighting indicates significant at 0.05 level. None significant at a Bonferroni corrected level (0.05/84=0.0006)

Table 27. Hazard Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Survival among Head and Neck Cancer Cases in the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, African Americans

		Coded Allele		Overall Deaths / Deaths from HNC / Alive						Overall Survival		Disease-Specific Survival	
Gene	SNP	Referent (A) / Variant (B)		AA			AB + BB			HR (95% CI)[a]	p-value	HR (95% CI)[a]	p-value
ERCC3													
(XPB)	rs4150496	G	A	95	30	83	66	28	59	0.98 (0.71, 1.36)	0.93	1.40 (0.82, 2.38)	0.22
	rs4150459	G	A	101	35	89	61	23	54	1.08 (0.78, 1.50)	0.65	1.14 (0.66, 1.98)	0.63
	rs1011019	C	T	94	34	89	68	24	54	1.06 (0.77, 1.47)	0.72	1.08 (0.62, 1.86)	0.78
	rs4150434	G	A	126	46	106	36	12	37	0.84 (0.57, 1.24)	0.38	0.79 (0.41, 1.55)	0.50
	rs4150416	T	G	39	13	46	122	44	97	1.32 (0.91, 1.90)	0.14	1.47 (0.78, 2.80)	0.23
	rs4150407	A	G	43	13	41	119	45	102	1.13 (0.79, 1.62)	0.49	1.35 (0.72, 2.53)	0.35
	rs4150402	G	A	94	34	89	68	24	54	1.06 (0.77, 1.47)	0.72	1.08 (0.62, 1.86)	0.78
XPC	rs2228001	A	C	91	32	89	71	26	54	1.18 (0.85, 1.63)	0.32	1.36 (0.79, 2.32)	0.26
	rs2228000	C	T	137	50	114	25	8	29	0.77 (0.49, 1.21)	0.26	0.65 (0.30, 1.42)	0.28
	rs3731124	A	C	136	49	116	26	9	27	0.91 (0.60, 1.40)	0.67	0.75 (0.37, 1.53)	0.43
	rs3731093	T	C	140	54	123	19	3	19	0.86 (0.51, 1.45)	0.57	0.44 (0.14, 1.43)	0.17
	rs3731089	G	A	140	54	123	22	4	20	0.91 (0.56, 1.48)	0.70	0.52 (0.19, 1.47)	0.22
	rs2733537	A	G	115	46	97	47	12	46	0.86 (0.60, 1.23)	0.40	0.59 (0.30, 1.13)	0.11
	rs2607755	T	C	70	27	41	92	31	102	0.62 (0.45, 0.86)	0.004	0.51 (0.30, 0.86)	0.01
	rs1902658	G	A	30	10	23	132	48	120	0.94 (0.62, 1.43)	0.78	0.87 (0.43, 1.76)	0.71
ERCC8	rs3117	T	C	72	21	54	90	37	89	0.81 (0.59, 1.12)	0.20	1.15 (0.66, 1.99)	0.62
CDK7	rs2972388	A	G	77	30	83	85	28	60	1.36 (0.98, 1.87)	0.06	1.04 (0.61, 1.77)	0.88
CCNH	rs2266691	A	G	140	52	117	22	6	26	0.83 (0.53, 1.32)	0.44	0.54 (0.23, 1.28)	0.16
	rs2266692	G	T	133	46	104	29	12	39	0.68 (0.45, 1.03)	0.07	0.80 (0.41, 1.53)	0.49
XPA	rs3176757	C	T	126	42	110	36	16	33	1.00 (0.68, 1.46)	0.98	1.42 (0.78, 2.59)	0.25
	rs3176753	T	C	123	40	102	39	18	41	0.89 (0.62, 1.29)	0.54	1.17 (0.66, 2.08)	0.58
	rs3176748	A	G	132	53	118	30	5	25	1.03 (0.68, 1.56)	0.88	0.40 (0.16, 1.02)	0.05
	rs3176658	C	T	141	51	119	21	7	24	0.89 (0.55, 1.44)	0.64	0.88 (0.38, 2.00)	0.76
	rs1800975	G	A	100	32	87	55	54	51	1.05 (0.74, 1.47)	0.80	1.44 (0.82, 2.55)	0.21
RAD23B	rs1805330	C	T	93	32	90	69	26	53	1.05 (0.76, 1.47)	0.76	1.15 (0.67, 1.99)	0.61
ERCC6	rs2228529	A	G	123	48	111	39	10	30	1.17 (0.81, 1.69)	0.41	0.74 (0.37, 1.49)	0.40
	rs2228527	A	G	115	44	103	47	14	40	1.04 (0.74, 1.48)	0.82	0.81 (0.44, 1.50)	0.51
	rs4253132	T	C	97	35	94	65	23	49	1.13 (0.82, 1.56)	0.46	1.17 (0.69, 1.99)	0.57
	rs2228528	G	A	107	40	105	54	18	38	1.46 (1.04, 2.04)	0.03	1.22 (0.69, 2.14)	0.50
DDB2													
(XPE)	rs2029298	A	G	43	16	47	119	42	96	1.23 (0.86, 1.76)	0.26	1.27 (0.71, 2.30)	0.42
	rs1685404	G	C	86	31	78	76	27	65	1.07 (0.77, 1.47)	0.70	0.97 (0.56, 1.66)	0.90
	rs2957873	A	G	49	20	41	112	38	102	0.95 (0.67, 1.35)	0.78	0.79 (0.46, 1.38)	0.41
	rs326224	G	A	43	14	37	119	44	106	1.12 (0.78, 1.60)	0.54	1.21 (0.66, 2.21)	0.55
	rs2306353	G	A	60	21	46	102	37	97	0.88 (0.64, 1.22)	0.45	0.93 (0.54, 1.59)	0.78
	rs326222	C	T	26	12	28	136	46	115	1.17 (0.76, 1.80)	0.47	0.88 (0.46, 1.68)	0.70
	rs901746	A	G	35	15	30	127	43	113	0.96 (0.66, 1.41)	0.85	0.79 (0.43, 1.44)	0.44
ERCC5													
(XPG)	rs2296147	T	C	101	32	92	60	25	51	1.07 (0.77, 1.48)	0.70	1.42 (0.84, 2.42)	0.19
	rs2296148	C	T	122	45	106	39	13	37	0.96 (0.66, 1.39)	0.81	0.93 (0.49, 1.75)	0.82
	rs4771436	T	G	110	35	94	52	23	49	0.90 (0.64, 1.26)	0.54	1.24 (0.73, 2.12)	0.43
	rs1047768	C	T	66	21	50	96	37	93	0.87 (0.63, 1.20)	0.39	1.06 (0.61, 1.84)	0.83
	rs2020915	G	A	103	42	102	59	16	41	1.22 (0.88, 1.70)	0.24	0.82 (0.45, 1.49)	0.52
	rs3818356	C	T	110	35	96	52	23	47	0.93 (0.66, 1.31)	0.68	1.27 (0.75, 2.18)	0.37
	rs4150355	C	T	119	39	99	43	19	44	0.92 (0.64, 1.34)	0.68	1.16 (0.65, 2.05)	0.62
	rs4150360	T	C	11	5	8	151	53	135	0.79 (0.42, 1.50)	0.48	0.65 (0.25, 1.70)	0.38
	rs4150383	G	A	131	42	111	31	16	32	0.88 (0.59, 1.31)	0.53	1.34 (0.75, 2.39)	0.33
	rs17655	C	G	44	19	46	118	39	97	1.09 (0.76, 1.56)	0.65	0.84 (0.47, 1.50)	0.56
	rs873601	A	G	14	8	16	148	50	127	1.16 (0.66, 2.02)	0.61	0.76 (0.35, 1.62)	0.47
	rs876430	C	T	15	8	17	147	50	126	1.17 (0.68, 2.00)	0.58	0.84 (0.39, 1.79)	0.65
	rs1051677	T	C	116	43	116	46	15	27	1.31 (0.92, 1.86)	0.14	1.15 (0.63, 2.11)	0.64
	rs1051685	A	G	77	30	61	85	28	82	0.84 (0.62, 1.15)	0.29	0.72 (0.43, 1.20)	0.20
ERCC4													
(XPF)	rs3136038	C	T	43	17	49	119	41	94	1.26 (0.88, 1.81)	0.20	1.13 (0.64, 2.01)	0.67
	rs744154	C	G	114	40	107	48	18	36	1.16 (0.82, 1.64)	0.42	1.27 (0.72, 2.26)	0.41
	rs3136085	G	C	92	34	81	70	24	62	1.06 (0.76, 1.46)	0.75	1.01 (0.59, 1.75)	0.96
	rs3136091	C	G	131	45	124	31	13	19	1.27 (0.84, 1.90)	0.25	1.55 (0.82, 2.94)	0.18
	rs3136130	G	T	39	16	36	123	42	107	1.04 (0.72, 1.51)	0.84	0.90 (0.50, 1.63)	0.74
	rs3136172	A	G	112	39	104	50	19	39	1.12 (0.80, 1.59)	0.51	1.24 (0.70, 2.19)	0.46
	rs2020955	T	C	101	37	92	61	21	51	1.11 (0.80, 1.55)	0.53	1.05 (0.60, 1.82)	0.86
RAD23A	rs2974752	A	G	39	12	38	116	42	100	1.11 (0.77, 1.62)	0.57	1.29 (0.67, 2.48)	0.45
	rs11558955	A	G	135	47	121	27	11	22	0.99 (0.65, 1.51)	0.97	1.14 (0.58, 2.22)	0.71

HR hazards ratio, CI confidence interval

a) HR for dominant genetic model (AB + BB vs AA). HRs adjusted for matching factors (age, sex, including pairwise interactions) and ancestry (% African ancestry)

Highlighting indicates significant at 0.05 level. None significant at a Bonferroni corrected level (0.05/79=0.0006)

Table 27 cont. Hazard Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Survival among Head and Neck Cancer Cases in the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, African Americans

		Coded Allele		Overall Deaths / Deaths from HNC / Alive						Overall Survival		Disease-Specific Survival	
Gene	SNP	Referent (A) / Variant (B)		AA			AB + BB			HR (95% CI)[a]	p-value	HR (95% CI)[a]	p-value
ERCC2 (XPD)	rs13181	T	G	86	31	87	76	27	55	1.24 (0.90, 1.70)	0.19	1.18 (0.70, 2.00)	0.54
	rs238418	C	A	5	4	3	157	54	139	0.87 (0.34, 2.27)	0.78	0.27 (0.09, 0.82)	0.02
	rs1799787	C	T	120	40	115	42	18	28	1.36 (0.95, 1.95)	0.09	1.65 (0.93, 2.91)	0.09
	rs3916874	G	C	142	53	126	20	5	17	0.94 (0.58, 1.54)	0.82	0.59 (0.23, 1.52)	0.27
	rs238416	G	A	129	44	114	32	14	29	1.04 (0.70, 1.55)	0.83	1.33 (0.72, 2.45)	0.36
	rs50872	C	T	116	42	107	46	16	36	1.08 (0.76, 1.54)	0.66	0.98 (0.54, 1.76)	0.94
	rs50871	T	G	120	36	109	42	22	34	1.07 (0.74, 1.54)	0.73	1.93 (1.11, 3.35)	0.02
	rs238407	A	T	114	39	112	48	19	31	1.22 (0.86, 1.72)	0.27	1.36 (0.77, 2.38)	0.29
	rs3810366	C	G	108	39	104	54	19	39	1.13 (0.81, 1.59)	0.47	1.04 (0.59, 1.83)	0.89
ERCC1	rs735482	A	C	83	31	73	79	27	70	0.94 (0.69, 1.29)	0.72	0.86 (0.51, 1.46)	0.58
	rs2336219	G	A	84	31	73	78	27	70	0.93 (0.67, 1.27)	0.63	0.87 (0.51, 1.47)	0.59
	rs3212964	G	A	111	43	96	49	15	47	0.98 (0.69, 1.38)	0.89	0.76 (0.41, 1.39)	0.37
	rs3212955	A	G	82	31	77	80	27	66	0.92 (0.67, 1.27)	0.62	0.92 (0.54, 1.55)	0.75
	rs3212948	C	G	5	3	4	157	55	139	0.64 (0.24, 1.73)	0.38	0.36 (0.09, 1.37)	0.13
	rs3212935	A	G	81	32	62	81	26	81	0.84 (0.61, 1.16)	0.28	0.65 (0.38, 1.10)	0.11
	rs3212930	T	C	131	44	119	31	14	24	1.09 (0.73, 1.62)	0.68	1.43 (0.77, 2.64)	0.26
LIG1	rs156641	G	A	129	43	105	33	15	38	0.76 (0.51, 1.14)	0.19	1.13 (0.61, 2.09)	0.70
	rs20580	C	A	33	8	29	129	50	113	1.00 (0.68, 1.48)	0.99	1.62 (0.76, 3.45)	0.21
	rs20579	C	T	83	26	67	79	32	76	0.91 (0.66, 1.26)	0.58	1.32 (0.77, 2.25)	0.31
	rs439132	A	G	88	27	84	74	31	59	1.10 (0.79, 1.52)	0.57	1.48 (0.86, 2.55)	0.15

HR hazards ratio, CI confidence interval

a) HR for dominant genetic model (AB + BB vs AA). HRs adjusted for matching factors (age, sex, including pairwise interactions) and ancestry (% African ancestry)

Highlighting indicates significant at 0.05 level. None significant at a Bonferroni corrected level (0.05/79=0.0006)

Figure 12. Kaplan-Meier Plots for Overall (OS) and Disease-Specific (DS) Survival by Genotype (solid line=0, dash line=1), CHANCE, Whites. Panel A, rs3136038 OS, Log-Rank p-value =0.02. Panel B, rs3136130 OS, Log-Rank p-value=0.01. Panel C, rs50871 OS, Log-Rank p-value=0.15. Panel D, rs3136038 DS, Log-Rank p-value=0.02. Panel E, rs3136130, DS, Log-Rank p-value=0.02. Panel F, rs50871 DS, Log-Rank p-value=0.04

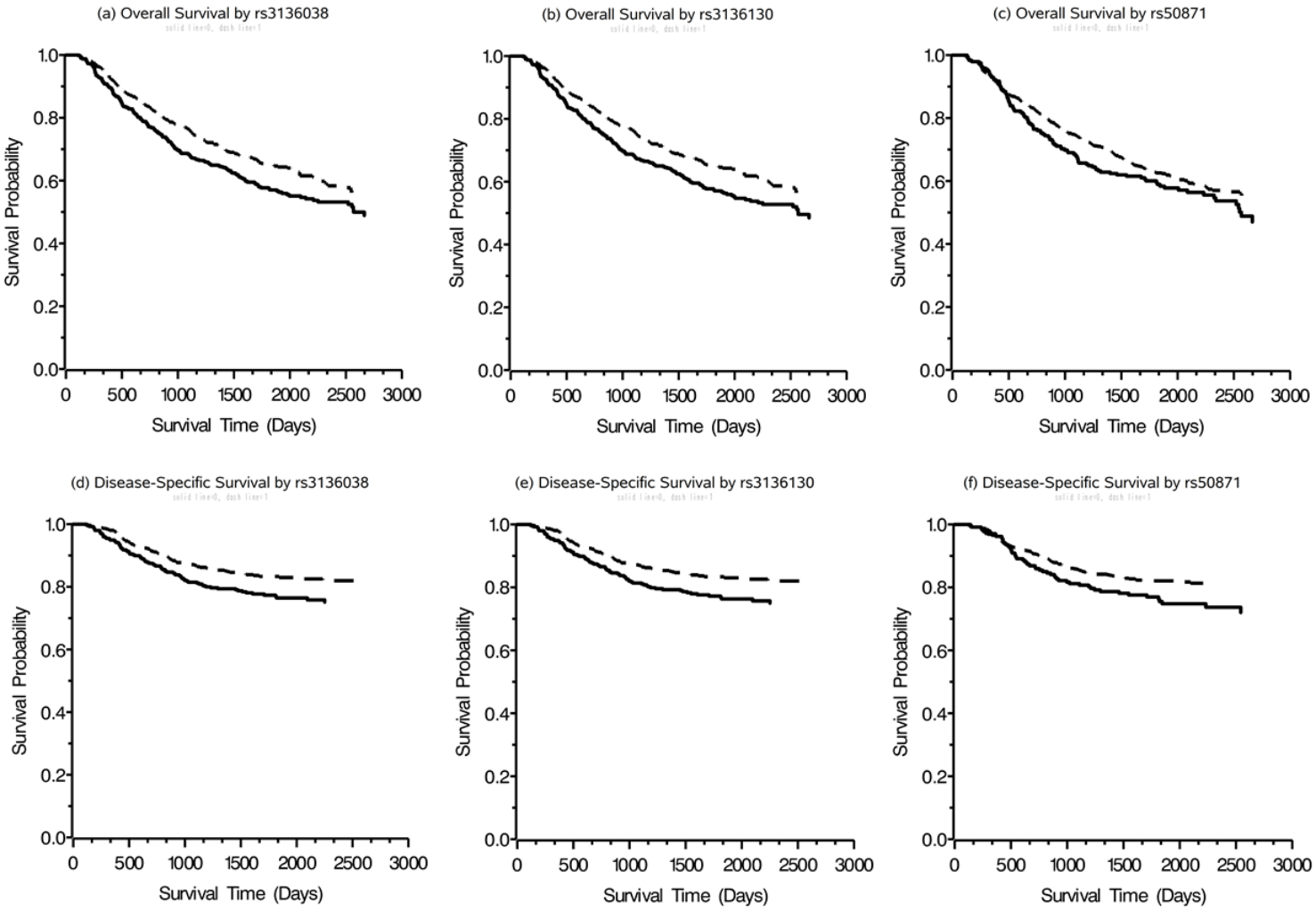
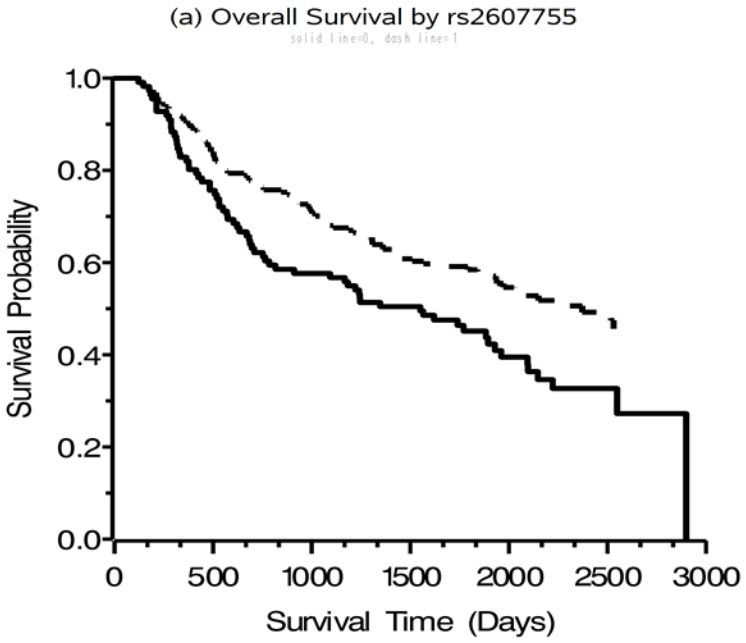
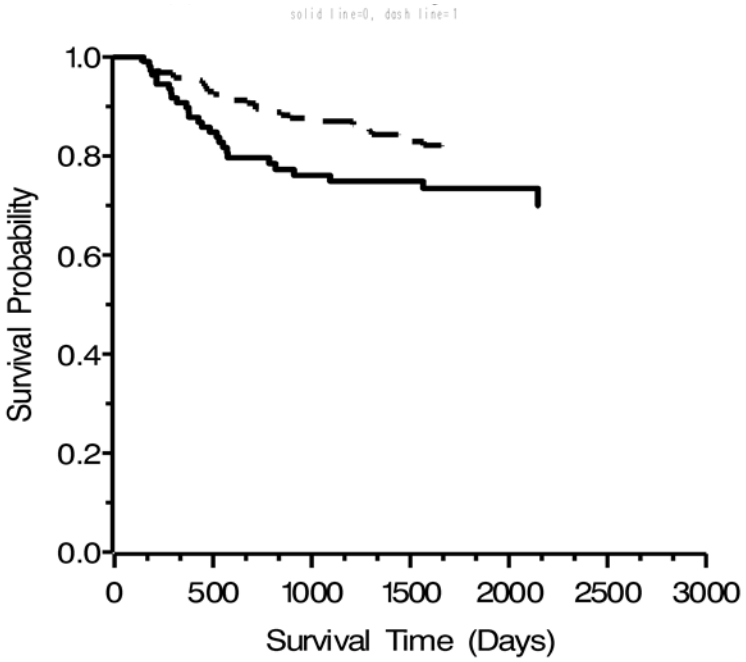


Figure 13. Kaplan-Meier Plots for Overall (OS) and Disease-Specific (DS) Survival by Genotype (solid line=0, dash line=1), CHANCE, African Americans. Panel A, rs2607755 OS, Log-Rank p-value=0.004. Panel B, rs2607755 DS, Log-Rank p-value=0.04.



(b) Disease-Specific Survival by rs2607755



CHAPTER 5

SUMMARY AND CONCLUSIONS

5.1 SUMMARY OF SPECIFIC AIMS

Nucleotide excision repair (NER) genes play an essential role in repairing DNA damage. Specifically, NER is the primary pathway for removing bulky DNA adducts (~30 damaged nucleotides) (123-125). Exogenous causes of bulky DNA adducts include a number of tobacco associated carcinogens, such as nitrosamines and benzopyrenes, as well as various cancer treatments, namely, radiotherapy and platinum-based chemotherapy (3,4,6,7,48). Researchers have described NER genes as a "double-edged sword" or "Janus, the two-faced Roman god" with respect to cancer progression (6). Specifically, functional NER genes are thought to protect against cancer incidence by repairing detrimental damage caused by carcinogens in cigarette smoke, among other sources (6). In contrast, radiation and platinum-based chemotherapy intentionally produce bulky DNA adducts in order to initiate cell death (apoptosis) of cancerous cells (6). Therefore, functional NER genes may lead to poorer survival by mitigating the effectiveness of cancer treatments (6). To test both aspects of this hypothesis with respect to head and neck cancer (HNC), the following research aims were explored in this dissertation. First, I assessed the individual and joint effects of polymorphisms in NER genes (15 genes, 84 SNPs) and smoking status (ever, frequency, and duration) on HNC risk. Second, I assessed the individual and joint effects of the same NER variants (15 genes, 84 SNPs) and treatment (combinations of chemotherapy, radiation therapy, and surgery) on risk of mortality among HNC cases.

5.2 SUMMARY OF RESULTS BY SPECIFIC AIM

5.2.1 Aim 1

Odds ratios for most variants in NER genes and HNC were close to the null value. Using the conventional analysis approach, 5 SNPs among whites and 4 SNPs among African Americans were associated with HNC at 0.05 alpha level, but none were associated at a Bonferroni corrected alpha level. Using hierarchical modelling to shrink estimates on the same gene towards each other, 1 SNP among whites and 1 SNP among African Americans remained associated with HNC. Among whites, rs4150403 on *ERCC3 (XPB)* was associated with increased HNC odds. Further, rs4150496 also on *ERCC3 (XPB)* suggestively associated with reduced HNC odds. Among African Americans, rs4253132 on *ERCC6* was associated with decreased HNC odds. Interactions between cigarette smoking and rs4253132 on *ERCC6*, rs2291120 on *DDB2,* and rs744154 on *ERCC4* suggested possible additive effects among whites. While interactions were significant at an uncorrected 0.05 alpha level, RERI estimates were generally imprecise and none were significant at a Bonferroni corrected alpha level. Further, HWE was questionable for rs4253132 of *ERCC6* among whites. Compared to the conventional method, ORs (95% CIs) and RERI point estimates for joint effects from the hierarchical model were similar.

5.2.2 Aim 2

Hazard ratios for variants in NER genes and HNC were close to the null value. No SNPs were significantly associated with overall or disease-specific survival at a Bonferroni corrected alpha level of 0.0006. However, 3 SNPs among whites and 1 SNP among African Americans were suggestively associated with both outcomes at an uncorrected 0.05 alpha level. Among whites, the variant genotypes of rs3136038 and rs3136130, which are in linkage disequilibrium (LD) on *ERCC4 (XPF)*, and rs50871 on *ERCC2* were modestly associated with better overall and disease-specific survival. Among African Americans, rs2607755 on *XPC* was modestly associated with better survival. Hazard

ratios for SNP-survival associations were of largest magnitude among individuals with stage 3 or 4 tumors. Interactions between rs2972388 of *CDK7* and radiation only, as well as radiation and chemotherapy, and rs2974752 of *RAD23A* and radiation and chemotherapy suggested possible additive effects among whites. While interactions were significant at a Bonferroni corrected 0.0006 alpha level, HWE was questionable for both rs2972388 and rs2974752.

5.3 SUMMARY OF RESULTS ACROSS SPECIFIC AIMS

5.3.1 Racial Differences

HNC incidence and patterns of risk factors such as cigarette smoking vary by race in United States (56,58). HNC survival also varies by race, with five-year survival rates among African Americans half those among whites (61,62). Further, genotype frequencies and linkage disequilibrium (LD) structure is known to vary by ancestral populations (129,203). Therefore, consideration of race-specific estimates was an important contribution of this dissertation.

Interesting differences in results by race were noted for both aims. For cigarette smoking-HNC associations, ORs were elevated among both whites and African Americans. However, the magnitude of the ORs among African Americans was noticeably higher than among whites. Differences in cigarette smoking-HNC associations by race using CHANCE data have been previously identified and published (57). Briefly, elevated HNC ORs among African American cigarette smokers were noted even when accounting for frequency and duration of smoking, cigarette product preferences (e.g., mentholated vs. non-mentholated), and HNC tumor site (57). Variation in gene-environment interactions may contribute to racial differences in cigarette smoking-HNC associations (57); though I was not able to explore interactions between cigarette smoking and NER SNPs among African Americans in this dissertation. Additional studies on racial differences in gene-environment interactions, as well as smoking cessation patterns, are warranted (57).

With respect to treatment, no substantial racial differences in HRs for either survival outcome were noted, with the exception of radiation only. Specifically, radiation only compared to surgery only was significantly associated with worse overall and disease-specific survival among whites, but not among African Americans. For models of platinum based-chemotherapy (yes vs. no), HRs were similarly reduced among both whites and African Americans. Although African Americans have a much higher mortality rate than whites, few studies have examined treatment-survival associations by race. In particular, clinical trials tended to not stratify effect estimates by race (209-211). Observational studies have presented mixed results. A study by Ragin et al. (212) reported modestly reduced overall survival among patients receiving radiation and/or chemotherapy and surgery with radiation and/or chemo compared to surgery only in the overall study population, though HRs were not statistically significant. Unfortunately, this study did not stratify treatment-survival HRs by race (212). However, the study did note that the proportions of patients receiving surgery only, radiation and/or chemotherapy only, and surgery with chemotherapy and/or radiation were similar between whites and African Americans (X^2 p-value=0.23) (212). A study of HNC using SEER data noted no difference in disease-specific survival among white and African Americans when models were adjusted for treatment; however, overall survival was modestly improved among whites (213). Murdock et al. noted worse survival among African Americans compared to whites when adjusting for treatment, though no difference in survival was noted for surgery with/without radiation compared to other treatment (214).

For both aims, SNP-HNC associations varied by race. For HNC incidence, a SNP on *ERCC3 (XPB)* was associated with elevated HNC risk among whites, while a single SNP on *ERCC6* was associated with reduced HNC risk among African Americans. This finding illustrated how a variant genotype of one SNP may be harmful while the variant genotype of another SNP may be beneficial, and that the direction of associations can vary by race. Not only were the effects of SNPs on HNC

different by race, but the genes implicated have considerably different functions within NER. In particular, *ERCC6* acts only on transcriptionally active DNA (123,124). Similarly, SNPs which appeared to be associated with survival among whites were not associated with survival among African Americans and vice-versa. Specifically, 2 SNPs, which were in LD, on *ERCC4 (XPF)* and a single SNP on *ERCC2* were suggestively associated with both overall and disease-specific survival among whites. In contrast, a single SNP on *XPC* was suggestively associated with both survival outcomes in African Americans. All three genes act during different phases of NER: *XPC* recognizes and binds to DNA adducts, *ERCC2* operates as a component of the TFIIH subunit to denature the double helix surrounding the adduct, and *ERCC4* creates an incision at the 5' end of a damage site (123,124). Since this was only the second study to consider associations between NER SNPs and HNC risk (15), and the first to consider survival, among African Americans, additional studies which consider race-specific effects are required.

5.3.2 "Double-Edged Sword"

As previously described, NER genes are hypothesized to be a "double-edged sword" or "Janus, the two headed Roman god" (6). In this dissertation I did not find conclusive evidence for this assertion. First, most SNPs were not associated with HNC incidence or survival. Second, those SNPs that were associated with HNC incidence were not associated with HNC survival, or vice-versa. Yet, associations were generally in the direction expected based on the outcome.

For HNC risk, variant genotypes of SNPs were generally hypothesized to be associated elevated HNC risk, though some may be associated with reduced HNC risk depending on the SNP. Among African Americans a single SNP was also associated with reduced HNC risk. Among whites, two SNPs on the same gene were associated with HNC, though one SNP was associated with elevated HNC risk and the other suggestively associated with reduced HNC risk demonstrating how the direction of associations can vary by SNP, gene, and race. While the function of many SNPs is

well understood (e.g., missense or nonsense mutations in the exon which are marked by amino acid changes) (215,216), a considerable portion of SNPs, including SNPs in this dissertation, occur in noncoding intronic regions. Although intronic SNPs can affect splicing (217), the exact consequence of each SNP is not always known. In particular, none of the SNPs associated with HNC outcomes in this dissertation have known function. It is also important to note that observed SNP-HNC associations may not be necessarily due to the specified SNP, but may rather reflect the effects of functional SNPs in LD with the specified SNP (218). As the complex interactions and function of genetic variants continue to be unraveled, our understanding of SNP-HNC associations, including direction of associations, will improve.

For HNC survival, it was believed that referent genotypes may mitigate treatment effects resulting in worse survival, though again some SNPs may have the opposite effect. Of the three SNPs associated with overall and disease-specific survival among whites and the one SNP among African Americans, all were associated with reduced HRs indicating improved survival as hypothesized. Though again, understanding SNP-survival associations will benefit from mounting functional information.

5.4 STRENGTHS AND LIMITATIONS

5.4.1 Strengths

The foremost strengths of this dissertation were the large, racially diverse study population and the broad evaluation of SNPs in NER genes. To my knowledge, this dissertation was the largest to evaluate both associations between SNPs in NER genes and HNC incidence and survival. Although two related studies included larger study populations to explore HNC incidence, these studies included a limited number of NER variant and defined the outcome as upper aero-digestive tract (UADT) cancers (HNC and esophageal cancers) (11,14). Most previous studies included only a couple hundred HNC cases and controls. Further, this dissertation was the first to report both NER SNP-HNC

risk and survival associations stratified by race (white and African American). One previous study reported NER SNP-UADT associations among African Americans, but included only 157 African Americans (15). As demonstrated in this dissertation, associations between NER variants and HNC incidence and survival vary by race, and were an important contribution to the literature.

In addition to including more individuals than previous studies, this dissertation also examined more SNPs in NER genes than any previous study. Previous studies on HNC incidence have collectively examined around 50 SNPs in 10 NER genes (4,5,8-46). For HNC survival, studies have considered even fewer SNPs, approximately 18 SNPs in 6 NER genes (7,47-55). This dissertation alone included 84 SNPs across 15 NER genes in whites and 79 SNPs across 14 genes in African Americans.

Other strengths of this dissertation project include utilization of hierarchical modeling and assessment of gene-environment interactions. Although the conventional approach to address multiple comparisons is to model one SNP at a time and then adjust the alpha level using the Bonferroni method, this approach is overly conservative and can result in false negatives because it assumes tests are independent, which is generally not the case with SNPs which may be in LD (164-166). However, not correcting for multiple comparisons would likely results in false positives (160,166). Therefore, hierarchical modeling has been advocated as a method which addresses multiple testing of correlated exposures by incorporating a SNP-gene matrix to account for clustering of SNP data by gene (164,165,167,168). In this sense, hierarchical modeling allows biology to inform the statistical model (164,165,168). Further, previous literature can be used to inform the prior value placed on the variance of the error term (164,165,167,168). In this dissertation I used a semi-Bayes approach to set this variation (τ^2) for SNP-HNC models to be 0.05, which corresponds to an expected OR between 0.6 to 1.6 (165). For joint effects of SNPs and cigarette smoking, τ^2 was set

to 0.35 to allow for ORs between 0.3 and 3.0 (165). To my knowledge, this is the first study to use hierarchical modeling to explore associations between NER variants and HNC risk.

To consider SNP-cigarette joint effects, several studies have stratified main SNP effects models by ever/never or light heavy cigarette smoking (4,9,10,13,15,16,24,26,27,30,31,33,35-38,40). In this dissertation, though, I formally calculated the RERI to assess interactions between SNPs and cigarette smoking. Further, several studies have assessed NER variant and survival associations within populations receiving the same treatment (47-51,53-55), but only one study has compared effects of a single NER SNP across strata of different treatment regimens (7). In this dissertation I considered joint effects of 84 SNPs and 6 treatment regimens.

5.4.2 Limitations

While exploration of gene-environment interactions was an asset to this dissertation, it was also limited. Despite the large sample size of CHANCE, RERI estimates were imprecise among whites. Among African Americans, small sample sizes were too small to reliably consider joint effects (though joint effects among African Americans are presented in the appendix solely as an exploratory analysis). HNC tumor site-specific estimates among African Americans were also limited by sparse numbers.

Another key limitation of this dissertation was incomplete capture of variation across some genes, especially among African Americans, since tagging SNPs were not selected for all genes and SNPs were selected based on the CEU population. Based on HapMap data (129,143), the proportion of variation captured by SNPs in this dissertation ranged from 0% for *CDK7* among CEU (Utah Residents with Northern and Western European Ancestry) and YRI (Yoruba in Ibadan, Nigeria) populations, to 76% and 53% for *ERCC1* among the CEU and YRI populations, respectively. Therefore, it is possible that some potentially meaningful LD blocks were overlooked. In addition, I did not estimate haplotypes. Further, some SNPs were excluded from analyses because the minor

allele frequency was less than 5%, though most of these SNPs were originally selected based on previous literature and not tagging. Therefore, the proportion of variation captures was likely not further compromised.

In addition, I did not consider proxy interviews (52 cases and 17 controls) since these occurred for individuals who died prior to interview, and therefore did not provide a biologic sample. If SNPs were related to aggressive tumors, then estimates for SNP-risk and SNP-survival associations may be slightly attenuated to the null (82,153). When SNP-survival associations were stratified by stage, associations were strongest among cases with stage 3 and 4 tumors.

For analyses of HNC survival, there were also limitations with respect to treatment, covariate and outcome measurements. While information on whether patients received (yes/no) surgery, radiation, and chemotherapy (including chemotherapy drug) was uniformly abstracted from patients' medical records, information on duration of treatment (e.g., start and end dates) and timing of treatments combinations (e.g., induction, adjuvant, or concurrent chemotherapy) were not complete. For example, nearly a quarter of cases who received chemotherapy were missing end dates for that treatment (138). Information on radiation and chemotherapy dose was also not available. Since many previous studies focused on a single treatment, including restricting the study population to patients with comparable frequencies and durations of treatment (47-55), defining treatment based on combinations of dichotomous variables was considered sufficient to explore gene-environment interactions. However, frequency and duration of treatment would have allowed for assessment of dose-response trends of main effects, as well as more detailed exploration of SNP-treatment join effects. Finally, treatment history beyond first course treatment was not available. Therefore, treatment was considered solely as the first-course combinations of dichotomous variables for surgery, radiation, and chemotherapy. However, first course treatment is

generally regarded as the best possibility for cure and subsequent treatments are considered less effective (65,67,72).

With respect to covariates, survival models were adjusted for cigarette smoking and alcohol drinking information that was ascertained at baseline based on behaviors prior to diagnosis since information on behavioral risk factors following diagnosis was not uniformly available. Further, CHANCE does not currently contain information on human papillomavirus (HPV) which is associated with improved survival among cases with oropharyngeal tumors (103). However, since HPV is unlikely to affect germline SNPs, it would not be considered a confounder of SNP main effects, though it may impact SNP-treatment joint effects. When SNP-survival associations were stratified by tumor site, estimates for oropharyngeal cancers were generally of the same direction and magnitude as overall HNC estimates, though oropharyngeal cancer estimates were imprecise due to low cell counts and were not statistically significant. There was not adequate sample size to stratify SNP-treatment joint effects by tumor site. Finally, with respect to outcome, CHANCE currently does not contain information on tumor recurrent disease so I was unable to consider disease-free or relapse-free survival.

5.5 IMPLICATIONS AND CONCLUSIONS

5.5.1 SNP Main Effects

As previously described, associations between NER genes and HNC incidence and survival are biologically plausible (3,6). Previous epidemiologic studies have varied with regard to which specific SNPs were investigated and often presented inconsistent evidence for associations between the same SNP and HNC incidence (4,5,8-46) and survival (7,47-55). For both HNC incidence and survival, SNPs on *ERCC2*, in particular rs13181, were the most commonly studied NER variants with mixed evidence for associations with HNC outcomes (4,5,9,10,16,17,19-21,24,29,30,32-34,36,37,47,48,50,53,54).

This dissertation evaluated more NER variants than all previous studies combined. While a few SNP-HNC associations were identified, results overall were mostly null. Specifically, I identified 1 SNPs on *ERCC3*, rs4150403, among whites and 1 SNP on *ERCC6*, rs4253132, among African Americans which were associated with HNC risk. With respect to HNC survival, no SNPs were statistically significantly associated at a Bonferroni corrected level. However, rs3136038 and rs3136130 which are in LD on *ERCC4 (XPF)* and rs50871 on *ERCC2* among whites and rs2607755 on *XPC* among African Americans were suggestively associated with both overall and disease-specific survival at an uncorrected 0.05 alpha level. The remaining 80 or so NER variants included in this dissertation did not appear to be associated with HNC outcomes.

Since many of the SNPs included in this dissertation had not been previously considered, additional studies of NER genes and HNC outcomes are needed to replicate the findings in this dissertation. In particular future studies should focus on *ERCC3 and ERCC4* variants among whites and *ERCC6* and *XPC* variants among African Americans rather than including only a few *ERCC2* variants among mostly European descent population as has been commonly done in the past. With respect to *ERCC2*, though, future studies should consider rs1799793, as this SNP was associated with HNC risk in previous studies but was not included in this dissertation.

Further, studies should select SNPs based on tagging methods in CEU and YRI (or ASW African ancestry in Southwest USA) population separately (129). While this dissertation included the majority of genes in the NER pathway, it did not uniformly include tag SNPs to completely capture variation within given genes. Selection of tag SNPs would also allow for informative haplotype estimation. Finally, it is important that future studies note null associations. Identifying the lack of an association can be just as meaningful as detecting an association. Reporting null associations is important for following-up early positive associations, avoiding publication bias, and informing future meta-analyses (206).

