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Nucleotide Excision Repair Gene Polymorphisms, Meat Intake and Colon Cancer Risk

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Abstract

Purpose—Much of the DNA damage from colon cancer-related carcinogens, including heterocyclic amines (HCA) and polycyclic aromatic hydrocarbons (PAH) from red meat cooked at high temperature, are repaired by the nucleotide excision repair (NER) pathway. Thus, we examined whether NER non-synonymous single nucleotide polymorphisms (nsSNPs) modified the association between red meat intake and colon cancer risk.

Methods—The study consists of 244 African-American and 311 white colon cancer cases and population-based controls (331 African Americans and 544 whites) recruited from 33 counties in North Carolina from 1996 to 2000. Information collected by food frequency questionnaire on meat intake and preparation methods were used to estimate HCA and benzo(a)pyrene (BaP, a PAH)

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Conflict of Interest statement

The authors declare that there are no conflicts of interest.

intake. We tested 7 nsSNPs in 5 NER genes: *XPC A499V* and *K939Q*, *XPD D312N* and *K751Q*, *XPF R415Q*, *XPG D1104H*, and *RAD23B A249V*. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated using unconditional logistic regression.

Results—Among African Americans, we observed a statistically significant positive association between colon cancer risk and *XPC 499 AV+VV* genotype (OR=1.7, 95% CI: 1.1, 2.7, *AA* as referent), and an inverse association with *XPC 939 QQ* (OR=0.3, 95%CI: 0.2, 0.8, *KK* as referent). These associations were not observed among whites. For both races combined, there was interaction between the *XPC 939* genotype, well-done red meat intake and colon cancer risk (OR=1.5, 95% CI=1.0, 2.2 for high well-done red meat and *KK* genotype as compared to low well-done red meat and *KK* genotype, $p_{interaction}$ =0.05).

Conclusions—Our data suggest that NER nsSNPs are associated with colon cancer risk and may modify the association between well-done red meat intake and colon cancer risk.

Keywords

Case-control study; colon cancer; diet; DNA repair; meat; polymorphism

1.0 Introduction

African Americans have higher colorectal cancer incidence and mortality compared to all other racial/ethnic groups in the U.S.[1]. Differences in socioeconomic status, access to health care, environmental and dietary exposures, and genetic susceptibility may explain the disparities, though the exact contribution of each factor is unknown [2, 3]. Red meat intake has been wellstudied as a risk factor for colorectal cancer[4]. High red meat intake was associated with a modest increased risk of colorectal cancer in three meta-analyses [5–8].

The hypothesized etiologically relevant components in red meat include heterocyclic amines (HCAs), polycyclic aromatic hydrocarbons (PAHs), saturated fat, and nitrosamines [9–13]. Heme iron has also been implicated in colon carcinogenesis, though a cohort study found no association between heme iron intake and risk of colorectal cancer in Canadian women [14]. We previously reported statistically significant associations with well-done and pan-fried red meat, as well as the HCA, 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline (DiMeIQx), for colon cancer in the North Carolina Colon Cancer Study (NCCCS), a population-based, case-control study, of African Americans and whites [15].

HCAs and PAHs are carcinogens that can cause bulky DNA lesions. These DNA adducts can be repaired by the nucleotide excision repair pathway (NER). The NER pathway involves multiple factors in damage recognition and damage repair [16–18]. The Xeroderma Pigmentosa Group C (XPC)-RAD23B complex recognizes DNA damage, which is followed by unwinding of the DNA helix around the damaged site by the transcription factor IIH (TFIIH) complex of proteins. The TFIIH complex includes ERCC2/XPD and ERCC3/XPB [19–21]. Next, ERCC5/XPG and ERCC1/XPF make 3’ and 5’ incisions to the lesion [22–24], and the gap is filled by repair synthesis and sealed by DNA ligase [25, 26]. Decreased NER capacity in the presence of accumulating DNA damage has been associated with sporadic colorectal cancer [18].

Multiple polymorphisms within genes involved in the NER pathway have been identified, [27] many of which have functional significance [17, 28, 29]. Several of these NER gene nsSNPs have been examined in relation to colorectal cancer risk, with equivocal results thus far [30]. However, few data are available for joint effects of meat intake and NER gene polymorphisms on colon cancer risk [31–34], particularly among African Americans, an underserved population with higher incidence of colon cancer than other racial/ethnic groups [35]. The presence of joint effects would provide support for an underlying mechanism for our previously reported HCA-colon cancer associations that would involve the NER pathway. In the present study, we examined joint effects of meat intake and seven nsSNPS in five genes involved in NER on colon cancer risk. These nsSNPS were selected based on their putative functional impact and previous evidence of colon cancer risk associations. We hypothesize that nsSNPs in genes in the NER pathway modify associations between meat and meat-derived carcinogen (heterocyclic amines and polycyclic aromatic hydrocarbons) intake and colon cancer risk, and the extent of the effect modification varies by race.

