Meat Intake, Heterocyclic Amine Exposure, and Metabolizing Enzyme Polymorphisms in Relation to Colorectal Polyp Risk

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Abstract

Most colorectal cancers arise from adenomatous polyps or certain hyperplastic polyps. Only a few studies have investigated potential genetic modifiers of the associations between meat intake and polyp risk, and results are inconsistent. Using data from the Tennessee Colorectal Polyp Study, a large colonoscopy-based study, including 1,002 polyp cases (557 adenoma only, 250 hyperplastic polyp only, 195 both polyps) and 1,493 polyp-free patients, we evaluated the association of colorectal polyp risk with carcinogen exposure from meat and genetic polymorphisms in enzymes involved in heterocyclic amine (HCA) metabolism, including N-acetyltransferase 1 (NAT1) and N-acetyltransferase 2 (NAT2), cytochrome P450 1A2 (CYP1A2), and aryl hydrocarbon receptor (AhR). Data on intake levels of meats by preparation methods, doneness preferences, and other lifestyle factors were obtained. Fourteen single nucleotide polymorphisms in the *AhR*, *CYP1A2*, *NAT1*, and *NAT2* genes were evaluated. No clear association was found for any polymorphisms with polyp risk. However, apparent interactions were found for intake of meat and HCAs with *AhR*, *NAT1*, and *NAT2* genotypes, and the interactions were statistically significant for the group with both adenomatous and hyperplastic polyps. Dose-response relationships with meat or HCA intake were found only among those with the *AhR GA/AA* (*rs2066853*) genotype, *NAT1* rapid, or *NAT2* rapid/intermediate acetylators but not among those with other genotypes of these genes. This dose-response relationship was more evident among those with both *AhR GA/AA* and the *NAT1* rapid acetylator than those without this genotype combination. These results provide strong evidence for a modifying effect of metabolizing genes on the association of meat intake and HCA exposure with colorectal polyp risk. (Cancer Epidemiol Biomarkers Prev 2008;17(2):320–9)

Introduction

Meat consumption, particularly red and processed meat consumption, has been linked to the increased risk of colorectal cancer in many previous epidemiologic studies (1). Mutagens, such as heterocyclic amines (HCA) and polycyclic aromatic hydrocarbons (PAH), are formed during high-temperature cooking of meats (2). These compounds are mutagenic in Ames/*Salmonella* assays and cause colon tumors in laboratory animals (3). To exert their mutagenic action, HCAs require enzyme-catalyzed activation consisting of *N*-oxidation by hepatic cytochrome P450 1A2 (CYP1A2) and other extrahepatic *P*450 isozymes followed by *O*-acetylation by *N*-acetyltransferase 1 (NAT1) and N-acetyltransferase 2 (NAT2; ref. 4). The aryl hydrocarbon receptor (AhR or dioxin receptor) is an important mediator for xenobiotic signaling to enhance the expression of phase I and II enzymes (5), which affects HCA metabolism. HCAs bind strongly to DNA after activation, and detectable levels of 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP)-DNA adducts in the colon mucosa of rats and humans have been found (3, 6). Rapid *NAT1* or *NAT2* acetylators, in conjunction with a preference for well-done meat, have been shown to be associated with colorectal cancer risk in some but not in other studies (7, 8).

Colorectal adenomatous polyps are well-established precursors of colorectal cancer (9). The association of red meat intake with the risk (10-12) and recurrence (13, 14) of colorectal adenomas has been evaluated in several previous studies with inconsistent results. Studies on the effects of genetic polymorphisms in the *CYP1A2*, *NAT1*, and *NAT2* genes and their combined effects on colorectal adenomas with well-done meat or HCA intake and these genetic polymorphisms in these genes have also been inconsistent (15-18). Hyperplastic polyps, formerly considered innocuous polyps, may have malignant potential

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through pathways other than the adenoma-carcinoma sequence and may be a precursor for microsatellite-instable (MSI) colorectal cancers (19). To our knowledge, only one study has evaluated the modifying effect of genes on the environmental factors in risk of hyperplastic polyps (20). In this study, we evaluated genetic polymorphisms of genes involved in HCA metabolism (*CYP1A2, NAT1, NAT2*, and *AhR*) and possible interactive effects of these genes with dietary intake of meat and HCAs in the risk of colorectal adenomatous and hyperplastic polyps in a large-scale colonoscopy-based study.

Materials and Methods

Tennessee Colorectal Polyp Study. The Tennessee Colorectal Polyp Study (TCPS) is an ongoing colonoscopy-based study being conducted in Nashville, TN. Eligible participants, ages between 40 and 75 years, were identified from patients scheduled for colonoscopy at the Vanderbilt Gastroenterology Clinic and the Veteran's Affairs Tennessee Valley Health System Nashville campus between February 1, 2003 and December 31, 2005. Excluded from the study were participants who had genetic colorectal cancer syndromes (e.g., hereditary nonpolyposis colorectal cancer or familial adenomatous polyposis), prior history of inflammatory bowel disease, adenomatous polyps, or any cancer other than non-melanoma skin cancer. The study was approved by the relevant committees for the use of human participants in research. Of these 4,617 eligible participants, 3,083 provided written informed consent (67%), and the majority of them (n = 2,752; 89.3%) were recruited either before or on the day of scheduled colonoscopy. A subset of participants (n = 331; 10.7%) were recruited after the colonoscopy largely because they were not timely identified to allow time for recruitment before the colonoscopy. Among the 3,083 participants, 2,678 (87%) completed a telephone interview and 2,355 (76%) completed a self-administered food frequency questionnaire (FFQ) developed for a similar population in the southern United States. Details for the FFQ used in this study have been described elsewhere (21). The median time between the colonoscopy and the completion of the survey was 13 days, and interviewers were blinded to the results of the colonoscopy. Of those who completed the telephone interviews, 98% of cases and 98% of controls donated a blood or buccal cell sample. For all participants recruited at the time of colonoscopy, blood or buccal cells were collected before the start of the colonoscopy. For participants recruited after colonoscopy, buccal cells were collected by the participant at home using a mouthwash kit and sent through the mail to the study laboratory for processing. These samples were processed on the same day, typically within 4 h of sample collection, and were stored at -80°C until relevant bioassays could be conducted.