5.5.2 SNP-Cigarette Smoking and SNP-Treatment Joint Effects

Cigarette smoking is strongly associated with increased risk of HNC (2), and a growing body of evidence suggests that cigarette smoking-HNC associations may be modified by NER genes (4,8-10,13,15,16,22,24,26-28,30,31,33,35-38,40,44). Further, cigarette smoking-HNC associations are marked by noticeably higher magnitude ORs among African Americans in comparison to whites, and racial variation in gene-environment interactions may contribute to such differences (57). However, only three suggestive SNP-cigarette interactions (rs4253132-smoking, rs2291120-smoking, and rs744154-smoking) were noted among whites in this dissertation.

With respect to survival, treatment is a strong predictor of outcome following HNC diagnosis (65,72). Historically HNC was treated with surgery and/or radiation therapy (65,72). However, following a series of clinical trials in the 1990s demonstrating survival benefits for treatment with radiation and chemotherapy following surgery, advanced tumors (stage 3 and 4) are increasingly treated with concurrent or induction chemotherapy (72). Both radiation and platinum-based chemotherapies irradiate cancerous cells by causing DNA adducts, among other forms of DNA damage (6,7,48). Since NER genes remove such adducts, functional process may actually mitigate intended treatment effects (6). Although three SNP-treatment interactions (rs2972388-radiation, rs2972388-radiation and chemotherapy, and rs2974752-radiation and chemotherapy) were significant at a Bonferroni-corrected alpha level among whites in this dissertation, these interactions all involved SNPs with inconsistent HWE evidence.

While the present study is the largest to date to consider SNP-cigarette smoking and SNP-treatment joint effects on HNC outcomes, estimates were imprecise among whites and inestimable among African Americans. Therefore, studies among even larger, racially diverse populations are needed. Given the potential resource burden of individual large studies, larger sample sizes could be efficiently achieved through pooling efforts, such as those conducted by the INHANCE consortium.

This would require coordination among existing and future studies to not only administer questionnaires to ascertain demographic and behavorial information, but to uniformly collect DNA samples to ascertain genetic information, medical records to ascertain treatment information, and death records to ascertain survival outcomes. Larger studies would also allow for tumor site and stage specific estimation of interactions, which I was unable to evaluate in this dissertation. As noted, SNP-HNC associations were stronger for some tumor site and stages than others. Therefore, joint effects are also likely to vary tumor site and stage. Finally, studies of SNP and treatment effects on HNC survival would benefit from more detailed treatment information; namely, dose and duration of treatment which I was unable to analyse.

5.5.3 Other Considerations for Future Studies

Given the prominent role of NER genes in repairing DNA damage, especially the types of damage caused by cigarette smoking and treatment, variants in this pathway were prime suspects for associations with HNC. However, other DNA repair pathways are also believed to contribute to HNC outcomes. In particular, base excision repair (BER) genes have a similar function to NER genes, namely removing DNA adducts (123,124). While NER processes remove bulky adducts, (~30 damaged nucleotides), BER genes repair smaller adducts (~1-13 damaged nucleotides) (123,124). Yet only about a dozen studies have investigated the effects of BER variants on HNC risk (131). Associations between *XRCC1* variants and HNC risk were consistently noted (131). For HNC survival, only half a dozen studies have considered the effects of 3 variants in 2 BER genes and none of these studies investigated interactions between BER SNPs and treatment (47,48,53,54,219,220), though a separate study on *XRCC1* expression did note important interactions with treatment (221). Therefore future studies, including the CHANCE study, could investigate associations between BER variants, particularly *XRCC1*, cigarette smoking, treatment, and HNC risk and survival. Other DNA repair pathways to be further investigated include homologous recombination and nonhomologous

end joining, as well as other specific DNA repair variants such as *FGFR4* and *CCND1* (131,222). Although future studies of other DNA repair variants may yield null results (similar to this dissertation), detecting null associations is important for sifting through biologically plausible genetic associations, as previously described.

The literature on genetics and HNC would further benefit from additional genome-wide association studies (GWAS). Previously, McKay et al. (81) conducted a GWAS for upper aerodigestive cancers (UADT); though, only 5% of cases included in this particular study had tumors of the esophagus. In the first phase of the study, associations between 294,620 SNPs and UADT cancers were examined in the Central Europe and ARCAGE study populations (2,230 UADT cases and 4,090 controls) (81). In the second phase, the top 19 SNPs associated with UADT cancer, as identified in phase 1, were then replicated using data from the INHANCE study population (6,514 UADT cases and 7,892 controls) (81). Five SNPs were found to be significantly associated with UADT cancers in both phases: rs4767364 in *ALDH2;* rs1494961in *HEL208* (related to the *ADH* genes); and rs1573496, rs1229984 and rs698 in *ADH7, AHD1B,*and *ADH1C,* respectively (81). All of these genes are known to function in alcohol metabolism, none in DNA repair (81).

Future GWAS studies should focus on more diverse populations, particularly African American populations. The McKay study included only 537 cases and 539 controls who were African American, which limited estimation among this population (81). In addition, GWAS studies assessing associations between common variants and HNC survival may yield informative results. Finally, it is important to keep in mind that even if GWAS or candidate gene studies do not detect a SNP main effect, that does not preclude important gene-environment interactions involving that SNP (223). Therefore, future GWAS and candidate gene studies should consider gene-environment interactions.

Finally, future studies which consider associations between gene and protein expression and HNC risk and survival may enhance the literature. Previously, 4 studies have investigated associations between expression of 8 NER genes or proteins (*ERCC3, XPA, XPC, ERCC6, ERCC5, ERCC4, ERCC2, ERCC1*) and HNC risk (12,42,43,224). In addition, 9 studies evaluated associations between expression of 2 genes or proteins (*ERCC1* and *ERCC4*) and survival among HNC cases (49,52,55,225-230). Single nucleotide polymorphisms are known to impact gene expression (231). Therefore, assessing associations between gene and protein expression and HNC risk and outcomes will further inform functional and mechanistic understanding of the genetic etiology of this disease (231). In addition, studies which utilize DNA and RNA extracted directly from tumor tissues could offer additional insights regarding germline and somatic mutations and gene expression with respect to HNC, particularly for response to treatment.

5.5.4 Public Health Implications

> As described by the US National Institute for Environmental Health Sciences (232):
>
> Almost all diseases result from a complex interaction between an individual's genetic make-up and environmental agents. Subtle differences in genetic factors cause people to respond differently to the same environmental exposure. This explains why some individuals have a fairly low risk of developing a disease as a result of an environmental insult, while others are much more vulnerable. As scientists learn more about how genetics and environmental factors work together to cause human diseases, they will be able to develop new strategies for the prevention and treatment of many illnesses (232).

A review in *Nature Genetics* by Hunter et al. (233) further discusses the public health significance of environmental and genetic research. The authors specifically assert that considering gene-environment interactions will help identify susceptible individuals, understand disease mechanisms, and inform tailored interventions and treatments (233).

In the context of this dissertation, strong associations between cigarette smoking and HNC risk were already well established in the literature (2). However, few studies had considered racial differences in smoking-HNC associations (57). A previous CHANCE study indicated higher magnitude

ORs among African Americans compared to whites, and gene-environment interactions were hypothesized to play a role (57). Since carcinogens in cigarette smoke can cause DNA adducts and NER process remove DNA adducts (3,124), smoking-NER variants interactions are biologically plausible factors for racial differences in HNC risk. Further, characterizing gene-environment interactions may help further elucidate why some non-smokers develop HNC and some smokers never develop HNC (4,234).

Beyond specifically assessing interactions between cigarette smoking and NER variants with respect to HNC, research regarding gene-environment has value in further clarifying the underlying mechanisms of cancer etiology more broadly. Insights into how environmental exposures are modified by DNA repair processes may be translated to other public health concerns. For example, air pollution is known to contain some carcinogens similar to tobacco smoke, such as polycyclic aromatic hydrocarbons (234,235); therefore, research regarding air pollution-cancer associations could benefit from epidemiologic investigation of cigarette smoking-NER variants effects with respect to cancer outcomes.

Finally, with respect to HNC survival, there still remains debate about optimal treatment. Although a series of clinical trials indicated survival advantages for the addition of chemotherapy to radiation therapy (72), concerns regarding dosing and potential side-effects, especially for less aggressive tumors, still remain (236,237). Further, only a few studies have examined treatment-survival associations among HNC cases by race (212-214). Again given the biologically established connection between treatment and the NER pathway (6), assessing treatment-NER variant interaction has the potential to inform mechanistic knowledge and help discern any racial differences in treatment response. Further research characterizing treatment response based on variants in biologically plausible pathways could have promising implications for targeted therapies (7,233).

5.5.5 Summary

In summary, this dissertation evaluated associations between 84 SNPs and HNC risk and survival among a large, racially diverse study population. SNP-HNC associations varied by race and outcome. The majority of SNPs were not associated with either HNC risk or survival, though two SNPs (one among whites and one among African Americans) were associated with HNC risk and four SNPs (three among whites and one among African Americans) were suggestively associated with HNC survival. A few suggestive SNP-cigarette or SNP-treatment interactions were also noted. Larger, perhaps pooled, studies are needed to confirm findings and more precisely estimate joint effects. In addition, future studies should include a larger number African Americans to estimate race-specific effects. Finally, studies which select SNPs to completely tag variation in genes and facilitate haplotype estimation, as well as studies of other DNA repair pathways are warranted. Characterizing independent and joint effects of behavorial/environmental and genetic exposures can help identify susceptible individuals, unravel disease mechanisms and etiology, and inform preventive and therapeutic strategies (233).

APPENDIX A

AIM 1 SUPPLEMENTAL TABLES REFERENCED IN CHAPTER 3

Table 1S. Odds Ratios for Environmental Tobacco Smoke and Head and Neck Cancer in the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study

	Never Active Cigarette Smoking			Ever Active Cigarette Smoking			Whites			African Americans		
Environmental Tobacco Smoke	**Controls**	**Cases**	**OR (95% I)[a]**	**Controls**	**Cases**	**OR (95% I)[a]**	**Controls**	**Cases**	**OR (95% I)[a]**	**Controls**	**Cases**	**OR (95% I)[a]**
Never	130	47		83	84		159	89		54	42	
Ever	378	116	0.84 (0.54, 1.33)	733	979	0.92 (0.62, 1.37)	914	832	0.87 (0.63, 1.19)	197	263	0.91 (0.45, 1.82)
Missing	0	0		1	1		1	1		0	0	
Work												
Never	215	70		199	246		476	291		116	108	
Ever	293	93	1.02 (0.69, 1.53)	618	816	1.07 (0.82, 1.39)	597	630	1.02 (0.81, 1.30)	135	197	1.11 (0.67, 1.86)
Missing	0	0		0	2		1	1		0	0	
Home												
Never	279	89		313	310		317	209		97	107	
Ever	229	74	1.03 (0.67, 1.58)	503	753	1.03 (0.81, 1.30)	757	711	1.09 (0.87, 1.36)	154	198	0.82 (0.49, 1.37)
Missing	0	0		1	1		0	2		0	0	
Work Duration (years)												
Never	215	70		199	246		317	209		97	107	
<10	84	27	0.96 (0.55, 1.68)	109	149	1.06 (0.73, 1.55)	155	128	0.94 (0.67, 1.33)	38	48	1.43 (0.67, 3.05)
10-19	76	24	0.99 (0.54, 1.79)	147	138	0.80 (0.56, 1.15)	184	122	0.82 (0.59, 1.14)	39	40	0.85 (0.40, 1.84)
20-29	69	21	0.93 (0.50, 1.73)	131	205	1.24 (0.88, 1.76)	164	181	1.19 (0.86, 1.64)	36	45	0.99 (0.48, 2.08)
30+	59	20	1.35 (0.69, 2.67)	223	305	1.13 (0.82, 1.55)	245	269	1.11 (0.82, 1.51)	37	56	1.33 (0.64, 2.77)
Missing	5	1		8	21		9	13		4	9	
P_{trend}			0.46			0.52			0.45			0.69
Home Duration (years)												
Never	279	89		313	310		476	291		116	108	
<10	98	35	1.02 (0.61, 1.71)	224	324	0.94 (0.71, 1.24)	255	271	1.02 (0.78, 1.32)	67	88	0.78 (0.43, 1.42)
10-19	50	17	1.31 (0.67, 2.57)	99	179	1.13 (0.79, 1.60)	114	140	1.27 (0.90, 1.79)	35	56	0.78 (0.38, 1.60)
20-29	32	7	0.62 (0.24, 1.62)	74	113	1.01 (0.68, 1.51)	96	94	0.98 (0.67, 1.43)	10	26	1.26 (0.41, 3.88)
30+	49	15	1.07 (0.48, 2.39)	104	132	1.14 (0.79, 1.65)	131	121	1.18 (0.84, 1.68)	22	26	0.81 (0.32, 2.06)
Missing	0	0		3	6		2	5		1	1	
P_{trend}			0.87			0.52			0.38			0.87

OR odds ratio, I interval estimates

[a]Odds ratios adjusted for matching factors (age, sex, and race, including pairwise interactions), education, alcohol drinking, and cigarette smoking

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

Table 2S. Odds Ratios for Single Nucleotide Polymorphisms (SNPs) in ERCC3 and Head and Neck Cancer Tumor Sites Using Hierarchical Regression for SNPs by Gene, the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, Whites

		Cases/Controls				
Tumor Site	**SNP**	**AA**		**AB + BB**		**OR (95% I)[a]**
Oral[a]	rs4150496	228	392	279	682	0.79 (0.60,1.04)
	rs1011019	240	548	267	526	0.98 (0.73,1.31)
	rs4150434	308	670	199	404	0.99 (0.77,1.27)
	rs4150416	210	481	297	593	0.97 (0.73,1.30)
	rs4150407	175	311	332	763	1.01 (0.76,1.35)
	rs4150403	394	904	113	170	1.32 (1.01,1.71)
Pharynx[b]	rs4150496	36	392	49	682	0.98 (0.66,1.46)
	rs1011019	43	548	42	526	1.04 (0.70,1.53)
	rs4150434	45	670	40	404	1.22 (0.79,1.87)
	rs4150416	41	481	44	593	0.94 (0.63,1.38)
	rs4150407	31	311	54	763	0.91 (0.60,1.36)
	rs4150403	67	904	18	170	1.18 (0.79,1.78)
Larynx[c]	rs4150496	137	392	191	682	0.82 (0.61,1.12)
	rs1011019	177	548	150	526	0.85 (0.62,1.17)
	rs4150434	193	670	134	404	0.96 (0.73,1.27)
	rs4150416	159	481	168	593	0.85 (0.62,1.16)
	rs4150407	112	311	215	763	0.83 (0.60,1.13)
	rs4150403	272	904	55	170	1.04 (0.77,1.40)
Oral[d]	rs4150496	55	392	74	682	0.87 (0.61,1.25)
	rs1011019	59	548	70	526	1.03 (0.72,1.47)
	rs4150434	85	670	44	404	0.92 (0.63,1.34)
	rs4150416	50	481	79	593	1.07 (0.75,1.54)
	rs4150407	42	311	87	763	0.98 (0.67,1.42)
	rs4150403	99	904	30	170	1.20 (0.84,1.72)
Oropharynx[3]	rs4150496	123	392	137	682	0.77 (0.56,1.06)
	rs1011019	125	548	134	526	0.98 (0.71,1.36)
	rs4150434	149	670	110	404	1.09 (0.80,1.49)
	rs4150416	110	481	149	593	0.97 (0.70,1.35)
	rs4150407	92	311	167	763	1.01 (0.73,1.41)
	rs4150403	204	904	55	170	1.19 (0.87,1.62)
NOS[f]	rs4150496	72	392	98	682	0.95 (0.67,1.34)
	rs1011019	82	548	88	526	1.04 (0.73,1.47)
	rs4150434	99	670	71	404	1.09 (0.77,1.54)
	rs4150416	76	481	94	593	0.93 (0.66,1.31)
	rs4150407	60	311	110	763	0.92 (0.65,1.31)
	rs4150403	131	904	39	170	1.30 (0.92,1.83)

OR odds ratio, I interval estimate

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

[a]Includes tumors with the following ICD codes:C01.9, C02.2, C02.4, C02.9, C03.0, C03.1, C03.9, C04.0, C04.9, C05.0, C05.1, C05.2, C05.3, C05.9, C06.0, C06.1, C06.2, C06.9, C09.0, C09.1, C09.9

[b]Includes tumors with the following ICD codes:C10.0, C10.9, C12.9, C13.0, C13.1, C13.9, C14.0

[c]Includes tumors with the following ICD codes: C32.0, C32.1, C32.2, C32,3, C32.9

[d]Includes tumors with the following ICD codes: C02.2, C0.3.0, C03.1, C03.9, C04.0, C0.4.9, C05.0, C06.0, C06.1, C06.2, C06.9

[e]Includes tumors with the following ICD codes: C01.9, C02.4, C05.1, C05.2, C09.0, C09.1, C09.9, C10.0, C10.9

[f]Includes tumors with the following ICD codes: C02.9, C05.9, C14.0

Table 3S. Odds Ratios for Single Nucleotide Polymorphisms (SNPs) in ERCC6 Genes and Laryngeal Cancer Using Hierarchical Regression for SNPs by Gene, the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, African Americans

		Cases/Controls				
Tumor Site	**SNP**	**AA**		**AB + BB**		**OR (95% I)[a]**
Larynx[b]	rs2228529	87	189	26	60	0.84 (0.56,1.27)
	rs2228527	81	175	33	76	0.88 (0.59,1.30)
	rs4253132	73	125	41	126	0.65 (0.44,0.97)
	rs2228528	79	182	34	69	0.91 (0.60,1.38)

OR odds ratio, I interval estimates

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

[b]Includes tumors with the following ICD codes: C32.0, C32.1, C32.2, C32,3, C32.9

Table 4S. Odds Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Head and Neck Cancer Using Conventional Logistic Regression for Individual SNPs, the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, Whites

		Coded Allele		Cases/Controls				AB + BB vs AA	
Gene	SNP	Referent (A)	Variant (B)	AA		AB + BB		OR (95% I)[a]	p-value[b]
ERCC3 (XPB)	rs4150496	G	A	401	392	520	682	0.75 (0.63, 0.90)	0.002
	rs1011019	C	T	462	548	460	526	1.02 (0.85, 1.22)	0.81
	rs4150434	G	A	548	670	374	404	1.13 (0.94, 1.35)	0.21
	rs4150416	T	G	410	481	509	593	1.00 (0.83, 1.20)	0.99
	rs4150407	A	G	318	311	604	763	0.78 (0.64, 0.95)	0.01
	rs4150403	G	A	736	904	186	170	1.34 (1.06, 1.70)	0.01
	rs4150402	G	A	462	548	460	525	1.03 (0.86, 1.23)	0.78
XPC	rs2228001	A	C	337	375	584	699	0.92 (0.77, 1.11)	0.40
	rs3731143	T	C	818	957	104	117	1.06 (0.80, 1.41)	0.70
	rs2228000	C	T	524	598	396	475	0.96 (0.80, 1.15)	0.64
	rs3731124	A	C	521	599	401	475	0.97 (0.81, 1.17)	0.78
	rs13099160	A	G	814	962	108	112	1.09 (0.82, 1.45)	0.56
	rs3731093	T	C	776	919	138	146	1.09 (0.84, 1.41)	0.52
	rs3731089	G	A	778	919	144	155	1.08 (0.84, 1.38)	0.56
	rs2733537	A	G	416	480	506	594	0.98 (0.82, 1.17)	0.82
	rs3731068	C	A	624	732	298	342	1.03 (0.85, 1.25)	0.77
	rs2607755	T	C	242	284	680	790	1.01 (0.82, 1.23)	0.95
	rs1902658	G	A	235	280	686	794	0.86 (0.70, 1.07)	0.17
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	609	710	313	364	1.01 (0.83, 1.22)	0.95
	rs3176748	A	G	440	510	482	564	0.96 (0.80, 1.15)	0.66
	rs2808667	C	T	814	950	106	124	1.05 (0.79, 1.39)	0.73
	rs2805835	G	C	727	848	195	226	1.02 (0.82, 1.28)	0.84
	rs3176689	A	T	622	728	300	346	0.98 (0.81, 1.18)	0.80
	rs3176683	T	C	818	944	104	130	0.92 (0.70, 1.22)	0.57
	rs3176658	C	T	699	792	223	282	0.93 (0.76, 1.14)	0.49
	rs1800975	G	A	420	473	465	563	0.96 (0.80, 1.15)	0.64
RAD23B	rs1805330	C	T	764	870	158	204	0.90 (0.71, 1.14)	0.39
	rs1805329	C	T	590	711	332	363	1.13 (0.93, 1.36)	0.21
ERCC6	rs2228529	A	G	597	661	313	396	0.88 (0.73, 1.06)	0.19
	rs2228527	A	G	598	665	324	409	0.89 (0.74, 1.07)	0.21
	rs4253132	T	C	723	829	199	245	0.95 (0.77, 1.18)	0.66
	rs2228528	G	A	637	746	284	328	1.01 (0.83, 1.22)	0.93
DDB2 (XPE)	rs2029298	A	G	425	478	497	596	0.95 (0.80, 1.14)	0.62
	rs4647709	C	T	766	902	156	172	1.06 (0.83, 1.35)	0.62
	rs2291120	T	C	685	812	237	262	1.02 (0.83, 1.25)	0.87
	rs1685404	G	C	418	502	504	572	1.04 (0.87, 1.25)	0.65
	rs2957873	A	G	643	711	279	363	0.87 (0.72, 1.05)	0.15
	rs326224	G	A	683	761	239	313	0.88 (0.72, 1.08)	0.22
	rs2306353	G	A	696	762	226	312	0.82 (0.67, 1.00)	0.05
	rs326222	C	T	484	526	438	548	0.89 (0.74, 1.06)	0.20
	rs901746	A	G	485	528	437	546	0.89 (0.75, 1.07)	0.21
ERCC5 (XPG)	rs2296147	T	C	280	303	637	765	0.90 (0.74, 1.09)	0.29
	rs4771436	T	G	563	659	359	415	1.03 (0.85, 1.23)	0.79
	rs1047768	C	T	319	377	603	696	1.03 (0.86, 1.25)	0.73
	rs3818356	C	T	563	659	357	413	1.03 (0.85, 1.23)	0.79
	rs4150351	A	C	595	692	327	382	0.99 (0.82, 1.20)	0.95
	rs4150355	C	T	402	428	520	646	0.85 (0.71, 1.02)	0.07
	rs4150360	T	C	275	316	647	758	0.79 (0.63, 1.00)	0.05
	rs4150383	G	A	630	749	292	325	1.08 (0.89, 1.31)	0.46
	rs4150386	A	C	724	836	198	237	0.96 (0.77, 1.19)	0.69
	rs17655	C	G	555	658	367	416	1.05 (0.88, 1.26)	0.59
	rs873601	A	G	464	539	458	535	1.00 (0.83, 1.19)	0.97
	rs4150393	A	G	702	844	220	230	1.15 (0.93, 1.42)	0.21

OR odds ratio, I interval estimates

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

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

Table 4S cont. Odds Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Head and Neck Cancer Using Conventional Logistic Regression for Individual SNPs, the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, Whites

		Coded Allele		Cases/Controls				AB + BB vs AA	
Gene	SNP	Referent (A)	Variant (B)	AA		AB + BB		OR (95% I)[a]	p-value[b]
ERCC5 (XPG)	rs876430	C	T	465	540	457	534	1.00 (0.83, 1.19)	0.97
	rs1051677	T	C	735	858	186	216	1.00 (0.80, 1.25)	0.97
	rs1051685	A	G	736	832	185	242	0.90 (0.72, 1.12)	0.34
ERCC4 (XPF)	rs3136038	C	T	402	490	520	584	1.07 (0.89, 1.28)	0.49
	rs1799798	G	A	757	901	165	173	1.15 (0.90, 1.46)	0.26
	rs744154	C	G	480	582	442	492	1.08 (0.90, 1.29)	0.41
	rs3136085	G	C	475	576	447	498	1.08 (0.90, 1.29)	0.41
	rs3136130	G	T	400	485	522	589	1.06 (0.88, 1.27)	0.54
	rs1800067	G	A	778	920	144	154	1.10 (0.86, 1.42)	0.44
	rs3136172	A	G	458	566	464	508	1.12 (0.93, 1.34)	0.23
RAD23A	rs2974752	A	G	333	424	561	617	1.16 (0.96, 1.40)	0.11
ERCC2 (XPD)	rs13181	T	G	381	437	534	633	0.95 (0.79, 1.14)	0.58
	rs238418	C	A	382	426	540	648	0.92 (0.77, 1.11)	0.38
	rs1799787	C	T	472	545	450	529	0.97 (0.81, 1.16)	0.75
	rs3916874	G	C	477	545	445	529	0.95 (0.80, 1.14)	0.60
	rs238416	G	A	369	468	552	604	1.17 (0.97, 1.40)	0.10
	rs50872	C	T	531	584	389	488	0.89 (0.74, 1.07)	0.20
	rs50871	T	G	242	258	680	815	0.89 (0.73, 1.10)	0.28
	rs238407	A	T	263	338	658	736	1.16 (0.95, 1.41)	0.14
	rs3810366	C	G	178	232	743	548	1.18 (0.94, 1.47)	0.15
ERCC1	rs735482	A	C	688	797	234	277	0.98 (0.80, 1.21)	0.86
	rs2336219	G	A	688	797	234	277	0.98 (0.80, 1.21)	0.86
	rs3212964	G	A	692	794	230	280	0.94 (0.77, 1.16)	0.57
	rs3212955	A	G	528	607	394	466	0.99 (0.82, 1.18)	0.90
	rs3212948	C	G	382	458	540	616	1.07 (0.89, 1.28)	0.49
	rs3212930	T	C	576	657	346	417	0.96 (0.80, 1.15)	0.63
LIG1	rs156641	G	A	370	440	552	634	1.01 (0.84, 1.22)	0.88
	rs20580	C	A	237	293	685	781	1.05 (0.86, 1.29)	0.63
	rs20579	C	T	691	826	231	248	1.09 (0.89, 1.35)	0.40

OR odds ratio, I interval estimates

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

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

Table 5S. Odds Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Head and Neck Cancer Using Conventional Logistic Regression for Individual SNPs, the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, African Americans

		Coded Allele		Cases/Controls				AB + BB vs AA	
Gene	SNP	Referent (A)	Variant (B)	AA		AB + BB		OR (95% I)[a]	p-value[b]
ERCC3									
(XPB)	rs4150496	G	A	178	136	125	115	0.80 (0.56, 1.14)	0.21
	rs4150459	G	A	190	164	115	87	1.23 (0.85, 1.78)	0.26
	rs1011019	C	T	183	143	122	108	0.84 (0.59, 1.19)	0.33
	rs4150434	G	A	232	186	73	65	1.00 (0.66, 1.50)	0.99
	rs4150416	T	G	85	76	219	175	1.13 (0.77, 1.65)	0.54
	rs4150407	A	G	84	68	221	183	0.97 (0.66, 1.43)	0.87
	rs4150402	G	A	183	143	122	108	0.84 (0.59, 1.19)	0.33
XPC	rs2228001	A	C	180	134	125	117	0.82 (0.57, 1.16)	0.26
	rs2228000	C	T	251	205	54	46	0.98 (0.62, 1.55)	0.95
	rs3731124	A	C	252	212	53	39	1.06 (0.66, 1.70)	0.80
	rs3731093	T	C	263	208	38	41	0.75 (0.46, 1.24)	0.27
	rs3731089	G	A	263	208	42	43	0.79 (0.49, 1.28)	0.34
	rs2733537	A	G	212	164	93	87	0.85 (0.59, 1.24)	0.40
	rs2607755	T	C	111	109	194	142	1.35 (0.94, 1.93)	0.10
	rs1902658	G	A	300	51	5	200	0.69 (0.46, 1.03)	0.07
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	221	48	30	1.39 (0.84, 2.30)	0.20
	rs2266692	G	T	237	202	68	48	1.18 (0.77, 1.82)	0.45
XPA	rs3176757	C	T	236	193	69	58	0.94 (0.62, 1.42)	0.77
	rs3176753	T	C	225	184	80	67	0.97 (0.65, 1.43)	0.87
	rs3176748	A	G	250	208	55	43	1.06 (0.66, 1.68)	0.82
	rs3176658	C	T	260	210	45	41	0.97 (0.60, 1.57)	0.92
	rs1800975	G	A	187	141	106	93	0.87 (0.60, 1.26)	0.47
RAD23B	rs1805330	C	T	183	160	122	91	1.16 (0.81, 1.66)	0.43
ERCC6	rs2228529	A	G	234	189	69	60	0.93 (0.62, 1.40)	0.72
	rs2228527	A	G	218	175	87	76	0.91 (0.62, 1.33)	0.63
	rs4253132	T	C	191	125	114	126	0.55 (0.38, 0.79)	0.001
	rs2228528	G	A	212	182	92	69	1.19 (0.80, 1.75)	0.39
DDB2									
(XPE)	rs2029298	A	G	90	88	215	163	1.26 (0.87, 1.82)	0.22
	rs1685404	G	C	164	140	141	111	1.12 (0.79, 1.60)	0.52
	rs2957873	A	G	90	82	214	169	1.11 (0.76, 1.61)	0.59
	rs326224	G	A	80	63	225	188	0.89 (0.60, 1.33)	0.58
	rs2306353	G	A	106	97	199	154	1.14 (0.80, 1.64)	0.47
	rs326222	C	T	54	50	251	201	1.15 (0.74, 1.80)	0.53
	rs901746	A	G	65	58	240	193	1.03 (0.67, 1.56)	0.90
ERCC5									
(XPG)	rs2296147	T	C	193	148	111	102	0.86 (0.60, 1.24)	0.43
	rs2296148	C	T	228	190	76	61	1.07 (0.71, 1.60)	0.76
	rs4771436	T	G	204	172	101	79	1.03 (0.71, 1.49)	0.87
	rs1047768	C	T	116	115	189	136	1.27 (0.89, 1.80)	0.18
	rs2020915	G	A	205	144	100	107	0.70 (0.49, 1.00)	0.05
	rs3818356	C	T	206	172	99	79	1.00 (0.69, 1.45)	0.99
	rs4150355	C	T	218	175	87	76	0.98 (0.67, 1.45)	0.93
	rs4150360	T	C	19	17	286	232	0.95 (0.67, 1.36)	0.80
	rs4150383	G	A	242	200	63	51	0.98 (0.64, 1.51)	0.93
	rs17655	C	G	90	70	215	181	0.96 (0.65, 1.41)	0.82
	rs873601	A	G	30	30	275	221	1.29 (0.74, 2.27)	0.37
	rs876430	C	T	32	30	273	221	1.22 (0.70, 2.11)	0.49
	rs1051677	T	C	232	184	73	67	0.85 (0.57, 1.27)	0.44
	rs1051685	A	G	138	117	167	133	0.98 (0.69, 1.39)	0.89

OR odds ratio, I interval estimates

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

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

Table 5S cont. Odds Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Head and Neck Cancer Using Conventional Logistic Regression for Individual SNPs, the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, African Americans

		Coded Allele		Cases/Controls				AB + BB vs AA	
Gene	SNP	Referent (A)	Variant (B)	AA		AB + BB		OR (95% I)[a]	p-value[b]
ERCC4									
(XPF)	rs3136038	C	T	92	84	213	167	1.14 (0.79, 1.66)	0.48
	rs744154	C	G	221	174	84	77	0.91 (0.62, 1.34)	0.63
	rs3136085	G	C	173	146	132	105	1.16 (0.81, 1.65)	0.41
	rs3136091	C	G	255	199	50	52	0.73 (0.47, 1.14)	0.17
	rs3136130	G	T	75	65	230	186	1.11 (0.74, 1.65)	0.61
	rs3136172	A	G	216	171	89	80	0.94 (0.64, 1.37)	0.74
	rs2020955	T	C	193	165	112	86	1.10 (0.76, 1.58)	0.62
RAD23A	rs2974752	A	G	77	62	216	170	1.06 (0.71, 1.59)	0.77
	rs11558955	A	G	256	214	49	37	1.18 (0.73, 1.92)	0.50
ERCC2									
(XPD)	rs13181	T	G	173	140	131	109	0.95 (0.67, 1.35)	0.77
	rs238418	C	A	8	11	296	240	1.57 (0.59, 4.21)	0.37
	rs1799787	C	T	235	192	70	59	0.95 (0.63, 1.44)	0.82
	rs3916874	G	C	268	226	37	25	1.15 (0.65, 2.04)	0.62
	rs238416	G	A	243	208	61	41	1.34 (0.85, 2.13)	0.21
	rs50872	C	T	223	158	82	93	0.64 (0.44, 0.92)	0.02
	rs50871	T	G	229	195	76	56	1.20 (0.79, 1.84)	0.40
	rs238407	A	T	226	190	79	61	1.07 (0.71, 1.62)	0.73
	rs3810366	C	G	212	180	93	71	1.11 (0.75, 1.64)	0.59
ERCC1	rs735482	A	C	156	122	149	129	0.87 (0.62, 1.23)	0.44
	rs2336219	G	A	157	126	148	125	0.92 (0.65, 1.30)	0.64
	rs3212964	G	A	207	142	96	107	0.65 (0.45, 0.93)	0.02
	rs3212955	A	G	159	142	146	109	1.21 (0.85, 1.72)	0.30
	rs3212948	C	G	9	6	296	245	0.82 (0.26, 2.54)	0.73
	rs3212935	A	G	143	125	162	125	1.19 (0.84, 1.69)	0.34
	rs3212930	T	C	250	205	55	46	1.00 (0.64, 1.57)	1.00
LIG1	rs156641	G	A	234	192	71	59	1.07 (0.70, 1.64)	0.74
	rs20580	C	A	62	57	242	194	1.21 (0.79, 1.84)	0.38
	rs20579	C	T	150	128	155	123	1.03 (0.73, 1.46)	0.87
	rs439132	A	G	172	136	133	115	0.87 (0.61, 1.24)	0.43

OR odds ratio, I interval estimates

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

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

Table 6S. Odds Ratios and Relative Excess Risk Estimates for Joint Effects of Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Ever Environmental Tobacco Smoke on Head and Neck Cancer Risk Using Conventional Logistic Regression, the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, Whites

		Coded Allele		Cases/Controls								OR (95% I)[d]			
Gene	SNP	Referent (A) / Variant (B)		ETS=0, SNP=0		ETS=0, SNP=1		ETS=1, SNP=0		ETS=1, SNP=1		ETS=1, SNP=0	ETS=0, SNP=1	ETS=1, SNP=1	RERI (95% CI)
ERCC3 (XPB)	rs4150496	G	A	46	58	43	101	355	334	476	580	0.65 (0.41, 1.04)	0.47 (0.26, 0.84)	0.51 (0.32, 0.80)	0.38 (0.03, 0.73)
	rs1011019	C	T	45	82	44	77	416	466	416	448	0.98 (0.63, 1.53)	1.40 (0.79, 2.49)	1.05 (0.67, 1.63)	-0.34 (-1.15, 0.48)
	rs4150434	G	A	44	106	45	53	504	563	328	351	1.23 (0.80, 1.88)	2.20 (1.22, 3.95)	1.14 (0.74, 1.76)	-1.29 (-2.63, 0.05)
	rs4150416	T	G	40	73	49	86	369	408	460	506	0.97 (0.61, 1.56)	1.32 (0.74, 2.36)	1.01 (0.63, 1.60)	-0.29 (-1.07, 0.50)
	rs4150407	A	G	35	52	54	107	283	259	549	655	0.70 (0.42, 1.18)	0.57 (0.32, 1.04)	0.57 (0.35, 0.93)	0.29 (-0.13, 0.71)
	rs4150403	G	A	70	136	19	23	665	767	167	147	0.92 (0.64, 1.31)	1.89 (0.91, 3.95)	1.18 (0.77, 1.79)	-0.63 (-2.03, 0.77)
	rs4150402	G	A	45	82	44	76	416	466	416	448	0.98 (0.63, 1.53)	1.43 (0.80, 2.54)	1.05 (0.67, 1.63)	-0.37 (-1.20, 0.47)
XPC	rs2228001	A	C	28	57	61	102	309	317	522	597	1.11 (0.64, 1.91)	1.28 (0.69, 2.36)	0.96 (0.56, 1.63)	-0.43 (-1.31, 0.45)
	rs3731143	T	C	80	145	9	14	737	812	95	102	0.87 (0.62, 1.21)	1.29 (0.50, 3.34)	1.00 (0.63, 1.57)	-0.16 (-1.42, 1.10)
	rs2228000	C	T	57	93	32	66	466	505	364	408	0.85 (0.56, 1.27)	0.92 (0.51, 1.65)	0.81 (0.53, 1.23)	0.05 (-0.53, 0.62)
	rs3731124	A	C	56	80	33	79	465	519	367	395	0.71 (0.47, 1.07)	0.65 (0.36, 1.17)	0.73 (0.48, 1.11)	0.37 (-0.04, 0.78)
	rs13099160	A	G	77	140	12	19	736	821	96	93	0.83 (0.59, 1.18)	0.95 (0.41, 2.23)	1.03 (0.65, 1.63)	0.24 (-0.63, 1.10)
	rs3731093	T	C	71	136	18	22	704	782	120	124	0.88 (0.62, 1.26)	1.45 (0.69, 3.06)	1.03 (0.66, 1.61)	-0.30 (-1.41, 0.81)
	rs3731089	G	A	71	136	18	23	706	782	126	132	0.89 (0.63, 1.27)	1.43 (0.68, 2.99)	1.04 (0.67, 1.60)	-0.28 (-1.36, 0.80)
	rs2733537	A	G	41	76	48	83	374	404	458	510	0.95 (0.59, 1.51)	1.20 (0.68, 2.14)	0.95 (0.60, 1.52)	-0.20 (-0.92, 0.53)
	rs3731068	C	A	70	96	19	63	553	636	279	278	0.64 (0.44, 0.94)	0.43 (0.22, 0.83)	0.73 (0.49, 1.09)	0.66 (0.34, 0.97)*
	rs2607755	T	C	29	35	60	124	213	249	619	665	0.61 (0.34, 1.11)	0.68 (0.36, 1.30)	0.66 (0.37, 1.18)	0.37 (-0.07, 0.82)
	rs1902658	G	A	28	33	61	126	207	247	624	667	0.58 (0.31, 1.07)	0.66 (0.34, 1.28)	0.65 (0.36, 1.18)	0.41 (-0.02, 0.84)
ERCC8	rs3117	T	C	39	58	50	101	297	338	535	576	0.77 (0.47, 1.26)	0.83 (0.46, 1.48)	0.76 (0.47, 1.23)	0.17 (-0.35, 0.68)
CDK7	rs2972388	A	G	23	46	66	113	243	289	589	625	0.94 (0.51, 1.74)	1.28 (0.66, 2.48)	1.07 (0.59, 1.95)	-0.15 (-0.97, 0.67)
XPA	rs3176757	C	T	58	99	31	60	550	610	282	304	0.84 (0.57, 1.25)	0.98 (0.54, 1.77)	0.87 (0.57, 1.32)	0.05 (-0.56, 0.66)
	rs3176748	A	G	41	84	48	75	398	425	434	489	0.94 (0.60, 1.48)	1.13 (0.64, 2.02)	0.90 (0.57, 1.41)	-0.18 (-0.87, 0.52)
	rs2808667	C	T	81	136	8	23	732	813	98	101	0.78 (0.56, 1.10)	0.62 (0.24, 1.61)	1.03 (0.65, 1.62)	0.62 (-0.05, 1.29)
	rs2805835	G	C	68	126	21	33	659	722	173	192	0.92 (0.64, 1.32)	1.31 (0.66, 2.60)	0.90 (0.59, 1.36)	-0.34 (-1.27, 0.59)
	rs3176689	A	T	59	109	30	50	562	618	270	296	0.96 (0.65, 1.42)	1.33 (0.72, 2.46)	0.90 (0.60, 1.36)	-0.39 (-1.25, 0.46)
	rs3176683	T	C	78	136	11	23	739	807	93	107	0.86 (0.61, 1.22)	1.00 (0.43, 2.30)	0.82 (0.52, 1.30)	-0.04 (-0.92, 0.84)
	rs3176658	C	T	69	113	20	46	630	678	202	236	0.81 (0.56, 1.17)	0.78 (0.40, 1.51)	0.79 (0.52, 1.18)	0.20 (-0.36, 0.75)
	rs1800975	G	A	43	67	42	86	377	405	422	477	0.82 (0.51, 1.30)	0.88 (0.49, 1.60)	0.79 (0.50, 1.26)	0.09 (-0.47, 0.65)
RAD23B	rs1805330	C	T	69	128	20	31	694	741	138	173	0.90 (0.63, 1.30)	1.09 (0.54, 2.18)	0.76 (0.49, 1.16)	-0.24 (-1.05, 0.58)
	rs1805329	C	T	65	108	24	51	524	602	308	312	0.78 (0.54, 1.14)	0.82 (0.42, 1.57)	0.87 (0.59, 1.29)	0.27 (-0.28, 0.83)
ERCC6	rs2228529	A	G	54	98	34	61	542	563	279	334	0.96 (0.64, 1.44)	1.19 (0.66, 2.15)	0.86 (0.56, 1.32)	-0.28 (-1.04, 0.47)
	rs2228527	A	G	54	98	35	61	543	567	289	347	0.96 (0.64, 1.44)	1.19 (0.66, 2.15)	0.86 (0.56, 1.31)	-0.29 (-1.05, 0.47)
	rs4253132	T	C	77	117	12	42	645	711	187	203	0.76 (0.53, 1.08)	0.50 (0.24, 1.08)	0.74 (0.49, 1.11)	0.48 (0.05, 0.91)
	rs2228528	G	A	69	126	20	33	567	620	264	294	0.91 (0.63, 1.31)	1.25 (0.63, 2.51)	0.88 (0.60, 1.30)	-0.28 (-1.18, 0.62)

OR odds ratio, I interval estimates

[a]Odds ratios adjusted for matching factors (age and sex including pairwise interactions), education, alcohol drinking, cigarette smoking, and percent African ancestry. 124 individuals missing alcohol drinking or cigarette smoking, and therefore dropped from models.

