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Modification by *N*-acetyltransferase 1 genotype on the association between dietary heterocyclic amines and colon cancer in a multiethnic study

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Abstract

Objective: Colorectal cancer incidence is greater among African Americans, compared to whites in the U.S., and may be due in part to differences in diet, genetic variation at metabolic loci, and/or the joint effect of diet and genetic susceptibility. We examined whether our previously reported associations between meat-derived heterocyclic amine (HCA) intake and colon cancer were modified by *N*-acetyltransferase 1 (NAT1) or 2 (NAT2) genotypes and whether there were differences by race.

Methods: In a population-based, case-control study of colon cancer, exposure to HCAs was assessed using a food-frequency questionnaire with a meat-cooking and doneness module, among African Americans (217 cases and 315 controls) and whites (290 cases and 534 controls).

Results: There was no association with NAT1*10 versus NAT1-non*10 genotypes for colon cancer. Among whites, there was a positive association for NAT2-"rapid/intermediate" genotype [odds ratio (OR)= 1.4; 95% confidence interval (CI)=1.0, 1.8], compared to the NAT2-"slow" that was not observed among African Americans. Colon cancer associations with HCA intake were modified by NAT1, but not NAT2, regardless of race. However, the "at-risk" NAT1 genotype differed by race. For example, among African Americans, the positive association with 2-amino-1-methyl-6-phenyl-imidazo[4,5-*b*]pyridine (PhIP) was confined to those with NAT1*10 genotype (OR=1.8; 95% CI=1.0, 3.3; P for interaction=0.02, comparing highest to lowest intake), but among whites, an association with 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) was confined to those with NAT1-non*10 genotype (OR=1.9; 95% CI=1.1, 3.1; P for interaction=0.03).

Conclusions: Our data indicate modification by NAT1 for HCA and colon cancer associations, regardless of race. Although the at-risk NAT1 genotype differs by race, the magnitude of the individual HCA-related associations in both race groups are similar. Therefore, our data do not support the hypothesis that NAT1 by HCA interactions contribute to differences in colorectal cancer incidence between African Americans and whites.

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Keywords

Acetyltransferases; amines; colon cancer; meat; polymorphism, genetic

1. Introduction

Colorectal cancer incidence rates have been declining in the U.S., with the steepest decline since 1990, especially among non-Hispanic whites [1]. Incidence rates (100,000/year) between 2000 and 2004 were higher among African-American males (72.6) and females (55.0), compared to whites males (60.4) and females (44.0) [2]. Contributing factors to the higher rates of colorectal cancer among African Americans may include dietary intake [3] and/or eating behavior [4], genetic variation at metabolic loci [5] and/or joint effects of both dietary factors and genetic susceptibility [6].

Heterocyclic amines (HCAs) are mutagens and animal carcinogens that are formed when meat is cooked at high temperatures by methods such as pan frying until it is well-done or has a charred appearance [7]. Consumption of pan-fried, well-done meat is a surrogate for HCA and PAH exposure [8], and may be positively associated with colon cancer [9]. Differences in meat intake patterns by doneness and cooking method have been observed among a population-based control sample of African Americans and whites in North Carolina, U.S. For example, among African-American controls, greater intake was observed for pan-fried red meat, well/very well-done red meat, white meat and pan-fried chicken intake, and the HCAs, 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx), and 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline (DiMeIQx), compared to white controls. In contrast, greater grilled/barbecued red meat intake was observed among white controls, compared to African-American controls [10].

HCAs require activation in order to exhibit carcinogenic potential [11]. The initial *N*-hydroxylation step occurs in the liver, and is catalyzed by cytochrome p4501A2 (CYP1A2) [12]. The resulting *N*-hydroxy HCA derivatives are thought to be stable enough to circulate to the colon [13,14] where they are activated by *N*-acetyltransferase 1 (NAT1) and 2 (NAT2) through *O*-acetylation leading to the formation of highly reactive *N*-acetoxy esters [15]. These compounds undergo spontaneous hydrolysis to form arylnitrenium ions; which have the potential to covalently bond with DNA to form adducts and thereby increase risk of mutagenesis and possibly colon cancer [16,17]. NAT1 and NAT2 expression in hepatic, as well as extrahepatic human tissues has been well documented, with recent mRNA localization to the surface epithelial cells of the colon and of the crypts of Lieberkuhn [18].