2.0 Materials and Methods

The NCCCS has been described in detail previously [36]. In brief, cases were selected through a rapid ascertainment system [37] established in conjunction with the North Carolina Central Cancer Registry and enrolled within one year of diagnosis. Cases were eligible if they were between 40 and 84 years of age at first primary diagnosis of invasive adenocarcinoma of the colon and diagnosed between 10/01/1996 and 09/30/2000. Controls were randomly selected from North Carolina Division of Motor Vehicle lists if they were under 65 years of age, or from the Center for Medicare and Medicaid Services list if they were 65 years or older. Of those who were eligible, 84% of cases and 62% of controls were interviewed. A total of 643 colon cancer cases (294 African Americans and 349 whites) and 1048 population-based controls (437 African Americans and 611 whites) were enrolled in the study. Cases and controls were frequency matched by race, sex and 5-year age group through a variation of randomized recruitment as previously described [38]. The study was approved by the School of Medicine Institutional Review Board at the University of North Carolina and by equivalent committees at the collaborating hospitals.

A 150-item food frequency questionnaire was used to measure usual dietary intake over the year prior to diagnosis for cases, or year prior to date of interview for controls [39]. The questionnaire was modified to assess individual exposure to dietary carcinogens based on a meat-cooking and doneness module developed by Sinha, *et al.* [40]. Details regarding the collection of dietary history and specifically HCA and PAH exposure have been previously described [15]. In brief, meat intake frequency data, cooking method, and level of doneness were used to estimate values of three HCAs [DiMeIQx, 2-amino-3,8-dimethylimidazo[4.5-f]quinoxaline (MeIQx), and 2-amino-1-methyl-6-phenyl-imidazo[4,5-b]pyridine (PhIP)], and one PAH (BaP) using an exposure-index that has been previously described in detail [40, 41].

Blood samples were obtained from 86% of cases and 83% of controls. Cases and controls who provided blood samples were more likely to be male, white, and never-smokers ($p<0.01$), as previously reported [36]. No other differences between those who provided

blood samples and those who did not were noted for variables such as age, education level, income, family history of colorectal cancer, or total meat intake. Genomic DNA was extracted using the PureGene® DNA isolation kit (Gentra Systems, Inc., Minneapolis, MN). Seven SNPs in five genes involved in DNA repair were genotyped. The MassARRAY system (Sequenom, Inc., San Diego, CA) was used to determine genotypes. Genotyping was first completed on a panel of 90 DNA samples from Coriell Institute for Medical Research (Camden, NJ) and compared to the reported genotype data on 2 websites: http://www.ncbi.nlm.nih.gov and http://egp.gs.washington.edu. As part of the quality control protocol, four control samples were genotyped with 92 patient samples on each 96-well plate, and study cases and controls were loaded on each plate to minimize systematic bias. The average call rate was >95% for the genotype assay. The concordance rate for the quality control samples was 100% and the concordance rate for the Coriell samples ranged from 91% to 100%. For each genotype, there was a 100% concordance rate for the 4 internal control samples on each plate. Hardy Weinberg Equilibrium [42] was examined among controls for each SNP stratified by race using a goodness of fit χ^2 test to compare the observed genotype frequencies with expected genotype frequencies calculated on the basis of the observed allele frequencies.

Unconditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) using SAS statistical software version 9.1. All tests were two-sided. Models presented here are adjusted for offset terms to account for randomized recruitment sampling method, used to maintain somewhat equal numbers by age, race and gender categories [43]. Additional adjustment of total energy intake, energy-adjusted fat intake, dietary fiber intake, and total meat intake were made for the main effect of diet and the joint effects. Based on previous findings for smoking history and colon cancer risk in this dataset [38], smoking status was evaluated as a potential confounder but it was ultimately not retained in the final adjusted model because its inclusion did not change effect estimates. Meat intake and meat-derived carcinogen variables were categorized into “low” versus “high” intake, based on median cutpoints within the control population. We examined the following meat and meat-derived carcinogen intake variables in the interaction analyses: total meat, total red meat, well-done/very well-done red meat, pan-fried red meat, total chicken/turkey, very well-done chicken/turkey, MeIQx, DiMeIQx, PhIP, and BaP.

A summary SNP variable was created summing the number of ‘at-risk’ alleles present for each SNP for each participant. In creating the summary SNP variable, we grouped alleles for each SNP according to hypothesized functional effects, frequency in the study population, and subsequent effect on cancer risk. For each gene, the ‘at-risk’ allele was defined as the less common (variant) allele, with the exception that for analyses stratified by race, the *XPC 939* less common allele was associated with reduced risk in this population, and thus, the more common allele was considered the ‘at-risk’ allele.