Interval estimates presented not corrected for multiple comparisons.

Highlighting indicates RERI significant at 0.05 level. Asterisks indicate RERI significant at a Bonferroni corrected level (0.05/84=0.0006).

Table 6S cont. Odds Ratios and Relative Excess Risk Estimates for Joint Effects of Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Ever Environmental Tobacco Smoke on Head and Neck Cancer Risk Using Conventional Logistic Regression, the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, Whites

		Coded Allele		Cases/Controls								OR (95% I)[d]			
Gene	SNP	Referent (A) / Variant (B)		ETS=0, SNP=0		ETS=0, SNP=1		ETS=1, SNP=0		ETS=1, SNP=1		ETS=1, SNP=0	ETS=0, SNP=1	ETS=1, SNP=1	RERI (95% CI)
DDB2															
(XPE)	rs2029298	A	G	44	71	45	88	381	407	451	507	0.92 (0.59, 1.45)	1.03 (0.58, 1.84)	0.83 (0.53, 1.31)	-0.12 (-0.77, 0.53)
	rs4647709	C	T	73	135	16	24	693	767	139	147	0.86 (0.60, 1.22)	1.10 (0.51, 2.36)	0.95 (0.62, 1.44)	-0.01 (-0.88, 0.86)
	rs2291120	T	C	73	110	16	49	611	701	221	213	0.73 (0.50, 1.05)	0.53 (0.27, 1.08)	0.78 (0.52, 1.17)	0.52 (0.10, 0.93)
	rs1685404	G	C	39	76	50	83	378	425	454	489	0.86 (0.54, 1.37)	1.15 (0.64, 2.04)	0.98 (0.62, 1.55)	-0.03 (-0.68, 0.63)
	rs2957873	A	G	66	108	23	51	576	603	256	311	0.90 (0.62, 1.31)	0.99 (0.52, 1.89)	0.77 (0.52, 1.15)	-0.12 (-0.81, 0.56)
	rs326224	G	A	67	110	22	49	615	651	217	263	0.90 (0.62, 1.30)	1.07 (0.56, 2.03)	0.82 (0.55, 1.23)	-0.14 (-0.87, 0.59)
	rs2306353	G	A	71	112	18	47	624	650	208	264	0.88 (0.61, 1.27)	0.88 (0.45, 1.74)	0.72 (0.48, 1.08)	-0.04 (-0.70, 0.61)
	rs326222	C	T	44	75	45	84	439	451	393	463	1.01 (0.65, 1.57)	1.14 (0.64, 2.02)	0.82 (0.52, 1.28)	-0.33 (-1.07, 0.41)
	rs901746	A	G	44	75	45	84	440	453	392	461	1.01 (0.65, 1.57)	1.14 (0.64, 2.02)	0.82 (0.52, 1.28)	-0.33 (-1.06, 0.41)
ERCC5															
(XPG)	rs2296147	T	C	26	43	63	114	254	260	573	650	0.79 (0.44, 1.43)	0.85 (0.45, 1.61)	0.74 (0.42, 1.31)	0.10 (-0.49, 0.70)
	rs4771436	T	G	58	100	31	59	504	559	328	355	0.88 (0.59, 1.31)	1.05 (0.58, 1.90)	0.86 (0.57, 1.29)	-0.07 (-0.73, 0.59)
	rs1047768	C	T	30	57	59	102	288	320	544	593	0.96 (0.57, 1.63)	1.15 (0.63, 2.10)	0.93 (0.56, 1.55)	-0.19 (-0.93, 0.55)
	rs3818356	C	T	58	100	31	59	504	559	326	353	0.88 (0.59, 1.31)	1.05 (0.58, 1.90)	0.86 (0.57, 1.30)	-0.07 (-0.73, 0.59)
	rs4150351	A	C	60	101	29	58	534	591	298	323	0.84 (0.56, 1.24)	0.92 (0.50, 1.68)	0.83 (0.55, 1.25)	0.07 (-0.51, 0.66)
	rs4150355	C	T	39	63	50	96	363	364	469	550	0.80 (0.49, 1.30)	0.81 (0.45, 1.46)	0.74 (0.46, 1.19)	0.12 (-0.41, 0.65)
	rs4150360	T	C	26	49	63	110	248	267	584	647	1.01 (0.58, 1.77)	1.16 (0.62, 2.16)	0.92 (0.54, 1.59)	-0.24 (-1.04, 0.55)
	rs4150383	G	A	60	111	29	48	569	638	263	276	0.92 (0.63, 1.35)	1.24 (0.67, 2.30)	0.90 (0.60, 1.36)	-0.26 (-1.06, 0.54)
	rs4150386	A	C	71	123	18	36	652	712	180	201	0.82 (0.57, 1.18)	0.80 (0.40, 1.60)	0.79 (0.52, 1.19)	0.17 (-0.43, 0.77)
	rs17655	C	G	50	100	39	59	504	557	328	357	0.87 (0.57, 1.30)	1.08 (0.60, 1.94)	0.92 (0.60, 1.40)	-0.03 (-0.68, 0.63)
	rs873601	A	G	42	81	47	78	421	457	411	457	0.84 (0.53, 1.32)	0.95 (0.53, 1.68)	0.83 (0.53, 1.30)	0.05 (-0.53, 0.62)
	rs4150393	A	G	73	123	16	36	628	721	204	193	0.80 (0.56, 1.15)	0.90 (0.44, 1.83)	0.98 (0.66, 1.48)	0.29 (-0.37, 0.95)
	rs876430	C	T	42	81	47	78	422	458	410	456	0.84 (0.53, 1.31)	0.95 (0.53, 1.68)	0.83 (0.53, 1.30)	0.05 (-0.53, 0.63)
	rs1051677	T	C	78	124	11	35	656	733	175	181	0.75 (0.53, 1.07)	0.49 (0.22, 1.12)	0.78 (0.52, 1.18)	0.54 (0.09, 0.99)
	rs1051685	A	G	69	119	20	40	666	712	165	202	0.81 (0.57, 1.17)	0.72 (0.37, 1.43)	0.71 (0.46, 1.08)	0.17 (-0.38, 0.72)
ERCC4															
(XPF)	rs3136038	C	T	41	75	48	84	360	414	472	500	0.76 (0.48, 1.21)	0.91 (0.51, 1.62)	0.86 (0.54, 1.36)	0.19 (-0.34, 0.72)
	rs1799798	G	A	71	133	18	26	686	767	146	147	0.89 (0.63, 1.27)	1.36 (0.65, 2.87)	1.00 (0.65, 1.53)	-0.26 (-1.30, 0.79)
	rs744154	C	G	48	85	41	74	431	496	401	418	0.76 (0.49, 1.17)	0.90 (0.51, 1.61)	0.89 (0.58, 1.38)	0.23 (-0.29, 0.75)
	rs3136085	G	C	47	84	42	75	427	491	405	423	0.75 (0.49, 1.17)	0.91 (0.51, 1.63)	0.90 (0.58, 1.39)	0.23 (-0.29, 0.75)
	rs3136130	G	T	39	75	50	84	360	409	472	505	0.80 (0.50, 1.29)	1.00 (0.56, 1.79)	0.90 (0.56, 1.43)	0.09 (-0.49, 0.68)
	rs1800067	G	A	78	137	11	22	699	782	133	132	0.81 (0.57, 1.14)	0.75 (0.31, 1.78)	0.93 (0.61, 1.42)	0.38 (-0.32, 1.07)
	rs3136172	A	G	46	82	43	77	411	483	421	431	0.74 (0.47, 1.15)	0.90 (0.50, 1.59)	0.90 (0.58, 1.40)	0.26 (-0.24, 0.77)
RAD23A	rs2974752	A	G	31	65	54	87	301	359	507	529	0.89 (0.53, 1.48)	1.17 (0.64, 2.14)	0.97 (0.58, 1.60)	-0.09 (-0.79, 0.62)

OR odds ratio, I interval estimates

[a]Odds ratios adjusted for matching factors (age and sex including pairwise interactions), education, alcohol drinking, cigarette smoking, and percent African ancestry. 124 individuals missing alcohol drinking or cigarette smoking, and therefore dropped from models.

Interval estimates presented not corrected for multiple comparisons.

Highlighting indicates RERI significant at 0.05 level. Asterisks indicate RERI significant at a Bonferroni corrected level (0.05/84=0.0006).

Table 6S cont. Odds Ratios and Relative Excess Risk Estimates for Joint Effects of Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Ever Environmental Tobacco Smoke on Head and Neck Cancer Risk Using Conventional Logistic Regression, the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, Whites

		Coded Allele		Cases/Controls								OR (95% I)[d]			
Gene	SNP	Referent (A) / Variant (B)		ETS=0, SNP=0		ETS=0, SNP=1		ETS=1, SNP=0		ETS=1, SNP=1		ETS=1, SNP=0	ETS=0, SNP=1	ETS=1, SNP=1	RERI (95% CI)
ERCC2															
(XPD)	rs13181	T	G	36	61	53	96	344	376	481	536	0.84 (0.51, 1.38)	1.01 (0.56, 1.82)	0.85 (0.52, 1.38)	0 (-0.62, 0.62)
	rs238418	C	A	36	60	53	99	345	366	487	548	0.84 (0.51, 1.39)	0.96 (0.53, 1.74)	0.84 (0.51, 1.37)	0.03 (-0.57, 0.63)
	rs1799787	C	T	45	87	44	72	426	458	406	456	0.91 (0.59, 1.42)	1.19 (0.67, 2.12)	0.95 (0.61, 1.47)	-0.15 (-0.86, 0.55)
	rs3916874	G	C	47	85	42	74	430	459	402	455	0.96 (0.62, 1.49)	1.14 (0.64, 2.03)	0.87 (0.56, 1.34)	-0.24 (-0.95, 0.47)
	rs238416	G	A	30	68	59	91	339	400	492	512	0.99 (0.59, 1.65)	1.38 (0.76, 2.51)	1.10 (0.66, 1.82)	-0.27 (-1.09, 0.55)
	rs50872	C	T	54	83	35	76	476	500	354	412	0.83 (0.55, 1.26)	0.83 (0.47, 1.50)	0.75 (0.49, 1.14)	0.08 (-0.46, 0.62)
	rs50871	T	G	23	36	66	123	218	222	614	691	1.07 (0.57, 2.02)	1.23 (0.63, 2.41)	0.98 (0.53, 1.80)	-0.32 (-1.23, 0.59)
	rs238407	A	T	26	48	63	111	237	290	594	624	0.81 (0.45, 1.44)	1.01 (0.54, 1.90)	0.89 (0.51, 1.56)	0.07 (-0.56, 0.71)
	rs3810366	C	G	19	37	70	122	159	195	672	719	0.76 (0.39, 1.45)	0.95 (0.48, 1.87)	0.84 (0.45, 1.56)	0.14 (-0.50, 0.77)
ERCC1	rs735482	A	C	66	118	23	41	621	678	211	236	0.86 (0.60, 1.25)	0.99 (0.51, 1.91)	0.84 (0.56, 1.26)	-0.01 (-0.70, 0.67)
	rs2336219	G	A	66	118	23	41	621	678	211	236	0.86 (0.60, 1.25)	0.99 (0.51, 1.91)	0.84 (0.56, 1.26)	-0.01 (-0.70, 0.67)
	rs3212964	G	A	66	117	23	42	625	676	207	238	0.85 (0.59, 1.24)	0.92 (0.48, 1.79)	0.80 (0.53, 1.21)	0.03 (-0.62, 0.68)
	rs3212955	A	G	55	89	34	70	472	518	360	395	0.79 (0.52, 1.20)	0.87 (0.49, 1.56)	0.84 (0.55, 1.27)	0.17 (-0.36, 0.70)
	rs3212948	C	G	40	64	49	95	341	394	491	520	0.70 (0.43, 1.14)	0.82 (0.46, 1.46)	0.81 (0.51, 1.30)	0.29 (-0.18, 0.76)
	rs3212930	T	C	56	98	33	61	519	559	313	355	0.85 (0.57, 1.27)	1.00 (0.56, 1.81)	0.87 (0.58, 1.33)	0.02 (-0.60, 0.64)
LIG1	rs156641	G	A	36	54	53	105	334	385	498	529	0.64 (0.39, 1.06)	0.74 (0.41, 1.33)	0.76 (0.46, 1.24)	0.38 (-0.04, 0.81)
	rs20580	C	A	22	27	67	132	215	265	617	649	0.47 (0.24, 0.92)	0.63 (0.31, 1.27)	0.65 (0.34, 1.22)	0.55 (0.17, 0.92)
	rs20579	C	T	69	111	20	48	621	714	211	200	0.73 (0.51, 1.06)	0.73 (0.38, 1.41)	1.01 (0.67, 1.53)	0.54 (0.04, 1.05)

OR odds ratio, I interval estimates

[a]Odds ratios adjusted for matching factors (age and sex including pairwise interactions), education, alcohol drinking, cigarette smoking, and percent African ancestry. 124 individuals missing alcohol drinking or cigarette smoking, and therefore dropped from models.

Interval estimates presented not corrected for multiple comparisons.

Highlighting indicates RERI significant at 0.05 level. Asterisks indicate RERI significant at a Bonferroni corrected level (0.05/84=0.0006).

APPENDIX B

AIM 1 SUPPLEMENTAL TABLES NOT REFERENCED IN CHAPTER 3

Table 1A. Odds Ratios and Relative Excess Risk Estimates for Joint Effects of Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Cigarette Smoking on Head and Neck Cancer Risk Using Exact Logistic Regression, the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, African Americans

		Coded Allele		Cases/Controls								OR (95% I)[a]			
Gene	SNP	Referent (A) / Variant (B)		Cigarette=0, SNP=0		Cigarette=0, SNP=1		Cigarette=1, SNP=0		Cigarette=1, SNP=1		Cigarette=1, SNP=0	Cigarette=0, SNP=1	Cigarette=1, SNP=1	RERI
ERCC3															
(XPB)	rs4150496	G	A	7	52	6	47	171	84	119	68	14.99 (6.42, 40.82)	0.95 (0.24, 3.56)	12.86 (5.42, 35.48)	-2.07
	rs4150459	G	A	9	66	4	33	181	98	111	54	13.44 (6.32, 32.04)	0.89 (0.19, 3.49)	14.89 (6.75, 36.6)	1.55
	rs1011019	C	T	10	60	3	39	173	83	119	69	12.40 (5.92, 28.59)	0.46 (0.08, 1.96)	10.25 (4.82, 23.96)	-1.62
	rs4150434	G	A	9	68	4	31	223	118	69	34	14.19 (6.74, 33.52)	0.98 (0.20, 3.83)	15.06 (6.51, 38.58)	0.90
	rs4150416	T	G	6	34	7	65	79	42	212	110	10.50 (3.94, 33.09)	0.61 (0.16, 2.4)	10.85 (4.33, 32.59)	0.74
	rs4150407	A	G	3	24	10	75	81	44	211	108	14.48 (4.06, 79.27)	1.07 (0.25, 6.52)	15.51 (4.56, 82.27)	0.97
	rs4150402	G	A	10	60	3	39	173	83	119	69	12.40 (5.92, 28.59)	0.46 (0.08, 1.96)	10.25 (4.82, 23.96)	-1.62
XPC	rs2228001	A	C	6	50	7	49	174	84	118	68	17.11 (6.96, 50.79)	1.19 (0.32, 4.61)	14.3 (5.73, 42.99)	-2.99
	rs2228000	C	T	11	83	2	16	240	122	52	30	14.75 (7.48, 31.87)	0.94 (0.09, 4.99)	12.85 (5.73, 31.1)	-1.85
	rs3731124	A	C	9	86	4	13	243	126	49	26	18.32 (8.83, 42.81)	2.9 (0.57, 12.46)	17.61 (7.37, 46.51)	-2.61
	rs3731093	T	C	12	84	1	13	251	124	37	28	14.09 (7.31, 29.45)	0.54 (0.01, 4.28)	9.1 (4, 22.01)	-4.53
	rs3731089	G	A	12	84	1	15	251	124	41	28	14.09 (7.31, 29.45)	0.47 (0.01, 3.64)	10.07 (4.47, 24.21)	-3.48
	rs2733537	A	G	10	67	3	32	202	97	90	55	13.85 (6.71, 31.55)	0.63 (0.1, 2.68)	10.84 (5.02, 25.66)	-2.64
	rs2607755	T	C	6	45	7	54	105	64	187	88	12.17 (4.81, 36.90)	0.97 (0.26, 3.78)	15.8 (6.4, 47.04)	3.66
	rs1902658	G	A	3	25	10	74	50	26	242	126	15.59 (4.19, 88.13)	1.12 (0.26, 6.86)	15.9 (4.72, 83.86)	0.19
ERCC8	rs3117	T	C	5	34	8	65	121	60	171	92	13.55 (4.93, 46.65)	0.84 (0.22, 3.52)	12.54 (4.66, 42.48)	-0.85
CDK7	rs2972388	A	G	9	52	4	47	151	80	141	72	10.81 (4.96, 26.28)	0.49 (0.1, 1.92)	11.21 (5.11, 27.38)	0.90
CCNH	rs2266691	A	G	8	90	5	9	249	131	43	21	21.25 (9.93, 52.31)	6.09 (1.29, 27.15)	22.41 (8.84, 63.81)	-3.93
	rs2266692	G	T	9	77	4	21	228	125	64	27	15.51 (7.43, 36.42)	1.62 (0.33, 6.56)	19.84 (8.42, 51.76)	3.70
XPA	rs3176757	C	T	8	74	5	25	228	119	64	33	17.61 (8.13, 43.73)	1.84 (0.43, 7.09)	17.6 (7.36, 47.45)	-0.85
	rs3176753	T	C	10	73	3	26	215	111	77	41	14.05 (6.88, 31.74)	0.84 (0.14, 3.63)	13.51 (6.13, 32.58)	-0.38
	rs3176748	A	G	11	78	2	21	239	130	53	22	12.96 (6.57, 28.02)	0.68 (0.07, 3.48)	16.69 (7.2, 41.86)	4.05
	rs3176658	C	T	9	85	4	14	251	125	41	27	18.85 (9.08, 44.07)	2.67 (0.53, 11.32)	14.05 (5.82, 37.32)	-6.47
	rs1800975	G	A	4	56	9	35	183	85	97	58	29.84 (10.52, 117.01)	3.55 (0.91, 17.02)	23.09 (7.93, 92.24)	-9.31
RAD23B	rs1805330	C	T	7	59	6	40	176	101	116	51	14.58 (6.33, 39.29)	1.26 (0.32, 4.75)	18.9 (7.91, 52.49)	4.06
ERCC6	rs2228529	A	G	12	77	1	21	222	112	68	39	12.64 (6.5, 26.62)	0.31 (0.01, 2.31)	11.03 (5.18, 25.16)	-0.92
	rs2228527	A	G	11	72	2	27	207	103	85	49	13.07 (6.53, 28.55)	0.49 (0.05, 2.46)	11.22 (5.29, 25.79)	-1.34
	rs4253132	T	C	9	50	4	49	182	75	110	77	13.36 (6.12, 32.5)	0.46 (0.1, 1.77)	7.87 (3.56, 19.31)	-4.94
	rs2228528	G	A	7	74	6	25	205	108	86	44	19.92 (8.79, 53.07)	2.51 (0.63, 9.69)	20.33 (8.45, 56.81)	-1.10
DDB2															
(XPE)	rs2029298	A	G	2	31	11	68	88	57	204	95	23.58 (5.63, 211.02)	2.49 (0.5, 24.46)	32.98 (8.11, 290.14)	7.91
	rs1685404	G	C	8	51	5	48	156	89	136	63	11.09 (4.94, 28.3)	0.67 (0.16, 2.5)	13.61 (5.96, 35.23)	2.86
	rs2957873	A	G	5	33	8	66	85	49	206	103	11.29 (4.02, 39.49)	0.8 (0.21, 3.37)	13.1 (4.89, 44.28)	2.01
	rs326224	G	A	4	25	9	74	76	38	216	114	12.27 (3.86, 52.02)	0.76 (0.19, 3.69)	11.76 (3.93, 47.64)	-0.27
	rs2306353	G	A	5	39	8	60	101	58	191	94	13.41 (4.91, 46.05)	1.04 (0.28, 4.35)	15.72 (5.92, 52.78)	2.27
	rs326222	C	T	2	18	11	81	52	32	240	120	14.28 (3.1, 135.06)	1.22 (0.23, 12.28)	17.88 (4.17, 161.4)	3.38
	rs901746	A	G	3	22	10	77	62	36	230	116	12.38 (3.38, 69.06)	0.95 (0.22, 5.85)	14.44 (4.21, 76.9)	2.11

OR odds ratio, I interval estimates

[a]Crude (not adjusted for matching factors or ancestry)

Table 1A cont. Odds Ratios and Relative Excess Risk Estimates for Joint Effects of Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Cigarette Smoking on Head and Neck Cancer Risk Using Exact Logistic Regression, the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, African Americans

		Coded Allele		Cases/Controls								OR (95% I)[a]			
Gene	SNP	Referent (A) / Variant (B)		Cigarette=0, SNP=0		Cigarette=0, SNP=1		Cigarette=1, SNP=0		Cigarette=1, SNP=1		Cigarette=1, SNP=0	Cigarette=0, SNP=1	Cigarette=1, SNP=1	RERI
ERCC5															
(XPG)	rs2296147	T	C	7	56	6	42	186	92	105	60	16.04 (6.93, 43.39)	1.14 (0.29, 4.3)	13.84 (5.81, 38.31)	-2.35
	rs2296148	C	T	10	72	3	27	218	118	73	34	13.22 (6.48, 29.84)	0.8 (0.13, 3.44)	15.19 (6.78, 37.24)	2.17
	rs4771436	T	G	8	65	5	34	196	107	96	45	14.78 (6.74, 37.03)	1.19 (0.28, 4.52)	17.07 (7.37, 44.78)	2.10
	rs1047768	C	T	5	45	8	54	111	70	181	82	14.12 (5.27, 47.79)	1.33 (0.35, 5.55)	19.68 (7.46, 65.86)	5.23
	rs2020915	G	A	9	67	4	32	196	77	96	75	18.77 (8.77, 44.99)	0.93 (0.19, 3.66)	9.45 (4.33, 22.98)	-9.26
	rs3818356	C	T	9	65	4	34	197	107	95	45	13.21 (6.23, 31.38)	0.85 (0.18, 3.33)	15.03 (6.7, 37.48)	1.97
	rs4150355	C	T	9	67	4	32	209	108	83	44	14.31 (6.77, 33.93)	0.93 (0.19, 3.66)	13.84 (6.14, 34.65)	-0.40
	rs4150360	T	C	1	8	12	90	18	9	274	142	14.78 (1.59, 748.17)	1.07 (0.12, 51.22)	15.35 (2.02, 687.38)	0.50
	rs4150383	G	A	11	73	2	26	231	127	61	25	12 (6.05, 26.04)	0.51 (0.05, 2.59)	15.85 (6.97, 38.99)	4.34
	rs17655	C	G	5	35	8	64	85	35	207	117	16.66 (5.86, 59.04)	0.88 (0.23, 3.67)	12.3 (4.63, 41.34)	-4.24
	rs873601	A	G	2	15	11	84	28	15	264	137	13.37 (2.59, 135.99)	0.98 (0.18, 10)	14.37 (3.27, 131.3)	1.01
	rs876430	C	T	2	15	11	84	30	15	262	137	14.32 (2.78, 145.25)	0.98 (0.18, 10)	14.26 (3.24, 130.31)	-0.05
	rs1051677	T	C	10	71	3	28	222	113	70	39	13.86 (6.78, 31.33)	0.76 (0.13, 3.26)	12.55 (5.64, 30.51)	-1.07
	rs1051685	A	G	6	47	7	51	132	70	160	82	14.62 (5.85, 43.92)	1.07 (0.29, 4.17)	15.14 (6.12, 45.17)	0.45
	rs17655	C	G	5	35	8	64	85	35	207	117	16.66 (5.86, 59.04)	0.88 (0.23, 3.67)	12.3 (4.63, 41.34)	-4.24
	rs873601	A	G	2	15	11	84	28	15	264	137	13.37 (2.59, 135.99)	0.98 (0.18, 10)	14.37 (3.27, 131.3)	1.01
	rs876430	C	T	2	15	11	84	30	15	262	137	14.32 (2.78, 145.25)	0.98 (0.18, 10)	14.26 (3.24, 130.31)	-0.05
	rs1051677	T	C	10	71	3	28	222	113	70	39	13.86 (6.78, 31.33)	0.76 (0.13, 3.26)	12.55 (5.64, 30.51)	-1.07
	rs1051685	A	G	6	47	7	51	132	70	160	82	14.62 (5.85, 43.92)	1.07 (0.29, 4.17)	15.14 (6.12, 45.17)	0.45
ERCC4															
(XPF)	rs3136038	C	T	4	31	9	68	88	53	204	99	12.69 (4.16, 52.24)	1.03 (0.26, 4.91)	15.84 (5.39, 63.48)	3.13
	rs744154	C	G	7	76	6	23	214	98	78	54	23.52 (10.37, 62.71)	2.8 (0.7, 10.87)	15.48 (6.49, 42.91)	-9.84
	rs3136085	G	C	6	64	7	35	167	82	125	70	21.52 (8.86, 63.35)	2.12 (0.56, 8.28)	18.84 (7.67, 55.98)	-3.79
	rs3136091	C	G	10	83	3	16	245	116	47	36	17.42 (8.61, 39.07)	1.55 (0.25, 6.98)	10.67 (4.69, 26.42)	-7.3
	rs3136130	G	T	4	29	9	70	71	36	221	116	14.02 (4.45, 59.11)	0.93 (0.24, 4.48)	13.72 (4.66, 55.01)	-0.23
	rs3136172	A	G	7	74	6	25	209	97	83	55	22.59 (9.94, 60.33)	2.51 (0.63, 9.69)	15.75 (6.62, 43.58)	-8.36
	rs2020955	T	C	9	68	4	31	184	97	108	55	14.22 (6.7, 33.86)	0.98 (0.2, 3.83)	14.66 (6.65, 35.98)	0.46
RAD23A	rs2974752	A	G	3	20	10	69	74	42	206	101	11.55 (3.16, 64.21)	0.97 (0.22, 5.98)	13.49 (3.87, 72.55)	1.98
	rs11558955	A	G	12	84	1	15	244	130	48	22	13.07 (6.79, 27.29)	0.47 (0.01, 3.64)	14.94 (6.54, 36.6)	2.41
ERCC2															
(XPD)	rs13181	T	G	5	62	8	37	168	78	123	72	26.43 (10.17, 87.58)	2.66 (0.71, 11.13)	20.95 (7.99, 69.88)	-7.14
	rs238418	C	A	1	5	12	94	7	6	284	146	5.33 (0.42, 314.49)	0.64 (0.06, 32.68)	9.68 (1.07, 461.59)	4.70
	rs1799787	C	T	6	76	7	23	229	116	63	36	24.83 (10.46, 71.87)	3.8 (0.98, 15.21)	21.73 (8.4, 67.27)	-5.89
	rs3916874	G	C	13	91	0	8	255	135	37	17				
	rs238416	G	A	9	82	4	15	234	126	57	26	16.82 (8.09, 39.39)	2.41 (0.48, 10.11)	19.53 (8.23, 51.28)	1.30
	rs50872	C	T	10	63	3	36	213	95	79	57	14.02 (6.77, 32.01)	0.53 (0.09, 2.23)	8.64 (3.97, 20.55)	-4.91

OR odds ratio, I interval estimates

[a]Crude (not adjusted for matching factors or ancestry)

Table 1A cont. Odds Ratios and Relative Excess Risk Estimates for Joint Effects of Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Cigarette Smoking on Head and Neck Cancer Risk Using Exact Logistic Regression, the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, African Americans

		Coded Allele		Cases/Controls								OR (95% I)[a]			
Gene	SNP	Referent (A) / Variant (B)		Cigarette=0, SNP=0		Cigarette=0, SNP=1		Cigarette=1, SNP=0		Cigarette=1, SNP=1		Cigarette=1, SNP=0	Cigarette=0, SNP=1	Cigarette=1, SNP=1	RERI
ERCC2 (XPD)	rs50871	T	G	10	80	3	19	219	115	73	37	15.14 (7.45, 34.06)	1.26 (0.2, 5.57)	15.53 (7, 37.68)	0.13
	rs238407	A	T	8	77	5	22	218	113	74	39	18.44 (8.51, 45.81)	2.17 (0.51, 8.45)	17.95 (7.67, 47.57)	-1.66
	rs3810366	C	G	8	72	5	27	204	108	88	44	16.88 (7.75, 42.11)	1.66 (0.39, 6.36)	17.72 (7.66, 46.48)	0.19
ERCC1	rs735482	A	C	10	38	3	61	146	84	146	68	6.56 (3.02, 15.55)	0.19 (0.03, 0.8)	8.09 (3.69, 19.32)	2.34
	rs2336219	G	A	10	40	3	59	147	86	145	66	6.79 (3.14, 16.03)	0.21 (0.03, 0.87)	8.71 (3.98, 20.76)	2.71
	rs3212964	G	A	12	51	1	47	195	91	95	60	9.05 (4.49, 19.58)	0.09 (0, 0.67)	6.67 (3.19, 14.91)	-1.47
	rs3212955	A	G	7	55	6	44	152	87	140	65	13.61 (5.84, 37.01)	1.07 (0.28, 4.03)	16.73 (7.09, 45.98)	3.05
	rs3212948	C	G	13	2	0	97	9	4	283	148				
	rs3212935	A	G	6	51	7	48	137	74	155	77	15.58 (6.29, 46.53)	1.24 (0.33, 4.8)	16.94 (6.86, 50.46)	1.13
	rs3212930	T	C	9	76	4	23	241	129	51	23	15.68 (7.52, 36.8)	1.46 (0.3, 5.87)	18.27 (7.54, 48.97)	2.13
LIG1	rs156641	G	A	9	78	4	21	225	114	67	38	16.99 (8.12, 39.97)	1.64 (0.34, 6.64)	15.03 (6.58, 38.06)	-2.6
	rs20580	C	A	3	21	10	78	59	36	232	116	11.25 (3.05, 63.02)	0.9 (0.21, 5.53)	13.91 (4.03, 74.29)	2.76
	rs20579	C	T	8	46	5	53	142	82	150	70	9.88 (4.34, 25.44)	0.55 (0.13, 2.05)	12.2 (5.34, 31.57)	2.78
	rs439132	A	G	8	50	5	49	164	86	128	66	11.82 (5.25, 30.21)	0.64 (0.15, 2.4)	12 (5.25, 31.06)	0.53

OR odds ratio, I interval estimates

[a]Crude (not adjusted for matching factors or ancestry)

Table 2A. Odds Ratios and Relative Excess Risk Estimates for Joint Effects of Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Cigarette Smoking on Head and Neck Cancer Risk Using Conventional Logistic Regression, the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, African Americans

		Coded Allele		Cases/Controls								OR (95% I)[a]			
Gene	SNP	Referent (A) / Variant (B)		Cigarette=0, SNP=0		Cigarette=0, SNP=1		Cigarette=1, SNP=0		Cigarette=1, SNP=1		Cigarette=1, SNP=0	Cigarette=0, SNP=1	Cigarette=1, SNP=1	RERI (95% CI)
ERCC3 (XPB)	rs4150496	G	A	7	52	6	47	171	84	119	68	10.62 (3.89, 28.98)	1.53 (0.42, 5.56)	7.64 (2.74, 21.31)	-3.51 (-9.85, 2.82)
	rs4150459	G	A	9	66	4	33	181	98	111	54	7.25 (2.90, 18.13)	0.83 (0.21, 3.29)	7.34 (2.83, 19.01)	0.26 (-3.71, 4.24)
	rs1011019	C	T	10	60	3	39	173	83	119	69	5.64 (2.29, 13.92)	0.35 (0.08, 1.56)	5.21 (2.07, 13.14)	0.22 (-2.61, 3.05)
	rs4150434	G	A	9	68	4	31	223	118	69	34	6.60 (2.71, 16.05)	0.91 (0.22, 3.73)	11.11 (4.1, 30.08)	4.60 (-2.58, 11.78)
	rs4150416	T	G	6	34	7	65	79	42	212	110	5.15 (1.56, 17.00)	0.58 (0.15, 2.17)	5.56 (1.79, 17.24)	0.83 (-2.17, 3.84)
	rs4150407	A	G	3	24	10	75	81	44	211	108	11.7 (2.63, 52.03)	1.32 (0.28, 6.22)	8.81 (2.08, 37.26)	-3.20 (-11.82, 5.41)
	rs4150402	G	A	10	60	3	39	173	83	119	69	5.64 (2.29, 13.92)	0.35 (0.08, 1.56)	5.21 (2.07, 13.14)	0.22 (-2.61, 3.05)
XPC	rs2228001	A	C	6	50	7	49	174	84	118	68	9.83 (3.44, 28.05)	1.30 (0.35, 4.81)	7.7 (2.65, 22.41)	-2.43 (-8.06, 3.20)
	rs2228000	C	T	11	83	2	16	240	122	52	30	6.76 (2.94, 15.57)	0.60 (0.11, 3.40)	8.51 (3.2, 22.66)	2.15 (-3.41, 7.70)
	rs3731124	A	C	9	86	4	13	243	126	49	26	10.85 (4.27, 27.53)	3.72 (0.75, 18.35)	11.01 (3.76, 32.29)	-2.55 (-11.73, 6.63)
	rs3731093	T	C	12	84	1	13	251	124	37	28	7.71 (3.40, 17.51)	0.99 (0.09, 10.5)	6.48 (2.42, 17.34)	-1.23 (-6.53, 4.08)
	rs3731089	G	A	12	84	1	15	251	124	41	28	7.65 (3.37, 17.35)	0.73 (0.07, 7.40)	6.87 (2.58, 18.29)	-0.51 (-5.57, 4.55)
	rs2733537	A	G	10	67	3	32	202	97	90	55	6.64 (2.73, 16.14)	0.60 (0.13, 2.65)	6.75 (2.65, 17.19)	0.52 (-3.14, 4.17)
	rs2607755	T	C	6	45	7	54	105	64	187	88	8.39 (2.59, 27.14)	1.35 (0.35, 5.23)	9.99 (3.13, 31.93)	1.25 (-3.53, 6.03)
	rs1902658	G	A	3	25	10	74	50	26	242	126	7.35 (1.54, 34.99)	0.81 (0.17, 3.77)	6.28 (1.42, 27.78)	-0.88 (-6.23, 4.47)
ERCC8	rs3117	T	C	5	34	8	65	121	60	171	92	8.36 (2.53, 27.66)	0.95 (0.24, 3.67)	7.01 (2.16, 22.73)	-1.29 (-6.07, 3.48)
CDK7	rs2972388	A	G	9	52	4	47	151	80	141	72	4.36 (1.73, 11.00)	0.25 (0.06, 0.99)	4.35 (1.70, 11.12)	0.74 (-1.47, 2.95)
CCNH	rs2266691	A	G	8	90	5	9	249	131	43	21	12.15 (4.63, 31.86)	6.33 (1.32, 30.29)	18.26 (5.64, 59.15)	0.78 (-14.86, 16.41)
	rs2266692	G	T	9	77	4	21	228	125	64	27	9.18 (3.64, 23.12)	2.27 (0.51, 10.04)	12.54 (4.34, 36.26)	2.09 (-6.43, 10.62)
XPA	rs3176757	C	T	8	74	5	25	228	119	64	33	9.61 (3.77, 24.47)	2.01 (0.50, 8.09)	9.88 (3.53, 27.7)	-0.73 (-7.26, 5.79)
	rs3176753	T	C	10	73	3	26	215	111	77	41	6.56 (2.77, 15.54)	0.52 (0.11, 2.38)	6.65 (2.64, 16.72)	0.57 (-3.21, 4.34)
	rs3176748	A	G	11	78	2	21	239	130	53	22	7.24 (3.13, 16.79)	0.80 (0.14, 4.67)	8.93 (3.13, 25.51)	1.89 (-4.54, 8.32)
	rs3176658	C	T	9	85	4	14	251	125	41	27	8.79 (3.70, 20.88)	1.91 (0.41, 8.88)	9.69 (3.48, 27.01)	-0.01 (-6.94, 6.93)
	rs1800975	G	A	4	56	9	35	183	85	97	58	13.28 (3.90, 45.21)	2.7 (0.67, 10.97)	11.95 (3.45, 41.34)	-3.03 (-11.46, 5.40)
RAD23B	rs1805330	C	T	7	59	6	40	176	101	116	51	8.92 (3.33, 23.88)	1.58 (0.43, 5.81)	9.99 (3.65, 27.35)	0.48 (-4.73, 5.70)
ERCC6	rs2228529	A	G	12	77	1	21	222	112	68	39	7.34 (3.27, 16.46)	0.57 (0.06, 5.38)	7.33 (2.88, 18.67)	0.42 (-4.08, 4.93)
	rs2228527	A	G	11	72	2	27	207	103	85	49	7.43 (3.19, 17.32)	0.75 (0.14, 4.06)	7.13 (2.82, 17.98)	-0.06 (-4.22, 4.10)
	rs4253132	T	C	9	50	4	49	182	75	110	77	6.64 (2.60, 16.95)	0.35 (0.09, 1.41)	4.04 (1.59, 10.31)	-1.94 (-5.72, 1.84)
	rs2228528	G	A	7	74	6	25	205	108	86	44	12.88 (4.80, 34.58)	4.10 (1.05, 15.98)	12.00 (4.14, 34.80)	-3.98 (-13.22, 5.26)
DDB2 (XPE)	rs2029298	A	G	2	31	11	68	88	57	204	95	15.51 (2.98, 80.81)	3.70 (0.66, 20.72)	24.13 (4.74, 122.76)	5.91 (-7.28, 19.11)
	rs1685404	G	C	8	51	5	48	156	89	136	63	5.62 (2.16, 14.56)	0.46 (0.12, 1.80)	5.60 (2.12, 14.80)	0.52 (-2.39, 3.44)
	rs2957873	A	G	5	33	8	66	85	49	206	103	4.95 (1.52, 16.19)	0.57 (0.15, 2.17)	5.60 (1.81, 17.34)	1.08 (-1.75, 3.91)
	rs326224	G	A	4	25	9	74	76	38	216	114	6.62 (1.81, 24.27)	0.68 (0.16, 2.90)	5.78 (1.68, 19.92)	-0.53 (-4.66, 3.61)
	rs2306353	G	A	5	39	8	60	101	58	191	94	6.82 (2.17, 21.48)	0.95 (0.25, 3.60)	7.91 (2.63, 23.82)	1.14 (-2.74, 5.02)
	rs326222	C	T	2	18	11	81	52	32	240	120	5.60 (1.01, 30.96)	0.78 (0.14, 4.55)	6.54 (1.27, 33.74)	1.15 (-2.55, 4.85)
	rs901746	A	G	3	22	10	77	62	36	230	116	5.38 (1.26, 22.88)	0.66 (0.14, 3.09)	5.77 (1.45, 22.91)	0.73 (-2.60, 4.06)
ERCC5 (XPG)	rs2296147	T	C	7	56	6	42	186	92	105	60	10.37 (3.82, 28.13)	1.75 (0.48, 6.35)	8.94 (3.21, 24.86)	-2.18 (-8.16, 3.8)
	rs2296148	C	T	10	72	3	27	218	118	73	34	6.90 (2.95, 16.10)	0.71 (0.15, 3.28)	8.35 (3.17, 22.00)	1.74 (-3.24, 6.73)