Interindividual differences in the acetylation or metabolic activation of HCAs have been reported [19]. In addition, NAT1 and NAT2 genotype frequencies vary by race [19,20], suggesting that racial differences in genetic susceptibility to HCAs may contribute to differences in colorectal cancer risk. Although several epidemiologic studies have evaluated whether genetic susceptibility at the NAT loci modify the association between surrogates of HCA exposure (e.g. meat doneness or cooking method) on risk of colon cancer [21-24], few data are available that measure individual HCA compounds in a multiethnic population-based sample. We investigated whether our previously reported findings [10] were modified by NAT1 or NAT2 genotype, and whether there were differences by race.

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2. Materials and methods

2.1. Study population

Cases and controls of the North Carolina Colon Cancer Study were selected from 33 counties in North Carolina, U.S., and frequency matched to cases by race (African American, white), age (<65, ≥65 years), and sex [25]. Details of the study design have been previously described [10]. In brief, cases were selected through a rapid ascertainment system [26] established in conjunction with the North Carolina Central Cancer Registry. 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 10/01/96 and 09/30/00. 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. The study was approved by the Institutional Review Board at the University of North Carolina School of Medicine and by equivalent committees at the collaborating hospitals.

In this study population, African American controls were younger, less educated, and although more likely to be never smokers, were also more likely to be long-term current smokers, compared to white controls. Statistically significant case-control differences were not observed for demographic or smoking characteristics, regardless of race, with the exception of age among African Americans [10]. Mean daily energy, total fat, total meat, red meat and the HCAs, DiMeIQx, MeIQx, and 2-amino-1-methyl-6-phenyl-imidazo[4,5-*b*]pyridine (PhIP) were greater among cases, compared to controls, regardless of race [10]. Dietary fiber was inversely associated with colorectal cancer [3], while calcium was only inversely associated among whites [27]. Although folate intake was not associated with colorectal cancer in this population [27], an approximate two-fold increase in risk was reported for those with low folate and the wild-type methylenetetrahydrofolate reductase genotype, regardless of race [28].

2.2. Exposure assessment

Questionnaires were administered in-person in the participants' homes, by specially trained registered nurses. Information was collected on lifestyle factors such as physical activity and tobacco use, as well as medical, family, and work histories, and use of over-the-counter medications. 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 selection for controls [29]. The questionnaire was modified to assess individual exposure to dietary carcinogens based on a meat-cooking and doneness module developed by Sinha, *et al.* [30]. Details regarding the collection of dietary history and specifically HCA and PAH exposure have been previously documented [10]. In brief, frequency, cooking method, and level of doneness of meat were used to estimate values of three HCAs (MeIQx, PhIP and DiMeIQx) using an exposure-index that has been previously described in detail [30,31].

2.3. Genotyping

Of the individuals with completed questionnaire data, 88% (93% of cases, and 85% of controls) also agreed to provide a blood sample for DNA analyses. We were able to successfully amplify DNA for NAT genotype from 93% of the collected blood samples, leaving 532 African Americans (217 cases and 315 controls), and 824 whites (290 cases and 534 controls) available for analysis. As previously reported [32], cases and controls who did not provide blood samples were more likely to be female ($P < 0.01$) and white ($P < 0.01$). There were no other significant differences, for example, by age, education level, income, family history of colorectal cancer, smoking status, or total meat intake [10,32].

