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Polymorphisms in base excision repair genes as colorectal cancer risk factors and modifiers of the effect of diets high in red meat

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Abstract

Background—A diet high in red meat is an established colorectal cancer (CRC) risk factor. Carcinogens generated during meat cooking have been implicated as causal agents, and can induce oxidative DNA damage, which elicits repair by the base excision repair (BER) pathway.

Methods—Using a family-based study we investigated the role of polymorphisms in four BER genes (*APEX1* Gln51His, Asp148Glu; *OGG1* Ser236Cys; *PARP* Val742Ala; *XRCC1* Arg194Trp, Arg280His, Arg399Gln) as potential CRC risk factors and modifiers of the association between high-red meat or poultry diets and CRC risk. We tested for gene-environment interactions using case-only analyses (N = 577) and compared statistically significant results to those obtained using case-unaffected sibling comparisons (N = 307 sibships).

Results—Carriers of the *APEX1* codon 51 Gln/His genotype had a reduced CRC risk compared to carriers of the Gln/Gln genotype (OR 0.15, 95% CI 0.03-0.69, p = 0.015). The association between higher red meat intake (>3 servings/week) and CRC was modified by the *PARP* Val762Ala SNP (case-only interaction p = 0.026). This SNP also modified the association between higher intake of high-temperature cooked red meat (case-only interaction p = 0.0009).

Conclusions—We report evidence that the BER pathway *PARP* gene modifies the association of diets high in red meat cooked at high temperatures with risk of CRC.

Impact—Our findings suggest a contribution to colorectal carcinogenesis of free radical damage as one of the possible harmful effects of a high-red meat diet.

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INTRODUCTION

Diets high in red meat are convincing colorectal cancer (CRC) risk factors (1). Our results, and those of others (2-4), support a role for chemical carcinogens that form in cooked or processed meats in CRC risk, such as heterocyclic amines (HCAs), polycyclic aromatic hydrocarbons (PAHs), and N-nitroso compounds (NOCs) (5). The latter can also form endogenously after red meat consumption (6).

Among the several types of DNA damage induced by meat carcinogens are oxidative base damage and single strand breaks, which are repaired by the base excision repair pathway (BER) (7). Polymorphisms in DNA repair pathways could affect the levels of DNA lesions that accumulate in the colorectal mucosa, thus influencing CRC risk. Previously, we reported interactions between a polymorphism in a bulky adduct repair gene and diets high in red meat on CRC risk (2). Only one study has reported data on one BER gene polymorphism jointly with red meat intake (8). In the present study, we examined whether single nucleotide polymorphisms (SNPs) in four genes that play key roles in BER (*APEX1, PARP, XRCC1,* and *OGG1*) were associated with CRC risk and whether they modified the effect of diets high in red meat and poultry, taking into account cooking practices.

METHODS

Study Subjects

We conducted a family-based case-control association study with subjects recruited from the USC Consortium of the Colon Cancer Family Registry (Colon-CFR)(2,9). Briefly, incident CRC cases (probands) and unaffected siblings and cousins were recruited through the population-based registries affiliated with USC Consortium component centers (9). Unaffected siblings in the families of the probands were selected as controls. All participants signed informed consent forms, donated a blood sample, and completed an in–person questionnaire that provided data on demographic, diet, physical activity and other lifestyle factors. Details on the ascertainment and eligibility criteria used by the USC Consortium have been published (9). In our analyses, we included affected probands (577) and unaffected siblings (362) recruited from the population-based registries between 1997-2002, for a total of 307 sibships.

Exposure assessment

We used data collected with the baseline risk factor questionnaire used by all Colon CFR sites (2,10): number of servings per week of red meat (beef, lamb, pork), red meat cooked by pan-frying/oven-broiling/grilling, level of doneness of red meat on the outside (lightly, medium or heavily browned), level of doneness on the inside (red, pink, brown), number of servings of poultry cooked by pan-frying/oven-broiling/grilling, and level of doneness of poultry on the outside (lightly, medium or heavily browned). All questions were asked in reference to the two years before the cancer diagnosis of the proband or date of interview for unaffected siblings.