The interaction between genotype and meat intake was examined by using high meat intake and the genotype’s hypothesized highest risk category (based on previous experimental and epidemiologic literature) as the common referent group and calculating ORs for each other combination of meat intake and genotype. Deviation from the multiplicative model was determined based on the fitness of the interaction term (between meat-related variables and

NER genotype) with the likelihood ratio test (LRT). LRT p-values for multiplicative interactions were considered statistically significant at $p < 0.10$ [44].

3.0 Results

Demographic characteristics of the study population have been described previously [15]. Briefly, the mean age of the study population was 65 years and the study population was 50% female. In general, cases and controls had similar intakes of fiber and folate, and controls consumed less fat and energy compared with cases, regardless of race [45]. A higher percentage of controls (41%) than cases (34%) were never smokers for whites only. Among whites, odds ratios were elevated for former smokers, individuals with more than 20 years of smoking, and those who smoked greater than one pack per day [38]. No associations for smoking were observed among African Americans. There were 546 cases (230 African Americans) and 855 controls (323 African Americans) with complete genotyping data. Genotype frequencies among controls were in HWE ($p>0.05$) for all nsSNPs examined among African Americans in the study, and were in HWE for all except for two nsSNPs among whites ($p=0.049$ for *XPF/ERCC4 R415Q* and $p=0.001$ for *RAD23B A249V*). Variant allele frequencies among controls are reported in Table 1. Four of the seven variant allele frequencies (i.e., *XPD/ERCC2 D312N, XPG/ERCC5 D1104H, XPC A499V,* and *RAD23B A249V*) for African Americans differed from whites in our study and from ranges reported in previous studies [30].

We observed a statistically significant positive association for the *XPC499 AV+VV* genotype (Table 2), among African Americans, but not whites. Also among African Americans, we observed a statistically significant decreased risk for the *XPC939 QQ* genotype as compared to the *KK* genotype. No substantial associations were observed for the other NER gene nsSNPs and risk of colon cancer, regardless of race (Table 2).

We first examined the effect of "high" (≥median) versus "low" (<median) meat intake on colon cancer stratified by genotype for each of the seven nsSNPs for all participants combined, and stratified by race. Results did not differ substantially between African Americans and whites, thus, we show results from the pooled analyses. Suggestive modification with total meat intake and colon cancer was observed by *XPD* homozygous variant versus homozygous wild-type genotypes (OR=1.7, 95% CI=0.8–3.5, p for interaction=0.09 for *D312N*; and OR=1.5, 95% CI=0.8–2.6, p for interaction=0.06 for *K751Q*). For well-done red meat (Table 3), statistically non-significant interaction was observed with the *XPC* 939 genotypes, such that individuals with the *KK* genotype and high well-done red meat intake were at moderately increased risk for colon cancer compared to the referent group of low well-done red meat intake and *KK* genotype (p for interaction=0.05). Increased risk with high well-done red meat intake was observed among individuals with *XPC 499 VV* (OR=1.8, 95% CI: 0.8, 4.2, p for interaction = 0.36) and *XPD 751 QQ* (OR=1.6, 95% CI: 0.9, 2.8, p for interaction=0.33) (Table 3), though these interactions did not reach statistical significance. For the remaining meat and meat-derived carcinogen intake variables, patterns of increasing risk with higher intake were not modified by NER genotypes (data not shown).

To account for the potential deleterious effect of having multiple ‘at-risk’ alleles in several genes within the NER pathway, we evaluated the interaction between meat and meat-derived carcinogen intake and number of ‘at-risk’ alleles for the NER gene nsSNPs in relation to colon cancer risk (Table 4). The increased risk of colon cancer for higher meat intake was strongest among those individuals with greater than or equal to four ‘at-risk’ alleles within the seven nsSNPs examined, though LRTs for multiplicative interaction were not statistically significant. The observed associations were similar for African Americans and whites when examined separately (data not shown).