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Genomic DNA was extracted from whole blood specimens using the PureGene® DNA isolation kit (Gentra Systems, Inc., Minneapolis, MN). We identified four NAT1 alleles (*3, *4, *10, *11) and five NAT2 alleles (*4, *5, *6, *7, *14), as defined by Vatsis *et al.* [33]. Two assays were used for *NAT1* genotyping. The first was the restriction fragment length polymorphism (RFLP)-polymerase chain reaction (PCR) assay [34]. The second assay was an allele specific (AS)-PCR, which was used to distinguish between the NAT1*10 and NAT1*3 alleles [34]. Optimal PCR conditions were slightly different from the published protocol. For the RFLP assay, the PCR cycles were as follows: denaturation at 94°C for 90 seconds, replication at 94°C for 10 seconds, 56°C for 30 seconds and 72°C for 45 seconds for 35 cycles, and elongation at 72°C for 4 minutes. For the AS assay, the PCR cycles were as follows: denaturation at 94°C for 3 minutes, replication at 94°C for 10 seconds, 53°C for 30 seconds and 72°C for 45 seconds for 30 cycles, and elongation at 72°C for 4 minutes. NAT2 genotyping was determined by RFLP-PCR methods, as previously described [35]. Optimized PCR cycles were as follows: denaturation at 94°C for 5 minutes, replication at 94°C for 30 seconds, 50°C for 30 seconds and 72°C for 90 seconds for 30 cycles, and elongation stage of 72°C for 4 minutes.

For quality control purposes, a 10% random sample of individuals were repeated for NAT1 and NAT2 genotyping to verify initial results. In addition, all assay results were confirmed by a second independent reader. Genomic DNA extracted from lymphoblastoid cell lines (Corriell Institute, Camden, NJ) were used as positive controls for each genotype and were included in every experiment.

2.4. Statistical analysis

NAT1 and *NAT2* allele and genotype frequencies were calculated among African-Americans and whites, cases and controls separately. Individuals were categorized as “NAT1*10” if an individual had at least one *10 allele, and “NAT1-non*10” if they had none, based on functional [17] and human studies [36]. Individuals were categorized as “NAT2-rapid” if they were homozygous for the wild-type *4 allele, “NAT2-intermediate” if they were heterozygous for the *4 allele, and “NAT2-slow” if they had any other combination of alleles. Observed NAT1 and NAT2 genotype frequencies among controls were compared to expected genotype frequencies, calculated on the basis of observed allele frequencies under the assumption of Hardy-Weinberg equilibrium (HWE) [37]. The Pearson chi-square statistic [with degrees of freedom (df) = number of alleles −1] was used to test whether the expected number of individuals was significantly different from the observed number of individuals with each genotype, stratified by race.

All meat (by type, cooking method, doneness preference) and HCA (MeIQx, DiMeIQx, PhIP) variables were derived from food frequency questionnaire responses. The HCA variables were derived by multiplying grams of meat intake (stratified by type, doneness and method) by the compound concentration (ng/day) measured in that meat type [10]. The meat and HCA variables were categorized into tertiles, based on the distributions among controls. If a continuous variable had more than 33.3 percent zero values, then quantiles were created by including all zero values in the reference group and dichotomizing the remaining values (e.g. >, ≤median value).

For continuous covariates, tertile cutpoints were determined based on the distributions among all controls. These covariates included: fruits, vegetables, dietary fiber, total fat, dietary folate, and total energy intake, physical activity, height, weight, and body mass index (kg/m^2). Fat intake was adjusted for total caloric intake using the residual method [38].

Adjusted odds ratios (ORs) and 95 percent confidence intervals (CIs) for colon cancer were calculated from unconditional logistic regression models [39]. PROC LOGISTIC of the

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software package SAS (version 9.1; SAS Institute, Cary, NC) was used with the option in the MODEL statement to incorporate offsets, which takes into account the selection probabilities by age, race, and sex [25]. Multivariable gene effects models included the following variables to adjust for potential confounding: five-year age groups (≤45, 46-50,…, ≥76 years) and sex. Multivariable main effects models included the previously mentioned variables for age and sex, in addition to race (African American, white), dietary fiber, total fat, and total energy intake, because they were either related both to colon cancer and meat-related variables, a greater than 10% change in beta estimates was observed for the main effect variable between unadjusted and adjusted models, or because there was compelling evidence from the literature for possible confounding. Covariates that were assessed, but did not fulfill the criteria mentioned above for confounding were mean daily folate intake (>276.6, ≤276.6 μg), smoking (never, former, current; never, formerly smoked <35 years, formerly smoked ≥35 years, currently smoke for <35 years, currently smoke for ≥35 years), mean BMI (>28.5, ≤28.5 kg/m^2), and alcohol intake in past year (ever, never beer, wine or liquor).