Colonoscopic procedures were done and reported using standard clinical protocols by the patient's gastroenterologist. Likewise, all pathology diagnoses were determined by hospital pathologists and reported as part of routine care. Data were abstracted from these colonoscopy and pathology reports to classify study participants into one of the following study groups: adenomatous polyps only, hyperplastic polyps only, presence of both adenomatous and hyperplastic polyps, and polyp-free patients. Polyp-free patients are used as the controls for this study. To be diagnosed as a polyp-free control, the participant had to have a complete colonoscopy reaching the cecum and be polyp-free at colonoscopy.

Assessment of Meat and HCA Intake. Details for the meat consumption questionnaire and meat mutagen calculation methods have been described previously (22). In brief, a telephone interview was conducted to obtain information on medication use, demographics, medical history, and lifestyle, including questions on usual intake frequency, portion size, and preparation of 11 meats (hamburgers or cheeseburgers from fast food, hamburgers or cheeseburgers not from fast food, beef steaks, pork chops or ham steaks, bacon, sausage, hot-dogs or franks, chicken, fish, meat gravies made with drippings, and short ribs or spareribs). For each meat item, we also asked how often the participant ate the meat according to different cooking methods; that is, oven broiled or oven baked, grilled or barbecued, pan fried, deep fried (for chicken and fish), and all other ways, for example, boiled, steamed, or microwaved.

Participants reported their usual preference level of meat doneness by using a series of three-color photographs representing increasing levels of doneness for each of the seven meat items evaluated in the study (hamburger patties, beef steaks, pork chops, bacon, grilled chicken, pan fried chicken, and pan fried or grilled fish). Each photograph was labeled with a number and represented a range of doneness from medium, well done, to very well done (hamburger patties and beef steaks) or from rare/just done, well done, to very well done (all other items). Participants were asked when they usually ate each food item, whether the item usually looked less done than photograph one, about the same as one, two, or three, or more than three. Participants were asked to have the food picture booklet, which was typically given to the participant in-person on the day of colonoscopy or in front of them during the telephone interview. At the beginning of the telephone interview, the trained interviewers verified that the participant had the food picture booklet in hand. In case that a participant had misplaced the booklet, that portion of the interview would be rescheduled for another time when a replacement booklet was received, generally within a few days.

Using the software application known as the Computerized Heterocyclic Amines Resource for Research in Epidemiology of Disease (2), we estimated the exposure level of 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (MeIQx), 2-amino-3,4,8-trimethylimidazo[4,5-*f*]quinoxaline (DiMeIQx), PhIP, benzo[*a*]pyrene (BaP), and mutagenic activity for each study participant.

Genotyping. Genotyping assays were processed using genomic DNA extracted from blood or buccal cells. The allelic discrimination of the *NAT2, CYP1A2*, and *AhR* gene polymorphisms were assessed with the ABI PRISM 7900 Sequence Detection Systems (Applied Biosystems) using TaqMan assay. The TaqMan Assay-on-Demand reagents are available for *NAT2* G590A (*rs1799930*), G857A (*rs1799931*), T341C (*rs1801280*), *CYP1A2* A-164C (*rs762551*), and *AhR* Arg^{554}Lys (*rs2066853*) from ABI. The

reagents for *NAT2* G191A (*rs1801279*) polymorphisms were obtained from ABI's Assay-by-Design service (primers were GGAGTTGGGCTTAGAGGCTATTTT and CAGAAGTTGATTGACCTGGAGACA; probes were VIC-CCACCCCGGTTTC and FAM-CCCACCCTGG-TTTC). The final volume for each reaction was 5 μL, consisting of 2.5 μL TaqMan Universal PCR Master Mix, 0.25 μL primers/TaqMan probes mix, and 5 ng genomic DNA. The PCR profile consisted of an initial denaturation step at 95°C for 10 min and 40 cycles of 92°C for 15 s and 60°C for 1 min. The fluorescence level was measured with the ABI PRISM 7900HT sequence detector. Allele frequencies were determined by ABI SDS software. The laboratory staff was blinded to the identity of the participants. Quality-control samples were included in the genotyping assays. Each 384-well plate contained 4 water blanks, 8 CEPH 1347-02 DNA, and 16 blinded quality-control samples. The blinded quality-control samples were taken from the second tube of study samples included in the study. Quality-control samples were distributed across separate 384-well plates. The concordance rate for the blinded quality-control samples was 100% for all of these single nucleotide polymorphisms (SNP). In addition, DNA of 45 Caucasian samples that were used in the HapMap and/or Perlegen projects was purchased from Coriell Cell Repositories (http://locus.umdnj.edu/ccr/) and genotyped for all five SNPs. The average consistency rate of the five SNPs was 99.3% compared with data from HapMap (http://www.hapmap.org) and Perlegen (http://genome.perlegen.com).

Allelic discrimination assays for the *NAT1* gene also used TaqMan primers and fluorogenic probes as described previously (23). The assay identifies a nucleotide at eight polymorphisms in the *NAT1* coding region or 3′ untranslated region: C97T (R33Stop), C190T (R64W), G445A (V149I), C559T (R187Stop), G560A (R187Q), A752T (D251V), T1088A (3′ untranslated region), and C1095A (3′ untranslated region).

***N*-Acetyltransferase Phenotype Imputation.** *NAT2* phenotypes were imputed by standard methods based on the functional activities of each allele (24). In addition to the SNPs examined in this study, there are other *NAT2* SNPs that were not checked. This has the potential to lead to genotype misclassification. However, the G590A, G857A, T341C, or G191A SNPs are signature SNPs of haplotype clusters associated with the slow acetylator phenotype (24). Thus, the following phenotype imputations were made based on codominant expression of rapid and slow acetylator *NAT2* alleles: slow acetylators were either homozygous for any of the four SNPs or heterozygous for two or more of the four SNPs, intermediate acetylators were heterozygous for one of the four SNPs, and rapid acetylators were homozygous for the common nucleotide at each of the four SNPs.

Unlike *NAT2*, there is no clear consensus for imputing *NAT1* phenotypes. However, in comparison with *NAT1* *3 and *4, the *NAT1* *14, *15, *17, *19, and *22 alleles have been associated with slow acetylation (25). We additionally hypothesized that the *10 and *11 alleles are rapid acetylation alleles based on previous literature (25, 26). However, these alleles are probably only slightly rapid, do not compensate for the slow alleles, and may only be rapid if in combination with or heterozygous with a *NAT1* *3 and *4 allele. Therefore, we considered any participants possessing slow alleles (*NAT1* *14, *15, *17, *19, and *22) to be a slow acetylator, any participants homozygous for rapid alleles (*NAT1* *10 and *11*) or in combination with a *NAT1* *3 and *4 allele to be a rapid acetylator, and all others as intermediate acetylators.