OR odds ratio, I interval estimates

[a]Odds ratios adjusted for matching factors (age and sex including pairwise interactions), education, alcohol drinking, and percent African ancestry

Table 2A cont. Odds Ratios and Relative Excess Risk Estimates for Joint Effects of Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Cigarette Smoking on Head and Neck Cancer Risk Using Conventional Logistic Regression, the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, African Americans

		Coded Allele		Cases/Controls								OR (95% I)[a]			
Gene	SNP	Referent (A) / Variant (B)		Cigarette=0, SNP=0		Cigarette=0, SNP=1		Cigarette=1, SNP=0		Cigarette=1, SNP=1		Cigarette=1, SNP=0	Cigarette=0, SNP=1	Cigarette=1, SNP=1	RERI (95% CI)
ERCC5 (XPG)	rs4771436	T	G	8	65	5	34	196	107	96	45	6.95 (2.73, 17.69)	0.85 (0.22, 3.25)	8.19 (3.03, 22.16)	1.39 (-3.00, 5.77)
	rs1047768	C	T	5	45	8	54	111	70	181	82	5.98 (1.97, 18.14)	0.95 (0.25, 3.57)	9.15 (3.04, 27.50)	3.22 (-1.42, 7.86)
	rs2020915	G	A	9	67	4	32	196	77	96	75	10.46 (4.08, 26.8)	0.92 (0.22, 3.89)	4.72 (1.79, 12.42)	-5.67 (-12.75, 1.41)
	rs3818356	C	T	9	65	4	34	197	107	95	45	6.25 (2.55, 15.33)	0.60 (0.15, 2.42)	7.30 (2.79, 19.08)	1.45 (-2.45, 5.35)
	rs4150355	C	T	9	67	4	32	209	108	83	44	9.13 (3.53, 23.63)	1.64 (0.39, 6.91)	9.26 (3.39, 25.34)	-0.51 (-6.19, 5.17)
	rs4150360	T	C	1	8	12	90	18	9	274	142	7.88 (0.65, 95.06)	0.86 (0.08, 9.64)	6.45 (0.65, 64.22)	-1.29 (-11.17, 8.6)
	rs4150383	G	A	11	73	2	26	231	127	61	25	6.03 (2.55, 14.27)	0.44 (0.08, 2.53)	8.05 (2.94, 22.00)	2.58 (-2.70, 7.85)
	rs17655	C	G	5	35	8	64	85	35	207	117	8.95 (2.54, 31.53)	0.92 (0.24, 3.57)	6.91 (2.11, 22.66)	-1.96 (-8.01, 4.08)
	rs873601	A	G	2	15	11	84	28	15	264	137	5.41 (0.81, 36.01)	0.57 (0.09, 3.71)	4.75 (0.83, 27.31)	-0.23 (-5.13, 4.68)
	rs876430	C	T	2	15	11	84	30	15	262	137	5.85 (0.88, 38.86)	0.57 (0.09, 3.71)	4.71 (0.82, 27.07)	-0.71 (-6.25, 4.83)
	rs1051677	T	C	10	71	3	28	222	113	70	39	7.06 (3.04, 16.40)	0.51 (0.10, 2.51)	5.75 (2.25, 14.67)	-0.83 (-4.68, 3.03)
	rs1051685	A	G	6	47	7	51	132	70	160	82	9.22 (3.11, 27.30)	0.95 (0.26, 3.48)	6.53 (2.25, 18.92)	-2.64 (-8.20, 2.92)
ERCC4 (XPF)	rs3136038	C	T	4	31	9	68	88	53	204	99	6.60 (1.79, 24.31)	0.98 (0.24, 3.96)	8.24 (2.33, 29.17)	1.66 (-2.33, 5.64)
	rs744154	C	G	7	76	6	23	214	98	78	54	10.16 (3.92, 26.34)	1.98 (0.51, 7.62)	9.19 (3.39, 24.92)	-1.95 (-8.10, 4.20)
	rs3136085	G	C	6	64	7	35	167	82	125	70	10.71 (3.86, 29.71)	2.38 (0.62, 9.06)	11.23 (4.07, 31.00)	-0.85 (-7.17, 5.47)
	rs3136091	C	G	10	83	3	16	245	116	47	36	8.76 (3.66, 21.00)	1.12 (0.23, 5.40)	5.48 (2.03, 14.80)	-3.40 (-8.99, 2.19)
	rs3136130	G	T	4	29	9	70	71	36	221	116	7.02 (1.93, 25.50)	0.95 (0.23, 3.97)	7.66 (2.26, 25.99)	0.70 (-3.54, 4.93)
	rs3136172	A	G	7	74	6	25	209	97	83	55	9.66 (3.71, 25.18)	1.86 (0.49, 7.11)	9.67 (3.57, 26.17)	-0.85 (-6.67, 4.97)
	rs2020955	T	C	9	68	4	31	184	97	108	55	8.98 (3.62, 22.29)	1.06 (0.26, 4.37)	6.58 (2.59, 16.68)	-2.46 (-7.50, 2.57)
RAD23A	rs2974752	A	G	3	20	10	69	74	42	206	101	3.55 (0.78, 16.21)	0.45 (0.10, 2.14)	3.77 (0.88, 16.14)	0.76 (-1.37, 2.89)
	rs11558955	A	G	12	84	1	15	244	130	48	22	7.06 (3.09, 16.13)	0.51 (0.05, 4.91)	7.39 (2.80, 19.47)	0.82 (-4.38, 6.01)
ERCC2 (XPD)	rs13181	T	G	5	62	8	37	168	78	123	72	14.78 (4.84, 45.09)	2.43 (0.65, 9.16)	10.13 (3.31, 31.03)	-6.08 (-15.95, 3.78)
	rs238418	C	A	1	5	12	94	7	6	284	146	2.54 (0.14, 44.85)	0.34 (0.03, 4.63)	2.84 (0.23, 34.55)	0.96 (-2.82, 4.74)
	rs1799787	C	T	6	76	7	23	229	116	63	36	14.05 (5.09, 38.78)	3.54 (0.94, 13.38)	9.44 (3.16, 28.26)	-7.14 (-17.63, 3.34)
	rs3916874	G	C	13	91	0	8	255	135	37	17				
	rs238416	G	A	9	82	4	15	234	126	57	26	9.27 (3.76, 22.85)	3.54 (0.76, 16.46)	15.13 (5.36, 42.65)	3.32 (-7.24, 13.88)
	rs50872	C	T	10	63	3	36	213	95	79	57	7.03 (2.84, 17.4)	0.43 (0.09, 1.99)	4.38 (1.71, 11.23)	-2.08 (-6.01, 1.85)
	rs50871	T	G	10	80	3	19	219	115	73	37	8.86 (3.61, 21.74)	1.60 (0.31, 8.30)	8.30 (3.04, 22.67)	-1.16 (-6.77, 4.45)
	rs238407	A	T	8	77	5	22	218	113	74	39	10.86 (4.22, 27.95)	3.55 (0.87, 14.39)	12.62 (4.58, 34.77)	-0.79 (-9.00, 7.41)
	rs3810366	C	G	8	72	5	27	204	108	88	44	9.22 (3.55, 23.96)	2.18 (0.55, 8.65)	11.99 (4.37, 32.87)	1.59 (-5.15, 8.32)
ERCC1	rs735482	A	C	10	38	3	61	146	84	146	68	2.84 (1.10, 7.36)	0.13 (0.03, 0.59)	3.95 (1.51, 10.29)	1.98 (-0.01, 3.97)
	rs2336219	G	A	10	40	3	59	147	86	145	66	2.87 (1.11, 7.43)	0.13 (0.03, 0.60)	3.98 (1.53, 10.36)	1.98 (-0.02, 3.98)
	rs3212964	G	A	12	51	1	47	195	91	95	60	3.72 (1.54, 8.99)	0.05 (0.01, 0.46)	3.08 (1.25, 7.64)	0.31 (-1.55, 2.16)
	rs3212955	A	G	7	55	6	44	152	87	140	65	6.86 (2.48, 18.95)	0.72 (0.19, 2.75)	6.37 (2.27, 17.89)	-0.21 (-3.84, 3.41)
	rs3212948	C	G	13	2	0	97	9	4	283	148				
	rs3212935	A	G	6	51	7	48	137	74	155	77	10.26 (3.40, 30.93)	1.91 (0.5, 7.28)	11.62 (3.86, 35.05)	0.45 (-5.37, 6.28)
	rs3212930	T	C	9	76	4	23	241	129	51	23	8.26 (3.29, 20.76)	1.24 (0.30, 5.17)	8.71 (3, 25.28.00)	0.21 (-5.77, 6.18)

OR odds ratio, I interval estimates

[a]Odds ratios adjusted for matching factors (age and sex including pairwise interactions), education, alcohol drinking, and percent African ancestry

Table 2A cont. Odds Ratios and Relative Excess Risk Estimates for Joint Effects of Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Cigarette Smoking on Head and Neck Cancer Risk Using Conventional Logistic Regression, the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, African Americans

		Coded Allele		Cases/Controls								OR (95% I)[a]			
Gene	SNP	Referent (A) / Variant (B)		Cigarette=0, SNP=0		Cigarette=0, SNP=1		Cigarette=1, SNP=0		Cigarette=1, SNP=1		Cigarette=1, SNP=0	Cigarette=0, SNP=1	Cigarette=1, SNP=1	RERI (95% CI)
LIG1	rs156641	G	A	9	78	4	21	225	114	67	38	9.37 (3.89, 22.60)	2.22 (0.51, 9.64)	9.12 (3.45, 24.15)	-1.47 (-7.97, 5.02)
	rs20580	C	A	3	21	10	78	59	36	232	116	4.68 (1.10, 19.95)	0.6 (0.13, 2.81)	5.43 (1.37, 21.59)	1.15 (-1.81, 4.10)
	rs20579	C	T	8	46	5	53	142	82	150	70	4.87 (1.85, 12.82)	0.49 (0.13, 1.89)	6.72 (2.55, 17.71)	2.36 (-0.92, 5.63)
	rs439132	A	G	8	50	5	49	164	86	128	66	7.67 (2.91, 20.20)	0.73 (0.20, 2.71)	5.71 (2.13, 15.35)	-1.69 (-5.88, 2.49)

OR odds ratio, I interval estimates

[a]Odds ratios adjusted for matching factors (age and sex including pairwise interactions), education, alcohol drinking, and percent African ancestry

Table 3A. Odds Ratios and Relative Excess Risk Estimates for Joint Effects of Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Cigarette Smoking on Head and Neck Cancer Risk Using Hierarchical Logistic Regression, the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, African Americans

		Coded Allele		Cases/Controls								OR (95% I)[a]			
Gene	SNP	Referent (A) / Variant (B)		Cigarette=0, SNP=0		Cigarette=0, SNP=1		Cigarette=1, SNP=0		Cigarette=1, SNP=1		Cigarette=1, SNP=0	Cigarette=0, SNP=1	Cigarette=1, SNP=1	RERI
ERCC3 (XPB)	rs4150496	G	A	7	52	6	47	171	84	119	68	9.51 (3.78, 23.93)	1.24 (0.41, 3.73)	7.08 (2.66, 18.86)	-2.68
	rs4150459	G	A	9	66	4	33	181	98	111	54	7.42 (3.09, 17.80)	0.88 (0.28, 2.77)	7.45 (2.91, 19.06)	0.15
	rs1011019	C	T	10	60	3	39	173	83	119	69	6.29 (2.63, 15.05)	0.49 (0.15, 1.57)	5.61 (2.23, 14.07)	-0.17
	rs4150434	G	A	9	68	4	31	223	118	69	34	7.04 (2.98, 16.63)	1.10 (0.34, 3.51)	11.43 (4.21, 31.04)	4.29
	rs4150416	T	G	6	34	7	65	79	42	212	110	5.90 (1.98, 17.56)	0.69 (0.22, 2.14)	6.17 (2.10, 18.16)	0.58
	rs4150407	A	G	3	24	10	75	81	44	211	108	9.87 (2.88, 33.79)	1.08 (0.32, 3.70)	7.64 (2.20, 26.52)	-2.31
	rs4150402	G	A	10	60	3	39	173	83	119	69	6.29 (2.63, 15.05)	0.49 (0.15, 1.57)	5.61 (2.23, 14.07)	-0.17
XPC	rs2228001	A	C	6	50	7	49	174	84	118	68	9.05 (3.47, 23.60)	1.13 (0.37, 3.41)	7.25 (2.63, 19.99)	-1.93
	rs2228000	C	T	11	83	2	16	240	122	52	30	7.17 (3.17, 16.20)	0.80 (0.22, 2.94)	8.64 (3.22, 23.13)	1.66
	rs3731124	A	C	9	86	4	13	243	126	49	26	9.34 (3.97, 21.96)	2.31 (0.63, 8.48)	10.22 (3.59, 29.12)	-0.42
	rs3731093	T	C	12	84	1	13	251	124	37	28	7.63 (3.44, 16.94)	0.90 (0.18, 4.48)	6.46 (2.41, 17.28)	-1.08
	rs3731089	G	A	12	84	1	15	251	124	41	28	7.75 (3.49, 17.21)	0.82 (0.17, 3.84)	6.90 (2.59, 18.39)	-0.67
	rs2733537	A	G	10	67	3	32	202	97	90	55	7.02 (2.98, 16.52)	0.71 (0.22, 2.35)	6.98 (2.75, 17.70)	0.24
	rs2607755	T	C	6	45	7	54	105	64	187	88	8.18 (2.85, 23.46)	1.30 (0.42, 4.05)	9.79 (3.31, 28.93)	1.31
	rs1902658	G	A	3	25	10	74	50	26	242	126	7.49 (2.03, 27.60)	0.82 (0.24, 2.88)	6.38 (1.71, 23.76)	-0.94
ERCC8	rs3117	T	C	5	34	8	65	121	60	171	92	8.15 (2.79, 23.78)	0.91 (0.29, 2.85)	6.87 (2.31, 20.47)	-1.19
CDK7	rs2972388	A	G	9	52	4	47	151	80	141	72	5.19 (2.12, 12.70)	0.38 (0.12, 1.16)	4.89 (1.91, 12.49)	0.32
CCNH	rs2266691	A	G	8	90	5	9	249	131	43	21	10.25 (4.26, 24.66)	3.85 (1.08, 13.75)	17.3 (5.48, 54.65)	4.20
	rs2266692	G	T	9	77	4	21	228	125	64	27	8.65 (3.64, 20.54)	1.92 (0.56, 6.54)	12.23 (4.29, 34.89)	2.66
XPA	rs3176757	C	T	8	74	5	25	228	119	64	33	8.87 (3.71, 21.24)	1.64 (0.51, 5.28)	9.49 (3.46, 26.03)	-0.02
	rs3176753	T	C	10	73	3	26	215	111	77	41	6.98 (3.02, 16.14)	0.65 (0.20, 2.18)	6.86 (2.73, 17.28)	0.23
	rs3176748	A	G	11	78	2	21	239	130	53	22	7.51 (3.32, 17.00)	0.95 (0.25, 3.63)	9.00 (3.14, 25.81)	1.54
	rs3176658	C	T	9	85	4	14	251	125	41	27	8.35 (3.65, 19.06)	1.58 (0.45, 5.59)	9.54 (3.45, 26.44)	0.62
	rs1800975	G	A	4	56	9	35	183	85	97	58	10.56 (3.67, 30.41)	1.93 (0.61, 6.05)	10.02 (3.26, 30.8)	-1.48
RAD23B	rs1805330	C	T	7	59	6	40	176	101	116	51	8.50 (3.40, 21.25)	1.44 (0.47, 4.34)	9.66 (3.65, 25.57)	0.73
ERCC6	rs2228529	A	G	12	77	1	21	222	112	68	39	7.56 (3.41, 16.77)	0.76 (0.17, 3.32)	7.39 (2.89, 18.89)	0.07
	rs2228527	A	G	11	72	2	27	207	103	85	49	7.58 (3.34, 17.23)	0.83 (0.23, 3.03)	7.20 (2.86, 18.12)	-0.21
	rs4253132	T	C	9	50	4	49	182	75	110	77	7.10 (2.90, 17.41)	0.41 (0.13, 1.30)	4.23 (1.68, 10.66)	-2.29
	rs2228528	G	A	7	74	6	25	205	108	86	44	10.57 (4.33, 25.79)	2.64 (0.84, 8.32)	10.62 (3.87, 29.18)	-1.59
DDB2 (XPE)	rs2029298	A	G	2	31	11	68	88	57	204	95	11.57 (3.23, 41.41)	2.64 (0.74, 9.44)	18.6 (5.03, 68.86)	5.40
	rs1685404	G	C	8	51	5	48	156	89	136	63	6.22 (2.50, 15.47)	0.58 (0.19, 1.79)	6.00 (2.30, 15.71)	0.20
	rs2957873	A	G	5	33	8	66	85	49	206	103	5.74 (1.94, 17.00)	0.70 (0.22, 2.17)	6.29 (2.13, 18.52)	0.85
	rs326224	G	A	4	25	9	74	76	38	216	114	7.05 (2.25, 22.11)	0.74 (0.22, 2.45)	6.07 (1.94, 19.01)	-0.71
	rs2306353	G	A	5	39	8	60	101	58	191	94	7.09 (2.50, 20.17)	1.01 (0.33, 3.11)	8.16 (2.87, 23.18)	1.06
	rs326222	C	T	2	18	11	81	52	32	240	120	6.53 (1.62, 26.26)	0.93 (0.23, 3.68)	7.47 (1.82, 30.65)	1.01
	rs901746	A	G	3	22	10	77	62	36	230	116	6.23 (1.79, 21.73)	0.79 (0.22, 2.78)	6.53 (1.87, 22.82)	0.50

OR odds ratio, I interval estimates

[a]Odds ratios adjusted for matching factors (age and sex including pairwise interactions), education, alcohol drinking, and percent African ancestry

Table 3A cont. Odds Ratios and Relative Excess Risk Estimates for Joint Effects of Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Cigarette Smoking on Head and Neck Cancer Risk Using Exact Logistic Regression, the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, African Americans

		Coded Allele		Cases/Controls								OR (95% I)[a]			
Gene	SNP	Referent (A) / Variant (B)		Cigarette=0, SNP=0		Cigarette=0, SNP=1		Cigarette=1, SNP=0		Cigarette=1, SNP=1		Cigarette=1, SNP=0	Cigarette=0, SNP=1	Cigarette=1, SNP=1	RERI
ERCC5															
(XPG)	rs2296147	T	C	7	56	6	42	186	92	105	60	9.37 (3.73, 23.51)	1.44 (0.48, 4.32)	8.34 (3.13, 22.25)	-1.46
	rs2296148	C	T	10	72	3	27	218	118	73	34	7.22 (3.16, 16.49)	0.85 (0.25, 2.89)	8.50 (3.21, 22.46)	1.43
	rs4771436	T	G	8	65	5	34	196	107	96	45	7.24 (2.97, 17.63)	0.94 (0.31, 2.88)	8.40 (3.14, 22.49)	1.22
	rs1047768	C	T	5	45	8	54	111	70	181	82	6.55 (2.34, 18.31)	1.09 (0.35, 3.36)	9.82 (3.40, 28.37)	3.18
	rs2020915	G	A	9	67	4	32	196	77	96	75	9.57 (3.99, 22.95)	0.73 (0.22, 2.44)	4.44 (1.75, 11.28)	-4.86
	rs3818356	C	T	9	65	4	34	197	107	95	45	6.73 (2.83, 15.99)	0.74 (0.23, 2.31)	7.61 (2.92, 19.88)	1.15
	rs4150355	C	T	9	67	4	32	209	108	83	44	8.57 (3.54, 20.72)	1.41 (0.43, 4.65)	8.90 (3.35, 23.67)	-0.07
	rs4150360	T	C	1	8	12	90	18	9	274	142	7.67 (1.49, 39.42)	0.84 (0.16, 4.47)	6.31 (1.15, 34.62)	-1.20
	rs4150383	G	A	11	73	2	26	231	127	61	25	6.71 (2.91, 15.50)	0.68 (0.19, 2.45)	8.40 (3.05, 23.13)	2.01
	rs17655	C	G	5	35	8	64	85	35	207	117	8.58 (2.82, 26.09)	0.88 (0.28, 2.73)	6.69 (2.24, 20.03)	-1.76
	rs873601	A	G	2	15	11	84	28	15	264	137	6.54 (1.51, 28.37)	0.69 (0.16, 2.93)	5.55 (1.28, 24.13)	-0.68
	rs876430	C	T	2	15	11	84	30	15	262	137	6.81 (1.58, 29.36)	0.66 (0.16, 2.80)	5.33 (1.24, 22.99)	-1.14
	rs1051677	T	C	10	71	3	28	222	113	70	39	7.34 (3.23, 16.69)	0.60 (0.17, 2.11)	5.84 (2.28, 14.94)	-1.10
	rs1051685	A	G	6	47	7	51	132	70	160	82	8.76 (3.25, 23.58)	0.87 (0.29, 2.63)	6.28 (2.29, 17.19)	-2.35
ERCC4															
(XPF)	rs3136038	C	T	4	31	9	68	88	53	204	99	7.01 (2.21, 22.28)	1.06 (0.33, 3.39)	8.66 (2.69, 27.87)	1.59
	rs744154	C	G	7	76	6	23	214	98	78	54	9.20 (3.80, 22.28)	1.57 (0.50, 4.89)	8.65 (3.29, 22.72)	-1.12
	rs3136085	G	C	6	64	7	35	167	82	125	70	9.46 (3.74, 23.93)	1.87 (0.61, 5.77)	10.28 (3.94, 26.81)	-0.04
	rs3136091	C	G	10	83	3	16	245	116	47	36	8.28 (3.61, 19.00)	0.90 (0.25, 3.26)	5.36 (2.00, 14.37)	-2.82
	rs3136130	G	T	4	29	9	70	71	36	221	116	7.27 (2.34, 22.60)	0.99 (0.30, 3.25)	7.88 (2.56, 24.26)	0.62
	rs3136172	A	G	7	74	6	25	209	97	83	55	8.92 (3.66, 21.73)	1.55 (0.50, 4.80)	9.20 (3.51, 24.15)	-0.26
	rs2020955	T	C	9	68	4	31	184	97	108	55	8.63 (3.64, 20.42)	0.94 (0.29, 3.07)	6.42 (2.58, 15.96)	-2.15
RAD23A	rs2974752	A	G	3	20	10	69	74	42	206	101	4.69 (1.25, 17.64)	0.62 (0.17, 2.23)	4.77 (1.25, 18.13)	0.46
	rs11558955	A	G	12	84	1	15	244	130	48	22	7.43 (3.32, 16.63)	0.73 (0.17, 3.23)	7.48 (2.82, 19.81)	0.31
ERCC2															
(XPD)	rs13181	T	G	5	62	8	37	168	78	123	72	11.83 (4.43, 31.54)	1.69 (0.56, 5.12)	8.55 (3.07, 23.77)	-3.97
	rs238418	C	A	1	5	12	94	7	6	284	146	5.53 (0.92, 33.25)	0.66 (0.10, 4.49)	5.14 (0.71, 37.23)	-0.05
	rs1799787	C	T	6	76	7	23	229	116	63	36	11.13 (4.49, 27.61)	2.20 (0.71, 6.75)	8.23 (2.92, 23.20)	-4.09
	rs3916874	G	C	13	91	0	8	255	135	37	17				
	rs238416	G	A	9	82	4	15	234	126	57	26	8.52 (3.66, 19.86)	2.70 (0.76, 9.56)	14.58 (5.25, 40.51)	4.35
	rs50872	C	T	10	63	3	36	213	95	79	57	7.35 (3.1, 17.43)	0.49 (0.14, 1.66)	4.51 (1.78, 11.42)	-2.33
	rs50871	T	G	10	80	3	19	219	115	73	37	8.35 (3.6, 19.41)	1.30 (0.35, 4.90)	8.00 (2.99, 21.40)	-0.65
	rs238407	A	T	8	77	5	22	218	113	74	39	9.45 (3.96, 22.56)	2.5 (0.77, 8.16)	11.64 (4.37, 30.98)	0.69
	rs3810366	C	G	8	72	5	27	204	108	88	44	8.62 (3.54, 20.96)	1.86 (0.58, 5.95)	11.49 (4.31, 30.64)	2.01

OR odds ratio, I interval estimates

[a]Odds ratios adjusted for matching factors (age and sex including pairwise interactions), education, alcohol drinking, and percent African ancestry

Table 3A cont. Odds Ratios and Relative Excess Risk Estimates for Joint Effects of Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Cigarette Smoking on Head and Neck Cancer Risk Using Exact Logistic Regression, the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, African Americans

		Coded Allele		Cases/Controls								OR (95% I)[a]			
Gene	SNP	Referent (A) / Variant (B)		Cigarette=0, SNP=0		Cigarette=0, SNP=1		Cigarette=1, SNP=0		Cigarette=1, SNP=1		Cigarette=1, SNP=0	Cigarette=0, SNP=1	Cigarette=1, SNP=1	RERI
ERCC1	rs735482	A	C	10	38	3	61	146	84	146	68	3.86 (1.54, 9.69)	0.28 (0.09, 0.88)	4.85 (1.86, 12.65)	1.71
	rs2336219	G	A	10	40	3	59	147	86	145	66	3.89 (1.56, 9.75)	0.28 (0.09, 0.89)	4.88 (1.87, 12.71)	1.70
	rs3212964	G	A	12	51	1	47	195	91	95	60	4.74 (2.00, 11.24)	0.17 (0.05, 0.61)	3.55 (1.42, 8.85)	-0.37
	rs3212955	A	G	7	55	6	44	152	87	140	65	7.13 (2.76, 18.44)	0.78 (0.25, 2.39)	6.55 (2.40, 17.86)	-0.36
	rs3212948	C	G	13	2	0	97	9	4	283	148				
	rs3212935	A	G	6	51	7	48	137	74	155	77	9.34 (3.46, 25.21)	1.64 (0.53, 5.04)	10.81 (3.85, 30.35)	0.83
	rs3212930	T	C	9	76	4	23	241	129	51	23	8.11 (3.40, 19.35)	1.18 (0.36, 3.87)	8.64 (3.00, 24.91)	0.36
LIG1	rs156641	G	A	9	78	4	21	225	114	67	38	8.64 (3.75, 19.89)	1.69 (0.49, 5.79)	8.80 (3.37, 22.96)	-0.53
	rs20580	C	A	3	21	10	78	59	36	232	116	5.72 (1.63, 20.16)	0.76 (0.21, 2.71)	6.42 (1.82, 22.69)	0.93
	rs20579	C	T	8	46	5	53	142	82	150	70	5.62 (2.22, 14.19)	0.67 (0.22, 2.03)	7.42 (2.84, 19.39)	2.14
	rs439132	A	G	8	50	5	49	164	86	128	66	7.69 (3.09, 19.14)	0.74 (0.24, 2.23)	5.72 (2.18, 15.02)	-1.70

OR odds ratio, I interval estimates

[a]Odds ratios adjusted for matching factors (age and sex including pairwise interactions), education, alcohol drinking, and percent African ancestry

Table 4A. Odds Ratios and Relative Excess Risk Estimates for Joint Effects of Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Ever Environmental Tobacco Smoke on Head and Neck Cancer Risk Using Conventional Logistic Regression, the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, African Americans

		Coded Allele		Cases/Controls								OR (95% I)[a]			
Gene	SNP	Referent (A) / Variant (B)		Cigarette=0, SNP=0		Cigarette=0, SNP=1		Cigarette=1, SNP=0		Cigarette=1, SNP=1		Cigarette=1, SNP=0	Cigarette=0, SNP=1	Cigarette=1, SNP=1	RERI (95% CI)
ERCC3 (XPB)	rs4150496	G	A	20	26	22	28	158	110	103	87	1.43 (0.53, 3.85)	1.57 (0.44, 5.65)	0.93 (0.34, 2.54)	-1.07 (-3.52, 1.38)
	rs4150459	G	A	27	44	15	10	163	120	100	77	0.95 (0.42, 2.15)	0.99 (0.23, 4.21)	0.88 (0.37, 2.11)	-0.05 (-1.59, 1.48)
	rs1011019	C	T	26	31	16	23	157	112	106	85	0.78 (0.32, 1.89)	0.61 (0.16, 2.29)	0.77 (0.32, 1.88)	0.38 (-0.53, 1.29)
	rs4150434	G	A	30	34	12	20	202	152	61	45	1.11 (0.48, 2.53)	2.18 (0.56, 8.45)	1.53 (0.59, 3.98)	-0.76 (-3.65, 2.14)
	rs4150416	T	G	14	22	28	32	71	54	191	143	0.75 (0.25, 2.27)	0.76 (0.21, 2.75)	0.81 (0.29, 2.25)	0.29 (-0.75, 1.34)
	rs4150407	A	G	10	18	32	36	74	50	189	147	1.76 (0.46, 6.69)	1.59 (0.37, 6.72)	1.16 (0.32, 4.16)	-1.19 (-4.29, 1.92)
	rs4150402	G	A	26	31	16	23	157	112	106	85	0.78 (0.32, 1.89)	0.61 (0.16, 2.29)	0.77 (0.32, 1.88)	0.38 (-0.53, 1.29)
XPC	rs2228001	A	C	25	22	17	32	155	112	108	85	0.90 (0.32, 2.49)	0.84 (0.23, 3.09)	0.79 (0.28, 2.23)	0.05 (-1.20, 1.30)
	rs2228000	C	T	34	46	8	8	217	159	46	38	0.92 (0.44, 1.93)	1.00 (0.13, 7.83)	0.96 (0.39, 2.33)	0.04 (-2.10, 2.19)
	rs3731124	A	C	37	43	5	11	215	169	48	28	0.70 (0.33, 1.52)	0.28 (0.05, 1.56)	1.00 (0.38, 2.59)	1.01 (0.22, 1.81)
	rs3731093	T	C	38	43	2	10	225	165	36	31	0.74 (0.35, 1.58)	0.08 (0.01, 0.75)	0.78 (0.29, 2.06)	0.95 (0.36, 1.54)
	rs3731089	G	A	38	43	4	11	225	165	38	32	0.73 (0.34, 1.56)	0.21 (0.03, 1.28)	0.76 (0.29, 1.99)	0.82 (0.17, 1.47)
	rs2733537	A	G	30	37	12	17	182	127	81	70	0.84 (0.37, 1.90)	0.61 (0.14, 2.60)	0.79 (0.34, 1.86)	0.34 (-0.67, 1.35)
	rs2607755	T	C	17	24	25	30	94	85	169	112	0.74 (0.27, 2.06)	0.86 (0.24, 3.04)	0.94 (0.35, 2.56)	0.35 (-0.70, 1.40)
	rs1902658	G	A	5	11	37	43	48	40	215	157	2.15 (0.4, 11.63)	2.04 (0.36, 11.52)	1.58 (0.32, 7.90)	-1.61 (-6.18, 2.97)
ERCC8	rs3117	T	C	24	24	18	30	102	70	161	127	0.68 (0.26, 1.78)	0.44 (0.12, 1.60)	0.64 (0.26, 1.60)	0.52 (-0.18, 1.22)
CDK7	rs2972388	A	G	21	36	21	18	139	96	124	101	1.80 (0.72, 4.51)	3.50 (0.92, 13.35)	1.31 (0.52, 3.28)	-2.99 (-8.01, 2.03)
CCNH	rs2266691	A	G	34	52	8	2	223	169	40	28	1.24 (0.59, 2.58)			
	rs2266692	G	T	31	43	11	10	206	159	57	38	0.86 (0.39, 1.85)	1.12 (0.20, 6.18)	1.35 (0.53, 3.42)	0.38 (-1.60, 2.36)
XPA	rs3176757	C	T	30	38	12	16	206	155	57	42	0.69 (0.30, 1.57)	0.47 (0.12, 1.91)	0.99 (0.38, 2.55)	0.83 (0, 1.66)
	rs3176753	T	C	30	38	12	16	195	146	68	51	1.04 (0.47, 2.30)	1.33 (0.31, 5.65)	0.90 (0.37, 2.20)	-0.47 (-2.51, 1.58)
	rs3176748	A	G	37	42	5	12	213	166	50	31	0.70 (0.32, 1.53)	0.33 (0.06, 1.68)	1.00 (0.37, 2.67)	0.97 (0.13, 1.82)
	rs3176658	C	T	37	44	5	10	223	166	40	31	0.77 (0.35, 1.69)	0.51 (0.10, 2.57)	1.02 (0.38, 2.72)	0.74 (-0.29, 1.77)
	rs1800975	G	A	26	26	15	25	161	115	91	68	0.42 (0.14, 1.21)	0.29 (0.07, 1.17)	0.53 (0.18, 1.57)	0.82 (0.38, 1.25)*
RAD23B	rs1805330	C	T	21	33	21	21	162	127	101	70	1.25 (0.50, 3.14)	2.10 (0.57, 7.73)	1.38 (0.53, 3.60)	-0.97 (-3.73, 1.79)
ERCC6	rs2228529	A	G	35	37	7	16	199	152	62	44	0.68 (0.31, 1.51)	0.28 (0.06, 1.35)	0.85 (0.33, 2.17)	0.89 (0.24, 1.55)
	rs2228527	A	G	34	35	8	19	184	140	79	57	0.67 (0.29, 1.50)	0.32 (0.07, 1.45)	0.81 (0.33, 2.00)	0.82 (0.19, 1.45)
	rs4253132	T	C	27	30	15	24	164	95	99	102	1.02 (0.40, 2.61)	0.63 (0.18, 2.24)	0.54 (0.21, 1.41)	-0.10 (-1.29, 1.09)
	rs2228528	G	A	30	37	12	17	182	145	80	52	0.86 (0.37, 1.97)	0.98 (0.24, 4.00)	1.17 (0.45, 3.01)	0.33 (-1.09, 1.74)
DDB2 (XPE)	rs2029298	A	G	9	18	33	36	81	70	182	127	1.80 (0.49, 6.66)	3.09 (0.72, 13.27)	2.28 (0.64, 8.12)	-1.61 (-5.78, 2.57)
	rs1685404	G	C	18	24	24	30	146	116	117	81	0.66 (0.21, 2.12)	0.56 (0.14, 2.15)	0.58 (0.18, 1.92)	0.36 (-0.52, 1.25)
	rs2957873	A	G	14	22	28	32	76	60	186	137	0.59 (0.19, 1.87)	0.57 (0.16, 2.13)	0.69 (0.23, 2.04)	0.52 (-0.24, 1.29)
	rs326224	G	A	12	14	30	40	68	49	195	148	0.63 (0.18, 2.23)	0.58 (0.15, 2.30)	0.64 (0.19, 2.11)	0.43 (-0.45, 1.31)
	rs2306353	G	A	17	25	25	29	89	72	174	125	0.44 (0.15, 1.24)	0.39 (0.11, 1.41)	0.64 (0.24, 1.72)	0.81 (0.33, 1.29)
	rs326222	C	T	8	14	34	40	46	36	217	161	1.03 (0.25, 4.24)	1.44 (0.33, 6.24)	1.26 (0.34, 4.65)	-0.21 (-2.21, 1.80)
	rs901746	A	G	12	15	30	39	53	43	210	154	0.52 (0.15, 1.82)	0.60 (0.15, 2.30)	0.70 (0.22, 2.20)	0.58 (-0.16, 1.33)

OR odds ratio, I interval estimates

[a]Odds ratios adjusted for matching factors (age and sex including pairwise interactions), education, alcohol drinking, and percent African ancestry

Highlighting indicates RERI significant at 0.05 level. Asterisks indicate RERI significant at a Bonferroni corrected level (0.05/79=0.0006).