SNP Selection and Genotyping

We genotyped *APEX1* Glu51His (rs1048945) and Asp148Glu (rs3136820), *OGG1* Ser236Cys (rs1052133), *PARP* Val742Ala (rs1136410), *XRCC1* Arg194Trp (rs1799782), Arg280His (rs25487), and Arg399Gln (rs25489). These SNPs were selected based on their putative impact on protein function and/or previous evidence of cancer risk associations (11-15). Genotypes were obtained using Taqman assays (ABI, Foster City, CA), including 6% duplicated samples for quality control. We observed 100% concordance between all duplicate samples, and call rates >99%.

Data Analysis

SNP analyses—The observed genotypic frequencies among Caucasian unaffected siblings (82.6% of all siblings) did statistically significantly differ those expected under Hardy-Weinberg equilibrium. We estimated odds ratios (ORs) and 95% confidence intervals (CI) for each genotype, and per allele ORs assuming a log-additive mode of action, using 1: N matched conditional logistic regression. Adjustment for age and gender did not change estimates by more than 10%; therefore, these terms were not included in final models. Haplotype probabilities including SNPs in proximate chromosomal locations were calculated using the E-M algorithm. Global tests for association of haplotype alleles with CRC were conducted using likelihood ratio tests.

Gene x Exposure (GxE) analyses—Given that we had data and samples available for 577 probands, but only 307 of these had siblings available for case-unaffected sibling comparisons, we decided to test for interaction using case-only analyses to maximize statistical power. We created dichotomous exposure variables of meat intake using the median among cousins as cutpoints (9) and tested for GxE interactions in case-only analyses using unadjusted unconditional logistic regression models with the dichotomized exposure as the outcome variable and the 7 individual SNPs as the independent variables. These obtained ORs are equivalent to interaction ORs (IORs), provided that the prevalence of the gene variants is independent of exposure prevalence (16). We tested this assumption of independence among the cousins of the probands, who are more representative of the underlying population than the unaffected siblings, and found no statistically significant association between any of the SNPs and the exposures. We evaluated the potential confounding effects of: age at interview, gender, history of Crohn's disease, ulcerative colitis irritable bowel syndrome, diverticulitis, diabetes and high cholesterol, marital status, folate supplements, weight 2 years before interview and at age 20, height, years lived in the USA, BMI, aspirin/ibuprofen use, physical activity, fruits and vegetables per week, level of education and income. Adjustment for these potential confounders did not change ORs for meat variables by greater than 10%. Hence, they were not included in interaction models. For 87.5% of the subjects, we also had dietary data obtained with an FFQ (10) for total energy intake, total protein and total saturated fat intake. Consideration of these variables did not change risk estimates by more than 10%, so were also not included in our final models. We considered potential heterogeneity of the GxE interactions by tumor sub-site (colon versus rectum), using methods we previously described (2). To confirm our significant case-only GxE ORs, we compared them to IORs computed using proband-unaffected siblings, testing for interactions on a multiplicative scale using conditional logistic regression models. To account for multiple testing we applied the Bonferroni correction. We present uncorrected ORs and CIs and indicate whether they were or not compatible with chance after Bonferroni correction. All tests were two-sided; all analyses were conducted using STATA version 11 (STATA Corporation, College Station, TX).

RESULTS

BER polymorphisms and CRC risk

When comparing probands to unaffected siblings we observed an inverse association between the *APEX1* codon 51 His allele and CRC risk (log-additive per His allele OR = 0.14; 95% CI = 0.03-0.66; p = 0.012) (Table 1). This finding was compatible with chance after Bonferroni correction. Analyses of *APEX1* haplotypes defined by the codons 51 and 148 polymorphisms (D' = 0.607; R^2 = 0.0130 among Whites) showed that the association between the codon 51 Gln allele and CRC risk is driven by the His^{51}-Asp^{148} haplotype (12 controls/6 cases) (OR for this haplotype= 0.17; 95% CI = 0.04-0.79, p = 0.024; global test p

= 0.015). There was no heterogeneity of the main effects by tumor site (colon vs rectum) for any of the 7 SNPs investigated.