Further details for classification of *NAT1* and *NAT2* genotypes and imputed phenotypes are provided in Appendices 1 and 2.

Statistical Analysis. Generalized linear models and Mantel-Haenszel χ^2 tests were used to compare the distribution of demographic characteristics and risk factors for colorectal polyps among case and control groups with adjustment for age and sex differences. Polytomous logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (95% CI) for the association between exposures and types of polyp by comparing multiple case groups with one common control group. ORs were adjusted for known risk factors for colorectal polyps and variables that showed different distributions among comparison groups [age, sex, study site, education, indication for colonoscopy, smoking, alcohol consumption, regularly exercised in the past 10 years, regular use of nonsteroidal anti-inflammatory drugs (NSAID), and total energy intake]. Total energy intake was derived using data from the FFQ. For those who did not provide FFQ information, energy intake level was imputed with age-specific (40-49, 50-59, 60-64, and ≥65 years) and sex-specific mean values. Stratified analyses for meat and HCA intake by genotype were done. ORs were estimated based on per decile increment of meat, HCA and BaP intake, and mutagenic activity stratified by genotype. The interactions between dietary variables (in decile increment) and genotypes were evaluated using the log-likelihood ratio test by comparing the model with and without the interaction terms. All analyses were carried out using SAS software (version 9.1).

For the current analysis, participants were limited to those with a confirmed diagnosis of adenomatous or hyperplastic polyp or clean colon. Excluded from the analysis were 7 participants diagnosed with colorectal cancer and 40 participants with a diagnosis other than polyps, an ambiguous colonoscopic procedure, or an unclear pathology evaluation. Also excluded were 91 participants with missing data in any of the meat consumption and doneness questions and one with missing genotyping information in any of the four genes. These exclusions were not mutually exclusive, and some participants met two or more the exclusion criteria. The final number of participants included in the analysis was 557 cases with adenomatous polyps only, 250 cases with hyperplastic polyps only, 195 cases with both adenomatous and hyperplastic polyps, and 1,493 polyp-free controls.

Results

The distribution of demographic and other characteristics for the three case groups and polyp-free controls are presented in Table 1. Compared with controls, patients in any of the case groups were more likely to be male, to be a smoker, to have lower educational attainment, and to have a lower household income. Additionally, cases with adenomatous polyps were older

Table 1. Characteristics of study participants by comparison groups, the TCPS, 2003-2005

Characteristic	Polyp type				
	Adenomatous only (n = 557)	Hyperplastic only (n = 250)	Concurrent adenomatous and hyperplastic (n = 195)	Controls (n = 1,493)	P*
Age (y), mean ± SD	59.6 ± 7.5	56.7 ± 7.0	59.8 ± 6.4	57.2 ± 7.8	<0.001
Sex (male), %	75.0	69.8	83.6	58.1	<0.001
Educational attainment (college or higher), %†	70.5	61.9	63.2	73.0	0.001
Race (White), %	83.7	92.0	89.7	86.2	0.007
Indication for colonoscopy (screening), %†	56.1	54.2	44.5	56.2	0.012
Family history of colorectal cancer, %†	13.5	12.4	18.6	12.3	0.439
Ever smoke cigarettes regularly, %†	58.1	72.1	82.3	52.3	<0.001
Ever consume alcohol regularly, %†	47.6	52.9	45.3	44.9	0.100
Exercise regularly, %†	51.3	50.8	47.1	56.3	0.032
Current NSAID user, %	50.8	57.3	54.3	57.4	0.074
BMI (kg/m^2), mean ± SE‡					
Male	28.9 ± 0.5	28.4 ± 0.8	28.9 ± 0.9	28.2 ± 0.4	0.119
Female	27.4 ± 1.1	28.1 ± 1.4	27.2 ± 2.2	27.6 ± 0.6	0.743
Height (cm), mean ± SE‡					
Male	179.5 ± 0.7	176.8 ± 1.0	179.9 ± 1.1	178.6 ± 0.5	0.031
Female	163.7 ± 1.1	163.9 ± 1.5	165.3 ± 2.3	163.7 ± 0.6	0.743

*Derived from ANOVA for continuous variables and χ^2 test for categorical variables.
†Standardized by age (40-49, 50-59, 60-64, and ≥65 y) and sex distribution of all study participants.
‡Standardized by age distribution (40-49, 50-59, 60-64, and ≥65 y) of all study participants.

than controls, whereas cases with hyperplastic polyps only were similar in age to controls.

Table 2 provides median and interquartile ranges for intake levels of total meat, red meat, HCAs, BaP, mutagenic activity, and total energy intake. In general, cases, particularly cases with hyperplastic polyps and cases with concurrent adenomatous and hyperplastic polyps, had a higher intake of meat and meat carcinogens, such as PhIP, MeIQx, and DiMeIQx, than polyp-free controls.

Shown in Table 3 are the distributions of *AhR* (*rs2066853*), *CYP1A2* (*rs762551*), *NAT2*, and *NAT1* genetic polymorphisms among colorectal polyp cases and polyp-free controls and their associations with polyp risk. With the exception of the *NAT1* genotype, no other genetic polymorphisms showed a statistically significant association with colorectal polyps. Rapid acetylator *NAT1* genotypes were associated with an elevated risk of adenomas (OR, 1.8; 95% CI, 1.0-3.2) compared with participants with slow acetylator genotypes. Participants with *NAT1* intermediate or rapid acetylator genotypes also showed a nonsignificantly increased risk for concurrent adenomatous and hyperplastic polyps in comparison with *NAT1* slow acetylators.

Table 4 presents associations of meat and meat mutagen intake with polyp risk stratified by genotypes.