Sensitivity analyses were conducted to evaluate whether removing information from the SNPs that were not in HWE would have any impact on the results presented. Odds ratios for those with high pan fried meat intake and having greater than or equal to four “at risk” alleles attenuated from 1.5 (95% CI: 1.1, 2.2) to 1.4 (95% CI: 1.0, 2.1) when alleles from *RAD23B A249V* and *XPF/ERCC4 R415Q*, which did not satisfy HWE among whites, were eliminated (data not shown). A similar pattern of attenuated effect and loss of statistical significance was observed for those with greater than or equal to four “at risk” alleles with higher MeIQx intake [from OR= 1.5 (95% CI: 1.1, 2.2) to OR= 1.3 (95% CI: 0.9, 2.0)], or with higher DiMeIQx intake [from OR= 1.6 (95% CI: 1.1, 2.3) to OR= 1.3 (95% CI: 0.8, 1.9)] when *RAD23B A249V* and *XPF/ERCC4 R415Q* were excluded. A non-statistically significant increased risk of colon cancer also was observed for higher BaP intake with greater than or equal to four “at risk” alleles OR= 1.3 (95% CI: 0.9, 1.9) once *RAD23B A249V* and *XPF R415Q* were excluded (data not shown).

4.0 Discussion

We examined the associations among colon cancer and seven nsSNPs in genes encoding five enzymes involved in NER, in a large, population-based, case-control study of African Americans and whites in North Carolina. We previously found positive associations for meat and HCA intake and colon cancer in this population, so we further examined whether genotype modified the association between meat and meat-derived carcinogen intake and colon cancer, and whether associations differed by race. We found modest evidence for modification of the effect of total meat intake on colon cancer by the *XPD 751 QQ* and *312NN* genotypes. For well-done red meat intake, there was evidence of interaction with the *XPC* 939 genotypes on colon cancer risk. Additionally, we observed the strongest associations for high intake of red meat, well-done red meat and pan-fried red meat, as well at the meat-derived carcinogens MeIQx and DiMeIQx, among individuals with four or more ‘at-risk’ alleles of the seven nsSNPs examined as compared to individuals with fewer ‘at-risk’ alleles.

We found no associations of single SNPs with colon cancer risk, with the exception of an increased risk for carriers of the V allele for *XPC A499V* and a decreased risk for carriers of the Q allele for *XPC K939Q* in African Americans only. Our findings support results from previous studies that have examined associations between these SNPs and colon cancer, rectal cancer, adenomatous polyps and hyperplastic polyps (reviewed in [31]). The variant allele frequencies among whites in our study were similar to those reported in other studies from the Naccarati et al. review [30], while variant allele frequencies among African

Americans were less than these for all nsSNPs examined except for *XPG D1104H* where the variant allele frequency was higher among African Americans as compared with whites. Our findings for no association are similar to the unexpected lack of statistically significant associations between polymorphisms in DNA repair genes and colorectal cancer risk in genome-wide association studies [46]. It is possible that the null findings are a result of multiple loci with small effects on risk and/or rare alleles with moderate effects and/or the heterogeneity of colorectal cancer.

We selected seven nsSNPS in five genes involved in NER based on functional implication of these SNPs and previous reports of associations with colon cancer. While these results are controversial [47], there is evidence that the homozygote variant genotypes for *XPD D312N* and/or *K751Q* are associated with higher DNA adduct levels [48–50], increased apoptotic response to UV-C irradiation [51], or reduced DNA repair capacity utilizing various DNA repair capacity assays [52–56]. However, one study observed no association between the *XPD K751Q* polymorphism and sister chromatid exchange frequencies or DNA adducts [57] and another study observed lower chromosomal aberration frequencies among individuals homozygous for the variant allele of *XPD K751Q* [58].

Less is known about the functional consequences of the other gene polymorphisms examined in this study; however, the SIFT program predicts functional consequences for the *XPF R415Q, XPC A499V* and *XPC K939Q* polymorphisms, and the PolyPhen algorithm predicts functional consequences for the *XPG D1104H* polymorphism [17]. In one study, no significant differences in DNA repair rate or single strand breaks were observed for the *XPG* and *XPC* polymorphisms, though there was a tendency toward increased repair capacity for *XPG HH* variant homozygotes compared to wildtype *DD* homozygotes, and reduced repair rate for the *XPC QQ* variant homozygotes compared to wild-type homozygotes [58]. In another study, the *RAD23B VV* and the *XPC 939 QQ* genotypes were associated with increased mutagen sensitivity compared with homozygote wild-type carriers, while other NER gene polymorphisms were not (*XPD K751Q, XPD D321N, XPG D1104H, XPC A499V*) [59].