Statistical interaction between NAT genotypes and meat-related intake on risk of colon cancer was evaluated based on deviation from the multiplicative model. Interaction variables were created for meat-related variables and NAT genotype (e.g. NAT1non-*10, *10 and NAT2-slow, -rapid/intermediate). Then, the fitness of the interaction term in the model was evaluated using the likelihood ratio test. Likelihood ratio tests were considered statistically significant at an alpha level of 0.10 to account for the low power of the test (p. 213-214 in [40]).

3. Results

NAT1 and NAT2 allele and genotype frequencies are presented in Table 1. Genotype frequencies among controls were in HWE for NAT1 (P = 0.98 among African Americans, P = 0.65 among whites, with df = 3), and for NAT2 (P = 0.55 among African Americans, P = 0.80 among whites, with df = 4). Among controls, we observed higher frequencies of the NAT1*10, NAT2-rapid, and NAT2-intermediate genotypes among African Americans, than among whites. There was no association with colon cancer for NAT1*10 versus NAT1-non*10 genotypes among African Americans or whites (Table 1). Among whites, there was a modest positive association for NAT2-intermediate genotype [odds ratio (OR)= 1.4; 95% confidence interval (CI)=1.0, 1.8], compared to the NAT2-slow genotype that was slightly attenuated when combined with the NAT2-rapid genotype. There was no association for NAT2-intermediate or combined rapid/intermediate genotypes among African Americans.

Stratified analyses by NAT1 and NAT2 genotype are presented for meat intake, and meat-derived HCA exposure in relation to colon cancer, separately for African Americans (Table 2) and whites (Table 3). Among African Americans, statistically significant positive associations were observed with pan-fried chicken and DiMeIQx, comparing highest to lowest intake, and with PhIP for mid-level intake (Table 2). These associations were confined to those with NAT1*10 genotype, and statistical interaction was present at the P<0.10 level. In contrast, interaction was not observed by NAT2 genotype (Table 2).

Statistically significant positive associations for colon cancer among whites were observed with well-done red meat, pan-fried red meat, and MeIQx (Table 3). These associations were confined to those with NAT1-non*10 genotype, in contrast to our findings among African Americans. Statistical interaction was observed with NAT1 for well-done red meat and MeIQx at the P<0.01 level. Statistical interaction was not observed between NAT2 genotype and meat intake or meat-derived HCA intake, except for a borderline statistically significant interaction for PhIP (Table 3).

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We examined possible interaction between NAT1 and NAT2 genotypes. NAT1 by NAT2 interactions were not observed for colon cancer overall (P for interaction=0.35), or among whites (P for interaction=0.37). However, interaction was observed among African Americans (P for interaction=0.06), where a positive association was present among those with NAT1*10 and NAT2-rapid/intermediate genotypes (OR=1.8; 95% CI: 0.9, 3.6), compared to those with NAT1-non*10 and NAT2-slow genotypes.

4. Discussion

Racial disparities for colon cancer cannot be explained solely by socioeconomic, behavior, environmental, lifestyle factors, or genetic factors, rather etiologic explanations for these disparities may include interactions between all of these factors [41]. Using data from a population-based case-control study, we observed statistically significant interaction between meat-derived HCA intake and NAT1 genotype, regardless of race. In addition, our data suggest that NAT1 acetylation of HCAs differs by race, where PhIP increased risk of colon cancer among African Americans with "fast" acetylation, and MeIQx increased risk among whites with "slow" acetylation.