Table 2. Median (25th, 75th percentiles) for meat and meat mutagen intake levels, the TCPS, 2003-2005

	Polyp type				
	Adenomatous only	Hyperplastic only	Concurrent adenomatous and hyperplastic	Controls	P*
Male					
Total meat (g/d)†	108.7 (66.1, 157.9)	117.1 (83.1, 167.1)	120.6 (68.8, 171.7)	106.3 (67.4, 154.7)	0.092
Red meat (g/d)†	64.7 (29.7, 100.6)	74.0 (37.2, 110.5)	69.1 (38.5, 116.1)	56.7 (26.7, 96.6)	0.001
MeIQx (ng/d)	51.9 (21.9, 107.6)	70.6 (28.3, 120.5)	60.6 (26.3, 116.0)	49.6 (21.3, 98.5)	0.004
PhIP (ng/d)	193.0 (88.2, 385.6)	234.9 (130.3, 423.3)	225.0 (112.7, 459.1)	221.2 (96.5, 401.5)	0.154
DiMeIQx (ng/d)	3.5 (1.3, 8.4)	4.4 (1.8, 9.3)	4.5 (1.9, 9.2)	3.6 (1.2, 7.7)	0.015
BaP (ng/d)	37.3 (12.6, 90.4)	56.4 (16.4, 113.8)	44.0 (15.7, 100.1)	46.5 (12.6, 103.4)	0.095
Mutagenic activity (revertants colony)	8,376 (4,702, 15,353)	10,031 (5,315, 19,686)	10,346 (5,081, 19,280)	9,316 (4,616, 16,103)	0.083
Total energy intake (kcal/d)‡	1,622 (1,209, 2,103)	1,700 (1,151, 2,106)	1,578 (1,279, 1,981)	1,582 (1,193, 2,030)	0.676
Female					
Total meat (g/d)	79.0 (48.0, 103.7)	83.2 (56.5, 117.6)	78.4 (57.1, 110.6)	72.8 (49.9, 109.3)	0.295
Red meat (g/d)	30.8 (13.7, 50.0)	39.3 (20.4, 58.7)	48.2 (23.9, 83.9)	26.5 (9.4, 52.1)	0.004
MeIQx (ng/d)	29.9 (11.4, 48.1)	34.0 (14.5, 66.4)	43.5 (20.3, 72.8)	24.7 (9.3, 51.5)	0.043
PhIP (ng/d)	178.4 (75.0, 327.2)	196.0 (84.9, 413.9)	148.5 (74.5, 274.2)	143.7 (60.9, 271.5)	0.039
DiMeIQx (ng/d)	2.7 (0.7, 5.1)	3.6 (1.8, 7.1)	3.5 (1.4, 6.4)	2.5 (0.8, 5.0)	0.054
BaP (ng/d)	24.9 (9.1, 62.3)	32.7 (11.2, 68.3)	21.7 (8.5, 58.1)	20.8 (6.5, 54.2)	0.063
Mutagenicity (revertants colony)	6,607 (3,884, 11,294)	6,885 (4,294, 13,968)	7,305 (5,351, 12,289)	6,540 (3,537, 10,593)	0.203
Total energy intake (kcal/d)‡	1,387 (1,017, 1,823)	1,491 (1,213, 1,767)	1,610 (1,152, 1,762)	1,462 (1,108, 1,802)	0.702

*Derived from the Kruskal-Wallis test.
†The red meat category includes hamburgers or cheeseburgers, beef steaks, pork chops or ham steaks, bacon, sausage, hotdogs or franks, and short ribs or spareribs. Total meat included all red meat items, chicken, and fish.
‡Among those who completed the FFQ.

Table 3. Association between genetic polymorphisms in the *AhR, CYP1A2, NAT2*, and *NAT1* genes and risk for colorectal polyps, the TCPS, 2003-2005

Gene	Controls	Polyp type					
		Adenomatous only		Hyperplastic only		Concurrent adenomatous and hyperplastic	
	n	*n*	OR (95% CI)*	*n*	OR (95% CI)*	*n*	OR (95% CI)*
AhR (*rs2066853*)							
GG	1,109	416	1.0 (Reference)	192	1.0 (Reference)	148	1.0 (Reference)
GA/AA	380	137	1.0 (0.8-1.2)	55	0.8 (0.6-1.1)	47	0.9 (0.6-1.3)
GA	331	121	1.0 (0.8-1.3)	51	0.9 (0.6-1.2)	41	0.9 (0.6-1.4)
AA	49	16	0.9 (0.5-1.6)	4	0.4 (0.2-1.3)	6	0.9 (0.4-2.2)
CYP1A2 (*rs762551*)							
AA	744	265	1.0 (Reference)	138	1.0 (Reference)	101	1.0 (Reference)
AC/CC	746	290	1.1 (0.9-1.3)	111	0.8 (0.6-1.1)	94	0.9 (0.7-1.3)
AC	617	237	1.1 (0.9-1.3)	94	0.8 (0.6-1.1)	74	0.9 (0.6-1.2)
CC	129	53	1.1 (0.8-1.6)	17	0.7 (0.4-1.2)	20	1.1 (0.7-1.9)
NAT2 †							
Slow acetylator	880	311	1.0 (Reference)	141	1.0 (Reference)	110	1.0 (Reference)
Intermediate acetylator	529	209	1.1 (0.9-1.4)	94	1.1 (0.8-1.5)	75	1.1 (0.8-1.5)
Rapid acetylator	80	34	1.2 (0.8-1.9)	12	0.9 (0.5-1.7)	10	1.0 (0.5-2.0)
NAT1 †							
Slow acetylator	69	15	1.0 (Reference)	11	1.0 (Reference)	5	1.0 (Reference)
Intermediate acetylator	806	300	1.7 (0.9-3.0)	137	1.1 (0.5-2.1)	113	2.3 (0.9-6.2)
Rapid acetylator	605	238	1.8 (1.0-3.2)	100	1.0 (0.5-2.1)	74	2.0 (0.8-5.5)

*Adjusted for age, sex, study site, educational attainment, indication for colonoscopy, smoking, alcohol consumption, physical activity, and regular NSAID use.
†Definitions for imputation of *NAT1* and *NAT2* acetylator status are presented in Appendices 1 and 2.