Table 4A cont. Odds Ratios and Relative Excess Risk Estimates for Joint Effects of Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Ever Environmental Tobacco Smoke on Head and Neck Cancer Risk Using Conventional Logistic Regression, the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, African Americans

		Coded Allele		Cases/Controls								OR (95% I)[a]			
Gene	SNP	Referent (A) / Variant (B)		Cigarette=0, SNP=0		Cigarette=0, SNP=1		Cigarette=1, SNP=0		Cigarette=1, SNP=1		Cigarette=1, SNP=0	Cigarette=0, SNP=1	Cigarette=1, SNP=1	RERI (95% CI)
ERCC5 (XPG)	rs2296147	T	C	27	29	15	25	166	119	96	77	0.62 (0.24, 1.56)	0.45 (0.12, 1.66)	0.72 (0.28, 1.88)	0.65 (-0.01, 1.32)
	rs2296148	C	T	30	42	12	12	198	148	64	49	1.39 (0.63, 3.06)	4.74 (1.09, 20.68)	1.32 (0.53, 3.29)	-3.80 (-10.86, 3.25)
	rs4771436	T	G	24	35	18	19	180	137	83	60	0.98 (0.41, 2.37)	1.25 (0.34, 4.64)	1.11 (0.43, 2.86)	-0.13 (-1.82, 1.56)
	rs1047768	C	T	12	24	30	30	104	91	159	106	1.24 (0.4, 3.88)	2.01 (0.53, 7.70)	1.65 (0.53, 5.09)	-0.60 (-3.09, 1.89)
	rs2020915	G	A	33	37	9	17	172	107	91	90	0.87 (0.37, 2.04)	0.32 (0.07, 1.35)	0.42 (0.17, 1.05)	0.24 (-0.55, 1.02)
	rs3818356	C	T	24	35	18	19	182	137	81	60	1 (0.41, 2.41)	1.25 (0.34, 4.63)	1.06 (0.41, 2.74)	-0.20 (-1.91, 1.52)
	rs4150355	C	T	29	32	13	22	189	143	74	54	0.55 (0.22, 1.36)	0.39 (0.10, 1.45)	0.88 (0.32, 2.36)	0.94 (0.31, 1.57)
	rs4150360	T	C	1	6	41	48	18	11	245	184				
	rs4150383	G	A	32	40	10	14	210	160	53	37	0.78 (0.35, 1.74)	0.62 (0.14, 2.66)	1.03 (0.39, 2.67)	0.63 (-0.43, 1.69)
	rs17655	C	G	12	22	30	32	78	48	185	149	1.70 (0.51, 5.74)	1.54 (0.40, 5.98)	1.09 (0.35, 3.45)	-1.15 (-3.98, 1.67)
	rs873601	A	G	4	11	38	43	26	19	237	178	1.77 (0.27, 11.63)	1.43 (0.24, 8.51)	1.20 (0.23, 6.39)	-1.00 (-4.82, 2.82)
	rs876430	C	T	4	11	38	43	28	19	235	178	1.95 (0.3, 12.64)	1.43 (0.24, 8.56)	1.19 (0.22, 6.35)	-1.19 (-5.33, 2.96)
	rs1051677	T	C	34	39	8	15	198	145	65	52	1.07 (0.49, 2.36)	1.22 (0.26, 5.85)	0.70 (0.29, 1.72)	-0.59 (-2.70, 1.52)
	rs1051685	A	G	21	30	21	23	117	87	146	110	0.63 (0.23, 1.74)	0.38 (0.10, 1.38)	0.51 (0.19, 1.39)	0.50 (-0.15, 1.15)
ERCC4 (XPF)	rs3136038	C	T	14	21	28	33	78	63	185	134	0.72 (0.22, 2.34)	0.84 (0.22, 3.19)	0.89 (0.29, 2.79)	0.33 (-0.74, 1.40)
	rs744154	C	G	37	42	5	12	184	132	79	65	0.88 (0.41, 1.9)	0.78 (0.13, 4.74)	0.93 (0.41, 2.11)	0.26 (-1.23, 1.76)
	rs3136085	G	C	18	28	24	26	155	118	108	79	1.01 (0.4, 2.58)	1.42 (0.40, 5.00)	1.24 (0.47, 3.26)	-0.19 (-1.97, 1.58)
	rs3136091	C	G	41	46	1	8	214	153	49	44	0.91 (0.44, 1.89)	0.12 (0.01, 2.37)	0.64 (0.27, 1.51)	0.60 (-0.02, 1.23)
	rs3136130	G	T	5	15	37	39	70	50	193	147	1.46 (0.31, 6.89)	1.92 (0.38, 9.72)	1.62 (0.36, 7.27)	-0.75 (-3.79, 2.29)
	rs3136172	A	G	37	41	5	13	179	130	84	67	0.85 (0.40, 1.83)	0.77 (0.13, 4.69)	0.98 (0.43, 2.24)	0.36 (-1.10, 1.82)
	rs2020955	T	C	17	32	25	22	176	133	87	64	1.1 (0.44, 2.76)	1.19 (0.33, 4.25)	0.82 (0.31, 2.20)	-0.47 (-2.23, 1.30)
RAD23A	rs2974752	A	G	10	16	31	34	67	46	185	136	1.50 (0.36, 6.17)	1.76 (0.39, 7.96)	1.30 (0.34, 4.99)	-0.96 (-3.97, 2.05)
	rs11558955	A	G	37	47	5	7	219	167	44	30	0.92 (0.44, 1.94)	0.94 (0.14, 6.20)	0.93 (0.36, 2.41)	0.06 (-1.83, 1.96)
ERCC2 (XPD)	rs13181	T	G	23	36	18	18	150	104	113	91	1.44 (0.55, 3.73)	1.61 (0.45, 5.79)	1.01 (0.39, 2.60)	-1.03 (-3.46, 1.40)
	rs238418	C	A	42	3	0	51	8	8	254	189				
	rs1799787	C	T	31	45	11	9	204	147	59	50	1.23 (0.55, 2.76)	1.99 (0.46, 8.56)	0.85 (0.34, 2.08)	-1.38 (-4.49, 1.74)
	rs3916874	G	C	40	48	2	6	228	178	35	19	0.85 (0.41, 1.76)	0.30 (0.03, 2.81)	0.75 (0.26, 2.13)	0.60 (-0.34, 1.55)
	rs238416	G	A	35	41	7	12	208	167	54	29	0.68 (0.31, 1.48)	0.54 (0.09, 3.06)	1.84 (0.71, 4.80)	1.63 (0.09, 3.16)
	rs50872	C	T	34	30	8	24	189	128	74	69	0.83 (0.37, 1.87)	0.30 (0.07, 1.33)	0.52 (0.22, 1.23)	0.40 (-0.29, 1.09)
	rs50871	T	G	34	39	8	15	195	156	68	41	0.78 (0.35, 1.77)	0.61 (0.14, 2.72)	0.93 (0.37, 2.37)	0.54 (-0.48, 1.56)
	rs238407	A	T	35	40	7	14	191	150	72	47	0.76 (0.34, 1.71)	0.77 (0.16, 3.70)	1.28 (0.51, 3.19)	0.74 (-0.53, 2.02)
	rs3810366	C	G	33	38	9	16	179	142	84	55	0.86 (0.38, 1.95)	1.26 (0.29, 5.52)	1.32 (0.54, 3.24)	0.20 (-1.62, 2.02)

OR odds ratio, I interval estimates

[a]Odds ratios adjusted for matching factors (age and sex including pairwise interactions), education, alcohol drinking, and percent African ancestry

Highlighting indicates RERI significant at 0.05 level. Asterisks indicate RERI significant at a Bonferroni corrected level (0.05/79=0.0006).

Table 4A cont. Odds Ratios and Relative Excess Risk Estimates for Joint Effects of Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Ever Environmental Tobacco Smoke on Head and Neck Cancer Risk Using Conventional Logistic Regression, the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, African Americans

		Coded Allele		Cases/Controls								OR (95% I)[a]			
Gene	SNP	Referent (A) / Variant (B)		Cigarette=0, SNP=0		Cigarette=0, SNP=1		Cigarette=1, SNP=0		Cigarette=1, SNP=1		Cigarette=1, SNP=0	Cigarette=0, SNP=1	Cigarette=1, SNP=1	RERI (95% CI)
ERCC1	rs735482	A	C	22	26	20	28	134	96	129	101	1.02 (0.40, 2.55)	1.33 (0.37, 4.82)	1.10 (0.43, 2.79)	-0.25 (-2.00, 1.50)
	rs2336219	G	A	22	27	20	27	135	99	128	98	1.01 (0.40, 2.52)	1.33 (0.37, 4.83)	1.11 (0.44, 2.83)	-0.23 (-1.98, 1.52)
	rs3212964	G	A	32	31	9	22	175	111	87	85	0.59 (0.24, 1.42)	0.18 (0.04, 0.73)	0.49 (0.19, 1.23)	0.72 (0.31, 1.14)
	rs3212955	A	G	18	33	24	21	141	109	122	88	1.90 (0.73, 4.94)	3.03 (0.81, 11.38)	1.22 (0.47, 3.21)	-2.71 (-7.23, 1.80)
	rs3212948	C	G	1	54	41	0	8	6	255	191				
	rs3212935	A	G	24	29	18	25	119	96	144	100	0.89 (0.35, 2.27)	1.11 (0.30, 4.11)	1.08 (0.42, 2.73)	0.08 (-1.38, 1.54)
	rs3212930	T	C	33	47	9	7	217	158	46	39	1.29 (0.60, 2.77)	3.79 (0.75, 19.18)	0.89 (0.35, 2.23)	-3.19 (-9.50, 3.13)
LIG1	rs156641	G	A	33	39	9	15	201	153	62	44	0.69 (0.30, 1.55)	0.45 (0.10, 1.94)	1.00 (0.39, 2.58)	0.87 (0.03, 1.70)
	rs20580	C	A	13	9	28	45	49	48	214	149	0.40 (0.09, 1.70)	0.50 (0.11, 2.29)	0.62 (0.16, 2.45)	0.73 (0.13, 1.32)
	rs20579	C	T	23	27	19	27	127	101	136	96	1.14 (0.44, 2.99)	1.84 (0.51, 6.60)	1.39 (0.53, 3.68)	-0.59 (-2.89, 1.71)
	rs439132	A	G	24	30	18	24	148	106	115	91	1.01 (0.41, 2.50)	0.88 (0.24, 3.27)	0.74 (0.29, 1.89)	-0.15 (-1.53, 1.23)

OR odds ratio, I interval estimates

[a]Odds ratios adjusted for matching factors (age and sex including pairwise interactions), education, alcohol drinking, and percent African ancestry

Highlighting indicates RERI significant at 0.05 level. Asterisks indicate RERI significant at a Bonferroni corrected level (0.05/79=0.0006).

APPENDIX C

AIM 2 SUPPLEMENTAL TABLES REFERENCED IN CHAPTER 4

Table 7S. Hazard Ratios for Select Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and and Survival by Stage among Head and Neck Cancer Cases in the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study

			Overall Deaths / Deaths from HNC / Alive						Overall Survival		Disease-Specific Survival	
Gene	**SNP**	**Stage**	**AA**			**AB + BB**			**HR (95% CI)[a]**	**p-value**	**HR (95% CI)[a]**	**p-value**
Whites												
ERCC4 (XPF)	rs3136038	1	29	8	65	37	8	90	1.16 (0.71, 1.91)	0.56	0.75 (0.27, 2.05)	0.58
		2	33	16	39	40	16	55	0.98 (0.61, 1.59)	0.95	0.78 (0.38, 1.59)	0.49
		3	32	13	36	33	15	56	0.71 (0.42, 1.21)	0.21	0.82 (0.37, 1.82)	0.63
		4	90	49	78	89	44	120	0.67 (0.49, 0.91)	0.01	0.63 (0.41, 0.96)	0.03
	rs3136130	1	30	8	64	36	8	91	1.09 (0.66, 1.79)	0.74	0.71 (0.26, 1.94)	0.51
		2	32	16	38	41	16	56	0.96 (0.59, 1.55)	0.86	0.73 (0.36, 1.49)	0.39
		3	32	13	37	33	15	55	0.74 (0.44, 1.25)	0.25	0.84 (0.38, 1.87)	0.68
		4	90	49	77	89	44	121	0.65 (0.48, 0.88)	0.01	0.62 (0.41, 0.93)	0.02
ERCC2 (XPD)	rs50871	1	17	5	32	49	11	123	0.68 (0.38, 1.21)	0.19	0.65 (0.22, 1.97)	0.45
		2	20	11	32	53	21	62	0.98 (0.56, 1.72)	0.95	0.77 (0.34, 1.71)	0.52
		3	23	10	20	42	18	72	0.61 (0.35, 1.05)	0.07	0.49 (0.21, 1.14)	0.10
		4	50	29	48	129	64	150	0.84 (0.6, 1.17)	0.30	0.71 (0.45, 1.11)	0.14
African Americans												
ERCC4 (XPF)	rs2607755	1	8	0	12	10	1	28	1.19 (0.39, 3.6)	0.76		
		2	10	3	7	18	3	18	0.62 (0.26, 1.49)	0.29	0.21 (0.01, 3.16)	0.26
		3	9	8	8	19	4	18	1.04 (0.42, 2.59)	0.93	0.62 (0.15, 2.65)	0.52
		4	43	20	14	45	19	38	0.62 (0.45, 0.86)	0.004	0.5 (0.26, 0.96)	0.04

HR hazards ratio, CI confidence interval

a) HR for dominant genetic model (AB + BB vs AA). HRs adjusted for matching factors (age, sex, including pairwise interactions) and ancestry (% African ancestry)

Table 8S. Hazard Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Treatment on Overall Survival among Head and Neck Cancer Cases in the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, Whites

		Coded Allele		Died/Alive																			
Gene	SNP	Referent (A) / Variant (B)		Surgery, Referent Genotype		Surgery, Variant Genotype		Radiation, Referent Genotype		Radiation, Variant Genotype		Surgery and Radiation, Referent Genotype		Surgery and Radiation, Variant Genotype		Radiation and Chemotherapy, Referent Genotype		Radiation and Chemotherapy, Variant Genotype		Surgery, Radiation, Chemotherapy, Referent Genotype		Surgery, Radiation, Chemotherapy, Variant Genotype	
ERCC3																							
(XPB)	rs4150496	G	A	31	64	37	80	37	30	40	53	35	50	50	55	40	53	62	65	22	36	21	51
	rs1011019	C	T	32	62	36	82	40	45	37	38	46	52	39	54	49	69	53	49	17	42	26	45
	rs4150434	G	A	48	86	20	58	41	53	36	30	50	58	35	48	63	64	39	54	24	56	19	31
	rs4150416	T	G	28	58	40	86	35	43	42	40	40	46	45	59	41	62	60	56	15	35	28	51
	rs4150407	A	G	23	55	45	89	28	27	49	56	26	38	59	68	35	41	67	77	19	26	24	61
	rs4150403	G	A	49	110	19	34	61	67	16	16	70	88	15	18	81	100	21	18	35	67	8	20
	rs4150402	G	A	32	62	36	82	40	45	37	38	46	52	39	54	49	69	53	49	17	42	26	45
XPC	rs2228001	A	C	25	56	43	88	32	33	45	50	27	41	58	64	37	45	65	73	12	26	31	61
	rs3731143	T	C	60	128	8	16	59	80	18	3	75	92	10	14	91	105	11	13	40	79	3	8
	rs2228000	C	T	37	77	31	67	42	51	35	32	47	63	37	43	52	62	49	56	29	58	14	29
	rs3731124	A	C	43	82	25	62	43	43	34	40	54	56	31	50	51	73	51	45	23	52	20	35
	rs13099160	A	G	59	128	9	16	66	76	11	7	77	94	8	12	89	105	13	13	37	75	6	12
	rs3731093	T	C	56	118	12	24	61	73	15	9	73	91	12	14	87	102	13	15	37	70	6	17
	rs3731089	G	A	56	119	12	25	61	73	16	10	73	91	12	15	87	103	15	15	37	70	6	17
	rs2733537	A	G	29	56	39	88	33	46	44	37	35	51	50	55	41	52	61	66	24	44	19	43
	rs3731068	C	A	48	99	20	45	54	52	23	31	63	70	22	36	61	85	41	33	28	61	15	26
	rs2607755	T	C	20	30	48	114	14	20	63	63	31	29	54	77	21	34	81	84	13	29	30	58
	rs1902658	G	A	19	28	49	116	14	20	63	63	31	26	54	80	21	33	81	85	13	29	30	57
ERCC8	rs3117	T	C	19	52	49	92	28	32	49	51	27	40	58	66	33	42	69	76	15	44	28	43
CDK7	rs2972388	A	G	20	33	48	111	15	30	62	53	26	27	59	79	29	39	73	79	18	27	25	60
XPA	rs3176757	C	T	48	101	20	43	60	53	17	30	55	65	30	41	60	80	42	38	28	54	15	33
	rs3176748	A	G	34	67	34	77	35	42	42	41	46	46	39	60	46	55	56	63	19	47	24	40
	rs2808667	C	T	59	120	9	24	68	69	9	14	75	94	9	12	95	106	6	12	40	79	3	8
	rs2805835	G	C	53	114	15	30	54	63	23	20	64	89	21	17	84	93	18	25	39	66	4	21
	rs3176689	A	T	43	95	25	49	60	56	17	27	61	72	24	34	68	81	34	37	31	50	12	37
	rs3176683	T	C	57	129	11	15	70	71	7	12	79	91	6	15	89	105	13	13	39	79	4	8
	rs3176658	C	T	54	102	14	42	57	61	20	22	61	78	24	28	85	95	17	23	29	68	14	19
	rs1800975	G	A	38	66	29	74	40	33	36	44	38	41	43	61	45	61	51	54	18	35	24	46
RAD23B	rs1805330	C	T	54	116	14	28	64	66	13	17	67	90	18	16	84	106	18	12	31	79	12	8
	rs1805329	C	T	48	95	20	49	51	49	26	34	55	63	30	43	65	66	37	52	34	59	9	28
ERCC6	rs2228529	A	G	46	101	21	42	55	56	22	25	53	60	31	44	64	74	36	42	29	53	14	33
	rs2228527	A	G	46	101	22	43	54	57	23	26	53	60	32	46	64	75	38	43	29	53	14	34
	rs4253132	T	C	54	112	14	32	55	65	22	18	68	88	17	18	76	91	26	27	34	73	9	14
	rs2228528	G	A	51	95	17	49	45	56	32	27	59	78	26	28	78	83	23	35	28	60	15	27

HR hazards ratio, CI confidence interval

a) HRs adjusted for matching factors (age and sex, including pairwise interactions), stage, anatomic site, ancestry (% African ancestry), education, cigarette smoking, and alcohol drinking
Highlighting indicates RERI significant at 0.05 level. Asterisks indicate RERI significant at a Bonferroni corrected level (0.05/84=0.0006).

Table 8S cont. Hazard Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Treatment on Overall Survival among Head and Neck Cancer Cases in the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, Whites

		Coded Allele		Died/Alive																			
Gene	SNP	Referent (A) / Variant (B)		Surgery, Referent Genotype		Surgery, Variant Genotype		Radiation, Referent Genotype		Radiation, Variant Genotype		Surgery and Radiation, Referent Genotype		Surgery and Radiation, Variant Genotype		Radiation and Chemotherapy, Referent Genotype		Radiation and Chemotherapy, Variant Genotype		Surgery, Radiation, Chemotherapy, Referent Genotype		Surgery, Radiation, Chemotherapy, Variant Genotype	
DDB2																							
(XPE)	rs2029298	A	G	29	60	39	84	34	40	43	43	38	51	47	55	48	58	54	60	19	45	24	42
	rs4647709	C	T	57	118	11	26	65	69	12	14	73	92	12	14	85	97	17	21	32	72	11	15
	rs2291120	T	C	50	113	18	31	62	50	15	33	59	87	26	19	76	84	26	34	30	68	13	19
	rs1685404	G	C	34	72	34	72	37	37	40	46	40	49	45	57	41	48	61	70	17	40	26	47
	rs2957873	A	G	46	102	22	42	53	59	24	24	56	74	29	32	66	85	36	33	33	65	10	22
	rs326224	G	A	51	103	17	41	57	65	20	18	60	73	25	33	71	93	31	25	36	69	7	18
	rs2306353	G	A	51	106	17	38	57	67	20	16	62	77	23	29	71	93	31	25	36	71	7	16
	rs326222	C	T	30	76	38	68	36	39	41	44	44	56	41	50	53	68	49	50	25	54	18	33
	rs901746	A	G	30	77	38	67	36	39	41	44	44	56	41	50	53	68	49	50	25	54	18	33
ERCC5																							
(XPG)	rs2296147	T	C	24	35	44	108	21	18	56	65	26	30	58	76	41	40	60	77	15	27	27	60
	rs4771436	T	G	34	92	34	52	52	54	25	29	47	59	38	47	63	76	39	42	28	54	15	33
	rs1047768	C	T	20	60	48	84	27	33	50	50	24	30	61	76	32	45	70	73	16	29	27	58
	rs3818356	C	T	34	92	34	51	52	54	25	29	47	59	38	47	63	76	38	42	28	54	15	33
	rs4150351	A	C	42	91	26	53	51	46	26	37	64	68	21	38	62	76	40	42	30	60	13	27
	rs4150355	C	T	35	51	33	93	29	37	48	46	33	46	52	60	58	51	44	67	18	39	25	48
	rs4150360	T	C	16	52	52	92	21	28	56	55	23	26	62	80	29	39	73	79	14	24	29	63
	rs4150383	G	A	38	106	30	38	56	60	21	23	54	68	31	38	71	83	31	35	31	57	12	30
	rs4150386	A	C	55	111	13	33	56	62	21	21	70	90	15	16	84	98	18	20	32	58	11	29
	rs17655	C	G	45	94	23	50	42	54	35	29	48	62	37	44	55	71	47	47	26	51	17	36
	rs873601	A	G	40	81	28	63	36	43	41	40	39	51	46	55	44	60	58	58	25	39	18	48
	rs4150393	A	G	49	105	19	39	61	56	16	27	73	82	12	24	76	90	26	28	32	73	11	14
	rs876430	C	T	40	81	28	63	36	43	41	40	39	51	46	55	45	60	57	58	25	39	18	48
	rs1051677	T	C	53	113	15	31	49	66	28	17	79	84	6	21	82	97	20	21	33	71	10	16
	rs1051685	A	G	53	116	15	27	63	65	14	18	63	84	22	22	82	98	20	20	34	70	9	17
ERCC4																							
(XPF)	rs3136038	C	T	35	54	33	90	30	33	47	50	44	42	41	64	54	51	48	67	18	38	25	49
	rs1799798	G	A	56	114	12	30	66	70	11	13	67	86	18	20	89	95	13	23	37	71	6	16
	rs744154	C	G	37	76	31	68	41	42	36	41	47	48	38	58	60	59	42	59	19	46	24	41
	rs3136085	G	C	37	75	31	69	39	42	38	41	46	49	39	57	60	59	42	59	19	44	24	43
	rs3136130	G	T	35	53	33	91	29	33	48	50	45	42	40	64	54	51	48	67	18	37	25	50
	rs1800067	G	A	55	126	13	18	64	73	13	10	71	86	14	20	91	96	11	22	35	74	8	13
	rs3136172	A	G	35	75	33	69	37	41	40	42	43	47	42	59	57	58	45	60	19	41	24	46
RAD23A	rs2974752	A	G	29	46	38	95	33	33	43	47	25	32	56	70	30	54	67	62	14	32	28	52

HR hazards ratio, CI confidence interval

a) HRs adjusted for matching factors (age and sex, including pairwise interactions), stage, anatomic site, ancestry (% African ancestry), education, cigarette smoking, and alcohol drinking
Highlighting indicates RERI significant at 0.05 level. Asterisks indicate RERI significant at a Bonferroni corrected level (0.05/84=0.0006).

Table 8S. Hazard Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Treatment on Overall Survival among Head and Neck Cancer Cases in the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, Whites

		Coded Allele		Died/Alive																			
Gene	SNP	Referent (A) / Variant (B)		Surgery, Referent Genotype		Surgery, Variant Genotype		Radiation, Referent Genotype		Radiation, Variant Genotype		Surgery and Radiation, Referent Genotype		Surgery and Radiation, Variant Genotype		Radiation and Chemotherapy, Referent Genotype		Radiation and Chemotherapy, Variant Genotype		Surgery, Radiation, Chemotherapy, Referent Genotype		Surgery, Radiation, Chemotherapy, Variant Genotype	
ERCC2																							
(XPD)	rs13181	T	G	25	61	42	83	29	41	46	42	40	38	45	67	40	50	61	67	14	37	28	50
	rs238418	C	A	26	60	42	84	30	41	47	42	40	39	45	67	39	49	63	69	15	37	28	50
	rs1799787	C	T	34	72	34	72	38	48	39	35	46	52	39	54	53	56	49	62	19	47	24	40
	rs3916874	G	C	39	74	29	70	42	31	35	52	44	55	41	51	58	58	44	60	23	49	20	38
	rs238416	G	A	26	58	42	86	37	35	40	48	29	43	56	63	40	48	62	69	18	33	25	54
	rs50872	C	T	40	71	28	72	42	49	35	33	52	62	33	44	55	70	47	48	31	53	12	34
	rs50871	T	G	15	36	53	108	22	23	55	60	27	21	58	85	33	26	69	92	11	26	32	61
	rs238407	A	T	21	32	47	112	23	23	54	59	29	33	56	73	29	28	73	90	16	26	27	61
	rs3810366	C	G	13	24	55	120	13	17	64	66	18	20	67	86	22	18	80	100	10	20	33	66
ERCC1	rs735482	A	C	53	111	15	33	58	68	19	15	58	76	27	30	71	98	31	20	31	57	12	30
	rs2336219	G	A	53	111	15	33	58	68	19	15	58	76	27	30	71	98	31	20	31	57	12	30
	rs3212964	G	A	53	111	15	33	58	68	19	15	59	77	26	29	71	99	31	19	32	57	11	30
	rs3212955	A	G	35	74	33	70	39	51	38	32	48	59	37	47	59	75	43	43	23	59	20	28
	rs3212948	C	G	27	55	41	89	30	42	47	41	35	40	50	66	42	56	60	62	16	35	27	52
	rs3212930	T	C	42	79	26	65	46	54	31	29	55	61	30	45	67	79	35	39	25	61	18	26
LIG1	rs156641	G	A	25	51	43	93	35	32	42	51	25	49	60	57	39	47	63	71	23	39	20	48
	rs20580	C	A	12	31	56	113	26	27	51	56	17	28	68	78	24	27	78	91	16	27	27	60
	rs20579	C	T	51	101	17	43	58	65	19	18	72	73	13	33	73	90	29	28	34	68	9	19

HR hazards ratio, CI confidence interval

a) HRs adjusted for matching factors (age and sex, including pairwise interactions), stage, anatomic site, ancestry (% African ancestry), education, cigarette smoking, and alcohol drinking
Highlighting indicates RERI significant at 0.05 level. Asterisks indicate RERI significant at a Bonferroni corrected level (0.05/84=0.0006).

Table 8S cont. Hazard Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Treatment on Overall Survival among Head and Neck Cancer Cases in the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, Whites

		HR (95% CI)[a]								
Gene	**SNP**	**Surgery, Variant Genotype**	**Radiation, Referent Genotype**	**Radiation, Variant Genotype**	**Surgery and Radiation, Referent Genotype**	**Surgery and Radiation, Variant Genotype**	**Radiation and Chemotherapy, Referent Genotype**	**Radiation and Chemotherapy, Variant Genotype**	**Surgery, Radiation and Chemotherapy, Referent Genotype**	**Surgery, Radiation, and Chemotherapy, Variant Genotype**
ERCC3										
(XPB)	rs4150496	0.72 (0.43, 1.19)	1.23 (0.71, 2.12)	1.36 (0.80, 2.32)	1.00 (0.58, 1.71)	0.94 (0.56, 1.56)	0.94 (0.53, 1.68)	0.95 (0.57, 1.60)	1.17 (0.62, 2.22)	0.60 (0.32, 1.12)
	rs1011019	0.93 (0.57, 1.53)	1.72 (1.01, 2.93)	1.36 (0.81, 2.30)	1.14 (0.69, 1.88)	1.14 (0.68, 1.9)	1.02 (0.61, 1.72)	1.24 (0.72, 2.12)	0.66 (0.34, 1.29)	1.24 (0.68, 2.25)
	rs4150434	0.73 (0.42, 1.27)	1.21 (0.75, 1.95)	1.75 (1.07, 2.89)	1.13 (0.71, 1.79)	0.97 (0.59, 1.59)	1.03 (0.64, 1.67)	1.03 (0.61, 1.75)	0.79 (0.44, 1.41)	0.96 (0.51, 1.80)
	rs4150416	1.13 (0.68, 1.87)	1.77 (1.01, 3.10)	1.64 (0.96, 2.79)	1.24 (0.72, 2.12)	1.29 (0.77, 2.17)	1.11 (0.64, 1.94)	1.34 (0.77, 2.32)	0.73 (0.36, 1.50)	1.32 (0.72, 2.41)
	rs4150407	0.87 (0.51, 1.49)	1.19 (0.64, 2.21)	1.64 (0.94, 2.85)	1.04 (0.56, 1.92)	1.07 (0.63, 1.84)	1.16 (0.62, 2.18)	1.00 (0.57, 1.75)	1.41 (0.70, 2.83)	0.67 (0.35, 1.29)
	rs4150403	1.26 (0.71, 2.25)	1.86 (1.20, 2.89)	1.22 (0.64, 2.32)	1.23 (0.81, 1.87)	1.26 (0.68, 2.33)	1.14 (0.73, 1.78)	1.64 (0.88, 3.03)	1.05 (0.63, 1.77)	0.86 (0.38, 1.95)
	rs4150402	0.93 (0.57, 1.53)	1.72 (1.01, 2.93)	1.36 (0.81, 2.30)	1.14 (0.69, 1.88)	1.14 (0.68, 1.90)	1.02 (0.61, 1.72)	1.24 (0.72, 2.12)	0.66 (0.34, 1.29)	1.24 (0.68, 2.25)
XPC	rs2228001	1.08 (0.64, 1.82)	1.49 (0.83, 2.66)	1.81 (1.05, 3.12)	0.88 (0.48, 1.63)	1.45 (0.87, 2.43)	1.14 (0.64, 2.05)	1.21 (0.70, 2.10)	0.90 (0.43, 1.89)	1.04 (0.56, 1.92)
	rs3731143	0.96 (0.43, 2.13)	1.39 (0.91, 2.10)	3.53 (1.84, 6.77)	1.14 (0.76, 1.71)	1.35 (0.66, 2.78)	1.18 (0.76, 1.82)	0.96 (0.46, 2.02)	0.99 (0.60, 1.63)	0.60 (0.18, 2.00)
	rs2228000	0.96 (0.58, 1.58)	1.58 (0.96, 2.59)	1.52 (0.89, 2.59)	1.13 (0.70, 1.85)	1.15 (0.69, 1.92)	1.05 (0.62, 1.76)	1.21 (0.71, 2.06)	0.95 (0.53, 1.70)	0.92 (0.46, 1.82)
	rs3731124	0.85 (0.50, 1.43)	1.65 (1.00, 2.72)	1.38 (0.84, 2.27)	1.36 (0.85, 2.17)	0.82 (0.49, 1.39)	0.90 (0.54, 1.50)	1.38 (0.83, 2.28)	0.92 (0.51, 1.67)	0.88 (0.48, 1.64)
	rs13099160	1.10 (0.52, 2.33)	1.57 (1.04, 2.37)	1.64 (0.80, 3.37)	1.21 (0.81, 1.79)	0.93 (0.43, 2.02)	1.08 (0.69, 1.67)	1.86 (0.95, 3.62)	0.93 (0.56, 1.54)	1.12 (0.45, 2.75)
	rs3731093	1.05 (0.54, 2.01)	1.47 (0.97, 2.25)	1.93 (1.03, 3.64)	1.19 (0.79, 1.79)	1.11 (0.57, 2.16)	1.08 (0.69, 1.68)	1.54 (0.79, 3.02)	1.00 (0.60, 1.68)	0.75 (0.31, 1.84)
	rs3731089	1.03 (0.53, 1.97)	1.48 (0.97, 2.26)	2.01 (1.08, 3.72)	1.19 (0.79, 1.79)	1.04 (0.53, 2.02)	1.07 (0.69, 1.67)	1.70 (0.89, 3.23)	1.00 (0.60, 1.66)	0.75 (0.31, 1.83)
	rs2733537	0.92 (0.56, 1.53)	1.43 (0.82, 2.49)	1.57 (0.93, 2.66)	1.08 (0.62, 1.86)	1.14 (0.69, 1.90)	0.92 (0.52, 1.63)	1.24 (0.72, 2.13)	1.00 (0.53, 1.87)	0.83 (0.43, 1.59)
	rs3731068	0.93 (0.54, 1.59)	1.78 (1.11, 2.84)	1.29 (0.75, 2.22)	1.32 (0.85, 2.04)	0.80 (0.45, 1.44)	0.93 (0.57, 1.51)	1.61 (0.95, 2.72)	0.87 (0.50, 1.53)	1.03 (0.53, 2.01)
	rs2607755	0.72 (0.42, 1.24)	1.17 (0.55, 2.50)	1.26 (0.72, 2.23)	1.21 (0.64, 2.27)	0.81 (0.46, 1.43)	0.68 (0.34, 1.36)	1.01 (0.56, 1.83)	0.81 (0.37, 1.79)	0.74 (0.38, 1.41)
	rs1902658	0.74 (0.43, 1.29)	1.20 (0.56, 2.58)	1.29 (0.73, 2.30)	1.31 (0.69, 2.49)	0.81 (0.45, 1.45)	0.71 (0.35, 1.43)	1.03 (0.57, 1.88)	0.83 (0.37, 1.86)	0.76 (0.39, 1.48)
ERCC8	rs3117	1.23 (0.71, 2.15)	1.37 (0.72, 2.59)	2.22 (1.24, 3.97)	1.05 (0.56, 2.00)	1.53 (0.87, 2.68)	1.07 (0.56, 2.03)	1.45 (0.81, 2.60)	0.97 (0.46, 2.06)	1.15 (0.59, 2.21)
CDK7	rs2972388	0.57 (0.33, 0.99)	0.61 (0.28, 1.29)	1.25 (0.72, 2.16)	0.77 (0.41, 1.44)	0.76 (0.44, 1.33)	0.58 (0.30, 1.11)	0.87 (0.49, 1.54)	0.95 (0.46, 1.94)	0.51 (0.26, 0.98)
XPA	rs3176757	0.98 (0.57, 1.68)	1.75 (1.13, 2.72)	1.15 (0.62, 2.12)	1.18 (0.75, 1.85)	1.13 (0.68, 1.87)	1.02 (0.63, 1.66)	1.33 (0.80, 2.22)	0.99 (0.56, 1.73)	0.88 (0.46, 1.69)
	rs3176748	0.93 (0.57, 1.53)	1.44 (0.85, 2.43)	1.61 (0.96, 2.69)	1.23 (0.75, 2.02)	1.03 (0.62, 1.71)	1.12 (0.66, 1.89)	1.11 (0.66, 1.88)	0.71 (0.38, 1.35)	1.21 (0.66, 2.22)
	rs2808667	0.55 (0.27, 1.14)	1.50 (1.00, 2.26)	1.04 (0.46, 2.34)	1.03 (0.69, 1.54)	1.17 (0.56, 2.47)	1.03 (0.67, 1.59)	0.90 (0.37, 2.20)	0.86 (0.52, 1.41)	0.78 (0.24, 2.61)
	rs2805835	1.19 (0.65, 2.19)	1.50 (0.97, 2.33)	2.08 (1.19, 3.63)	1.11 (0.73, 1.70)	1.54 (0.89, 2.67)	1.21 (0.77, 1.91)	1.04 (0.56, 1.94)	1.18 (0.72, 1.96)	0.29 (0.09, 0.97)
	rs3176689	1.10 (0.65, 1.84)	1.86 (1.17, 2.96)	1.21 (0.66, 2.21)	1.24 (0.80, 1.93)	1.11 (0.63, 1.95)	1.17 (0.72, 1.90)	1.25 (0.72, 2.15)	1.22 (0.70, 2.13)	0.66 (0.32, 1.32)
	rs3176683	1.29 (0.67, 2.51)	1.69 (1.13, 2.54)	1.36 (0.53, 3.45)	1.31 (0.88, 1.96)	0.64 (0.27, 1.54)	1.23 (0.79, 1.91)	1.04 (0.53, 2.06)	0.99 (0.60, 1.64)	0.91 (0.31, 2.61)
	rs3176658	0.61 (0.33, 1.12)	1.41 (0.92, 2.16)	1.35 (0.74, 2.44)	1.02 (0.67, 1.56)	1.04 (0.61, 1.79)	1.01 (0.64, 1.57)	1.05 (0.55, 2.00)	0.76 (0.44, 1.30)	1.11 (0.55, 2.24)
	rs1800975	0.66 (0.40, 1.10)	1.47 (0.88, 2.46)	1.17 (0.69, 1.96)	1.03 (0.61, 1.74)	0.83 (0.50, 1.37)	0.77 (0.45, 1.32)	1.02 (0.61, 1.72)	0.78 (0.41, 1.48)	0.77 (0.42, 1.42)
RAD23B	rs1805330	1.56 (0.85, 2.88)	1.72 (1.13, 2.62)	1.69 (0.85, 3.37)	1.20 (0.79, 1.83)	1.43 (0.79, 2.60)	1.14 (0.73, 1.80)	1.69 (0.93, 3.09)	0.85 (0.50, 1.45)	1.66 (0.83, 3.33)
	rs1805329	0.81 (0.47, 1.40)	1.49 (0.95, 2.34)	1.46 (0.85, 2.52)	1.20 (0.77, 1.88)	0.96 (0.58, 1.60)	1.08 (0.67, 1.72)	1.12 (0.67, 1.89)	0.99 (0.58, 1.70)	0.70 (0.32, 1.49)
ERCC6	rs2228529	0.89 (0.52, 1.54)	1.53 (0.97, 2.44)	1.47 (0.84, 2.58)	1.23 (0.78, 1.95)	0.99 (0.59, 1.66)	0.97 (0.59, 1.57)	1.49 (0.86, 2.57)	1.14 (0.65, 1.99)	0.68 (0.34, 1.34)
	rs2228527	0.94 (0.55, 1.60)	1.58 (1.00, 2.51)	1.50 (0.85, 2.63)	1.25 (0.79, 1.99)	1.02 (0.61, 1.69)	0.99 (0.61, 1.61)	1.48 (0.86, 2.54)	1.15 (0.66, 2.02)	0.68 (0.34, 1.34)
	rs4253132	0.90 (0.48, 1.68)	1.41 (0.92, 2.17)	1.99 (1.14, 3.48)	1.11 (0.73, 1.68)	1.20 (0.67, 2.15)	1.17 (0.75, 1.81)	0.95 (0.53, 1.67)	0.93 (0.55, 1.55)	0.90 (0.42, 1.94)
	rs2228528	0.65 (0.36, 1.18)	1.30 (0.83, 2.03)	1.66 (0.98, 2.79)	0.99 (0.64, 1.51)	1.23 (0.73, 2.08)	1.04 (0.66, 1.64)	0.98 (0.55, 1.75)	0.86 (0.50, 1.48)	0.86 (0.44, 1.65)

HR hazards ratio, CI confidence interval

a) HRs adjusted for matching factors (age and sex, including pairwise interactions), stage, anatomic site, ancestry (% African ancestry), education, cigarette smoking, and alcohol drinking
Highlighting indicates RERI significant at 0.05 level. Asterisks indicate RERI significant at a Bonferroni corrected level (0.05/84=0.0006).