We examined whether interaction was present between meat and meat-derived carcinogen intake and NER genotypes on colon cancer risk. Four previous studies have examined meat intake and up to six NER gene polymorphisms in relation to colorectal cancer with mixed results [31–34]. We found evidence for interaction for total meat intake and the *XPD D312N* and the *K751Q* SNPs (LRT p-values=0.09 and 0.06, respectively). Similarly, using a case-only analysis in a family based case-control study, Joshi et al. reported an interaction between *XPD* polymorphisms *D312N* and *K751Q* and intake of heavily browned red meat in relation to colorectal cancer risk (p for interaction = 0.09 and p = 0.006, respectively) [34]. This is in contrast to the Yeh et al. study which found no interaction for the *XPD K751Q* genotype and meat intake on colorectal cancer risk [32]. We also found increased risk for high well-done red meat intake among homozygote wild-type genotype carriers for the *XPC K939Q* SNP (p for interaction =0.05), which is consistent with our finding that the variant allele carriers (and not the wild-type allele carriers) for this SNP were at reduced risk for colon cancer among African Americans in our study. This is in contrast to Berndt et al. [33] who found no interaction between red meat intake and *XPC* polymorphisms in relation to

colorectal cancer risk. Hansen et al. [31] reported statistically significant interaction between red meat intake and the *XPC K939Q* SNP in relation to colorectal cancer, but in contrast with our finding, the highest risk was among those with the homozygous variant genotype (*QQ*). Differences across these studies may be explained by the outcome measured, as we examined colon cancer only, while other studies examined these interactions in relation to colorectal cancer (both colon and rectal cancer combined). Contrasting results may also be related to the different dietary intake of the populations studied (two of the other studies were in Taiwan or Denmark which have different ranges in meat intake than the U.S.) and the method of dietary assessment utilized, as well as difference in dietary behaviors and patterns between racial/ethnic groups [60, 61]. In addition, given the multiple comparisons made in ours and other studies, the role of chance in explaining these few statistically significant findings cannot be discarded.

Given that many genes are involved in DNA repair, the effect of multiple functional polymorphisms in genes encoding for DNA repair enzymes may be expected to be stronger than the effect of any one individual polymorphism [62]. Supporting this, a previous study found a significant dose-response relationship between increasing number of adverse alleles for *XPC-PAT, XPC K939Q, XPA A23G and RAD23B A249V* SNPs and higher mutagen sensitivity as measured by benzo(a)pyrene diol epoxide (BPDE)-induced chromatid breaks in peripheral blood lymphocytes in healthy humans [59]. Our results also lend support to this by showing increased risk for those individuals with the most number of ‘at-risk’ alleles and highest meat intake compared to individuals with fewer ‘at-risk’ alleles and low meat intake. To our knowledge, ours is the first report to examine the interaction between a combined NER gene variable and meat or meat-derived carcinogen intake and colon cancer. Other studies are needed to replicate our findings and perhaps include additional genes of interest. For example, some studies suggest that polymorphisms in xenobiotic-metabolizing enzymes (XME) may play significant role in colon cancer by detoxifying meat-related carcinogens, thereby reducing their bioavailability and deleterious effects [63, 64].

While this was a modestly-sized case-control study, we may have limited power to examine interactions between diet and genotype, particularly when stratifying by race. Results were similar across racial groups for interaction results, and therefore presented among all participants combined in order to increase power and improve stability of the estimates. Limitations inherent to self-reported dietary intake in case-control studies include the potential for differential recall bias, where cases may recall usual diet differently from controls because of the impact of disease on dietary habits. This could result in odds ratios for meat-genotype associations with colon cancer that are biased either away from or toward the null value [65]. We reported that the genotype frequencies of two SNPs were not in HWE among white controls (i.e., *XPF/ERCC4 R415Q* and *RAD23B A249V*). A possible cause of deviations from HWE includes genotyping error [66], therefore, as a sensitivity analysis, we excluded information from these two SNPs from the combined “at-risk” allele’s assessment. There was no change in the resulting odds ratio among whites, suggesting that if genotyping measurement errors exist they did not impact our main findings. Another limitation includes the ascertainment of only one or two SNPs per gene. Other SNPs in these and other NER genes may be causative. Measuring these other SNPs and gene haplotypes in

future studies are needed to better characterize the role of DNA repair in the HCA-colon cancer pathway.

A major strength of the study is the inclusion of a large proportion of African Americans, an underrepresented population in previous studies. Another strength of our study was the use of a rapid ascertainment method to identify men and women within one year after diagnosis of colon cancer, thus limiting the opportunity for survival bias to influence our findings. Our results indicate that while variant allele frequencies and associations between the *XPC A499V* and *K939Q* and colon cancer may differ by race, the effects of genotype and meat intake on colon cancer were similar across racial groups. This study lends support to the idea that the NER DNA repair pathway may be involved in the mechanism relating dietary HCAs and PAHs to colon cancer.