Due to a small number of participants with a *NAT2* rapid acetylating status, this group of participants was combined with the *NAT2* intermediate acetylator group. Similarly, *NAT1* slow acetylators were combined with *NAT1* intermediate acetylators to enhance statistical power in interaction analyses. Positive associations with intake of meat and meat mutagens were observed primarily for the case group with concurrent adenomatous and hyperplastic polyps and predominantly among participants with the *GA/AA* genotypes in *AhR* (*rs2066853*) or *NAT1* rapid acetylator status. With the exception of the BaP, all other six exposure variables showed a significant dose-response relationship with the risk of concurrent adenomatous and hyperplastic polyps in participants with an *A* allele in *AhR* (*rs2066853*) or who were *NAT1* rapid acetylators. On the other hand, none of the seven exposure variables evaluated in the study showed any significant dose-response relationship with concurrent adenomatous and hyperplastic polyps among participants with *AhR GG* genotype or who were *NAT1* slow or intermediate acetylators. Statistical tests were significant for several gene-diet interactions evaluated in this study. For example, the OR (95% CI) for a decile increment in total meat intake was 1.32 (1.14-1.52) for participants carrying the *A* allele of the *AhR* gene and only 0.98 (0.91-1.05) for participants homozygous for the *G* allele (*P* for interaction = 0.002). Several positive interactions were also noted for *NAT2* genotypes. However, the pattern of the association was less consistent than that observed for *AhR* and *NAT1* genotypes.

Because a significant modifying effect was mainly observed for the *AhR* and *NAT1* genes, we combined the risk genotypes for these two genes (Table 5). Participants who had risk genotypes for both genes (*AhR GA/AA* and *NAT1* rapid acetylator) had the highest risk for concurrent adenomatous and hyperplastic polyps if they also consumed a high amount of total meat (OR, 1.57; 95% CI, 1.23-2.01; *P* for interaction = 0.019) or red meat (OR, 1.60; 95% CI, 1.23-2.09; *P* for interaction = 0.023). They were also at an increased risk if they had high intake of MeIQx, PhIP, or DiMeIQx (*P* for interaction = 0.048, 0.055, and 0.115, respectively).

Discussion

Our study evaluated not only colorectal adenomas but also hyperplastic polyps in relation to well-done meat intake and genetic polymorphisms in carcinogen-metabolizing enzymes. We found that a high intake of meat and HCAs was associated with an increased risk of polyps, primarily for the status of concurrent adenomatous and hyperplastic polyps among individuals who carried high-activity genotypes for the *NAT1* or *NAT2* genes or the *AhR A* allele (*rs2066853*). However, we did not observe any consistent modifying effects of these genotypes on the association of meat and HCA exposure with the risk of polyps among patients who had only adenomas.

The *NAT2* or *NAT1* genotypes were not found to be directly associated with colorectal cancer risk in previous studies (7). However, high red meat or MeIQx intake in combination with rapid acetylator genotypes was related to increased risk for colorectal cancer in several studies (8, 17, 19, 27-29). The functional significance for specific *NAT2* polymorphisms has been well established through measurement of catalytic activity for the *N*-acetylation of a sulfonamide drug and an aromatic amine carcinogen (30). *NAT1* appears to be expressed in many extrahepatic tissues, including the colon (31). HCAs, which are produced during high-temperature cooking of meats, are activated by *O*-acetylation (32). The role of *N*-acetyltransferase as a determinant of colorectal cancer risk has been supported by animal studies. Purewal et al. reported a 2-fold higher number of aberrant crypt foci

Table 4. Association of meat and HCA intake levels with colorectal polyp risk stratified by polymorphisms in the *AhR, CYP1A2, NAT2*, and *NAT1* genes, the TCPS, 2003-2005