BER polymorphisms, red meat, and poultry intake and CRC risk

The associations between diets higher (> 3 servings/week) in total red meat intake or higher in red meat cooked by pan-frying, oven-broiling or grilling and CRC was modified by the *PARP* Val762Ala polymorphism (total red meat case-only IOR = 1.41, p = 0.0255; high temperature cooked red meat case-only IOR = 1.66, p = 0.0009) (Table 2). CRC cases who ate more than 3 servings per week of total red meat or red meat cooked using high-temperature methods were more likely to carry one or two copies of the Ala allele rather than the Val/Val genotype. The finding for total red meat intake was compatible with chance after Bonferroni correction, whereas the finding for high-temperature cooked red meat remained statistically significant.

We found evidence that *XRCC1* Arg399Gln SNP might modify the association between meat level of doneness on the outside (case-only IOR = 0.76, p = 0.049) or the inside (case-only IOR = 0.75, p = 0.022) with CRC risk (Table 2). Both findings were compatible with chance after Bonferroni correction.

We found no evidence that any of these GxE interactions differed by tumor subsite, nor evidence that any of the 7 SNPs investigated modified the relation between higher intake of high-temperature cooked poultry or poultry level of doneness and CRC risk (data not shown).

We compared the statistically significant findings we described above for the *PARP* Val762Ala SNP to results of proband-sibling GxE interaction, analyses for which we had lower statistical power. When considering total red meat intake, the IOR were of similar magnitude to case-case analyses (IOR = 1.54; 95% CI = 0.83-2.86; p = 0.170), albeit not statistically significant (Table 3). When considering red meat cooked by high temperature methods, sibship analyses confirmed the previously observed interaction (IOR = 2.30; 95% CI = 1.20-4.38; p = 0.012), indicating a stronger association between higher intake of high-temperature cooked red meat and CRC among carriers of one or two copies of the Ala allele (OR for intake of > 3 servings/week of high-temperature cooked red meat per Ala allele = 2.64; 95% CI = 1.54-4.51; p = <0.0001) than among carriers of two copies of the Val allele (OR for > 3 servings/week of high-temperature cooked meat among Val/Val carriers = 1.17; 95% CI = 0.76-1.77; p = 0.484)(Table 3). We found no evidence of heterogeneity by tumor site for this interaction (data not shown). A comparison of the *XRCC1* Arg399Gln findings to results of proband-sibling GxE interaction analyses showed little support for an interaction between this SNP and level of doneness of red meat (Table 3).

DISCUSSION

We report an association between the *APEX1* Glu51His SNP and CRC risk and a modifier role for the *PARP* Val762Ala SNP on the effect of diets higher in high-temperature cooked red meat. Given the role PARP plays in oxidative damage repair, our findings support a contribution of free radicals from diets high in red meat to colorectal carcinogenesis.

PARP participates in DNA single strand break detection and transcription regulation. Changes in PARP expression levels have been linked to colorectal carcinogenesis (17). Previously, we reported a positive association between the *PARP* Lys940Arg, which is rare among Caucasians, and CRC risk among Singapore Chinese (18). Positive associations between the *PARP* Val762Val SNP and other cancers have been reported (19-21). Recently, we reported that *PARP* Val762Val modifies the association between diets high in n-3-PUFA

and rectal cancer risk (22). Our observation of a stronger association between high intake of high-temperature cooked red meat and CRC risk among carriers of the *PARP* codon 762 Ala allele is consistent with the reported reduced DNA repair activity of the protein encoded by this allele (11), which might lead to compromised BER proficiency and thus increased cancer risk. The multiple roles of PARP in DNA repair, transcription regulation, and colorectal carcinogenesis, might explain why we found stronger evidence of a modifier role for a SNP on this and not other BER genes. We did not see heterogeneity of gene-meat interactions across tumor subsites, suggesting that the modifying role of *PARP* may not change throughout the colorectum.