Table 8S cont. Hazard Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Treatment on Overall Survival among Head and Neck Cancer Cases in the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, Whites

		HR (95% CI)[a]								
Gene	**SNP**	**Surgery, Variant Genotype**	**Radiation, Referent Genotype**	**Radiation, Variant Genotype**	**Surgery and Radiation, Referent Genotype**	**Surgery and Radiation, Variant Genotype**	**Radiation and Chemotherapy, Referent Genotype**	**Radiation and Chemotherapy, Variant Genotype**	**Surgery, Radiation and Chemotherapy, Referent Genotype**	**Surgery, Radiation, and Chemotherapy, Variant Genotype**
DDB2										
(XPE)	rs2029298	0.76 (0.46, 1.27)	1.20 (0.68, 2.10)	1.46 (0.88, 2.44)	0.93 (0.55, 1.58)	1.06 (0.64, 1.75)	0.93 (0.54, 1.61)	1.02 (0.61, 1.72)	0.68 (0.35, 1.30)	0.96 (0.52, 1.77)
	rs4647709	0.88 (0.43, 1.81)	1.54 (1.02, 2.34)	1.59 (0.80, 3.16)	1.12 (0.74, 1.67)	1.35 (0.68, 2.69)	1.14 (0.73, 1.78)	1.08 (0.57, 2.02)	0.81 (0.48, 1.37)	1.79 (0.84, 3.80)
	rs2291120	1.14 (0.65, 1.99)	1.87 (1.22, 2.86)	0.93 (0.47, 1.86)	1.01 (0.65, 1.57)	2.02 (1.18, 3.45)	1.17 (0.73, 1.88)	1.24 (0.70, 2.18)	0.95 (0.55, 1.64)	1.09 (0.54, 2.20)
	rs1685404	0.99 (0.60, 1.65)	1.70 (1.00, 2.89)	1.45 (0.85, 2.45)	1.22 (0.72, 2.06)	1.11 (0.67, 1.85)	0.96 (0.55, 1.67)	1.30 (0.76, 2.21)	0.88 (0.45, 1.71)	1.01 (0.55, 1.86)
	rs2957873	1.08 (0.64, 1.84)	1.59 (1.01, 2.49)	1.68 (0.96, 2.96)	1.17 (0.75, 1.83)	1.23 (0.73, 2.08)	1.10 (0.68, 1.78)	1.33 (0.78, 2.26)	0.99 (0.58, 1.71)	0.91 (0.43, 1.92)
	rs326224	0.81 (0.45, 1.45)	1.43 (0.93, 2.21)	1.73 (0.97, 3.10)	1.12 (0.73, 1.72)	1.07 (0.63, 1.82)	0.99 (0.63, 1.58)	1.38 (0.80, 2.37)	0.92 (0.54, 1.54)	0.79 (0.34, 1.84)
	rs2306353	0.81 (0.45, 1.45)	1.40 (0.91, 2.17)	1.87 (1.05, 3.35)	1.13 (0.74, 1.73)	1.04 (0.60, 1.80)	1.00 (0.63, 1.59)	1.38 (0.80, 2.37)	0.90 (0.53, 1.52)	0.88 (0.38, 2.05)
	rs326222	1.13 (0.68, 1.87)	1.69 (0.98, 2.92)	1.67 (1.00, 2.80)	1.34 (0.80, 2.23)	1.15 (0.69, 1.93)	1.15 (0.67, 1.98)	1.29 (0.76, 2.18)	0.96 (0.52, 1.78)	1.07 (0.56, 2.06)
	rs901746	1.13 (0.68, 1.88)	1.69 (0.98, 2.93)	1.67 (1.00, 2.81)	1.34 (0.80, 2.24)	1.15 (0.69, 1.93)	1.16 (0.67, 1.99)	1.29 (0.76, 2.19)	0.97 (0.52, 1.79)	1.08 (0.56, 2.06)
ERCC5										
(XPG)	rs2296147	0.75 (0.44, 1.27)	1.28 (0.66, 2.50)	1.31 (0.77, 2.22)	1.20 (0.65, 2.23)	0.86 (0.50, 1.48)	1.02 (0.56, 1.85)	0.88 (0.49, 1.56)	0.81 (0.39, 1.69)	0.74 (0.39, 1.40)
	rs4771436	1.28 (0.78, 2.11)	1.89 (1.16, 3.08)	1.53 (0.85, 2.77)	1.02 (0.73, 1.97)	1.47 (0.87, 2.47)	1.24 (0.74, 2.07)	1.36 (0.78, 2.40)	1.15 (0.64, 2.06)	0.94 (0.47, 1.90)
	rs1047768	1.36 (0.79, 2.36)	1.79 (0.95, 3.37)	2.10 (1.16, 3.79)	1.26 (0.66, 2.40)	1.56 (0.88, 2.75)	1.29 (0.67, 2.48)	1.53 (0.84, 2.79)	1.34 (0.63, 2.82)	1.12 (0.57, 2.18)
	rs3818356	1.29 (0.78, 2.13)	1.90 (1.16, 3.09)	1.53 (0.85, 2.77)	1.20 (0.73, 1.98)	1.47 (0.87, 2.47)	1.25 (0.75, 2.09)	1.34 (0.76, 2.36)	1.14 (0.63, 2.06)	0.95 (0.47, 1.90)
	rs4150351	0.94 (0.56, 1.58)	2.01 (1.24, 3.24)	1.09 (0.63, 1.87)	1.21 (0.77, 1.91)	0.92 (0.52, 1.63)	1.07 (0.65, 1.76)	1.15 (0.68, 1.94)	0.90 (0.52, 1.56)	0.96 (0.47, 1.95)
	rs4150355	0.73 (0.44, 1.21)	1.07 (0.61, 1.89)	1.54 (0.94, 2.54)	1.08 (0.62, 1.86)	0.94 (0.58, 1.54)	1.17 (0.69, 1.98)	0.78 (0.45, 1.36)	0.77 (0.40, 1.48)	0.86 (0.46, 1.59)
	rs4150360	1.40 (0.78, 2.50)	1.63 (0.81, 3.29)	2.27 (1.23, 4.19)	1.49 (0.75, 2.95)	1.51 (0.83, 2.75)	1.37 (0.68, 2.74)	1.53 (0.82, 2.88)	1.43 (0.64, 3.19)	1.14 (0.57, 2.27)
	rs4150383	1.54 (0.93, 2.55)	1.96 (1.24, 3.11)	1.54 (0.84, 2.85)	1.27 (0.79, 2.03)	1.58 (0.93, 2.69)	1.34 (0.82, 2.19)	1.38 (0.78, 2.45)	1.24 (0.70, 2.18)	0.93 (0.45, 1.90)
	rs4150386	1.22 (0.64, 2.31)	1.53 (1.00, 2.36)	2.07 (1.15, 3.70)	1.14 (0.75, 1.72)	1.64 (0.88, 3.07)	1.12 (0.72, 1.77)	1.50 (0.81, 2.77)	1.06 (0.62, 1.79)	0.79 (0.39, 1.63)
	rs17655	1.05 (0.62, 1.78)	1.39 (0.86, 2.24)	2.03 (1.21, 3.41)	1.12 (0.70, 1.78)	1.27 (0.77, 2.10)	1.14 (0.70, 1.87)	1.19 (0.71, 2.01)	0.99 (0.55, 1.77)	0.91 (0.48, 1.71)
	rs873601	0.92 (0.55, 1.53)	1.36 (0.81, 2.27)	1.73 (1.04, 2.86)	1.02 (0.62, 1.69)	1.23 (0.76, 1.99)	1.08 (0.64, 1.82)	1.13 (0.68, 1.88)	1.12 (0.62, 2.03)	0.73 (0.39, 1.38)
	rs4150393	0.98 (0.56, 1.69)	1.89 (1.22, 2.95)	0.99 (0.54, 1.83)	1.24 (0.81, 1.89)	0.81 (0.41, 1.59)	1.07 (0.67, 1.71)	1.29 (0.74, 2.25)	0.83 (0.49, 1.42)	1.41 (0.66, 2.98)
	rs876430	0.92 (0.55, 1.53)	1.36 (0.81, 2.27)	1.73 (1.04, 2.86)	1.02 (0.62, 1.69)	1.23 (0.76, 1.99)	1.10 (0.65, 1.86)	1.10 (0.66, 1.84)	1.12 (0.62, 2.03)	0.73 (0.39, 1.38)
	rs1051677	0.84 (0.46, 1.54)	1.32 (0.84, 2.07)	1.97 (1.17, 3.31)	1.25 (0.83, 1.86)	0.46 (0.18, 1.18)	1.14 (0.73, 1.78)	0.97 (0.53, 1.79)	0.85 (0.51, 1.44)	1.22 (0.58, 2.57)
	rs1051685	0.96 (0.53, 1.73)	1.58 (1.03, 2.41)	1.37 (0.70, 2.70)	1.08 (0.70, 1.67)	1.40 (0.79, 2.45)	1.11 (0.70, 1.75)	1.19 (0.63, 2.21)	0.91 (0.54, 1.55)	1.01 (0.45, 2.28)
ERCC4										
(XPF)	rs3136038	0.63 (0.38, 1.04)	1.20 (0.70, 2.06)	1.30 (0.80, 2.12)	1.16 (0.72, 1.88)	0.73 (0.44, 1.22)	1.10 (0.67, 1.83)	0.74 (0.44, 1.25)	0.76 (0.39, 1.46)	0.74 (0.41, 1.33)
	rs1799798	0.85 (0.45, 1.62)	1.55 (1.02, 2.35)	1.39 (0.65, 2.95)	1.10 (0.72, 1.67)	1.30 (0.73, 2.33)	1.16 (0.74, 1.83)	0.89 (0.45, 1.78)	0.98 (0.59, 1.64)	0.61 (0.21, 1.77)
	rs744154	1.00 (0.60, 1.66)	1.59 (0.97, 2.63)	1.58 (0.95, 2.63)	1.39 (0.86, 2.22)	0.95 (0.57, 1.59)	1.36 (0.84, 2.22)	0.91 (0.54, 1.55)	0.88 (0.47, 1.67)	0.99 (0.55, 1.79)
	rs3136085	0.99 (0.59, 1.64)	1.51 (0.91, 2.50)	1.65 (1.00, 2.72)	1.36 (0.85, 2.18)	0.96 (0.58, 1.60)	1.37 (0.84, 2.23)	0.90 (0.53, 1.52)	0.92 (0.49, 1.74)	0.96 (0.53, 1.73)
	rs3136130	0.62 (0.38, 1.03)	1.15 (0.67, 1.98)	1.32 (0.81, 2.14)	1.19 (0.73, 1.92)	0.70 (0.42, 1.17)	1.11 (0.67, 1.85)	0.73 (0.43, 1.23)	0.76 (0.40, 1.47)	0.73 (0.41, 1.32)
	rs1800067	1.31 (0.70, 2.45)	1.58 (1.04, 2.41)	2.26 (1.16, 4.40)	1.28 (0.85, 1.94)	1.00 (0.53, 1.91)	1.26 (0.81, 1.97)	0.86 (0.41, 1.78)	0.98 (0.58, 1.64)	1.07 (0.47, 2.41)
	rs3136172	1.05 (0.64, 1.74)	1.51 (0.90, 2.54)	1.72 (1.04, 2.85)	1.38 (0.85, 2.25)	1.02 (0.61, 1.69)	1.37 (0.83, 2.27)	0.97 (0.57, 1.64)	0.98 (0.52, 1.87)	0.95 (0.53, 1.72)
RAD23A	rs2974752	0.67 (0.40, 1.12)	1.49 (0.84, 2.63)	1.15 (0.68, 1.95)	0.81 (0.44, 1.49)	0.93 (0.56, 1.56)	0.59 (0.32, 1.09)	1.06 (0.61, 1.82)	0.62 (0.30, 1.28)	0.77 (0.42, 1.42)

HR hazards ratio, CI confidence interval

a) HRs adjusted for matching factors (age and sex, including pairwise interactions), stage, anatomic site, ancestry (% African ancestry), education, cigarette smoking, and alcohol drinking
Highlighting indicates RERI significant at 0.05 level. Asterisks indicate RERI significant at a Bonferroni corrected level (0.05/84=0.0006).

Table 8S cont. Hazard Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Treatment on Overall Survival among Head and Neck Cancer Cases in the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, Whites

		HR (95% CI)[a]								
Gene	**SNP**	**Surgery, Variant Genotype**	**Radiation, Referent Genotype**	**Radiation, Variant Genotype**	**Surgery and Radiation, Referent Genotype**	**Surgery and Radiation, Variant Genotype**	**Radiation and Chemotherapy, Referent Genotype**	**Radiation and Chemotherapy, Variant Genotype**	**Surgery, Radiation and Chemotherapy, Referent Genotype**	**Surgery, Radiation, and Chemotherapy, Variant Genotype**
ERCC2										
(XPD)	rs13181	1.20 (0.71, 2.03)	1.50 (0.83, 2.73)	1.88 (1.07, 3.30)	1.48 (0.84, 2.59)	1.16 (0.67, 2.01)	1.34 (0.74, 2.43)	1.19 (0.67, 2.12)	0.74 (0.34, 1.57)	1.19 (0.64, 2.23)
	rs238418	1.17 (0.70, 1.96)	1.56 (0.87, 2.81)	1.91 (1.10, 3.32)	1.50 (0.86, 2.61)	1.13 (0.66, 1.95)	1.33 (0.74, 2.41)	1.21 (0.68, 2.13)	0.80 (0.38, 1.67)	1.19 (0.64, 2.22)
	rs1799787	1.09 (0.66, 1.81)	1.56 (0.92, 2.66)	1.78 (1.04, 3.03)	1.31 (0.78, 2.19)	1.15 (0.68, 1.95)	1.40 (0.81, 2.42)	1.04 (0.60, 1.80)	0.80 (0.41, 1.56)	1.21 (0.66, 2.24)
	rs3916874	0.68 (0.41, 1.14)	1.51 (0.93, 2.44)	1.13 (0.67, 1.90)	1.04 (0.65, 1.68)	0.90 (0.55, 1.48)	0.98 (0.59, 1.62)	0.95 (0.57, 1.58)	0.79 (0.44, 1.42)	0.80 (0.43, 1.51)
	rs238416	1.09 (0.65, 1.81)	1.78 (1.01, 3.13)	1.57 (0.92, 2.69)	0.99 (0.55, 1.78)	1.37 (0.82, 2.27)	1.13 (0.64, 2.00)	1.26 (0.73, 2.17)	1.22 (0.63, 2.37)	0.86 (0.46, 1.63)
	rs50872	0.71 (0.42, 1.19)	1.28 (0.77, 2.11)	1.84 (1.11, 3.07)	0.95 (0.59, 1.54)	1.03 (0.61, 1.73)	0.95 (0.57, 1.59)	0.98 (0.58, 1.66)	0.87 (0.49, 1.54)	0.64 (0.31, 1.30)
	rs50871	1.20 (0.65, 2.20)	1.72 (0.85, 3.48)	1.81 (0.97, 3.37)	2.19 (1.10, 4.34)	1.11 (0.60, 2.05)	1.48 (0.73, 2.96)	1.24 (0.66, 2.35)	1.04 (0.44, 2.43)	1.10 (0.55, 2.19)
	rs238407	0.65 (0.38, 1.11)	1.26 (0.65, 2.47)	1.30 (0.74, 2.27)	0.76 (0.41, 1.43)	0.89 (0.52, 1.53)	0.97 (0.51, 1.84)	0.80 (0.45, 1.40)	0.80 (0.39, 1.63)	0.61 (0.32, 1.17)
	rs3810366	0.85 (0.45, 1.61)	0.95 (0.40, 2.30)	1.49 (0.77, 2.86)	1.09 (0.50, 2.39)	1.00 (0.52, 1.91)	1.29 (0.60, 2.80)	0.94 (0.48, 1.84)	0.81 (0.33, 1.97)	0.83 (0.40, 1.73)
ERCC1	rs735482	1.19 (0.64, 2.18)	1.55 (1.01, 2.39)	1.93 (1.07, 3.51)	1.21 (0.78, 1.86)	1.22 (0.72, 2.07)	1.10 (0.70, 1.75)	1.45 (0.84, 2.51)	1.02 (0.60, 1.74)	0.91 (0.46, 1.84)
	rs2336219	1.19 (0.64, 2.18)	1.55 (1.01, 2.39)	1.93 (1.07, 3.51)	1.21 (0.78, 1.86)	1.22 (0.72, 2.07)	1.10 (0.70, 1.75)	1.45 (0.84, 2.51)	1.02 (0.60, 1.74)	0.91 (0.46, 1.84)
	rs3212964	1.19 (0.65, 2.19)	1.55 (1.01, 2.39)	1.93 (1.06, 3.51)	1.21 (0.79, 1.86)	1.22 (0.72, 2.07)	1.09 (0.69, 1.72)	1.51 (0.87, 2.60)	1.05 (0.62, 1.79)	0.85 (0.41, 1.74)
	rs3212955	1.07 (0.65, 1.76)	1.57 (0.93, 2.65)	1.71 (1.00, 2.91)	1.13 (0.69, 1.86)	1.33 (0.78, 2.26)	1.16 (0.68, 1.95)	1.25 (0.71, 2.18)	0.79 (0.42, 1.48)	1.32 (0.70, 2.49)
	rs3212948	1.11 (0.67, 1.85)	1.55 (0.87, 2.78)	1.77 (1.03, 3.04)	1.25 (0.71, 2.19)	1.23 (0.72, 2.09)	1.26 (0.71, 2.25)	1.19 (0.68, 2.08)	0.89 (0.43, 1.84)	1.08 (0.58, 2.02)
	rs3212930	0.79 (0.48, 1.31)	1.54 (0.95, 2.48)	1.26 (0.73, 2.18)	1.14 (0.72, 1.81)	0.91 (0.53, 1.56)	1.04 (0.64, 1.69)	1.03 (0.60, 1.79)	0.70 (0.39, 1.26)	1.21 (0.64, 2.29)
LIG1	rs156641	0.85 (0.51, 1.43)	1.39 (0.78, 2.45)	1.44 (0.84, 2.47)	0.84 (0.46, 1.53)	1.17 (0.70, 1.97)	0.90 (0.50, 1.63)	1.12 (0.65, 1.93)	0.87 (0.46, 1.66)	0.83 (0.42, 1.62)
	rs20580	1.15 (0.61, 2.17)	1.51 (0.72, 3.15)	1.87 (0.97, 3.61)	1.01 (0.46, 2.22)	1.38 (0.72, 2.64)	1.17 (0.55, 2.51)	1.28 (0.65, 2.51)	1.15 (0.52, 2.58)	0.99 (0.47, 2.09)
	rs20579	0.95 (0.54, 1.66)	1.68 (1.07, 2.63)	1.32 (0.72, 2.41)	1.28 (0.84, 1.95)	0.76 (0.40, 1.47)	1.07 (0.68, 1.70)	1.34 (0.77, 2.31)	1.02 (0.60, 1.74)	0.70 (0.31, 1.55)

HR hazards ratio, CI confidence interval

a) HRs adjusted for matching factors (age and sex, including pairwise interactions), stage, anatomic site, ancestry (% African ancestry), education, cigarette smoking, and alcohol drinking
Highlighting indicates RERI significant at 0.05 level. Asterisks indicate RERI significant at a Bonferroni corrected level (0.05/84=0.0006).

Table 8S cont. Hazard Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Treatment on Overall Survival among Head and Neck Cancer Cases in the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, Whites

		RERI (95% CI)[a]			
Gene	SNP	Radiation x SNP	Radiation and Surgery x SNP	Radiation and Chemotherapy x SNP	Surgery, Radiation and Chemotherapy x SNP
ERCC3 (XPB)	rs4150496	0.42 (-0.33, 1.16)	0.23 (-0.35, 0.81)	0.30 (-0.25, 0.84)	-0.29 (-1.09, 0.52)
	rs1011019	-0.29 (-1.25, 0.67)	0.07 (-0.62, 0.76)	0.29 (-0.35, 0.92)	0.65 (-0.06, 1.36)
	rs4150434	0.81 (-0.02, 1.65)	0.11 (-0.54, 0.75)	0.27 (-0.32, 0.86)	0.43 (-0.24, 1.11)
	rs4150416	-0.25 (-1.3, 0.80)	-0.08 (-0.87, 0.72)	0.10 (-0.63, 0.82)	0.45 (-0.34, 1.24)
	rs4150407	0.57 (-0.23, 1.37)	0.16 (-0.52, 0.84)	-0.03 (-0.74, 0.69)	-0.61 (-1.66, 0.45)
	rs4150403	-0.91 (-2.13, 0.32)	-0.24 (-1.25, 0.78)	0.24 (-0.82, 1.30)	-0.45 (-1.49, 0.59)
	rs4150402	-0.29 (-1.25, 0.67)	0.07 (-0.62, 0.76)	0.29 (-0.35, 0.92)	0.65 (-0.06, 1.36)
XPC	rs2228001	0.24 (-0.71, 1.18)	0.49 (-0.19, 1.16)	-0.01 (-0.74, 0.72)	0.06 (-0.78, 0.89)
	rs3731143	2.19 (0, 4.37)	0.25 (-0.94, 1.43)	-0.18 (-1.19, 0.84)	-0.34 (-1.46, 0.78)
	rs2228000	-0.01 (-0.93, 0.90)	0.06 (-0.65, 0.77)	0.21 (-0.44, 0.85)	0.01 (-0.76, 0.79)
	rs3731124	-0.12 (-1.03, 0.78)	-0.38 (-1.15, 0.38)	0.63 (0.02, 1.24)	0.12 (-0.61, 0.84)
	rs13099160	-0.03 (-1.45, 1.39)	-0.37 (-1.49, 0.74)	0.68 (-0.65, 2.01)	0.09 (-1.18, 1.35)
	rs3731093	0.41 (-0.90, 1.72)	-0.13 (-1.12, 0.86)	0.42 (-0.68, 1.53)	-0.30 (-1.30, 0.70)
	rs3731089	0.51 (-0.80, 1.81)	-0.18 (-1.14, 0.78)	0.6 (-0.51, 1.72)	-0.27 (-1.26, 0.71)
	rs2733537	0.21 (-0.64, 1.06)	0.14 (-0.53, 0.82)	0.39 (-0.20, 0.98)	-0.09 (-0.85, 0.67)
	rs3731068	-0.42 (-1.4, 0.57)	-0.45 (-1.24, 0.35)	0.75 (0, 1.50)	0.23 (-0.57, 1.03)
	rs2607755	0.37 (-0.47, 1.21)	-0.12 (-0.88, 0.65)	0.61 (0.13, 1.09)	0.20 (-0.49, 0.89)
	rs1902658	0.35 (-0.51, 1.22)	-0.24 (-1.08, 0.60)	0.58 (0.09, 1.08)	0.19 (-0.53, 0.90)
ERCC8	rs3117	0.62 (-0.38, 1.62)	0.24 (-0.55, 1.03)	0.15 (-0.61, 0.92)	-0.06 (-0.97, 0.86)
CDK7	rs2972388	1.07 (0.55, 1.60)*	0.43 (-0.07, 0.92)	0.72 (0.33, 1.10)*	-0.01 (-0.72, 0.70)
XPA	rs3176757	-0.58 (-1.59, 0.42)	-0.03 (-0.78, 0.73)	0.33 (-0.38, 1.04)	-0.08 (-0.89, 0.73)
	rs3176748	0.23 (-0.62, 1.09)	-0.14 (-1.07, 0.79)	0.06 (-0.59, 0.71)	0.56 (-0.16, 1.28)
	rs2808667	-0.02 (-1.01, 0.97)	0.59 (-0.33, 1.50)	0.32 (-0.56, 1.19)	0.37 (-0.65, 1.39)
	rs2805835	0.38 (-0.85, 1.62)	0.24 (-0.76, 1.24)	-0.37 (-1.33, 0.59)	-1.09 (-2.12, -0.06)
	rs3176689	-0.75 (-1.85, 0.35)	-0.23 (-1.05, 0.60)	-0.02 (-0.79, 0.75)	-0.66 (-1.58, 0.26)
	rs3176683	-0.63 (-2.19, 0.94)	-0.96 (-2.08, 0.16)	-0.48 (-1.56, 0.61)	-0.38 (-1.67, 0.92)
	rs3176658	0.33 (-0.55, 1.20)	0.41 (-0.23, 1.05)	0.44 (-0.26, 1.13)	0.75 (-0.04, 1.53)
	rs1800975	0.03 (-0.76, 0.82)	0.14 (-0.45, 0.72)	0.59 (0.11, 1.07)	0.33 (-0.27, 0.93)
RAD23B	rs1805330	-0.59 (-2.06, 0.88)	-0.33 (-1.57, 0.90)	-0.01 (-1.26, 1.23)	0.25 (-1.11, 1.61)
	rs1805329	0.16 (-0.73, 1.05)	-0.05 (-0.75, 0.65)	0.24 (-0.41, 0.89)	-0.11 (-0.88, 0.66)
ERCC6	rs2228529	0.04 (-0.91, 0.99)	-0.13 (-0.88, 0.61)	0.63 (-0.09, 1.35)	-0.36 (-1.18, 0.47)
	rs2228527	-0.02 (-0.99, 0.95)	-0.17 (-0.93, 0.58)	0.55 (-0.16, 1.27)	-0.42 (-1.26, 0.43)
	rs4253132	0.68 (-0.45, 1.81)	0.20 (-0.66, 1.05)	-0.12 (-0.87, 0.64)	0.08 (-0.81, 0.97)
	rs2228528	0.07 (-0.15, 1.56)	0.59 (-0.08, 1.26)	0.29 (-0.35, 0.94)	0.34 (-0.34, 1.03)

HR hazards ratio, CI confidence interval

a) HRs adjusted for matching factors (age and sex, including pairwise interactions), stage, anatomic site, ancestry (% African ancestry), education, cigarette smoking, and alcohol drinking.

Highlighting indicates RERI significant at 0.05 level. Asterisks indicate RERI significant at a Bonferroni corrected level (0.05/84=0.0006).

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		RERI (95% CI)[a]			
Gene	**SNP**	**Radiation x SNP**	**Radiation and Surgery x SNP**	**Radiation and Chemotherapy x SNP**	**Surgery, Radiation and Chemotherapy x SNP**
DDB2 (XPE)	rs2029298	0.51 (-0.22, 1.24)	0.36 (-0.20, 0.93)	0.33 (-0.22, 0.88)	0.52 (-0.08, 1.13)
	rs4647709	0.17 (-1.04, 1.39)	0.36 (-0.69, 1.42)	0.06 (-0.82, 0.94)	1.1 (-0.25, 2.45)
	rs2291120	-1.07 (-2.19, 0.04)	0.87 (-0.16, 1.90)	-0.07 (-0.92, 0.78)	0 (-0.95, 0.95)
	rs1685404	-0.25 (-1.22, 0.72)	-0.10 (-0.85, 0.66)	0.35 (-0.28, 0.98)	0.14 (-0.61, 0.89)
	rs2957873	0.01 (-1.04, 1.06)	-0.02 (-0.83, 0.79)	0.15 (-0.63, 0.92)	-0.17 (-1.07, 0.73)
	rs326224	0.50 (-0.53, 1.52)	0.15 (-0.58, 0.87)	0.58 (-0.17, 1.33)	0.07 (-0.76, 0.90)
	rs2306353	0.66 (-0.42, 1.74)	0.10 (-0.63, 0.83)	0.57 (-0.18, 1.32)	0.17 (-0.70, 1.04)
	rs326222	-0.15 (-1.15, 0.86)	-0.31 (-1.15, 0.52)	0 (-0.75, 0.76)	-0.02 (-0.87, 0.83)
	rs901746	-0.15 (-1.16, 0.86)	-0.32 (-1.16, 0.51)	0 (-0.76, 0.75)	-0.02 (-0.88, 0.83)
ERCC5 (XPG)	rs2296147	0.27 (-0.55, 1.10)	-0.09 (-0.84, 0.66)	0.12 (-0.48, 0.71)	0.17 (-0.50, 0.84)
	rs4771436	-0.64 (-1.79, 0.51)	-0.01 (-0.85, 0.84)	-0.15 (-0.98, 0.67)	-0.48 (-1.45, 0.49)
	rs1047768	-0.05 (-1.23, 1.14)	-0.07 (-1.00, 0.87)	-0.12 (-1.03, 0.78)	-0.58 (-1.75, 0.59)
	rs3818356	-0.66 (-1.82, 0.50)	-0.03 (-0.88, 0.82)	-0.20 (-1.03, 0.63)	-0.49 (-1.46, 0.48)
	rs4150351	-0.86 (-1.93, 0.20)	-0.23 (-0.99, 0.52)	0.14 (-0.52, 0.81)	0.11 (-0.69, 0.91)
	rs4150355	0.73 (0.02, 1.44)	0.13 (-0.50, 0.76)	-0.12 (-0.76, 0.52)	0.36 (-0.26, 0.97)
	rs4150360	0.24 (-0.95, 1.43)	-0.38 (-1.50, 0.73)	-0.24 (-1.23, 0.75)	-0.69 (-1.99, 0.62)
	rs4150383	-0.96 (-2.24, 0.33)	-0.22 (-1.21, 0.78)	-0.49 (-1.48, 0.49)	-0.85 (-1.97, 0.26)
	rs4150386	0.31 (-1.00, 1.62)	0.29 (-0.88, 1.46)	0.15 (-0.92, 1.23)	-0.48 (-1.50, 0.54)
	rs17655	0.60 (-0.43, 1.62)	0.11 (-0.66, 0.87)	0.01 (-0.73, 0.75)	-0.12 (-0.95, 0.71)
	rs873601	0.45 (-0.43, 1.33)	0.29 (-0.38, 0.95)	0.13 (-0.52, 0.78)	-0.30 (-1.12, 0.51)
	rs4150393	-0.88 (-1.92, 0.17)	-0.41 (-1.24, 0.43)	0.24 (-0.54, 1.01)	0.60 (-0.47, 1.66)
	rs876430	0.45 (-0.43, 1.33)	0.29 (-0.38, 0.95)	0.08 (-0.58, 0.74)	-0.30 (-1.12, 0.51)
	rs1051677	0.81 (-0.20, 1.81)	-0.63 (-1.44, 0.18)	-0.01 (-0.76, 0.73)	0.53 (-0.44, 1.49)
	rs1051685	-0.16 (-1.25, 0.93)	0.36 (-0.51, 1.23)	0.12 (-0.70, 0.95)	0.15 (-0.81, 1.10)
ERCC4 (XPF)	rs3136038	0.48 (-0.21, 1.16)	-0.06 (-0.66, 0.54)	0.01 (-0.55, 0.57)	0.35 (-0.22, 0.93)
	rs1799798	-0.02 (-1.19, 1.16)	0.35 (-0.50, 1.20)	-0.12 (-0.95, 0.71)	-0.22 (-1.15, 0.70)
	rs744154	-0.01 (-0.95, 0.93)	-0.43 (-1.23, 0.37)	-0.45 (-1.21, 0.32)	0.11 (-0.65, 0.88)
	rs3136085	0.15 (-0.77, 1.06)	-0.38 (-1.17, 0.40)	-0.46 (-1.23, 0.31)	0.05 (-0.73, 0.82)
	rs3136130	0.55 (-0.12, 1.22)	-0.11 (-0.72, 0.51)	-0.01 (-0.57, 0.55)	0.35 (-0.23, 0.92)
	rs1800067	0.37 (-1.22, 1.96)	-0.59 (-1.65, 0.46)	-0.72 (-1.79, 0.35)	-0.22 (-1.38, 0.94)
	rs3136172	0.16 (-0.77, 1.09)	-0.42 (-1.23, 0.40)	-0.46 (-1.25, 0.33)	-0.08 (-0.90, 0.73)
RAD23A	rs2974752	0 (-0.82, 0.81)	0.45 (-0.09, 0.98)	0.80 (0.36, 1.24)*	0.48 (-0.06, 1.03)

HR hazards ratio, CI confidence interval

a) HRs adjusted for matching factors (age and sex, including pairwise interactions), stage, anatomic site, ancestry (% African ancestry), education, cigarette smoking, and alcohol drinking

Highlighting indicates RERI significant at 0.05 level. Asterisks indicate RERI significant at a Bonferroni corrected level (0.05/84=0.0006).

Table 8S cont. Hazard Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Treatment on Overall Survival among Head and Neck Cancer Cases in the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, Whites

		RERI (95% CI)[a]			
Gene	**SNP**	**Radiation x SNP**	**Radiation and Surgery x SNP**	**Radiation and Chemotherapy x SNP**	**Surgery, Radiation and Chemotherapy x SNP**
ERCC2 (XPD)	rs13181	0.17 (-0.82, 1.17)	-0.52 (-1.48, 0.43)	-0.35 (-1.24, 0.53)	0.25 (-0.54, 1.05)
	rs238418	0.18 (-0.82, 1.17)	-0.54 (-1.48, 0.41)	-0.30 (-1.15, 0.56)	0.23 (-0.57, 1.02)
	rs1799787	0.12 (-0.84, 1.09)	-0.25 (-1.06, 0.56)	-0.46 (-1.30, 0.39)	0.31 (-0.47, 1.09)
	rs3916874	-0.06 (-0.84, 0.73)	0.18 (-0.41, 0.77)	0.29 (-0.24, 0.83)	0.33 (-0.28, 0.95)
	rs238416	-0.29 (-1.33, 0.75)	0.29 (-0.41, 1.00)	0.04 (-0.68, 0.76)	-0.45 (-1.40, 0.51)
	rs50872	0.86 (0.01, 1.70)	0.37 (-0.22, 0.95)	0.32 (-0.23, 0.87)	0.06 (-0.59, 0.71)
	rs50871	-0.11 (-1.29, 1.07)	-1.28 (-2.87, 0.31)	-0.43 (-1.47, 0.62)	-0.14 (-1.17, 0.90)
	rs238407	0.39 (-0.40, 1.18)	0.48 (-0.02, 0.98)	0.18 (-0.41, 0.77)	0.16 (-0.47, 0.79)
	rs3810366	0.69 (-0.11, 1.48)	0.06 (-0.78, 0.90)	-0.21 (-1.16, 0.75)	0.17 (-0.62, 0.97)
ERCC1	rs735482	0.19 (-1.06, 1.45)	-0.17 (-1.10, 0.76)	0.16 (-0.75, 1.08)	-0.29 (-1.28, 0.69)
	rs2336219	0.19 (-1.06, 1.45)	-0.17 (-1.10, 0.76)	0.16 (-0.75, 1.08)	-0.29 (-1.28, 0.69)
	rs3212964	0.19 (-1.06, 1.44)	-0.18 (-1.10, 0.75)	0.23 (-0.70, 1.15)	-0.40 (-1.39, 0.59)
	rs3212955	0.06 (-0.90, 1.03)	0.12 (-0.63, 0.88)	0.02 (-0.70, 0.74)	0.45 (-0.36, 1.26)
	rs3212948	0.11 (-0.86, 1.08)	-0.13 (-0.93, 0.68)	-0.18 (-0.96, 0.60)	0.08 (-0.73, 0.89)
	rs3212930	-0.07 (-0.92, 0.79)	-0.02 (-0.69, 0.64)	0.2 (-0.39, 0.80)	0.72 (-0.01, 1.45)
LIG1	rs156641	0.20 (-0.62, 1.02)	0.48 (-0.10, 1.06)	0.36 (-0.20, 0.92)	0.10 (-0.59, 0.80)
	rs20580	0.21 (-0.81, 1.23)	0.22 (-0.61, 1.04)	-0.04 (-0.93, 0.84)	-0.31 (-1.38, 0.75)
	rs20579	-0.31 (-1.35, 0.73)	-0.46 (-1.28, 0.36)	0.32 (-0.45, 1.08)	-0.27 (-1.12, 0.58)

HR hazards ratio, CI confidence interval

a) HRs adjusted for matching factors (age and sex, including pairwise interactions), stage, anatomic site, ancestry (% African ancestry), education, cigarette smoking, and alcohol drinking

Highlighting indicates RERI significant at 0.05 level. Asterisks indicate RERI significant at a Bonferroni corrected level (0.05/84=0.0006).