Gene	Intake	Polyp type					
		Adenomatous only		Hyperplastic only		Concurrent adenomatous and hyperplastic	
		OR (95% CI)*	P_{int} †	OR (95% CI)*	P_{int} †	OR (95% CI)*	P_{int} †
AhR (*rs2066853*)							
GG	Total meat	0.99 (0.94-1.03)		1.04 (0.98-1.10)		0.98 (0.91-1.05)	
	Red meat	1.01 (0.96-1.06)		1.04 (0.98-1.11)		1.02 (0.95-1.10)	
	MeIQx	1.00 (0.95-1.04)		1.04 (0.98-1.11)		1.02 (0.95-1.09)	
	PhIP	0.99 (0.95-1.04)		1.04 (0.98-1.10)		0.98 (0.92-1.05)	
	DiMeIQx	0.98 (0.94-1.03)		1.04 (0.98-1.10)		1.01 (0.95-1.08)	
	BaP	0.99 (0.95-1.04)		1.06 (1.00-1.12)		0.98 (0.92-1.05)	
	Mutagenic activity	0.97 (0.93-1.02)		1.01 (0.95-1.07)		0.99 (0.93-1.06)	
GA/AA	Total meat	1.02 (0.94-1.10)	0.685	1.12 (1.00-1.26)	0.185	1.32 (1.14-1.52)	0.002
	Red meat	1.02 (0.94-1.11)	0.691	1.06 (0.94-1.20)	0.796	1.28 (1.11-1.49)	0.047
	MeIQx	1.00 (0.92-1.09)	0.706	1.10 (0.98-1.23)	0.681	1.20 (1.05-1.38)	0.102
	PhIP	1.01 (0.94-1.09)	0.988	1.11 (0.99-1.23)	0.328	1.20 (1.06-1.35)	0.030
	DiMeIQx	1.02 (0.95-1.10)	0.408	1.16 (1.03-1.30)	0.233	1.20 (1.06-1.36)	0.067
	BaP	1.00 (0.93-1.08)	0.863	1.05 (0.94-1.18)	0.892	1.11 (0.98-1.26)	0.205
	Mutagenic activity	1.02 (0.94-1.10)	0.463	1.15 (1.03-1.28)	0.088	1.22 (1.07-1.38)	0.036
CYP1A2 (*rs762551*)							
AA	Total meat	1.02 (0.97-1.08)		1.08 (1.01-1.17)		1.04 (0.96-1.13)	
	Red meat	1.03 (0.97-1.10)		1.06 (0.98-1.14)		1.05 (0.96-1.15)	
	MeIQx	0.99 (0.93-1.05)		1.03 (0.96-1.11)		1.01 (0.93-1.10)	
	PhIP	1.01 (0.96-1.07)		1.04 (0.97-1.12)		1.01 (0.93-1.09)	
	DiMeIQx	0.99 (0.94-1.05)		1.07 (0.99-1.14)		1.04 (0.96-1.13)	
	BaP	0.99 (0.93-1.04)		1.05 (0.98-1.13)		0.98 (0.90-1.06)	
	Mutagenic activity	0.98 (0.93-1.04)		1.04 (0.97-1.11)		1.00 (0.93-1.09)	
AC/CC	Total meat	0.97 (0.92-1.03)	0.307	1.03 (0.95-1.12)	0.394	1.05 (0.96-1.15)	0.980
	Red meat	1.01 (0.95-1.06)	0.673	1.05 (0.96-1.14)	0.756	1.11 (1.01-1.22)	0.425
	MeIQx	1.01 (0.95-1.06)	0.587	1.07 (0.99-1.16)	0.772	1.11 (1.02-1.22)	0.057
	PhIP	0.99 (0.94-1.04)	0.773	1.07 (0.99-1.15)	0.682	1.07 (0.98-1.16)	0.294
	DiMeIQx	1.00 (0.95-1.05)	0.798	1.05 (0.97-1.13)	0.719	1.06 (0.98-1.15)	0.416
	BaP	1.02 (0.97-1.08)	0.264	1.07 (0.99-1.15)	0.842	1.06 (0.98-1.16)	0.163
	Mutagenic activity	0.99 (0.94-1.05)	0.567	1.04 (0.96-1.12)	0.996	1.08 (0.99-1.18)	0.117
NAT2 ‡							
Slow acetylator	Total meat	1.02 (0.97-1.07)		107 (0.99-1.15)		0.98 (0.91-1.06)	
	Red meat	1.02 (0.96-1.08)		1.04 (0.96-1.12)		0.99 (0.91-1.08)	
	MeIQx	1.01 (0.96-1.07)		1.03 (0.95-1.10)		1.01 (0.93-1.10)	
	PhIP	1.01 (0.96-1.06)		1.06 (0.99-1.13)		1.01 (0.94-1.09)	
	DiMeIQx	1.03 (0.98-1.08)		1.04 (0.98-1.12)		1.03 (0.96-1.11)	
	BaP	1.02 (0.97-1.07)		1.06 (0.99-1.14)		0.97 (0.90-1.05)	
	Mutagenic activity	1.00 (0.95-1.05)		1.03 (0.96-1.10)		1.01 (0.93-1.09)	
Rapid or intermediate acetylator	Total meat	0.98 (0.92-1.04)	0.368	1.06 (0.97-1.14)	0.885	1.12 (1.02-1.22)	0.039
	Red meat	1.02 (0.96-1.09)	0.709	1.08 (0.99-1.18)	0.412	1.20 (1.08-1.32)	0.014
	MeIQx	0.98 (0.92-1.04)	0.626	1.09 (1.00-1.18)	0.247	1.11 (1.01-1.22)	0.264
	PhIP	0.99 (0.94-1.05)	0.546	1.04 (0.97-1.13)	0.918	1.06 (0.97-1.15)	0.402
	DiMeIQx	0.95 (0.90-1.01)	0.072	1.08 (1.00-1.17)	0.500	1.07 (0.98-1.17)	0.516
	BaP	0.98 (0.92-1.04)	0.224	1.06 (0.98-1.15)	0.953	1.07 (0.97-1.17)	0.187
	Mutagenic activity	0.98 (0.92-1.03)	0.565	1.05 (0.97-1.13)	0.766	1.07 (0.98-1.17)	0.402
NAT1 ‡							
Slow or intermediate acetylator	Total meat	0.98 (0.93-1.03)		1.04 (0.97-1.12)		0.99 (0.92-1.07)	
	Red meat	1.00 (0.94-1.05)		1.02 (0.95-1.10)		1.03 (0.95-1.12)	
	MeIQx	1.00 (0.95-1.05)		1.04 (0.97-1.12)		1.01 (0.93-1.09)	
	PhIP	1.00 (0.95-1.05)		1.06 (0.99-1.14)		1.00 (0.93-1.07)	
	DiMeIQx	0.99 (0.94-1.04)		1.08 (1.00-1.15)		1.02 (0.94-1.10)	
	BaP	1.01 (0.96-1.06)		1.04 (0.97-1.11)		0.98 (0.91-1.06)	
	Mutagenic activity	0.99 (0.94-1.04)		1.06 (0.99-1.13)		1.00 (0.93-1.08)	
Rapid acetylator	Total meat	1.03 (0.97-1.09)	0.728	1.09 (1.00-1.18)	0.868	1.15 (1.04-1.27)	0.044
	Red meat	1.05 (0.99-1.12)	0.868	1.10 (1.00-1.20)	0.415	1.17 (1.06-1.31)	0.069
	MeIQx	1.00 (0.94-1.06)	0.543	1.05 (0.97-1.15)	0.911	1.14 (1.03-1.27)	0.068
	PhIP	1.01 (0.96-1.07)	0.880	1.04 (0.97-1.13)	0.519	1.10 (1.00-1.20)	0.230
	DiMeIQx	1.00 (0.95-1.06)	0.750	1.03 (0.95-1.12)	0.349	1.10 (1.00-1.21)	0.291
	BaP	0.99 (0.94-1.05)	0.286	1.09 (1.00-1.19)	0.930	1.08 (0.98-1.19)	0.365
	Mutagenic activity	0.99 (0.94-1.05)	0.589	1.02 (0.94-1.10)	0.298	1.10 (1.01-1.21)	0.232

*ORs were estimated for a 10% increment of intake and adjusted for age, sex, study site, educational attainment, indication for colonoscopy, smoking, alcohol consumption, physical activity, and regular NSAID use.
†*P* values for interactions of dietary exposure and genotype were derived from the log-likelihood ratio test.
‡Definitions for imputation of acetylator status for *NAT2* and *NAT1* are presented in Appendices 1 and 2.

Table 5. Association between meat and HCA intake levels and colorectal polyp risk stratified by combination of risk genotypes of the *AhR* and *NAT1* genes on colorectal polyp risk, the TCPS, 2003-2005