Although genetic variation is greater within race/ethnic groups than between, individual single nucleotide polymorphisms may occur uniquely within specific race/ethnic populations resulting in allele frequencies that differ between race/ethnic populations and could account for racial differences in disease susceptibility [42]. To test this hypothesis we measured NAT1 and NAT2 polymorphisms in a population-based sample of African Americans and whites. We observed a greater frequency of the NAT1*10 and NAT2-rapid/intermediate genotypes among African-American controls, than among white controls. NAT genotype frequencies observed in our study population were similar to other case-control studies in the U.S. [43, 44]. Also similar to our findings, in a study of black South Africans, a greater frequency of NAT2 high activity alleles, compared to whites. Black South Africans have among the lowest incidence of colon cancer in the world [45], suggesting that the magnitude of association between NAT2 rapid genotypes and colon cancer may be lower in populations of African versus European decent. In support of this hypothesis, we observed a weak positive association for colon cancer with the NAT2-rapid/intermediate genotype versus NAT2-slow, among whites but not African Americans. In addition no association was observed for NAT1*10, regardless of race. Our findings among whites were consistent with previous epidemiologic studies that reported null to weak positive associations for NAT1*10 versus NAT1-non*10, and NAT2-rapid/intermediate versus NAT2-slow and colon cancer [19,46,47], with some exceptions from small studies [34,48].

We observed that NAT1 genotype differentially modified the association between dietary sources of HCA exposure and colon cancer by race, where positive associations were present among African Americans with the NAT1*10 genotype, and among whites with the NAT1-non*10 genotype. Although NAT1 polymorphisms contribute to differential *N*- and *O*-acetylation of HCAs [15] and NAT1 activity is greater than NAT2 in the colon [49], few epidemiologic studies have evaluated NAT1 as a potential modifier of meat and colorectal cancer associations [50,51]. From a case-control study in Germany, Lilla, *et al.* reported stronger positive associations with frequency of red meat consumption among NAT1*10 than among NAT1-non*10, but interaction was not statistically significant [50]. In a small (N=102 colorectal cases) case-control study, interaction was not observed between red meat and NAT1 genotype, but this may be due to inadequate power [51].

There is epidemiologic evidence for differential effects of acetylation by race. For example, Probst, *et al.*, reported an inverse association between NAT2 "rapid" genotypes and colorectal adenomas among African Americans, but an increased risk among whites [52]. Mechanistic

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explanations for differences by race include the differential effect of individual NAT alleles on HCA acetylation [53]. Our data support this explanation, since we observed differences in NAT allele frequencies by race. Another mechanistic explanation is that genetic variation by race exists in other genes that are relevant for HCA metabolism, such as GSTs [54] and CYP1A2 [12] that are upstream from NAT. Epidemiologic support for this explanation has been observed where increased risk with well-done red meat only among those with rapid CYP1A2 and NAT2 in a case-control study of colorectal cancer [55].

Another explanation for our finding includes the effect of unmeasured heterogeneity in other xenobiotic metabolism genes and/or other environmental factors that may be related to differences in cancer risk between race/ethnic groups [56]. For example, functional data suggest that there was differential mutagenic potential for PhIP depending on genetic variability [57]. One likely suspect is differential glucuronidation of the PhIP intermediate, where greater activity makes the intermediate unavailable for further activation and eventually DNA damage [58]. We have previously reported interaction between UDP-glucuronosyltransferase (UGT) 1A7 and DiMeIQx, although differences by race were not observed [32].

Our findings of no modification by NAT2 genotype for HCA-colon cancer associations supports findings from a recent computational study in which observed differences in mutagenic activity between PhIP and MeIQx intermediates were not related to acetylation with NAT2 [59]. There have been several epidemiologic studies that have investigated meat intake and modification by NAT2 genotype for colorectal cancer [44,50,60,61]. However, few studies have incorporated information on meat cooking method and/or doneness level [21-24,55,62]. Most relevant is that our findings support those of Le Marchand, *et al.*, where no difference was reported for well-done red meat and colon cancer by NAT2 genotype, because this population-based, case-control study used similar methods of HCA estimation to our study [55].