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Abbreviations

BaP	benzo(a)pyrene
BPDE	benzo(a)pyrene diol epoxide
CI	confidence interval
DiMeIQX	2-amino-3, 4, 8-trimethylimidazo[4,5-f]quinoxaline
HCA	heterocyclic amine
LRT	likelihood ratio test
MeIQx	2-amino-3,8-dimethylimidazo[4.5-f]quinoxaline
NCCCS	North Carolina Colon Cancer Study
NER	nucleotide excision repair
nsSNP	non-synonymous single nucleotide polymorphism
OR	odds ratio
PAH	polycyclic aromatic hydrocarbon
PhIP	2-amino-1-methyl-6-phenyl-imidazo[4,5-b]pyridine
RR	relative risk
XP	Xeroderma Pigmentosa

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Highlights

- We examined DNA repair gene polymorphisms, red meat intake, and colon cancer risk
- Main effects of seven SNPs and interactions with diet were examined by race
- Two SNPs were associated with risk of colon cancer among African Americans
- High meat carcinogen intake and presence of >3 at-risk alleles jointly increased risk

Table 1

Comparison of DNA repair gene variant allele frequencies among controls by race and with previous studies

Gene/SNPs	African Americans	Whites	Reference ranges from Naccarati et al.[24] review paper
XPD/ERCC2 D312N	0.10	0.34	0.33 – 0.37
XPD/ERCC2 K751Q	0.24	0.36	0.07 – 0.39
XPF/ERCC4 R415Q	0.02	0.08	0.07 – 0.11
XPG/ERCC5 D1104H	0.45	0.21	0.21 – 0.28
XPC A499V	0.07	0.26	0.23 – 0.24
XPC K939Q	0.32	0.40	0.40 – 0.42
RAD23B A249V	0.04	0.19	0.17 – 0.20

Table 2

Association between DNA repair genotypes and colon cancer risk by race

	African Americans			Whites		
	Cases/controls	**OR[a]**	**95% CI**	**Cases/controls**	**OR[a]**	**95%CI**
XPD/ERCC2						
DD	170 / 258	1.0	Ref	136 / 230	1.0	Ref
DN	45 / 60	1.1	(0.7, 1.8)	119 / 238	0.8	(0.6, 1.1)
NN	5 / 3	2.7	(0.6, 11.9)	40 / 57	1.2	(0.7, 1.8)
DN+NN	50 / 63	1.2	(0.8, 1.9)	159 / 295	0.9	(0.7, 1.2)
XPD/ERCC2						
KK	128 / 186	1.0	Ref	114 / 209	1.0	Ref
KQ	83 / 115	1.1	(0.8, 1.6)	136 / 251	1.0	(0.7, 1.3)
QQ	13 / 19	1.0	(0.5, 2.1)	49 / 65	1.3	(0.9, 2.1)
KQ+QQ	96 / 134	1.1	(0.8, 1.5)	185 / 316	1.1	(0.8, 1.4)
XPF/ERCC4						
RR	217 / 307	1.0	Ref	251 / 455	1.0	Ref
RQ	8 / 16	0.8	(0.3, 1.8)	52 / 74	1.3	(0.9, 1.9)
QQ	1 / 0	--	--	1 / 7	0.3	(0.03, 2.1)
RQ+QQ	9 / 16	0.8	(0.4, 1.9)	53 / 81	1.2	(0.8, 1.7)
XPG/ERCC5						
DD	65 / 100	1.0	Ref	183 / 335	1.0	Ref
DH	120 / 151	1.2	(0.8, 1.8)	100 / 170	1.1	(0.8, 1.5)
HH	39 / 66	0.9	(0.5, 1.5)	15 / 27	1.1	(0.5, 2.0)
DH+HH	159 / 217	1.1	(0.8, 1.6)	113 / 197	1.1	(0.8, 1.5)
XPC A499V						
AA	175 / 276	1.0	Ref	177 / 293	1.0	Ref
AV	51 / 47	1.7	(1.1, 2.6)	104 / 207	0.8	(0.6, 1.1)
VV	2 / 0	--	--	22 / 35	1.0	(0.6, 1.8)
AV+VV	53 / 47	1.7	(1.1, 2.7)	126 / 242	0.9	(0.7, 1.2)
XPC K939Q						
KK	126 / 149	1.0	Ref	103 / 191	1.0	Ref

	African Americans			Whites		
	Cases/controls	**OR[a]**	**95% CI**	**Cases/controls**	**OR[a]**	**95%CI**
KQ	91 / 142	0.8	(0.6, 1.2)	148 / 252	1.1	(0.8, 1.5)
QQ	9 / 31	0.3	(0.2, 0.8)	52 / 89	1.1	(0.7, 1.6)
KQ+QQ	100 / 173	0.7	(0.5, 1.0)	200 / 341	1.1	(0.8, 1.5)
RAD23B A249V						
AA	203 / 292	1.0	Ref	195 / 327	1.0	Ref
AV	20 / 28	0.9	(0.5, 1.7)	99 / 182	0.9	(0.7, 1.2)
VV	--	--	--	3 / 8	0.7	(0.2, 2.5)
AV+VV	20 / 28	0.9	(0.5, 1.7)	102 / 190	0.9	(0.7, 1.2)
# **'At-Risk' Alleles**[b]						
0 or 1	49 / 69	1.0	Ref	25 / 49	1.0	Ref
2 or 3	105 / 164	0.9	(0.6, 1.4)	93 / 181	0.9	(0.5, 1.6)
4 or 5	44 / 61	1.0	(0.6, 1.8)	111 / 185	1.1	(0.6, 1.8)
6 or more	6 / 6	1.1	(0.3, 3.9)	42 / 69	1.1	(0.6, 2.0)