Carriers of the *APEX1* codon 51 Histidine allele had reduced CRC risk, an inverse association driven by the His^{51}-Asp^{148} haplotype. Two other studies have reported positive associations between the *APEX1* codon 148 Glu variant allele and CRC risk (23,24); neither of them investigated the Gln51His SNP. Similar estimates for the association of the haplotypes formed by these SNPs with colorectal adenomas have previously been reported (25). The APEX1 protein removes DNA apurinic/apyrimidinic sites as part of the BER pathway, and participates in the activation of various transcription factors. It is still unknown if the Gln51His SNP affects APE1 function.

The family-based design of our study provides reassurance that our results are unlikely to be confounded by population admixture. Two limitations in our study are that the selected SNPs do not account for all genetic variation in each of the selected genes from the BER pathway and that some of our findings are based on relatively small numbers. Therefore, larger studies using tagSNPs will be needed to confirm our findings.

In summary, our findings suggest a contribution to colorectal carcinogenesis of free radical damage as one of the possible harmful effects of red meat intake.

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Table 1

Base excision repair SNPs and colorectal cancer risk

		Colorectal Cancer			
Gene	**MAF[a]**	**Co/Ca**	**OR[b]**	**95% CI**	**p- value**
APEX1 Glu51His	0.04				
Gln/Gln		332/294	1.0[Ref]		
Gln/His		28/14	0.15	0.03-0.69	0.015
His/His		1/0	-	-	-
APEX1 Asp148Glu	0.47				
Asp/Asp		108/102	1.0[Ref]		
Asp/Glu		167/137	0.76	0.49-1.19	0.235
Glu/Glu		84/65	0.72	0.40-1.32	0.289
per allele Glu OR[c]			0.84	0.62-1.14	0.275
OGG1 Ser326Cys	0.19				
Ser/Ser		217/172	1.0[Ref]		
Ser/Cys		127/117	1.33	0.87-2.04	0.186
Cys/Cys		18/19	1.89	0.71-5.04	0.203
per allele Cys OR[c]			1.34	0.92-1.97	0.120
PARP Val762Ala	0.17				
Val/Val		239/196	1.0[Ref]		
Val/Ala		110/100	1.15	0.73-1.80	0.547
Ala/Ala		12/12	1.43	0.50-4.09	0.505
per allele Ala OR[c]			1.16	0.79-1.72	0.439
XRCC1 Arg194Trp	0.07				
Arg/Arg		303/261	1.0[Ref]		
Arg/Trp		53/43	0.78	0.42-1.42	0.397
Trp/Trp		4/1	-	-	-
per allele Trp OR[c]			0.67	0.37-1.21	0.188
XRCC1 Arg280His	0.03				
Arg/Arg		337/290	1.0[Ref]		

Gene	MAF[a]	Colorectal Cancer Co/Ca	OR[b]	95% CI	p- value
Arg/His		24/18	0.83	0.37-1.83	0.638
His/His		0/0	-	-	-
XRCC1 Arg399Gln	0.40				
Arg/Arg		136/120	1.0[Ref]		
Arg/Gln		181/144	0.87	0.58-1.31	0.501
Gln/Gln		43/41	0.98	0.50-1.94	0.960
per allele Trp OR[c]			0.94	0.69-1.30	0.748

[a] MAF, minor allele frequency, estimated among unaffected siblings;

[b] Unadjusted;