Table 9S. Hazard Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Platinum-Based Chemotherapy on Overall Survival among Head and Neck Cancer Cases in the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, Whites

		Coded Allele		Died/Alive								HR (95% CI)[a]			
Gene	SNP	Referent (A) / Variant (B)		No Platinum-Based Chemotherapy, Referent Genotype		No Platinum-Based Chemotherapy, Variant Genotype		Platinum-Based Chemotherapy, Referent Genotype		Platinum-Based Chemotherapy, Variant Genotype		No Platinum-Based Chemotherapy, Variant Genotype	Platinum-Based Chemotherapy, Referent Genotype	Platinum-Based Chemotherapy, Variant Genotype	RERI (95% CI)
ERCC3															
(XPB)	rs4150496	G	A	107	144	132	191	61	89	83	114	0.91 (0.69, 1.19)	0.74 (0.50, 1.11)	0.63 (0.44, 0.90)	-0.02 (-0.39, 0.34)
	rs1011019	C	T	125	159	114	177	66	112	78	91	0.86 (0.66, 1.13)	0.55 (0.38, 0.80)	0.78 (0.54, 1.13)	0.37 (0.05, 0.69)
	rs4150434	G	A	144	200	95	136	86	118	58	85	1.01 (0.76, 1.33)	0.69 (0.49, 0.98)	0.72 (0.49, 1.07)	0.02 (-0.35, 0.40)
	rs4150416	T	G	109	147	130	188	56	98	87	104	0.99 (0.75, 1.30)	0.58 (0.39, 0.87)	0.81 (0.56, 1.17)	0.24 (-0.11, 0.58)
	rs4150407	A	G	79	120	160	216	52	67	92	136	1.08 (0.81, 1.43)	0.89 (0.58, 1.37)	0.68 (0.47, 0.99)	-0.29 (-0.75, 0.17)
	rs4150403	G	A	188	267	51	69	115	166	29	37	0.90 (0.65, 1.26)	0.66 (0.48, 0.91)	0.84 (0.53, 1.34)	0.28 (-0.18, 0.74)
	rs4150402	G	A	125	159	114	177	66	112	78	91	0.86 (0.66, 1.13)	0.55 (0.38, 0.80)	0.78 (0.54, 1.13)	0.37 (0.05, 0.69)
XPC	rs2228001	A	C	88	131	151	204	47	71	97	132	1.27 (0.95, 1.68)	0.73 (0.48, 1.11)	0.84 (0.59, 1.22)	-0.15 (-0.60, 0.29)
	rs3731143	T	C	202	303	37	33	131	182	13	21	1.46 (0.99, 2.15)	0.77 (0.56, 1.05)	0.52 (0.28, 0.97)	-0.70 (-1.36, -0.04)
	rs2228000	C	T	131	193	107	143	82	118	61	85	0.98 (0.75, 1.28)	0.68 (0.48, 0.97)	0.71 (0.49, 1.05)	0.05 (-0.30, 0.41)
	rs3731124	A	C	142	183	97	153	73	123	71	80	0.80 (0.61, 1.06)	0.54 (0.37, 0.79)	0.75 (0.52, 1.08)	0.40 (0.10, 0.71)
	rs13099160	A	G	211	301	28	35	124	178	20	25	0.93 (0.61, 1.42)	0.66 (0.48, 0.90)	1.02 (0.61, 1.71)	0.43 (-0.19, 1.05)
	rs3731093	T	C	199	285	39	47	122	170	20	32	1.05 (0.73, 1.51)	0.69 (0.50, 0.95)	0.80 (0.48, 1.34)	0.06 (-0.48, 0.60)
	rs3731089	G	A	199	286	40	50	122	171	22	32	1.04 (0.73, 1.48)	0.68 (0.50, 0.93)	0.85 (0.52, 1.40)	0.14 (-0.40, 0.67)
	rs2733537	A	G	102	155	137	181	65	94	79	109	1.02 (0.77, 1.33)	0.67 (0.45, 0.98)	0.74 (0.51, 1.08)	0.06 (-0.30, 0.42)
	rs3731068	C	A	168	223	71	113	89	144	55	59	0.81 (0.60, 1.09)	0.56 (0.39, 0.79)	0.85 (0.58, 1.25)	0.49 (0.14, 0.84)
	rs2607755	T	C	66	81	173	255	34	61	110	142	0.82 (0.61, 1.11)	0.52 (0.32, 0.83)	0.65 (0.45, 0.94)	0.31 (-0.01, 0.62)
	rs1902658	G	A	65	76	174	260	34	60	110	142	0.80 (0.59, 1.08)	0.52 (0.32, 0.83)	0.64 (0.44, 0.93)	0.32 (0.01, 0.63)
ERCC8	rs3117	T	C	78	125	161	211	48	86	96	117	1.38 (1.03, 1.84)	0.71 (0.47, 1.10)	0.93 (0.64, 1.34)	-0.17 (-0.63, 0.30)
CDK7	rs2972388	A	G	65	92	174	244	45	64	99	139	0.99 (0.73, 1.34)	0.64 (0.41, 1.00)	0.72 (0.49, 1.06)	0.10 (-0.27, 0.47)
XPA	rs3176757	C	T	168	220	71	116	88	133	56	70	0.87 (0.65, 1.17)	0.63 (0.44, 0.89)	0.74 (0.50, 1.09)	0.24 (-0.11, 0.59)
	rs3176748	A	G	119	156	120	180	64	101	80	102	0.96 (0.73, 1.26)	0.65 (0.45, 0.94)	0.73 (0.51, 1.05)	0.13 (-0.22, 0.47)
	rs2808667	C	T	211	286	27	50	134	183	9	20	0.71 (0.46, 1.09)	0.68 (0.50, 0.92)	0.61 (0.30, 1.24)	0.22 (-0.30, 0.75)
	rs2805835	G	C	179	269	60	67	122	157	22	46	1.32 (0.97, 1.80)	0.82 (0.59, 1.12)	0.51 (0.30, 0.86)	-0.62 (-1.15, -0.10)
	rs3176689	A	T	171	224	68	112	96	131	48	72	0.85 (0.63, 1.15)	0.68 (0.49, 0.96)	0.64 (0.43, 0.95)	0.1 (-0.25, 0.46)
	rs3176683	T	C	215	294	24	42	127	182	17	21	0.80 (0.51, 1.26)	0.70 (0.51, 0.95)	0.61 (0.35, 1.06)	0.11 (-0.38, 0.60)
	rs3176658	C	T	180	244	59	92	114	161	30	42	0.85 (0.62, 1.16)	0.66 (0.48, 0.91)	0.76 (0.48, 1.20)	0.25 (-0.16, 0.67)
	rs1800975	G	A	120	141	112	181	64	95	73	99	0.75 (0.57, 0.99)	0.55 (0.37, 0.80)	0.66 (0.45, 0.96)	0.36 (0.07, 0.65)
RAD23B	rs1805330	C	T	192	275	47	61	114	183	30	20	1.27 (0.91, 1.79)	0.65 (0.47, 0.89)	1.11 (0.72, 1.71)	0.19 (-0.40, 0.78)
	rs1805329	C	T	156	209	83	127	101	124	43	79	0.91 (0.69, 1.22)	0.71 (0.51, 0.99)	0.62 (0.41, 0.94)	0 (-0.37, 0.36)

HR hazards ratio, CI confidence interval

a) HRs adjusted for matching factors (age and sex, including pairwise interactions), education, cigarette smoking, alcohol drinking, stage, ancestry (% African ancestry), surgery and/or radiation treatment.

Highlighting indicates RERI significant at 0.05 level. None significant at a Bonferroni corrected level (0.05/84=0.0006).

Table 9S cont. Hazard Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Platinum-Based Chemotherapy on Overall Survival among Head and Neck Cancer Cases in the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, Whites

		Coded Allele		Died/Alive								HR (95% CI)[a]			
Gene	SNP	Referent (A) / Variant (B)		No Platinum-Based Chemotherapy, Referent Genotype		No Platinum-Based Chemotherapy, Variant Genotype		Platinum-Based Chemotherapy, Referent Genotype		Platinum-Based Chemotherapy, Variant Genotype		No Platinum-Based Chemotherapy, Variant Genotype	Platinum-Based Chemotherapy, Referent Genotype	Platinum-Based Chemotherapy, Variant Genotype	RERI (95% CI)
ERCC6	rs2228529	A	G	158	218	79	113	94	127	48	73	0.90 (0.67, 1.21)	0.65 (0.46, 0.92)	0.72 (0.49, 1.08)	0.17 (-0.19, 0.53)
	rs2228527	A	G	157	219	82	117	94	128	50	75	0.91 (0.68, 1.22)	0.66 (0.46, 0.93)	0.72 (0.48, 1.06)	0.15 (-0.21, 0.51)
	rs4253132	T	C	184	268	55	68	110	161	34	42	1.15 (0.83, 1.59)	0.75 (0.55, 1.04)	0.62 (0.40, 0.96)	-0.29 (-0.75, 0.18)
	rs2228528	G	A	160	230	79	106	105	142	38	61	1.07 (0.80, 1.43)	0.72 (0.52, 1.01)	0.70 (0.46, 1.06)	-0.10 (-0.52, 0.33)
DDB2 (XPE)	rs2029298	A	G	104	152	135	184	66	103	78	100	1.04 (0.79, 1.37)	0.64 (0.43, 0.94)	0.79 (0.55, 1.13)	0.11 (-0.26, 0.48)
	rs4647709	C	T	201	281	38	55	116	168	28	35	1.09 (0.75, 1.59)	0.68 (0.50, 0.94)	0.87 (0.54, 1.40)	0.10 (-0.45, 0.64)
	rs2291120	T	C	177	253	62	83	106	149	38	54	1.12 (0.82, 1.52)	0.72 (0.51, 1.00)	0.74 (0.49, 1.14)	-0.09 (-0.54, 0.36)
	rs1685404	G	C	113	161	126	175	59	85	85	118	0.95 (0.72, 1.25)	0.62 (0.42, 0.92)	0.73 (0.50, 1.07)	0.17 (-0.17, 0.50)
	rs2957873	A	G	160	238	79	98	97	148	47	55	1.08 (0.81, 1.44)	0.69 (0.49, 0.97)	0.79 (0.53, 1.17)	0.02 (-0.40, 0.44)
	rs326224	G	A	174	244	65	92	105	160	39	43	1.00 (0.74, 1.35)	0.66 (0.48, 0.92)	0.83 (0.54, 1.26)	0.17 (-0.27, 0.60)
	rs2306353	G	A	176	253	63	83	105	162	39	41	1.01 (0.74, 1.37)	0.66 (0.48, 0.92)	0.85 (0.55, 1.29)	0.17 (-0.27, 0.62)
	rs326222	C	T	114	173	125	163	76	121	68	82	0.97 (0.74, 1.28)	0.64 (0.44, 0.93)	0.75 (0.52, 1.09)	0.14 (-0.21, 0.50)
	rs901746	A	G	114	174	125	162	76	121	68	82	0.97 (0.74, 1.28)	0.64 (0.44, 0.93)	0.75 (0.52, 1.09)	0.14 (-0.22, 0.50)
ERCC5 (XPG)	rs2296147	T	C	73	83	165	252	57	67	85	135	0.81 (0.60, 1.08)	0.64 (0.41, 0.98)	0.57 (0.38, 0.84)	0.12 (-0.21, 0.46)
	rs4771436	T	G	138	208	101	128	89	128	55	75	1.11 (0.84, 1.45)	0.72 (0.51, 1.01)	0.75 (0.51, 1.11)	-0.07 (-0.47, 0.32)
	rs1047768	C	T	76	125	163	211	46	72	98	131	1.21 (0.90, 1.62)	0.74 (0.47, 1.14)	0.83 (0.57, 1.21)	-0.12 (-0.56, 0.33)
	rs3818356	C	T	138	208	101	127	89	128	54	75	1.11 (0.84, 1.46)	0.72 (0.51, 1.02)	0.74 (0.50, 1.10)	-0.09 (-0.49, 0.31)
	rs4150351	A	C	162	208	77	128	92	133	52	70	0.74 (0.56, 1.00)	0.63 (0.45, 0.89)	0.63 (0.42, 0.93)	0.25 (-0.06, 0.56)
	rs4150355	C	T	101	134	138	202	76	91	68	112	0.96 (0.73, 1.26)	0.77 (0.52, 1.13)	0.62 (0.42, 0.91)	-0.11 (-0.50, 0.27)
	rs4150360	T	C	65	108	174	228	41	61	103	142	1.18 (0.87, 1.6)	0.75 (0.47, 1.20)	0.80 (0.55, 1.18)	-0.13 (-0.59, 0.33)
	rs4150383	G	A	155	237	84	99	100	138	44	65	1.17 (0.88, 1.55)	0.74 (0.53, 1.04)	0.73 (0.48, 1.09)	-0.19 (-0.62, 0.25)
	rs4150386	A	C	186	264	53	72	118	156	26	47	1.34 (0.97, 1.87)	0.74 (0.53, 1.02)	0.76 (0.48, 1.21)	-0.32 (-0.89, 0.24)
	rs17655	C	G	143	212	96	124	80	120	64	83	1.17 (0.88, 1.54)	0.75 (0.52, 1.06)	0.75 (0.51, 1.10)	-0.16 (-0.58, 0.25)
	rs873601	A	G	122	177	117	159	68	97	76	106	1.10 (0.84, 1.45)	0.78 (0.53, 1.13)	0.70 (0.48, 1.02)	-0.18 (-0.58, 0.23)
	rs4150393	A	G	188	246	51	90	108	160	36	43	0.73 (0.53, 1.01)	0.62 (0.45, 0.86)	0.74 (0.48, 1.15)	0.39 (0.03, 0.76)
	rs876430	C	T	122	177	117	159	69	97	75	106	1.10 (0.84, 1.45)	0.79 (0.54, 1.15)	0.69 (0.48, 1.00)	-0.20 (-0.61, 0.21)
	rs1051677	T	C	187	266	52	69	116	166	28	37	0.95 (0.68, 1.32)	0.71 (0.52, 0.97)	0.63 (0.39, 1.02)	-0.02 (-0.45, 0.40)
	rs1051685	A	G	186	267	53	68	116	167	28	36	1.05 (0.76, 1.45)	0.70 (0.51, 0.96)	0.74 (0.47, 1.19)	-0.01 (-0.47, 0.46)

HR hazards ratio, CI confidence interval

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		Coded Allele		Died/Alive								HR (95% CI)[a]			
Gene	SNP	Referent (A) / Variant (B)		No Platinum-Based Chemotherapy, Referent Genotype		No Platinum-Based Chemotherapy, Variant Genotype		Platinum-Based Chemotherapy, Referent Genotype		Platinum-Based Chemotherapy, Variant Genotype		No Platinum-Based Chemotherapy, Variant Genotype	Platinum-Based Chemotherapy, Referent Genotype	Platinum-Based Chemotherapy, Variant Genotype	RERI (95% CI)
ERCC4															
(XPF)	rs3136038	C	T	113	129	126	207	71	89	73	114	0.75 (0.57, 0.98)	0.68 (0.47, 0.99)	0.53 (0.37, 0.77)	0.11 (-0.20, 0.42)
	rs1799798	G	A	196	272	43	64	124	165	20	38	0.98 (0.69, 1.40)	0.73 (0.53, 1.00)	0.56 (0.32, 0.97)	-0.15 (-0.63, 0.32)
	rs744154	C	G	129	166	110	170	79	106	65	97	0.87 (0.66, 1.14)	0.73 (0.51, 1.05)	0.59 (0.40, 0.85)	-0.01 (-0.35, 0.33)
	rs3136085	G	C	126	166	113	170	79	104	65	99	0.90 (0.69, 1.19)	0.76 (0.53, 1.09)	0.59 (0.40, 0.85)	-0.07 (-0.43, 0.28)
	rs3136130	G	T	113	128	126	208	71	88	73	115	0.74 (0.56, 0.97)	0.69 (0.47, 1.00)	0.53 (0.36, 0.77)	0.10 (-0.20, 0.41)
	rs1800067	G	A	198	288	41	48	124	168	20	35	1.11 (0.78, 1.59)	0.73 (0.53, 1.00)	0.64 (0.38, 1.07)	-0.2 (-0.72, 0.32)
	rs3136172	A	G	119	163	120	173	76	100	68	103	0.94 (0.72, 1.24)	0.77 (0.53, 1.11)	0.61 (0.42, 0.89)	-0.10 (-0.47, 0.27)
RAD23A	rs2974752	A	G	90	111	142	215	45	87	93	111	0.84 (0.63, 1.12)	0.45 (0.28, 0.70)	0.72 (0.50, 1.04)	0.44 (0.15, 0.73)
ERCC2															
(XPD)	rs13181	T	G	99	141	137	194	55	86	87	116	1.00 (0.76, 1.32)	0.69 (0.46, 1.02)	0.70 (0.49, 1.02)	0.01 (-0.36, 0.39)
	rs238418	C	A	101	141	138	195	55	85	89	118	0.98 (0.75, 1.28)	0.69 (0.46, 1.02)	0.70 (0.48, 1.01)	0.03 (-0.33, 0.40)
	rs1799787	C	T	123	174	116	162	73	102	71	101	1.00 (0.77, 1.31)	0.74 (0.51, 1.07)	0.67 (0.46, 0.97)	-0.08 (-0.45, 0.29)
	rs3916874	G	C	128	162	111	174	81	106	63	97	0.78 (0.60, 1.03)	0.63 (0.43, 0.90)	0.62 (0.43, 0.90)	0.21 (-0.09, 0.51)
	rs238416	G	A	94	136	145	200	58	81	86	121	1.14 (0.87, 1.51)	0.78 (0.52, 1.16)	0.75 (0.52, 1.09)	-0.17 (-0.59, 0.25)
	rs50872	C	T	142	184	97	150	84	121	60	82	0.98 (0.74, 1.30)	0.67 (0.47, 0.95)	0.63 (0.42, 0.93)	-0.02 (-0.39, 0.34)
	rs50871	T	G	65	81	174	255	45	51	99	152	0.87 (0.64, 1.17)	0.70 (0.45, 1.10)	0.61 (0.42, 0.90)	0.05 (-0.34, 0.43)
	rs238407	A	T	76	89	163	246	45	53	99	150	0.97 (0.72, 1.30)	0.77 (0.50, 1.18)	0.59 (0.41, 0.86)	-0.15 (-0.56, 0.27)
	rs3810366	C	G	47	61	192	275	32	38	112	164	1.03 (0.72, 1.47)	0.85 (0.52, 1.42)	0.68 (0.45, 1.04)	-0.20 (-0.73, 0.33)
ERCC1	rs735482	A	C	177	256	62	80	101	154	43	49	1.10 (0.81, 1.51)	0.69 (0.49, 0.95)	0.80 (0.53, 1.20)	0.01 (-0.44, 0.45)
	rs2336219	G	A	177	256	62	80	101	154	43	49	1.10 (0.81, 1.51)	0.69 (0.49, 0.95)	0.80 (0.53, 1.20)	0.01 (-0.44, 0.45)
	rs3212964	G	A	178	257	61	79	102	155	42	48	1.10 (0.81, 1.51)	0.69 (0.50, 0.95)	0.80 (0.53, 1.21)	0.01 (-0.44, 0.46)
	rs3212955	A	G	126	187	113	149	83	132	61	71	1.14 (0.87, 1.51)	0.70 (0.49, 1.00)	0.81 (0.56, 1.19)	-0.03 (-0.44, 0.37)
	rs3212948	C	G	96	138	143	198	58	90	86	113	1.07 (0.82, 1.41)	0.74 (0.49, 1.10)	0.73 (0.51, 1.05)	-0.08 (-0.48, 0.31)
	rs3212930	T	C	147	197	92	139	94	138	50	65	0.84 (0.63, 1.11)	0.64 (0.45, 0.90)	0.69 (0.46, 1.02)	0.21 (-0.12, 0.54)
LIG1	rs156641	G	A	90	134	149	202	61	85	83	118	1.08 (0.82, 1.44)	0.69 (0.47, 1.02)	0.77 (0.53, 1.13)	0 (-0.39, 0.39)
	rs20580	C	A	57	87	182	249	40	53	104	150	1.28 (0.93, 1.77)	0.86 (0.54, 1.37)	0.82 (0.55, 1.23)	-0.31 (-0.84, 0.22)
	rs20579	C	T	187	241	52	95	107	156	37	47	0.78 (0.56, 1.08)	0.65 (0.47, 0.91)	0.68 (0.44, 1.04)	0.25 (-0.12, 0.61)

HR hazards ratio, CI confidence interval

a) HRs adjusted for matching factors (age and sex, including pairwise interactions), education, cigarette smoking, alcohol drinking, stage, ancestry (% African ancestry), surgery and/or radiation treatment.

Highlighting indicates RERI significant at 0.05 level. None significant at a Bonferroni corrected level (0.05/84=0.0006).

APPENDIX D

AIM 2 SUPPLEMENTAL TABLES NOT REFERENCED IN CHAPTER 4

Table 5A. Hazard Ratios for Select Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and and Survival by Tumor Site among Head and Neck Cancer Cases in the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study

			Overall Deaths / Deaths from HNC / Alive						Overall Survival		Disease-Specific Survival	
Gene	**SNP**	**Tumor Site**		**AA**			**AB + BB**		**HR (95% CI)[a]**	**p-value**	**HR (95% CI)[a]**	**p-value**
Whites												
ERCC4 (XPF)	rs3136038	oral cavity	88	42	123	103	47	193	0.79 (0.59, 1.05)	0.10	0.73 (0.48, 1.11)	0.14
		pharynx	31	12	12	15	2	28	0.27 (0.12, 0.57)	0.001	0.12 (0.02, 0.66)	0.01
		larynx	65	32	83	81	34	100	1.09 (0.78, 1.52)	0.63	0.85 (0.52, 1.40)	0.53
		oral cavity b	24	12	32	40	17	33	1.66 (0.97, 2.84)	0.06	1.43 (0.66, 3.13)	0.37
		oropharynx	35	13	67	47	21	111	0.78 (0.49, 1.23)	0.28	0.89 (0.43, 1.83)	0.75
		hypopharynx	17	6	1	8	2	8	0.06 (0.01, 0.32)	0.001	0.11 (0.00, 2.96)	0.19
		HNC NOS	43	23	35	23	9	69	0.34 (0.20, 0.58)	0.0001	0.25 (0.11, 0.56)	0.001
	rs3136130	oral cavity	88	42	122	103	47	194	0.78 (0.58, 1.04)	0.09	0.72 (0.47, 1.10)	0.13
		pharynx	31	12	13	15	2	27	0.28 (0.13, 0.60)	0.001	0.13 (0.02, 0.68)	0.02
		larynx	65	32	81	81	34	102	1.06 (0.76, 1.48)	0.74	0.84 (0.51, 1.37)	0.48
		oral cavity b	24	12	32	40	17	33	1.66 (0.97, 2.84)	0.06	1.43 (0.66, 3.13)	0.37
		oropharynx	35	13	68	47	21	110	0.79 (0.50, 1.24)	0.30	0.90 (0.44, 1.87)	0.78
		hypopharynx	17	6	1	8	2	8	0.06 (0.01, 0.32)	0.001	0.11 (0.00, 2.96)	0.19
		HNC NOS	43	23	34	23	9	70	0.33 (0.19, 0.56)	5.00E-05	0.24 (0.11, 0.54)	0.001
ERCC2 (XPD)	rs50871	oral cavity	51	29	80	140	60	236	0.91 (0.66, 1.26)	0.57	0.67 (0.43, 1.05)	0.08
		pharynx	12	3	10	34	11	30	1.40 (0.64, 3.07)	0.40	2.05 (0.4, 10.35)	0.39
		larynx	47	23	42	99	43	141	0.60 (0.42, 0.87)	0.01	0.51 (0.29, 0.87)	0.01
		oral cavity b	12	6	15	52	23	50	1.14 (0.59, 2.21)	0.69	0.99 (0.39, 2.54)	0.99
		oropharynx	23	13	42	59	21	136	0.88 (0.54, 1.46)	0.63	0.50 (0.25, 1.02)	0.06
		hypopharynx	10	3	3	15	5	6	1.22 (0.40, 3.73)	0.73	0.88 (0.05, 14.72)	0.93
		HNC NOS	18	10	30	48	22	74	1.09 (0.60, 1.96)	0.78	0.84 (0.38, 1.87)	0.68
African Americans												
ERCC4 (XPF)	rs2607755	oral cavity	36	13	17	47	20	49	0.56 (0.35, 0.90)	0.02	0.69 (0.32, 1.47)	0.34
		pharynx	11	7	5	17	6	9	0.54 (0.21, 1.41)	0.21	0.35 (0.10, 1.23)	0.10
		larynx	23	7	19	28	5	44	0.73 (0.40, 1.33)	0.31	0.43 (0.13, 1.42)	0.17
		oral cavity b	15	5	2	12	4	14	0.07 (0.02, 0.24)	2.43E-05	0.09 (0.01, 0.67)	0.02
		oropharynx	17	6	7	29	14	20	1.13 (0.56, 2.28)	0.74	1.03 (0.33, 3.15)	0.96
		hypopharynx	5	4	2	9	3	5	0.30 (0.02, 4.57)	0.39		
		HNC NOS	10	5	11	14	5	19	0.74 (0.31, 1.72)	0.48	0.48 (0.13, 1.76)	0.27

HR hazards ratio, CI confidence interval, HNC head and neck cancer, NOS not otherwise specified

a) HR for dominant genetic model (AB + BB vs AA). HRs adjusted for matching factors (age, sex, including pairwise interactions) and ancestry (% African ancestry)

See Table 2S in Appendix A for ICD codes used to categorize sites.

Table 6A. Hazard Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Treatment on Overall Survival among Head and Neck Cancer Cases in the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, African Americans

		Coded Allele		Died/Alive																			
Gene	SNP	Referent (A) / Variant (B)		Surgery, Referent Genotype		Surgery, Variant Genotype		Radiation, Referent Genotype		Radiation, Variant Genotype		Surgery and Radiation, Referent Genotype		Surgery and Radiation, Variant Genotype		Radiation and Chemotherapy, Referent Genotype		Radiation and Chemotherapy, Variant Genotype		Surgery, Radiation, Chemotherapy, Referent Genotype		Surgery, Radiation, Chemotherapy, Variant Genotype	
ERCC3																							
(XPB)	rs4150496	G	A	16	15	10	15	13	16	10	15	28	21	10	11	29	22	26	14	7	9	9	3
	rs4150459	G	A	18	18	8	13	17	21	7	10	24	21	14	11	31	21	24	15	9	7	7	5
	rs1011019	C	T	10	22	16	9	16	19	8	12	19	19	19	13	35	22	20	14	12	6	4	6
	rs4150434	G	A	25	23	1	8	17	24	7	7	30	18	8	14	39	30	16	6	12	10	4	2
	rs4150416	T	G	5	11	21	20	9	9	15	22	8	11	29	21	12	12	43	24	4	2	12	10
	rs4150407	A	G	9	8	17	23	6	10	18	21	11	9	27	23	13	10	42	26	3	4	13	8
	rs4150402	G	A	10	22	16	9	16	19	8	12	19	19	19	13	35	22	20	14	12	6	4	6
XPC	rs2228001	A	C	17	22	9	9	11	16	13	15	26	24	12	8	26	19	29	17	8	8	8	4
	rs2228000	C	T	26	25	0	6	22	28	2	3	29	22	9	10	43	29	12	7	16	9	0	3
	rs3731124	A	C	23	23	3	8	20	26	4	5	33	26	5	6	46	31	9	5	13	9	3	3
	rs3731093	T	C	20	28	4	3	22	27	2	4	33	28	4	4	52	28	3	8	11	11	5	0
	rs3731089	G	A	20	28	6	3	22	27	2	4	33	28	5	4	52	28	3	8	11	11	5	1
	rs2733537	A	G	20	22	6	9	20	25	4	6	24	19	14	13	40	22	15	14	11	8	5	4
	rs2607755	T	C	9	5	17	26	6	10	18	21	15	6	23	26	27	14	28	22	12	5	4	7
	rs1902658	G	A	3	2	23	29	3	5	21	26	6	3	32	29	12	11	43	25	5	1	11	11
ERCC8	rs3117	T	C	8	13	18	18	13	15	11	16	19	13	19	19	24	10	31	26	6	2	10	10
CDK7	rs2972388	A	G	11	17	15	14	11	17	13	14	16	17	22	15	28	27	27	9	10	5	6	7
CCNH	rs2266691	A	G	24	23	2	8	21	27	3	4	33	25	5	7	47	32	8	4	12	10	4	2
	rs2266692	G	T	21	23	5	8	17	21	7	10	32	24	6	8	46	25	9	11	15	10	1	2
XPA	rs3176757	C	T	21	25	5	6	18	25	6	6	29	23	9	9	44	27	11	9	11	9	5	3
	rs3176753	T	C	18	19	8	12	18	25	6	6	30	23	8	9	42	25	13	11	12	9	4	3
	rs3176748	A	G	24	21	2	10	18	27	6	4	33	27	5	5	45	33	10	3	11	9	5	3
	rs3176658	C	T	23	26	3	5	23	24	1	7	31	27	7	5	46	33	9	3	16	9	0	3
	rs1800975	G	A	18	22	6	9	16	19	7	12	20	18	16	13	33	21	20	11	11	7	5	5
RAD23B	rs1805330	C	T	10	17	16	14	16	19	8	12	24	18	14	14	31	24	24	12	10	11	6	1
ERCC6	rs2228529	A	G	18	23	8	7	18	23	6	8	30	28	8	4	42	30	13	5	12	7	4	5
	rs2228527	A	G	17	20	9	11	17	23	7	8	30	26	8	6	37	27	18	9	11	7	5	5
	rs4253132	T	C	15	16	11	15	15	25	9	6	22	23	16	9	34	21	21	15	9	8	7	4
	rs2228528	G	A	17	24	9	7	16	19	8	12	28	25	10	7	33	26	21	10	12	10	4	2
DDB2																							
(XPE)	rs2029298	A	G	6	8	20	23	12	8	12	23	13	9	25	23	10	15	45	21	2	7	14	5
	rs1685404	G	C	20	21	6	10	11	15	13	16	21	16	17	16	27	20	28	16	6	5	10	7
	rs2957873	A	G	6	8	20	23	7	9	16	22	12	9	26	23	16	11	39	25	7	4	9	8
	rs326224	G	A	5	9	21	22	5	6	19	25	12	8	26	24	15	11	40	25	5	3	11	9
	rs2306353	G	A	8	10	18	21	10	11	14	20	15	9	23	23	19	12	36	24	7	4	9	8

HR hazards ratio, CI confidence interval

a) HRs adjusted for matching factors (age and sex, including pairwise interactions), stage, anatomic site, ancestry (% African ancestry), education, cigarette smoking, and alcohol drinking
Highlighting indicates significant at 0.05 level. None significant at a Bonferroni corrected level (0.05/79=0.0006).

Table 6A cont. Hazards Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Treatment on Overall Survival among Head and Neck Cancer Cases in the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, African Americans

		Coded Allele		Died/Alive																			
Gene	SNP	Referent (A) / Variant (B)		Surgery, Referent Genotype		Surgery, Variant Genotype		Radiation, Referent Genotype		Radiation, Variant Genotype		Surgery and Radiation, Referent Genotype		Surgery and Radiation, Variant Genotype		Radiation and Chemotherapy, Referent Genotype		Radiation and Chemotherapy, Variant Genotype		Surgery, Radiation, Chemotherapy, Referent Genotype		Surgery, Radiation, Chemotherapy, Variant Genotype	
	rs326222	C	T	1	3	25	28	5	6	19	25	6	6	32	26	11	9	44	27	3	4	13	8
	rs901746	A	G	3	5	23	26	7	6	17	25	8	6	30	26	13	9	42	27	3	4	13	8
ERCC5																							
(XPG)	rs2296147	T	C	21	20	5	11	13	23	11	8	20	20	17	12	36	21	19	15	9	7	7	5
	rs2296148	C	T	19	24	7	7	18	21	6	10	30	28	8	4	41	23	13	13	12	9	4	3
	rs4771436	T	G	21	16	5	15	20	20	4	11	22	23	16	9	37	25	18	11	8	10	8	2
	rs1047768	C	T	12	7	14	24	8	12	16	19	15	12	23	20	24	14	31	22	5	5	11	7
	rs2020915	G	A	15	26	11	5	17	20	7	11	26	17	12	15	33	29	22	7	11	9	5	3
	rs3818356	C	T	21	17	5	14	20	20	4	11	22	23	16	9	37	26	18	10	8	10	8	2
	rs4150355	C	T	20	21	6	10	16	20	8	11	26	24	12	8	42	25	13	11	12	8	4	4
	rs4150360	T	C	2	0	24	31	1	5	23	26	5	0	33	32	0	2	55	34	3	1	13	11
	rs4150383	G	A	23	22	3	9	21	23	3	8	29	25	9	7	44	30	11	6	11	10	5	2
	rs17655	C	G	3	9	23	22	6	13	18	18	15	8	23	24	14	13	41	23	6	2	10	10
	rs873601	A	G	1	4	25	27	2	5	22	26	6	2	32	30	2	4	53	32	3	1	13	11
	rs876430	C	T	1	4	25	27	2	5	22	26	6	2	32	30	3	5	52	31	3	1	13	11
	rs1051677	T	C	19	27	7	4	19	25	5	6	25	23	13	9	36	30	19	6	14	10	2	2
	rs1051685	A	G	8	9	18	22	12	13	12	18	19	11	19	21	30	21	25	15	7	7	9	5
ERCC4																							
(XPF)	rs3136038	C	T	3	9	23	22	10	9	14	22	11	10	27	22	13	16	42	20	4	4	12	8
	rs744154	C	G	19	21	7	10	16	26	8	5	23	23	15	9	41	29	14	7	12	7	4	5
	rs3136085	G	C	18	19	8	12	12	25	12	6	19	14	19	18	30	16	25	20	11	7	5	5
	rs3136091	C	G	22	27	4	4	18	28	6	3	30	27	8	5	46	31	9	5	12	10	4	2
	rs3136130	G	T	5	10	21	21	9	8	15	23	9	5	29	27	12	10	43	26	3	3	13	9
	rs3136172	A	G	18	21	8	10	16	26	8	5	23	23	15	9	40	27	15	9	12	6	4	6
	rs2020955	T	C	20	23	6	8	13	25	11	6	23	17	15	15	31	18	24	18	12	9	4	3
RAD23																							
A	rs2974752	A	G	5	11	20	20	6	4	17	27	11	12	24	19	13	11	40	21	2	5	14	7
	rs11558955	A	G	20	28	6	3	20	25	4	6	32	28	6	4	46	31	9	5	14	8	2	4
ERCC2	rs13181																						
(XPD)		T	G	11	20	15	11	14	21	10	9	20	20	18	12	31	19	24	17	8	6	8	6
	rs238418	C	A	1	1	25	30	1	1	23	30	1	7	37	24	1	1	54	35	1	0	15	12
	rs1799787	C	T	16	26	10	5	17	27	7	4	28	25	10	7	45	26	10	10	12	10	4	2
	rs3916874	G	C	22	29	4	2	22	27	2	4	33	28	5	4	49	30	6	6	14	11	2	1
	rs238416	G	A	23	21	3	10	16	24	7	7	27	29	11	3	49	31	6	5	11	8	5	4
	rs50872	C	T	17	23	9	8	17	25	7	6	27	27	11	5	41	24	14	12	11	7	5	5

HR hazards ratio, CI confidence interval

a) HRs adjusted for matching factors (age and sex, including pairwise interactions), stage, anatomic site, ancestry (% African ancestry), education, cigarette smoking, and alcohol drinking
Highlighting indicates significant at 0.05 level. None significant at a Bonferroni corrected level (0.05/79=0.0006).

Table 6A cont. Hazard Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Treatment on Overall Survival among Head and Neck Cancer Cases in the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, African Americans

		Coded Allele		Died/Alive																			
Gene	SNP	Referent (A) / Variant (B)		Surgery, Referent Genotype		Surgery, Variant Genotype		Radiation, Referent Genotype		Radiation, Variant Genotype		Surgery and Radiation, Referent Genotype		Surgery and Radiation, Variant Genotype		Radiation and Chemotherapy, Referent Genotype		Radiation and Chemotherapy, Variant Genotype		Surgery, Radiation, Chemotherapy, Referent Genotype		Surgery, Radiation, Chemotherapy, Variant Genotype	
	rs50871	T	G	19	25	7	6	16	20	8	11	25	25	13	7	46	31	9	5	13	7	3	5
	rs238407	A	T	17	23	9	8	14	23	10	8	24	27	14	5	47	30	8	6	10	8	6	4
	rs3810366	C	G	17	22	9	9	14	21	10	10	22	25	16	7	44	27	11	9	9	8	7	4
ERCC1	rs735482	A	C	13	13	13	18	13	20	11	11	20	18	18	14	25	17	30	19	10	4	6	8
	rs2336219	G	A	13	13	13	18	13	20	11	11	20	18	18	14	25	17	30	19	11	4	5	8
	rs3212964	G	A	19	18	7	13	16	24	8	7	28	25	8	7	33	20	22	16	12	8	4	4
	rs3212955	A	G	10	19	16	12	11	15	13	16	19	16	19	16	32	20	23	16	9	7	7	5
	rs3212948	C	G	0	1	36	30	0	0	24	31	3	0	35	32	1	2	54	34	1	1	15	11
	rs3212935	A	G	12	16	14	15	11	17	13	14	20	13	18	19	27	12	28	24	9	4	7	8
	rs3212930	T	C	19	25	7	6	18	25	6	6	33	28	5	4	47	30	8	6	12	10	4	2
LIG1	rs156641	G	A	19	22	7	9	17	20	7	11	29	25	9	7	48	30	7	6	13	7	3	5
	rs20580	C	A	3	6	23	25	5	5	19	25	6	5	32	27	17	11	38	25	1	2	15	10
	rs20579	C	T	9	15	17	16	13	13	11	18	21	15	17	17	33	18	22	18	7	6	9	6
	rs439132	A	G	14	17	12	14	13	15	11	16	26	21	12	11	23	23	32	13	10	7	6	5

HR hazards ratio, CI confidence interval

a) HRs adjusted for matching factors (age and sex, including pairwise interactions), stage, anatomic site, ancestry (% African ancestry), education, cigarette smoking, and alcohol drinking
Highlighting indicates significant at 0.05 level. None significant at a Bonferroni corrected level (0.05/79=0.0006).