[a] Adjusted for age, gender and offsets

[b] The 'at-risk' allele was defined as follows: *XPD D312N*: N allele; *XPD K751Q*: Q allele; *XPF R415Q*: Q allele; *XPD D1104H*: H allele; *XPC A499V*: V allele; *XPCK939Q*: K allele; *RAD23B A249V*: V allele. The *XPC 939* less common allele was associated with reduced risk in this population, thus the more common allele was considered the 'at-risk' allele.

Table 3

Association between well-done red meat intake and colon cancer by DNA repair genotype

	All Participants						
	Low well-done red meat[a]			High well-done red meat[a]			P for interaction[c]
	Cases/controls	OR[b]	95% CI	Cases/controls	OR[b]	95%CI	
Overall	212 / 431	1.0	Ref	324 / 431	1.1	(0.9, 1.4)	
XPD/ERCC2							
DD	116 / 231	1.0	Ref	190 / 257	1.0	(0.8, 1.4)	
DN	67 / 157	0.8	(0.6, 1.2)	97 / 141	1.1	(0.8, 1.6)	
NN	23 / 38	1.3	(0.7, 2.3)	22 / 22	1.4	(0.7, 2.7)	0.63
DN+NN	90 / 195	0.9	(0.6, 1.3)	119 / 163	1.1	(0.8, 1.6)	0.46
XPD/ERCC2							
KK	91 / 174	1.0	Ref	151 / 221	1.0	(0.7, 1.4)	
KQ	92 / 197	0.9	(0.6, 1.3)	127 / 169	1.1	(0.8, 1.6)	
QQ	23 / 48	1.0	(0.6, 1.8)	39 / 36	1.6	(0.9, 2.8)	0.33
KQ+QQ	115 / 245	0.9	(0.7, 1.3)	166 / 205	1.2	(0.8, 1.7)	0.21
XPF/ERCC4							
RR	183 / 377	1.0	Ref	285 / 385	1.1	(0.9, 1.5)	
RQ	25 / 47	1.1	(0.7, 1.9)	35 / 43	1.3	(0.8, 2.2)	
QQ	1 / 7	0.3	(0.04, 2.6)	1 / 0	--	--	0.63
RQ+QQ	26 / 54	1.0	(0.6, 1.7)	36 / 43	1.3	(0.8, 2.2)	0.73
XPG/ERCC5							
DD	108 / 226	1.0	Ref	140 / 209	1.0	(0.7, 1.5)	
DH	78 / 162	1.0	(0.7, 1.4)	142 / 159	1.3	(0.9, 1.9)	
HH	21 / 38	1.1	(0.6, 2.0)	33 / 55	0.9	(0.5, 1.5)	0.36
DH+HH	99 / 200	1.0	(0.7, 1.4)	175 / 214	1.2	(0.9, 1.7)	0.45
XPC A499V							
AA	140 / 276	1.0	Ref	212 / 293	1.1	(0.8, 1.4)	
AV	63 / 130	1.0	(0.7, 1.4)	92 / 124	1.1	(0.8, 1.6)	
VV	8 / 24	0.7	(0.3, 1.7)	16 / 11	1.8	(0.8, 4.2)	0.36

All Participants							
	Low well-done red meat[a]			High well-done red meat[a]			P for interaction[c]
	Cases/controls	OR[b]	95% CI	Cases/controls	OR[b]	95%CI	
AV+VV	71 / 154	0.9	(0.6, 1.3)	108/135	1.2	(0.8, 1.7)	0.44
XPC K939Q							
KK	81 / 176	1.0	Ref	148 / 164	1.5	(1.0, 2.2)	
KQ	102 / 192	1.3	(0.9, 1.8)	137 / 202	1.2	(0.8, 1.7)	
QQ	27 / 60	1.0	(0.6, 1.8)	34 / 60	0.9	(0.6, 1.6)	0.15
KQ+QQ	129 / 252	1.2	(0.8, 1.7)	171 / 262	1.1	(0.8, 1.6)	0.05
RAD23B							
AA	149 / 296	1.0	Ref	249 / 323	1.1	(0.8, 1.4)	
AV	53 / 117	0.9	(0.6, 1.3)	66 / 93	1.2	(0.8, 1.7)	
VV	2 / 4	0.8	(0.2, 4.8)	1 / 4	0.6	(0.1, 5.2)	0.65
AV+VV	55 / 121	0.9	(0.6, 1.3)	67 / 97	1.1	(0.8, 1.7)	0.43