[c] per allele OR assuming a log-additive model

Table 2

Case-only analyses of interactions of BER polymorphisms with red meat intake

		OR[a]	95% CI	p-value
Total red meat intake	≤3 or >3 servings per week[c]			
PARP Val762Ala				
Val/Val	189/198	1.0[Ref]		
Val/Ala	62/106	1.63	1.13-2.37	0.010
Ala/Ala	9/12	1.28	0.52-3.09	0.594
per Ala allele OR[b]		*1.41*	*1.04-1.91*	*0.026*
Red meat cooked by pan-frying, oven-broiling or grilling	≤3 or >3 servings per week[c]			
PARP Val762Ala				
Val/Val	240/144	1.0[Ref]		
Val/Ala	81/87	1.79	1.24-2.58	0.002
Ala/Ala	9/12	2.22	0.91-5.40	0.078
per Ala allele OR[b]		*1.66*	*1.23-2.25*	*0.0009*
Level of doneness of red meat from outside	Light or Medium/Heavy[d]			
XRCC1 Arg399Gln				
Arg/Arg	113/127	1.0[Ref]		
Arg/Gln	137/124	0.81	0.57-1.14	0.227
Gln/Gln	44/26	0.53	0.30-0.91	0.021
per Gln allele OR[b]		*0.76*	*0.58-0.99*	*0.050*
Level of doneness of red meat from inside	Red or Pink/Brown[e]			
XRCC1 Arg399Gln				
Arg/Arg	113/127	1.0[Ref]		
Arg/Gln	137/124	0.81	0.57-1.14	0.227
Gln/Gln	44/26	0.53	0.30-0.91	0.021
per Gln allele OR[b]		*0.75*	*0.59-0.96*	*0.022*

[a] Case-only analyses were done using unadjusted unconditional logistic regression models using the dichotomized exposure as the outcome variable, using individual SNPs as the independent variables to obtain ORs that would be equivalent to interaction OR (IOR).

[b] Unadjusted per allele ORs assuming a log-additive model;

[c] ≤3 servings per week as referent group;

[d] Light or Medium as referent group;

[e] Red or pink as referent group.

Table 3

PARP Val762Ala or *XRCC1* Arg399Gln and red meat interactions: case-sib comparisons

	Co/Ca ≤ 3 servings per week	Co/Ca > 3 servings per week	OR[a]	95% CI	p-value
Total red meat intake					
***PARP* Val762Ala**					
Val/Val	126/92	112/104	1.53	0.98-2.39	0.061
Val/Ala	57/35	53/65	2.19	1.21-3.93	0.009
Ala/Ala	8/4	4/8	4.81	0.76-30.5	0.096
per Ala allele			*2.31*	*1.38-3.87*	*0.001*
interaction OR[b] = 1.54 (95% CI = 0.83-2.86; p = 0.170)					
Red meat cooked by pan-frying, oven-broiling or grilling					
***PARP* Val762Ala**					
Val/Val	149/118	89/76	1.17	0.76-1.78	0.484
Val/Ala	75/50	35/50	2.52	1.37-4.65	0.003
Ala/Ala	9/4	3/8	7.73	1.04-57.2	0.045
per Ala allele			2.64	1.51-4.51	<0.0001
interaction OR[b] = 2.30 (95% CI = 1.20-4.39; p = 0.012)					
	Co/Ca Light/Medium brown	Co/Ca Heavily brown	OR[c]	95% CI	p-value
Level of doneness of red meat from outside					
***XRCC1* Arg399Gln**					
Arg/Arg	93/82	42/38	0.96	0.55-1.69	0.896
Arg/GLn	129/98	51/46	1.26	0.75-2.10	0.383
Gln/Gln	33/31	10/10	1.25	0.47-3.30	0.659
per Gln allele			*1.17*	*0.79-1.73*	*0.433*
interaction OR[b] = 1.16 (95% CI = 0.70-1.92; p = 0.572)					
	Co/Ca Red/Pink	Co/Ca Brown	OR[d]	95% CI	p-value
Level of doneness of red meat on the inside					
***XRCC1* Arg399Gln**					
Arg/Arg	71/55	64/65	1.33	0.79-2.26	0.276

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	Co/Ca ≤ 3 servings per week	Co/Ca > 3 servings per week	OR[a]	95% CI	p-value
Arg/GLn	93/72	88/72	1.11	0.69-1.79	0.659
Gln/Gln	26/23	17/18	1.09	0.45-2.63	0.851
per Gln allele			*1.14*	*0.80-1.63*	*0.471*
interaction OR[b] = 0.86 (95% CI = 0.54-1.37; p = 0.531)					

[a] OR for > 3 servings/week versus ≤ 3 servings per week within each genotype subgroup;

[b] OR from interaction term between gene and exposure in models used to test for overall GxE interaction;

[c] OR for heavily brown versus light/medium brown within each genotype subgroup;

[d] OR for brown versus red/pink within each genotype subgroup.