Table 6A cont. Hazard Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Treatment on Overall Survival among Head and Neck Cancer Cases in the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, African Americans

		HR (95% CI)[a]								
Gene	**SNP**	**Surgery, Variant Genotype**	**Radiation, Referent Genotype**	**Radiation, Variant Genotype**	**Surgery and Radiation, Referent Genotype**	**Surgery and Radiation, Variant Genotype**	**Radiation and Chemotherapy, Referent Genotype**	**Radiation and Chemotherapy, Variant Genotype**	**Surgery, Radiation and Chemotherapy, Referent Genotype**	**Surgery, Radiation, and Chemotherapy, Variant Genotype**
ERCC3 (XPB)	rs4150496	0.76 (0.31, 1.84)	0.85 (0.36, 1.97)	0.78 (0.32, 1.91)	1.02 (0.51, 2.03)	0.83 (0.35, 1.96)	0.76 (0.37, 1.55)	1.16 (0.54, 2.47)	0.43 (0.16, 1.17)	1.17 (0.44, 3.14)
	rs4150459	0.59 (0.24, 1.48)	0.80 (0.37, 1.71)	0.90 (0.32, 2.57)	0.80 (0.40, 1.59)	1.13 (0.49, 2.58)	0.74 (0.35, 1.55)	0.91 (0.43, 1.92)	0.61 (0.23, 1.63)	0.58 (0.22, 1.55)
	rs1011019	1.71 (0.74, 4.00)	1.38 (0.57, 3.33)	1.20 (0.43, 3.41)	1.23 (0.53, 2.85)	1.80 (0.78, 4.15)	1.48 (0.66, 3.36)	1.07 (0.44, 2.61)	1.32 (0.51, 3.43)	0.49 (0.12, 1.94)
	rs4150434	0.20 (0.03, 1.58)	0.72 (0.34, 1.50)	1.36 (0.50, 3.65)	1.15 (0.62, 2.13)	0.58 (0.24, 1.38)	0.82 (0.44, 1.53)	0.95 (0.43, 2.08)	0.64 (0.28, 1.48)	0.75 (0.23, 2.40)
	rs4150416	1.09 (0.38, 3.12)	1.11 (0.34, 3.70)	1.02 (0.33, 3.13)	0.78 (0.23, 2.61)	1.36 (0.47, 3.88)	0.85 (0.26, 2.80)	1.18 (0.41, 3.41)	1.15 (0.27, 4.85)	0.75 (0.23, 2.48)
	rs4150407	0.68 (0.29, 1.59)	0.61 (0.19, 1.91)	0.83 (0.34, 2.06)	0.68 (0.26, 1.77)	0.90 (0.40, 2.03)	0.65 (0.25, 1.72)	0.76 (0.33, 1.74)	0.35 (0.08, 1.48)	0.64 (0.24, 1.68)
	rs4150402	1.71 (0.74, 4.00)	1.38 (0.57, 3.33)	1.20 (0.43, 3.41)	1.23 (0.53, 2.85)	1.80 (0.78, 4.15)	1.48 (0.66, 3.36)	1.07 (0.44, 2.61)	1.32 (0.51, 3.43)	0.49 (0.12, 1.94)
XPC	rs2228001	0.92 (0.38, 2.25)	0.78 (0.32, 1.89)	1.11 (0.49, 2.53)	1.01 (0.52, 1.98)	1.07 (0.47, 2.42)	0.76 (0.36, 1.60)	1.12 (0.56, 2.22)	0.75 (0.29, 1.95)	0.66 (0.25, 1.78)
	rs2228000		0.82 (0.42, 1.61)	0.60 (0.13, 2.75)	0.93 (0.51, 1.68)	0.62 (0.25, 1.53)	0.79 (0.42, 1.45)	0.80 (0.35, 1.80)	0.64 (0.30, 1.38)	
	rs3731124	0.47 (0.13, 1.62)	0.86 (0.43, 1.73)	0.94 (0.29, 3.07)	0.93 (0.50, 1.73)	0.97 (0.33, 2.82)	0.86 (0.46, 1.61)	0.81 (0.30, 2.16)	0.61 (0.27, 1.40)	0.77 (0.20, 2.94)
	rs3731093	1.68 (0.51, 5.56)	1.19 (0.59, 2.44)	0.82 (0.17, 4.06)	1.22 (0.64, 2.33)	1.50 (0.46, 4.92)	1.25 (0.65, 2.38)	0.21 (0.04, 1.06)	0.67 (0.27, 1.63)	
	rs3731089	1.91 (0.71, 5.17)	1.17 (0.58, 2.39)	0.80 (0.16, 3.93)	1.17 (0.62, 2.21)	1.72 (0.57, 5.18)	1.20 (0.63, 2.27)	0.21 (0.04, 1.03)	0.63 (0.26, 1.53)	1.79 (0.60, 5.34)
	rs2733537	0.74 (0.28, 1.96)	0.94 (0.45, 1.96)	0.82 (0.26, 2.61)	0.99 (0.50, 1.95)	0.97 (0.43, 2.16)	1.00 (0.51, 1.95)	0.65 (0.28, 1.48)	0.62 (0.25, 1.51)	0.83 (0.27, 2.56)
	rs2607755	0.31 (0.12, 0.79)	0.45 (0.14, 1.41)	0.39 (0.15, 1.04)	1.05 (0.40, 2.80)	0.28 (0.11, 0.72)	0.55 (0.21, 1.45)	0.25 (0.10, 0.68)	0.28 (0.09, 0.85)	0.21 (0.05, 0.79)
	rs1902658	0.46 (0.12, 1.72)	0.55 (0.10, 3.04)	0.50 (0.13, 1.89)	1.24 (0.27, 5.75)	0.48 (0.13, 1.78)	0.32 (0.07, 1.36)	0.53 (0.14, 2.02)	0.68 (0.13, 3.62)	0.29 (0.07, 1.24)
ERCC8	rs3117	1.33 (0.52, 3.40)	1.30 (0.47, 3.56)	1.13 (0.40, 3.19)	1.48 (0.59, 3.69)	1.20 (0.47, 3.07)	1.39 (0.54, 3.56)	1.06 (0.43, 2.66)	1.05 (0.32, 3.42)	0.82 (0.28, 2.43)
CDK7	rs2972388	1.33 (0.57, 3.08)	0.93 (0.37, 2.37)	1.52 (0.60, 3.84)	1.06 (0.46, 2.47)	1.44 (0.64, 3.24)	0.80 (0.35, 1.87)	1.76 (0.78, 4.00)	1.35 (0.47, 3.87)	0.57 (0.19, 1.72)
CCNH	rs2266691	0.41 (0.09, 1.90)	0.83 (0.41, 1.68)	0.86 (0.23, 3.20)	0.97 (0.54, 1.76)	0.68 (0.22, 2.14)	0.81 (0.43, 1.51)	1.19 (0.48, 2.95)	0.55 (0.24, 1.27)	1.23 (0.38, 3.97)
	rs2266692	0.83 (0.28, 2.44)	1.04 (0.49, 2.20)	0.86 (0.33, 2.27)	1.01 (0.55, 1.87)	1.39 (0.49, 3.92)	1.09 (0.58, 2.03)	0.61 (0.24, 1.56)	0.84 (0.38, 1.85)	0.24 (0.03, 1.87)
XPA	rs3176757	1.62 (0.55, 4.75)	0.97 (0.47, 2.01)	2.04 (0.67, 6.20)	1.15 (0.61, 2.17)	1.24 (0.53, 2.91)	1.16 (0.61, 2.20)	0.67 (0.26, 1.71)	0.75 (0.32, 1.77)	0.89 (0.30, 2.65)
	rs3176753	0.85 (0.35, 2.07)	1.00 (0.48, 2.06)	0.69 (0.21, 2.25)	1.09 (0.58, 2.05)	0.82 (0.31, 2.18)	0.86 (0.45, 1.68)	1.14 (0.49, 2.64)	0.78 (0.34, 1.84)	0.53 (0.16, 1.79)
	rs3176748	0.20 (0.04, 0.93)	0.67 (0.32, 1.38)	1.04 (0.38, 2.83)	0.85 (0.46, 1.56)	0.53 (0.18, 1.54)	0.66 (0.35, 1.26)	0.99 (0.42, 2.31)	0.48 (0.20, 1.16)	0.65 (0.22, 1.93)
	rs3176658	0.70 (0.15, 3.21)	1.15 (0.59, 2.25)	0.22 (0.03, 1.70)	0.98 (0.53, 1.79)	1.52 (0.57, 4.04)	0.87 (0.47, 1.60)	1.54 (0.61, 3.89)	0.79 (0.37, 1.70)	
	rs1800975	1.40 (0.45, 4.35)	1.16 (0.53, 2.53)	1.02 (0.36, 2.87)	1.03 (0.51, 2.09)	1.59 (0.75, 3.36)	1.11 (0.56, 2.22)	1.20 (0.55, 2.60)	0.91 (0.37, 2.21)	0.78 (0.26, 2.36)
RAD23B	rs1805330	1.45 (0.61, 3.42)	1.35 (0.54, 3.39)	1.06 (0.38, 2.98)	1.70 (0.76, 3.79)	0.97 (0.38, 2.45)	1.05 (0.46, 2.39)	1.46 (0.61, 3.48)	0.69 (0.25, 1.90)	1.85 (0.59, 5.73)
ERCC6	rs2228529	1.24 (0.48, 3.23)	0.93 (0.44, 2.01)	1.26 (0.43, 3.68)	1.07 (0.54, 2.09)	1.27 (0.50, 3.22)	0.90 (0.45, 1.82)	1.51 (0.65, 3.54)	0.92 (0.38, 2.23)	0.54 (0.16, 1.78)
	rs2228527	0.93 (0.36, 2.42)	0.89 (0.40, 1.96)	1.15 (0.41, 3.25)	1.08 (0.53, 2.18)	0.94 (0.37, 2.42)	0.83 (0.39, 1.78)	1.22 (0.55, 2.72)	0.77 (0.30, 1.94)	0.62 (0.20, 1.91)
	rs4253132	0.97 (0.42, 2.23)	0.92 (0.41, 2.07)	1.11 (0.42, 2.88)	0.92 (0.44, 1.91)	1.40 (0.64, 3.06)	0.98 (0.47, 2.04)	1.01 (0.45, 2.24)	0.58 (0.22, 1.5)	1.18 (0.41, 3.44)
	rs2228528	1.14 (0.47, 2.77)	1.10 (0.49, 2.44)	0.98 (0.37, 2.60)	0.98 (0.50, 1.91)	1.99 (0.81, 4.88)	0.82 (0.40, 1.68)	1.42 (0.65, 3.13)	0.80 (0.34, 1.89)	0.65 (0.17, 2.56)
DDB2 (XPE)	rs2029298	1.36 (0.50, 3.71)	2.20 (0.69, 7.03)	0.97 (0.33, 2.86)	1.41 (0.49, 4.01)	1.38 (0.53, 3.61)	0.88 (0.28, 2.79)	1.41 (0.53, 3.73)	0.31 (0.06, 1.62)	1.42 (0.48, 4.24)
	rs1685404	0.71 (0.27, 1.85)	0.80 (0.32, 1.99)	0.99 (0.46, 2.17)	1.20 (0.60, 2.39)	0.82 (0.39, 1.71)	0.77 (0.38, 1.56)	1.07 (0.53, 2.15)	0.55 (0.18, 1.66)	0.75 (0.31, 1.80)
	rs2957873	1.24 (0.46, 3.31)	1.30 (0.39, 4.34)	1.01 (0.35, 2.93)	1.48 (0.52, 4.20)	1.18 (0.44, 3.14)	1.00 (0.33, 3.01)	1.14 (0.44, 2.97)	0.98 (0.28, 3.44)	0.77 (0.25, 2.37)
	rs326224	2.17 (0.70, 6.76)	2.38 (0.58, 9.70)	1.62 (0.49, 5.33)	2.07 (0.63, 6.82)	1.87 (0.60, 5.81)	1.33 (0.39, 4.54)	1.87 (0.62, 5.66)	1.21 (0.27, 5.4)	1.33 (0.39, 4.56)
	rs2306353	1.24 (0.49, 3.15)	1.63 (0.56, 4.69)	0.90 (0.32, 2.54)	1.59 (0.62, 4.11)	1.06 (0.42, 2.67)	0.96 (0.35, 2.61)	1.12 (0.47, 2.71)	0.96 (0.29, 3.19)	0.76 (0.26, 2.20)
	rs326222	2.17 (0.27, 17.58)	2.29 (0.23, 22.95)	2.04 (0.24, 17.15)	3.34 (0.36, 31.39)	2.07 (0.26, 16.40)	2.23 (0.25, 19.79)	1.98 (0.24, 16.16)	0.98 (0.09, 10.77)	1.73 (0.21, 14.60)
	rs901746	1.50 (0.43, 5.30)	2.05 (0.47, 8.98)	1.27 (0.34, 4.77)	2.73 (0.66, 11.33)	1.34 (0.38, 4.69)	1.43 (0.37, 5.58)	1.32 (0.38, 4.61)	0.68 (0.12, 3.8)	1.18 (0.31, 4.52)
ERCC5 (XPG)	rs2296147	0.63 (0.23, 1.77)	0.76 (0.35, 1.64)	1.27 (0.51, 3.17)	0.78 (0.39, 1.55)	1.35 (0.66, 2.76)	0.99 (0.51, 1.93)	0.81 (0.37, 1.75)	0.76 (0.29, 1.97)	0.65 (0.25, 1.70)
	rs2296148	1.77 (0.68, 4.59)	1.18 (0.57, 2.47)	0.80 (0.25, 2.59)	1.09 (0.57, 2.07)	1.81 (0.72, 4.58)	1.50 (0.76, 2.94)	0.59 (0.25, 1.39)	0.78 (0.33, 1.84)	0.88 (0.27, 2.87)
	rs4771436	0.42 (0.15, 1.20)	0.86 (0.42, 1.76)	0.51 (0.14, 1.80)	0.77 (0.39, 1.53)	1.00 (0.48, 2.08)	0.74 (0.38, 1.44)	0.90 (0.42, 1.90)	0.44 (0.17, 1.13)	0.95 (0.35, 2.53)
	rs1047768	0.48 (0.21, 1.14)	0.56 (0.21, 1.50)	0.75 (0.31, 1.82)	0.91 (0.40, 2.07)	0.62 (0.28, 1.34)	0.68 (0.30, 1.51)	0.63 (0.29, 1.37)	0.36 (0.11, 1.15)	0.56 (0.21, 1.47)
	rs2020915	1.71 (0.72, 4.06)	1.33 (0.60, 2.97)	0.95 (0.35, 2.57)	1.58 (0.78, 3.19)	0.94 (0.41, 2.13)	1.02 (0.50, 2.10)	1.61 (0.73, 3.53)	0.84 (0.34, 2.10)	0.99 (0.33, 2.94)

HR hazards ratio, CI confidence interval

a) HRs adjusted for matching factors (age and sex, including pairwise interactions), education, cigarette smoking, alcohol drinking, stage, and ancestry (% African ancestry).

Highlighting indicates significant at 0.05 level. None significant at a Bonferroni corrected level (0.05/79=0.0006).

Table 6A cont. Hazard Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Treatment on Overall Survival among Head and Neck Cancer Cases in the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, African Americans

		HR (95% CI)[a]								
Gene	**SNP**	**Surgery, Variant Genotype**	**Radiation, Referent Genotype**	**Radiation, Variant Genotype**	**Surgery and Radiation, Referent Genotype**	**Surgery and Radiation, Variant Genotype**	**Radiation and Chemotherapy, Referent Genotype**	**Radiation and Chemotherapy, Variant Genotype**	**Surgery, Radiation and Chemotherapy, Referent Genotype**	**Surgery, Radiation, and Chemotherapy, Variant Genotype**
ERCC5 (XPG)	rs3818356	0.46 (0.16, 1.30)	0.88 (0.43, 1.82)	0.53 (0.15, 1.88)	0.79 (0.40, 1.57)	1.03 (0.50, 2.15)	0.73 (0.38, 1.42)	1.01 (0.47, 2.14)	0.46 (0.18, 1.17)	0.98 (0.36, 2.61)
	rs4150355	0.88 (0.33, 2.34)	1.06 (0.49, 2.30)	0.84 (0.33, 2.14)	0.88 (0.45, 1.71)	1.60 (0.71, 3.61)	0.89 (0.45, 1.74)	1.06 (0.45, 2.49)	0.76 (0.32, 1.81)	0.59 (0.18, 1.92)
	rs4150360									
	rs4150383	0.45 (0.13, 1.59)	0.92 (0.46, 1.85)	0.50 (0.11, 2.24)	0.94 (0.50, 1.75)	0.93 (0.39, 2.23)	0.8 (0.43, 1.49)	1.24 (0.53, 2.92)	0.58 (0.25, 1.36)	0.97 (0.29, 3.20)
	rs17655	1.61 (0.43, 6.03)	1.08 (0.23, 5.03)	1.59 (0.43, 5.95)	2.21 (0.60, 8.21)	1.29 (0.35, 4.76)	1.04 (0.27, 4.01)	1.61 (0.46, 5.73)	1.60 (0.33, 7.75)	0.94 (0.23, 3.77)
	rs873601	2.33 (0.29, 18.84)	1.62 (0.13, 19.61)	2.23 (0.28, 17.87)	2.87 (0.31, 26.61)	2.32 (0.29, 18.23)	1.44 (0.11, 18.15)	2.20 (0.28, 17.28)	2.90 (0.27, 31.76)	1.52 (0.18, 12.79)
	rs876430	2.34 (0.29, 18.92)	1.62 (0.13, 19.7)	2.24 (0.28, 17.95)	2.88 (0.31, 26.62)	2.33 (0.30, 18.30)	1.58 (0.15, 17.00)	2.22 (0.28, 17.42)	2.92 (0.27, 31.94)	1.52 (0.18, 12.83)
	rs1051677	1.51 (0.56, 4.05)	1.12 (0.55, 2.30)	0.91 (0.24, 3.35)	1.07 (0.55, 2.08)	1.56 (0.72, 3.37)	0.91 (0.47, 1.79)	1.50 (0.69, 3.24)	0.91 (0.40, 2.11)	0.52 (0.11, 2.36)
	rs1051685	0.87 (0.35, 2.16)	1.02 (0.37, 2.83)	0.81 (0.30, 2.20)	1.53 (0.61, 3.85)	0.71 (0.29, 1.78)	0.86 (0.34, 2.16)	0.88 (0.34, 2.27)	0.61 (0.19, 1.92)	0.74 (0.25, 2.23)
ERCC4 (XPF)	rs3136038	2.40 (0.65, 8.81)	3.04 (0.74, 12.56)	1.52 (0.39, 5.91)	1.97 (0.50, 7.71)	2.35 (0.65, 8.50)	1.15 (0.28, 4.74)	2.62 (0.71, 9.68)	1.56 (0.31, 7.84)	1.50 (0.37, 6.19)
	rs744154	0.87 (0.35, 2.19)	0.80 (0.37, 1.74)	1.34 (0.50, 3.60)	0.87 (0.44, 1.74)	1.49 (0.68, 3.24)	0.84 (0.42, 1.68)	1.22 (0.54, 2.73)	0.82 (0.34, 1.98)	0.47 (0.13, 1.71)
	rs3136085	0.59 (0.23, 1.53)	0.63 (0.28, 1.44)	1.38 (0.55, 3.50)	1.00 (0.49, 2.07)	0.84 (0.40, 1.78)	0.92 (0.45, 1.90)	0.66 (0.30, 1.44)	0.68 (0.27, 1.68)	0.51 (0.16, 1.55)
	rs3136091	1.21 (0.40, 3.65)	0.91 (0.44, 1.86)	1.61 (0.56, 4.65)	1.05 (0.57, 1.96)	1.52 (0.62, 3.75)	0.97 (0.51, 1.83)	1.21 (0.50, 2.94)	0.74 (0.32, 1.73)	0.84 (0.23, 3.08)
	rs3136130	1.31 (0.45, 3.85)	1.52 (0.43, 5.34)	1.10 (0.36, 3.37)	1.84 (0.54, 6.32)	1.25 (0.43, 3.59)	1.10 (0.33, 3.69)	1.29 (0.43, 3.89)	0.91 (0.15, 5.33)	0.93 (0.28, 3.09)
	rs3136172	0.94 (0.39, 2.29)	0.81 (0.37, 1.78)	1.37 (0.51, 3.70)	0.89 (0.44, 1.79)	1.52 (0.69, 3.35)	0.86 (0.42, 1.74)	1.22 (0.54, 2.75)	0.93 (0.38, 2.25)	0.40 (0.11, 1.46)
	rs2020955	0.82 (0.30, 2.22)	0.82 (0.38, 1.78)	1.42 (0.56, 3.64)	1.21 (0.61, 2.38)	0.88 (0.42, 1.88)	1.09 (0.55, 2.18)	0.76 (0.36, 1.59)	0.74 (0.31, 1.75)	0.62 (0.19, 2.00)
RAD23A	rs2974752	1.52 (0.55, 4.20)	2.56 (0.72, 9.09)	1.13 (0.38, 3.33)	1.39 (0.46, 4.25)	1.56 (0.57, 4.28)	1.24 (0.41, 3.77)	1.61 (0.59, 4.41)	1.83 (0.31, 10.67)	1.05 (0.34, 3.24)
	rs11558955	1.68 (0.54, 5.21)	1.11 (0.56, 2.23)	0.81 (0.22, 3.02)	1.21 (0.66, 2.22)	0.90 (0.33, 2.45)	0.97 (0.52, 1.81)	1.36 (0.52, 3.52)	0.92 (0.42, 2.02)	0.23 (0.03, 1.79)
ERCC2 (XPD)	rs13181	2.40 (1.05, 5.48)	1.33 (0.54, 3.23)	1.73 (0.66, 4.51)	1.47 (0.66, 3.24)	1.91 (0.84, 4.34)	1.6 (0.71, 3.58)	1.34 (0.60, 2.99)	1.04 (0.37, 2.92)	1.2 (0.43, 3.32)
	rs238418									
	rs1799787	2.72 (1.11, 6.68)	1.06 (0.49, 2.32)	2.26 (0.80, 6.39)	1.36 (0.68, 2.71)	1.92 (0.78, 4.70)	1.41 (0.70, 2.85)	0.87 (0.35, 2.20)	0.96 (0.4, 2.29)	1.18 (0.31, 4.47)
	rs3916874	1.79 (0.54, 5.93)	1.12 (0.56, 2.24)	0.85 (0.18, 4.07)	1.23 (0.67, 2.28)	0.93 (0.32, 2.70)	1.06 (0.56, 2.00)	1.08 (0.40, 2.93)	0.79 (0.35, 1.8)	0.87 (0.18, 4.22)
	rs238416	0.48 (0.14, 1.69)	0.78 (0.36, 1.67)	0.98 (0.37, 2.58)	0.74 (0.40, 1.38)	2.54 (1.11, 5.77)	0.83 (0.44, 1.57)	0.83 (0.30, 2.28)	0.75 (0.32, 1.76)	0.47 (0.16, 1.38)
	rs50872	1.36 (0.56, 3.32)	0.86 (0.39, 1.90)	1.98 (0.70, 5.60)	1.17 (0.60, 2.28)	1.19 (0.49, 2.87)	1.22 (0.61, 2.46)	0.72 (0.30, 1.76)	0.77 (0.31, 1.90)	0.95 (0.31, 2.92)
	rs50871	1.65 (0.65, 4.20)	1.15 (0.54, 2.47)	1.04 (0.40, 2.74)	1.12 (0.58, 2.16)	1.44 (0.65, 3.19)	1.03 (0.54, 1.98)	1.42 (0.57, 3.54)	1.00 (0.44, 2.29)	0.48 (0.13, 1.81)
	rs238407	1.51 (0.63, 3.62)	0.87 (0.38, 2.02)	1.46 (0.61, 3.51)	1.01 (0.51, 2.00)	1.89 (0.85, 4.21)	1.10 (0.56, 2.15)	1.05 (0.42, 2.65)	1.03 (0.42, 2.53)	0.68 (0.24, 1.90)
	rs3810366	1.35 (0.56, 3.21)	0.92 (0.39, 2.14)	1.22 (0.52, 2.90)	0.94 (0.47, 1.88)	1.81 (0.84, 3.93)	1.06 (0.53, 2.12)	1.03 (0.45, 2.36)	0.99 (0.39, 2.51)	0.71 (0.26, 1.90)
ERCC1	rs735482	0.74 (0.32, 1.69)	0.65 (0.27, 1.59)	1.10 (0.45, 2.72)	0.85 (0.38, 1.9)	0.96 (0.43, 2.18)	0.83 (0.36, 1.87)	0.81 (0.36, 1.82)	1.00 (0.37, 2.68)	0.40 (0.13, 1.20)
	rs2336219	0.73 (0.32, 1.69)	0.65 (0.26, 1.57)	1.11 (0.45, 2.74)	0.85 (0.38, 1.91)	0.96 (0.43, 2.18)	0.82 (0.36, 1.86)	0.81 (0.36, 1.82)	1.06 (0.40, 2.80)	0.34 (0.11, 1.09)
	rs3212964	0.54 (0.22, 1.34)	0.67 (0.30, 1.48)	1.08 (0.42, 2.75)	0.78 (0.4, 1.52)	1.02 (0.43, 2.43)	0.77 (0.38, 1.54)	0.75 (0.34, 1.62)	0.60 (0.25, 1.45)	0.53 (0.16, 1.76)
	rs3212955	2.10 (0.90, 4.86)	1.36 (0.53, 3.48)	1.56 (0.61, 4.00)	2.14 (0.93, 4.92)	1.23 (0.54, 2.84)	1.83 (0.82, 4.07)	1.03 (0.44, 2.43)	1.10 (0.41, 2.95)	1.10 (0.37, 3.29)
	rs3212948									
	rs3212935	1.02 (0.44, 2.32)	0.83 (0.34, 2.07)	1.12 (0.44, 2.87)	1.12 (0.51, 2.45)	1.03 (0.45, 2.37)	1.17 (0.52, 2.6)	0.84 (0.38, 1.85)	1.02 (0.37, 2.79)	0.56 (0.20, 1.62)
	rs3212930	1.97 (0.76, 5.12)	1.03 (0.49, 2.15)	1.64 (0.57, 4.77)	1.30 (0.70, 2.41)	0.87 (0.27, 2.77)	1.13 (0.59, 2.15)	0.92 (0.35, 2.39)	0.81 (0.35, 1.87)	0.95 (0.26, 3.50)
LIG1	rs156641	0.99 (0.37, 2.64)	1.12 (0.53, 2.40)	0.83 (0.30, 2.26)	1.14 (0.60, 2.19)	0.94 (0.38, 2.32)	1.02 (0.53, 1.93)	0.78 (0.29, 2.08)	0.97 (0.42, 2.26)	0.34 (0.09, 1.30)
	rs20580	1.28 (0.36, 4.60)	1.03 (0.19, 5.64)	1.29 (0.35, 4.80)	1.47 (0.34, 6.40)	1.32 (0.38, 4.65)	0.93 (0.24, 3.64)	1.33 (0.37, 4.75)	1.06 (0.1, 11.74)	0.90 (0.23, 3.54)
	rs20579	1.76 (0.72, 4.29)	1.81 (0.65, 5.04)	1.17 (0.44, 3.12)	1.46 (0.62, 3.42)	1.64 (0.67, 4.01)	1.49 (0.62, 3.57)	1.31 (0.53, 3.27)	1.01 (0.34, 2.97)	1.08 (0.37, 3.19)
	rs439132	0.92 (0.39, 2.13)	0.93 (0.40, 2.17)	0.93 (0.37, 2.38)	1.18 (0.58, 2.43)	0.77 (0.32, 1.86)	0.70 (0.32, 1.55)	1.31 (0.60, 2.88)	0.84 (0.34, 2.10)	0.58 (0.19, 1.78)

HR hazards ratio, CI confidence interval

a) HRs adjusted for matching factors (age and sex, including pairwise interactions), education, cigarette smoking, alcohol drinking, stage, and ancestry (% African ancestry).

Highlighting indicates significant at 0.05 level. None significant at a Bonferroni corrected level (0.05/79=0.0006).

Table 6A cont. Hazard Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Treatment on Overall Survival among Head and Neck Cancer Cases in the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, African Americans

		RERI (95% CI)[a]			
Gene	**SNP**	**Surgery, Variant Genotype**	**Radiation, Referent Genotype**	**Radiation, Variant Genotype**	**Surgery and Radiation, Referent Genotype**
ERCC3 (XPB)	rs4150496	0.17 (-0.86, 1.20)	0.05 (-0.97, 1.08)	0.64 (-0.19, 1.47)	0.99 (-0.13, 2.11)
	rs4150459	0.52 (-0.51, 1.55)	0.74 (-0.14, 1.61)	0.59 (-0.15, 1.33)	0.38 (-0.47, 1.22)
	rs1011019	-0.89 (-2.86, 1.08)	-0.15 (-1.77, 1.47)	-1.13 (-3.00, 0.75)	-1.55 (-3.72, 0.63)
	rs4150434	1.44 (0.08, 2.79)	0.22 (-0.62, 1.07)	0.93 (0.19, 1.68)	0.90 (-0.04, 1.85)
	rs4150416	-0.18 (-1.78, 1.42)	0.48 (-0.60, 1.57)	0.24 (-0.89, 1.36)	-0.49 (-2.46, 1.47)
	rs4150407	0.55 (-0.30, 1.40)	0.55 (-0.19, 1.28)	0.43 (-0.28, 1.14)	0.61 (-0.11, 1.33)
	rs4150402	-0.89 (-2.86, 1.08)	-0.15 (-1.77, 1.47)	-1.13 (-3.00, 0.75)	-1.55 (-3.72, 0.63)
XPC	rs2228001	0.41 (-0.77, 1.60)	0.13 (-1.01, 1.28)	0.43 (-0.50, 1.37)	-0.01 (-1.15, 1.12)
	rs2228000				
	rs3731124	0.61 (-0.61, 1.84)	0.58 (-0.58, 1.73)	0.48 (-0.43, 1.40)	0.69 (-0.45, 1.83)
	rs3731093	-1.05 (-3.6, 1.49)	-0.41 (-3.04, 2.22)	-1.72 (-4.09, 0.65)	
	rs3731089	-1.29 (-3.72, 1.14)	-0.36 (-2.88, 2.16)	-1.91 (-4.16, 0.34)	0.24 (-2.15, 2.63)
	rs2733537	0.14 (-1.09, 1.37)	0.24 (-0.76, 1.24)	-0.09 (-1.06, 0.88)	0.48 (-0.62, 1.58)
	rs2607755	0.63 (0.10, 1.16)	-0.09 (-1.16, 0.98)	0.39 (-0.20, 0.97)	0.61 (0.16, 1.05)
	rs1902658	0.49 (-0.47, 1.44)	-0.22 (-2.12, 1.68)	0.75 (0.29, 1.21)	0.14 (-1.17, 1.46)
ERCC8	rs3117	-0.5 (-2.24, 1.23)	-0.61 (-2.30, 1.07)	-0.66 (-2.3, 0.98)	-0.56 (-2.28, 1.15)
CDK7	rs2972388	0.27 (-1.19, 1.73)	0.05 (-1.24, 1.34)	0.63 (-0.50, 1.76)	-1.1 (-3.01, 0.82)
CCNH	rs2266691	0.62 (-0.68, 1.92)	0.30 (-0.73, 1.33)	0.97 (-0.15, 2.09)	1.27 (-0.20, 2.74)
	rs2266692	-0.01 (-1.32, 1.3)	0.54 (-1.03, 2.12)	-0.31 (-1.45, 0.83)	-0.44 (-1.67, 0.79)
XPA	rs3176757	0.45 (-2.11, 3.01)	-0.53 (-2.49, 1.44)	-1.11 (-3.06, 0.84)	-0.48 (-2.42, 1.46)
	rs3176753	-0.16 (-1.38, 1.06)	-0.11 (-1.27, 1.05)	0.42 (-0.62, 1.47)	-0.10 (-1.21, 1.01)
	rs3176748	1.17 (0.13, 2.21)	0.48 (-0.22, 1.17)	1.12 (0.38, 1.87)	0.96 (0.23, 1.70)
	rs3176658	-0.63 (-2.06, 0.80)	0.84 (-0.90, 2.58)	0.98 (-0.64, 2.59)	
	rs1800975	-0.54 (-2.48, 1.40)	0.16 (-1.58, 1.89)	-0.31 (-2.02, 1.41)	-0.53 (-2.38, 1.32)
RAD23B	rs1805330	-0.74 (-2.56, 1.08)	-1.17 (-3.05, 0.70)	-0.03 (-1.36, 1.29)	0.71 (-1.16, 2.58)
ERCC6	rs2228529	0.08 (-1.65, 1.80)	-0.04 (-1.59, 1.51)	0.37 (-1.08, 1.81)	-0.62 (-2.17, 0.93)
	rs2228527	0.34 (-1.08, 1.76)	-0.06 (-1.32, 1.19)	0.46 (-0.60, 1.52)	-0.07 (-1.28, 1.14)
	rs4253132	0.22 (-1.05, 1.48)	0.51 (-0.56, 1.58)	0.05 (-0.95, 1.05)	0.63 (-0.66, 1.92)
	rs2228528	-0.26 (-1.74, 1.23)	0.87 (-0.84, 2.59)	0.47 (-0.73, 1.67)	-0.29 (-1.71, 1.14)
DDB2 (XPE)	rs2029298	-1.6 (-4.55, 1.35)	-0.39 (-2.15, 1.37)	0.16 (-1.13, 1.44)	0.75 (-0.51, 2.02)
	rs1685404	0.49 (-0.59, 1.56)	-0.09 (-1.15, 0.97)	0.59 (-0.25, 1.43)	0.49 (-0.47, 1.44)
	rs2957873	-0.52 (-2.42, 1.38)	-0.54 (-2.29, 1.21)	-0.09 (-1.43, 1.24)	-0.45 (-2.16, 1.26)
	rs326224	-1.93 (-5.93, 2.07)	-1.37 (-4.39, 1.66)	-0.63 (-2.86, 1.61)	-1.05 (-3.85, 1.76)
	rs2306353	-0.96 (-3.05, 1.13)	-0.77 (-2.56, 1.03)	-0.07 (-1.33, 1.19)	-0.44 (-2.07, 1.19)
	rs326222	-1.42 (-7.13, 4.28)	-2.44 (-10.25, 5.36)	-1.42 (-6.73, 3.89)	-0.42 (-3.91, 3.07)
	rs901746	-1.29 (-4.67, 2.10)	-1.90 (-6.03, 2.24)	-0.61 (-2.85, 1.63)	0 (-1.78, 1.78)

HR hazards ratio, CI confidence interval

a) HRs adjusted for matching factors (age and sex, including pairwise interactions), education, cigarette smoking, alcohol drinking, stage, and ancestry (% African ancestry).

Highlighting indicates significant at 0.05 level. None significant at a Bonferroni corrected level (0.05/79=0.0006).

Table 6A cont. Hazard Ratios for Single Nucleotide Polymorphisms (SNPs) in Nucleotide Excision Repair (NER) Genes and Treatment on Overall Survival among Head and Neck Cancer Cases in the Carolina Head and Neck Cancer Epidemiology (CHANCE) Study, African Americans

		RERI (95% CI)[a]			
Gene	**SNP**	**Surgery, Variant Genotype**	**Radiation, Referent Genotype**	**Radiation, Variant Genotype**	**Surgery and Radiation, Referent Genotype**
ERCC5 (XPG)	rs2296147	0.88 (-0.33, 2.08)	0.94 (-0.06, 1.93)	0.18 (-0.69, 1.06)	0.25 (-0.79, 1.3)
	rs2296148	-1.15 (-3.22, 0.92)	-0.05 (-2.16, 2.07)	-1.67 (-3.78, 0.44)	-0.66 (-2.63, 1.31)
	rs4771436	0.22 (-0.69, 1.14)	0.80 (0.04, 1.56)	0.73 (0.05, 1.42)	1.08 (0.15, 2.00)
	rs1047768	0.71 (-0.01, 1.44)	0.23 (-0.56, 1.01)	0.47 (-0.14, 1.07)	0.72 (0.10, 1.33)
	rs2020915	-1.09 (-3.05, 0.86)	-1.35 (-3.29, 0.59)	-0.12 (-1.74, 1.49)	-0.56 (-2.37, 1.25)
	rs3818356	0.19 (-0.77, 1.14)	0.78 (-0.02, 1.58)	0.82 (0.07, 1.56)	1.06 (0.10, 2.03)
	rs4150355	-0.10 (-1.38, 1.17)	0.83 (-0.46, 2.13)	0.29 (-0.79, 1.37)	-0.05 (-1.25, 1.14)
	rs4150360				
	rs4150383	0.13 (-0.94, 1.19)	0.55 (-0.43, 1.52)	1.00 (-0.06, 2.05)	0.94 (-0.28, 2.16)
	rs17655	-0.10 (-2.18, 1.97)	-1.54 (-4.94, 1.87)	-0.04 (-1.77, 1.69)	-1.27 (-4.65, 2.10)
	rs873601	-0.71 (-5.20, 3.78)	-1.88 (-8.45, 4.69)	-0.56 (-4.64, 3.52)	-2.72 (-11.21, 5.78)
	rs876430	-0.72 (-5.24, 3.79)	-1.88 (-8.46, 4.69)	-0.70 (-4.89, 3.49)	-2.74 (-11.28, 5.81)
	rs1051677	-0.73 (-2.68, 1.23)	-0.02 (-1.74, 1.71)	0.08 (-1.58, 1.74)	-0.90 (-2.75, 0.94)
	rs1051685	-0.08 (-1.33, 1.18)	-0.69 (-2.29, 0.91)	0.15 (-0.78, 1.08)	0.26 (-0.75, 1.27)
ERCC4 (XPF)	rs3136038	-2.92 (-8.41, 2.56)	-1.03 (-4.18, 2.13)	0.06 (-1.95, 2.07)	-1.46 (-5.15, 2.23)
	rs744154	0.67 (-0.75, 2.09)	0.74 (-0.40, 1.89)	0.50 (-0.54, 1.54)	-0.22 (-1.44, 0.99)
	rs3136085	1.16 (-0.03, 2.35)	0.25 (-0.63, 1.12)	0.15 (-0.65, 0.94)	0.24 (-0.65, 1.13)
	rs3136091	0.49 (-1.49, 2.48)	0.25 (-1.54, 2.05)	0.03 (-1.57, 1.62)	-0.11 (-1.86, 1.64)
	rs3136130	-0.73 (-2.99, 1.52)	-0.91 (-3.34, 1.53)	-0.12 (-1.60, 1.36)	-0.29 (-2.25, 1.67)
	rs3136172	0.62 (-0.84, 2.08)	0.69 (-0.48, 1.86)	0.43 (-0.62, 1.47)	-0.47 (-1.76, 0.82)
	rs2020955	0.78 (-0.59, 2.14)	-0.15 (-1.31, 1.02)	-0.16 (-1.24, 0.92)	0.06 (-1.09, 1.20)
RAD23A	rs2974752	-1.95 (-5.56, 1.66)	-0.35 (-2.15, 1.44)	-0.14 (-1.72, 1.44)	-1.29 (-4.81, 2.22)
	rs11558955	-0.98 (-3.26, 1.29)	-0.99 (-3.16, 1.17)	-0.29 (-2.48, 1.90)	-1.38 (-3.51, 0.75)
ERCC2 (XPD)	rs13181	-1.00 (-3.33, 1.33)	-0.95 (-3.12, 1.21)	-1.65 (-3.96, 0.65)	-1.24 (-3.5, 1.02)
	rs238418	0.13 (-0.94, 1.19)	0.55 (-0.43, 1.52)	1.00 (-0.06, 2.05)	0.94 (-0.28, 2.16)
	rs1799787	-0.52 (-3.50, 2.47)	-1.16 (-3.88, 1.55)	-2.26 (-5.03, 0.52)	-1.50 (-4.31, 1.31)
	rs3916874	-1.06 (-3.63, 1.52)	-1.09 (-3.52, 1.34)	-0.76 (-3.07, 1.54)	-0.71 (-3.25, 1.84)
	rs238416	0.73 (-0.36, 1.81)	2.32 (0.36, 4.27)	0.52 (-0.49, 1.53)	0.24 (-0.69, 1.17)
	rs50872	0.76 (-1.27, 2.79)	-0.34 (-1.88, 1.20)	-0.86 (-2.41, 0.69)	-0.18 (-1.72, 1.37)
	rs50871	-0.76 (-2.59, 1.07)	-0.33 (-2.11, 1.46)	-0.26 (-2.11, 1.60)	-1.16 (-3.03, 0.70)
	rs238407	0.07 (-1.57, 1.72)	0.36 (-1.33, 2.06)	-0.56 (-2.17, 1.05)	-0.87 (-2.55, 0.81)
	rs3810366	-0.04 (-1.53, 1.46)	0.53 (-0.99, 2.05)	-0.38 (-1.79, 1.03)	-0.63 (-2.17, 0.91)
ERCC1	rs735482	0.72 (-0.23, 1.67)	0.38 (-0.49, 1.24)	0.24 (-0.55, 1.04)	-0.33 (-1.54, 0.88)
	rs2336219	0.73 (-0.22, 1.68)	0.38 (-0.49, 1.24)	0.25 (-0.55, 1.04)	-0.45 (-1.72, 0.82)
	rs3212964	0.88 (-0.16, 1.91)	0.70 (-0.25, 1.65)	0.44 (-0.23, 1.11)	0.39 (-0.44, 1.22)
	rs3212955	-0.89 (-3.06, 1.27)	-2.01 (-4.56, 0.55)	-1.90 (-4.23, 0.44)	-1.09 (-3.21, 1.02)

HR hazards ratio, CI confidence interval

a) HRs adjusted for matching factors (age and sex, including pairwise interactions), education, cigarette smoking, alcohol drinking, stage, and ancestry (% African ancestry).

Highlighting indicates significant at 0.05 level. None significant at a Bonferroni corrected level (0.05/79=0.0006).

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		RERI (95% CI)[a]			
Gene	**SNP**	**Surgery, Variant Genotype**	**Radiation, Referent Genotype**	**Radiation, Variant Genotype**	**Surgery and Radiation, Referent Genotype**
ERCC1	rs3212948	0.27 (-0.93, 1.47)	-0.10 (-1.26, 1.06)	-0.35 (-1.52, 0.83)	-0.47 (-1.85, 0.91)
	rs3212935	-0.35 (-2.84, 2.14)	-1.40 (-3.60, 0.80)	-1.18 (-3.24, 0.88)	-0.83 (-3.04, 1.38)
	rs3212930	-0.29 (-1.69, 1.12)	-0.20 (-1.53, 1.14)	-0.22 (-1.45, 1.00)	-0.62 (-1.98, 0.73)
LIG1	rs156641	-0.02 (-1.92, 1.89)	-0.42 (-2.67, 1.83)	0.12 (-1.29, 1.53)	-0.44 (-3.31, 2.44)
	rs20580	-1.39 (-3.85, 1.07)	-0.57 (-2.37, 1.22)	-0.93 (-2.80, 0.93)	-0.68 (-2.56, 1.20)
	rs20579	0.09 (-1.05, 1.23)	-0.33 (-1.50, 0.84)	0.69 (-0.18, 1.57)	-0.18 (-1.32, 0.97)
	rs439132	0.27 (-0.93, 1.47)	-0.10 (-1.26, 1.06)	-0.35 (-1.52, 0.83)	-0.47 (-1.85, 0.91)

HR hazards ratio, CI confidence interval

a) HRs adjusted for matching factors (age and sex, including pairwise interactions), education, cigarette smoking, alcohol drinking, stage, and ancestry (% African ancestry).

Highlighting indicates significant at 0.05 level. None significant at a Bonferroni corrected level (0.05/79=0.0006).

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