[a] Low intake: < median (21.5 g/day) intake; high intake: >= median intake

[b] Adjusted for age, race, gender, offsets, total energy intake, energy-adjusted fat intake, dietary fiber intake, and total meat intake

[c] p-value for likelihood ratio test; for each SNP, the first value represents the p-value comparing the three genotypes, the second value represents the p-value comparing the heterozygotes + homozygous variant genotypes to the homozygous wild-type genotype

Table 4

Association between colon cancer risk and meat and meat-derived carcinogen intake and DNA repair genotype

	Overall		# 'at-risk' alleles[d]				
			0–3 alleles		≥4 alleles		
	Cases/controls	OR (95% CI)	Cases/controls[e]	OR (95% CI)	Cases/controls[e]	OR (95% CI)	$P_{interaction}$[f]
Red Meat (g/day)[a]							
<28.4	210 / 431	1.0 (Ref)	104 / 220	1.0 (Ref)	88 / 178	1.0 (0.7, 1.4)	0.46
≥28.4	326 / 431	1.1 (0.9, 1.4)	169 / 243	1.1 (0.8, 1.6)	115 / 143	1.3 (0.9, 1.9)	
Pan fried red meat (g/day)[a]							
<8.9	202 / 431	1.0 (Ref)	95 / 212	1.0 (Ref)	87 / 180	1.2 (0.9, 1.7)	0.68
≥8.9	334 / 431	1.3 (1.0, 1.7)	178 / 251	1.1 (0.8, 1.7)	116 / 141	1.5 (1.1, 2.2)	
Well-done red meat (g/day)[a]							
<21.5	212 / 431	1.0 (Ref)	103 / 215	1.0 (Ref)	86 / 180	1.0 (0.7, 1.5)	0.32
≥21.5	324 / 431	1.1 (0.9, 1.4)	170 / 248	1.0 (0.7, 1.5)	117 / 141	1.4 (1.0, 2.0)	
MeIQx (ng/day) [b]							
<37.3	197 / 431	1.0 (Ref)	95 / 211	1.0 (Ref)	83 / 180	1.2 (0.9, 1.7)	0.57
≥37.3	339 / 431	1.3 (1.0, 1.7)	178 / 252	1.1 (0.8, 1.6)	120 / 141	1.5 (1.1, 2.2)	
DiMeIQx (ng/day)[b]							
<2.4	206 / 431	1.0 (Ref)	95 / 219	1.0 (Ref)	87 / 170	1.4 (1.0, 1.9)	0.65
≥2.4	330 / 431	1.3 (1.0, 1.7)	178 / 244	1.3 (0.9, 1.9)	116/ 151	1.6 (1.1, 2.3)	
PhIP (ng/day)[b]							
<45.9	228 / 431	1.0 (Ref)	123 / 231	1.0 (Ref)	83 / 163	1.0 (0.7, 1.3)	0.41
≥45.9	308 / 431	1.1 (0.8, 1.3)	150 / 232	1.1 (0.7, 1.5)	120 / 158	1.2 (0.9, 1.8)	
BaP (ng/day)[c]							
<7.7	242 / 431	1.0 (Ref)	130 / 255	1.0 (Ref)	87 / 136	1.1 (0.8, 1.5)	0.19
≥7.78	294 / 431	1.0 (0.8, 1.3)	143 / 208	1.4 (1.0, 2.0)	116 / 185	1.1 (0.8, 1.6)	

[a] Adjusted for age, race, gender, offsets, total energy intake, energy-adjusted fat intake, dietary fiber intake, and total meat intake

[b] Adjusted for age, race, gender, offsets, total energy intake, energy-adjusted fat intake, dietary fiber intake, and other HCA variables

[c] Adjusted for age, race, gender, offsets, total energy intake, energy-adjusted fat intake, dietary fiber intake

[d] The 'at-risk' allele was defined as follows: *XPD D312N*: N allele; *XPD K751Q*: Q allele; *XPF R415Q*: Q allele; *XPD D1104H*: H allele; *XPC A499V*: V allele; *XPCK939Q*: K allele; *RAD23B A249V*: V allele

[e] Total sample size may not add up to overall sample size due to missing data for some genotypes

[f] P-values for likelihood ratio test