Genotypes	Intake	Polyp type					
		Adenomatous only		Hyperplastic only		Concurrent adenomatous and hyperplastic	
		OR (95% CI)*	P_{int} †	OR (95% CI)*	P_{int} †	OR (95% CI)*	P_{int} †
Low risk ‡	Total meat	0.98 (0.93-1.04)		1.03 (0.95-1.12)		0.94 (0.86-1.02)	
	Red meat	1.02 (0.96-1.08)		1.04 (0.96-1.14)		0.99 (0.91-1.09)	
	MeIQx	1.01 (0.95-1.07)		1.03 (0.95-1.12)		1.00 (0.91-1.09)	
	PhIP	0.99 (0.93-1.04)		1.05 (0.97-1.13)		0.97 (0.90-1.06)	
	DiMeIQx	0.98 (0.93-1.04)		1.05 (0.97-1.13)		1.01 (0.93-1.10)	
	BaP	1.02 (0.96-1.07)		1.05 (0.98-1.14)		0.97 (0.89-1.05)	
	Mutagenic activity	0.98 (0.93-1.04)		1.02 (0.95-1.10)		0.98 (0.90-1.06)	
Intermediate risk ‡	Total meat	0.99 (0.93-1.06)		1.05 (0.97-1.13)		1.10 (0.99-1.21)	
	Red meat	0.99 (0.93-1.06)		1.00 (0.92-1.09)		1.11 (1.00-1.23)	
	MeIQx	0.98 (0.92-1.04)		1.04 (0.96-1.13)		1.06 (0.96-1.17)	
	PhIP	1.02 (0.97-1.08)		1.04 (0.97-1.13)		1.02 (0.93-1.12)	
	DiMeIQx	1.01 (0.95-1.07)		1.05 (0.97-1.14)		1.05 (0.96-1.15)	
	BaP	0.97 (0.91-1.03)		1.03 (0.95-1.12)		1.02 (0.92-1.12)	
	Mutagenic activity	0.99 (0.93-1.05)		1.03 (0.96-1.12)		1.05 (0.95-1.15)	
High risk ‡	Total meat	1.09 (0.98-1.21)	0.699	1.25 (1.03-1.51)	0.433	1.57 (1.23-2.01)	0.019
	Red meat	1.15 (1.02-1.30)	0.472	1.31 (1.06-1.63)	0.275	1.60 (1.23-2.09)	0.023
	MeIQx	1.06 (0.94-1.19)	0.634	1.12 (0.92-1.35)	0.957	1.48 (1.14-1.92)	0.048
	PhIP	1.01 (0.91-1.12)	0.766	1.13 (0.94-1.34)	0.940	1.39 (1.11-1.74)	0.055
	DiMeIQx	1.04 (0.93-1.15)	0.934	1.14 (0.95-1.36)	0.997	1.37 (1.10-1.71)	0.115
	BaP	1.08 (0.97-1.22)	0.384	1.17 (0.97-1.41)	0.569	1.26 (1.02-1.54)	0.323
	Mutagenic activity	1.04 (0.94-1.15)	0.981	1.13 (0.95-1.35)	0.943	1.31 (1.08-1.60)	0.079

*ORs were estimated for a 10% increment of intake and adjusted for age, sex, study site, educational attainment, indication for colonoscopy, smoking, alcohol consumption, physical activity, and regular NSAID use.
†*P* values for interactions of dietary exposure and genotype were derived from log-likelihood ratio test.
‡Defined as ''low-risk'' genotypes *AhR GG* or *NAT1* slow or intermediate acetylator, ''intermediate-risk'' genotypes *AhR GG* or *NAT1* rapid acetylator or *AhR GA/AA* or *NAT1* slow or intermediate acetylator, and ''high-risk'' genotypes *AhR GA/AA* or *NAT1* rapid acetylator.

and higher colon PhIP-DNA adduct levels in rapid acetylator rats compared with slow acetylator rats when they were fed 0.04% PhIP (33). In addition, Nerurkar et al. also showed that rapid acetylator mice had 3-fold more DNA adducts formed by the food carcinogen 2-amino-3-methyl-imidazo[4,5-*f*]quinoline in the colon mucosa than slow acetylator mice (34). *O*-acetyltransferase activity has been observed in colon tissues, and colon tissues obtained from cancer patients have been shown to possess high levels of *O*-acetyltransferase, suggesting an etiologic association between acetylation phenotype and colorectal carcinoma (6). Our results, which suggest that a high intake of meat and HCAs increase the risk for polyps among participants with high activity *NAT1* or *NAT2* genotypes, are consistent with a hypothesis based on the metabolic pathway of HCAs.

CYP1A2 catalyzes the initial activation of HCA to produce *N*-hydroxy-HCA for *O*-acetylation by *NAT1* and *NAT2* (4). The high activity *CYP1A2* phenotype has shown a nonsignificant increased risk for colorectal adenoma (15) or cancer (8, 35). Although *CYP1A2* is highly inducible by environmental and dietary factors, such as smoking and HCAs, *CYP1A2* activity is under strong genetic control (36). Correlations between *CYP1A2* genotypes and phenotypes, which are often assessed using the caffeine urinary metabolite ratio, have been inconsistent. The *CYP1A2 *1F* (*rs762551*) polymorphism, a *C* > *A* substitution in intron 1 at position 734, has been associated with *CYP1A2* activity in several studies (37, 38). However, it remains unclear which of the *A* and *C* alleles are associated with a high activity of this enzyme (37-39), and one study reported no difference in enzyme activity by genotypes (40). The *CYP1A2 *1F* polymorphism was not related to colorectal cancer risk in one study (35), but another study suggested an increased risk for colorectal cancer among those with the *C* allele (41). Elevated risk for colorectal cancer was observed among participants who had high intake of well-done meat, who smoked cigarettes, or who carried the *NAT2* genotype or the rapid *CYP1A2* phenotype (8). Yet, no interactive effect of MeIQx and the *CYP1A2* phenotype was observed for colorectal adenoma risk (15). We did not find any significant modifying effect of the *CYP1A2* (*rs762551*) polymorphism on association between meat, HCA intake, or colorectal polyp risk despite the suggested functional significance of this polymorphism on HCA metabolism.

AhR is a key regulator of transcriptional expression for the CYP1 family of genes (5). The $Arg^{554}Lys$ polymorphism (*rs2066853*) is located in exon 10 of this gene, a region associated with transactivity of other genes (42). No study has evaluated the *AhR* gene polymorphism for association with colorectal cancer risk. A recent report, which determined the level of DNA damage in peripheral blood lymphocytes using the alkaline comet assay, observed a higher level of DNA damage in participants with a variant *rs2066853* genotype than those with the *GG* genotype among coke-oven workers (43). This result is consistent with our finding that participants with an *A* allele were more vulnerable to environmental carcinogen exposure.

Few studies have compared the risk factors associated with adenomatous and hyperplastic polyps (44, 45). Only

Appendix A. *NAT1* diplotypes and imputed phenotypes

Diplotypes	Phenotypes	Frequency (%)
*10/*10	Rapid	4.7
*10/*11A	Rapid	0.4
*10/*11B	Rapid	0.1
*10/*14A	Slow	0.5
*10/*15	Slow	0.1
*10/*22	Slow	0.1
*11A/*14A	Slow	0.1
*11A/*15	Slow	0.1
*11A/*22	Slow	0.1
*3/*10	Rapid	1.8
*3/*11A	Rapid	0.2
*3/*14A	Slow	0.1
*3/*14B	Slow	0.1
*3/*3	Intermediate	0.1
*4/*10	Rapid	30.9
*4/*11A or *3/*11B	Rapid	2.9
*4/*11B	Rapid	0.2
*4/*14A or *10/*14B	Slow	2.2
*4/*14B	Slow	0.2
*4/*15	Slow	0.2
*4/*17	Slow	0.1
*4/*22	Slow	0.4
*4/*3	Intermediate	4.6
*4/*4	Intermediate	50.0

one study has investigated the association of metabolizing gene polymorphisms and their interactions with meat intake in the risk adenomatous and hyperplastic polyps and found no evidence for an interaction (20). Hyperplastic polyps are commonly detected in the large intestine and have generally not been regarded as having malignant potential (19). However, recent studies have suggested that some hyperplastic polyps may develop into cancer via pathways other than the adenoma-carcinoma sequence (19). Ten percent to 15% of colorectal cancers show MSI and do not share common molecular pathways with the adenoma-carcinoma sequence (19). This group of colorectal cancers is characterized by defective nucleotide mismatch repair and aberrant DNA methylation. It has been reported that individuals with colorectal cancers with MSI are more likely to harbor serrated or hyperplastic polyps than individuals with cancers without MSI (46). Epidemiologic studies have reported that the risk factor profiles for MSI tumors, and tumor without MSI are different (47-50). Patients with MSI colon cancers had significantly higher dietary exposure to HCAs than patients with microsatellite-stable colon cancers, and the risk of MSI colon cancer was increased 3-fold among patients who preferred to eat very well done red meat (50). In contrast, Diergaarde et al. found that red meat consumption was higher among patients with a microsatellite stable tumor than patients with a MSI tumor (47). Slattery et al. did not find any association between red meat intake and MSI status of colon cancer (49), whereas Lüchtenborg et al. found mixed results dependent on the type of meat (48). The reasons for the inconsistent finding are unclear, and additional research is needed.

In our study, most of the statistically significant interactions between carcinogen-metabolizing genotypes and meat carcinogen exposures were observed for the status of concurrent hyperplastic and adenomatous polyps. Our results are consistent with a previous study of Goode et al. (20), in which the increased risk associated with meat intake was most prominent among patients with both types of polyps than patients with only one type of polyps. The reasons for these findings are not clear. It is possible that HCA exposures may induce multiple premalignant loci in the colon, which is characterized by the presence of both adenomatous and hyperplastic polyps. It is also possible that individuals with certain characteristics may be more likely to develop both adenomatous and hyperplastic polyps in the colon after HCA exposure than participants without these characteristics. Sessile serrated adenomas have attracted considerable attention recently, given their potential to develop invasive MSI colorectal cancer. These adenomas show a mixed hyperplastic and adenomatous morphology (51). It is possible that HCA exposure may be more closely related to the risk of sessile serrated adenomas than other polyps. Additional research is needed in the future to reveal potential mechanisms for the findings observed in our study.

Strengths of our study include a large sample size, a detailed exposure assessment, and the use of a colonoscopy-based approach to classify study groups. Dietary surveys, however, were conducted after the colonoscopy; thus, similar to other studies, recall bias could be a concern. However, because the diagnosis of polyps cannot influence the genotype of study participants and the genotype is unlikely to be related to meat intake and

Appendix B. Four *NAT2* SNPs and imputed genotypes and phenotypes

G590A	G857A	T341C	G191A	*NAT2* genotype	Imputed *NAT2* phenotype	Frequency (%)
A/A	G/G	T/T	G/G	*6/*6	Slow	9.0
A/G	A/G	T/T	G/G	*6/*7	Slow	1.8
A/G	G/G	C/C	G/G	*5/*5	Slow	0.1
A/G	G/G	C/T	G/G	*5/*6	Slow	24.4
A/G	G/G	T/T	A/G	*6/*14	Slow	0.6
A/G	G/G	T/T	G/G	*4/*6	Intermediate	14.1
G/G	A/A	T/T	G/G	*7/*7	Slow	0.2
G/G	A/G	C/T	G/G	*5/*7	Slow	2.6
G/G	A/G	T/T	G/G	*4/*7	Intermediate	1.5
G/G	G/G	C/C	G/G	*5/*5	Slow	19.1
G/G	G/G	C/T	A/G	*5/*14	Slow	0.2
G/G	G/G	C/T	G/G	*4/*5	Intermediate	20.6
G/G	G/G	T/T	A/A	*14/*14	Slow	0.1
G/G	G/G	T/T	A/G	*4/*14	Intermediate	0.2
G/G	G/G	T/T	G/G	*4/*4	Rapid	5.6

meat carcinogen exposure, out study resembles closely the case scenario of ''Mendelian randomization,'' a concept that has attracted considerable attention in studying gene-environment interaction (52). It is believed that observational studies that meet Mendelian randomization criteria are akin to randomized control trials, in which potentials for recall bias and confounding are minimized. In other words, our results regarding gene-environment interactions are unlikely to be explained by information bias and confounding effects (51). Multiple comparisons involving the evaluation of several meat and meat mutagen intakes could increase type I errors. However, the patterns of the association between different meats, HCA items, and colorectal polyp risks were consistent across genotype strata; therefore, the effect of chance related to multiple comparisons can not entirely explain our findings. Because only one polymorphism for the *AhR* and *CYP1A2* genes was evaluated, a more comprehensive evaluation of the genetic information could provide further information on the modifying effect of these genes on meat and HCA intake. There was a suggestive main gene effect of *NAT1* gene on adenomatous polyp risk; however, the number of participants with *NAT1* slow acetylating status was small, affecting the stability of risk estimate. Because participants from the Veteran's Affairs clinic are mainly veterans, the difference in sex distribution is inevitable. However, we adjusted the analyses by study site as well as sex. Relatively low response rates for the FFQ could introduce a selection bias; however, the results excluding participants without FFQ showed very similar associations with the results from all participants who responded to the meat questions.

In summary, our results suggest that genetic polymorphisms involved in metabolic activation of HCAs may modify the risk of colorectal polyps. Our study provides strong evidence for a role of gene-diet interaction in the etiology of colorectal tumors.

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