A strength of our study, and a possible reason for previous inconsistent findings of meat-NAT genotype interactions for colorectal cancer, is the use of rigorous methods to estimate dietary HCAs [63]. High-quality exposure assessment is particularly important in estimating interaction with genetic polymorphisms, such as NAT1 and NAT2. By definition they have low-penetrance and are common in the population, so the association with disease is driven by the exposure and not by the presence of polymorphisms [64]. However, poor exposure assessment does not automatically result in biased gene-environment interactions [65].

Misclassification of gene effects may be a source of bias in these data, because genotype data was used to make assumptions about metabolic activity. Previously, epidemiologic studies have categorized NAT1 genotypes based on the presence of the *10 allele, because it contains a DNA sequence variant at the polyadenylation site which increases mRNA stability and possibly metabolic activity [36,66]. However, this categorization for NAT1 may no longer be appropriate [67]. One reason is that a novel NAT1 allele (NAT1*14A) was identified, and determined to be associated with a 15-20 fold reduction in affinity for p-aminosalicylic, a NAT1-selective substrate [68], whereas NAT1*10 was not [69,70]. The RFLP PCR-based genotyping methods used in this study, can not be used to distinguish between the NAT1*10 and NAT1*14A alleles. It has been estimated that using the RFLP genotyping methods misclassifies about 3% of the NAT1*14 alleles as NAT1*10 [71], which would result in a bias of the observed odds ratio toward the null, given that NAT1*10 genotype is not associated with diet among controls in these data (data not shown).

Incomplete NAT2 genotype-phenotype correlation may be another source of bias in our study. We examined three NAT2 SNPs, and although strong evidence exists for their correlation with

acetylation phenotype [72,73], we have misclassified some rapid acetylators as "slow" and visa versa. An analysis of the potential bias introduced in measuring three versus eleven NAT2 SNPs concluded that minimal misclassification and only slight biases in interaction estimates would result [74].

Our data indicate modification by NAT1 for HCA and colon cancer associations, regardless of race. Although the at-risk NAT1 genotype differs by race, the magnitude of the individual HCA-related associations in both race groups are similar. Therefore, our data do not support the hypothesis that NAT1 by HCA interactions contribute to differences in colorectal cancer incidence between African Americans and whites.

Reducing risk of colorectal cancer can be furthered with research on the genetic susceptibility of modifiable exposures, including dietary factors [75]. For example, chemopreventive strategies are currently being investigated to reduce the effects of HCA exposure that activate detoxification pathways in general [76], or specifically by activation CYP1A2 [77] and GSTs [78]. Reducing red meat intake, particularly pan fried meat, and increasing intake of foods known enhance detoxification enzymes remain to be important for reducing risk of colon cancer among both African Americans and whites.

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Table 1

NAT1 and NAT2 allele and genotype frequencies and odds ratios for colon cancer in African Americans and whites (North Carolina Colon Cancer Study)

	African Americans			Whites		
	Cases	**Controls**	**OR (95% CI)[a]**	**Cases**	**Controls**	**OR (95% CI)[a]**
NAT1						
n	208	299		282	528	
Allele frequency (n)[b]						
NAT1*3	0.07 (28)	0.07 (39)		0.05 (26)	0.04 (43)	
NAT1*4	0.48 (201)	0.45 (271)		0.73 (414)	0.76 (801)	
NAT1*10	0.45 (186)	0.48 (286)		0.20 (114)	0.18 (187)	
NAT1*11	0.00 (1)	0.00 (2)		0.02 (10)	0.02 (25)	
Chi-square *P*-value		0.793[c]			0.496	
Genotype frequency (n)[d]						
NAT1-non*10	0.31 (65)	0.28 (83)	1.0 (ref)	0.66 (186)	0.68 (360)	1.0 (ref)
NAT1*10	0.69 (143)	0.72 (216)	0.8 (0.6, 1.2)	0.34 (96)	0.32 (168)	1.1 (0.8, 1.5)
Chi-square *P*-value		0.395			0.520	
NAT2						
n	215	307		285	523	
Allele frequency (n)[b]						
NAT2*4	0.38 (164)	0.38 (236)		0.29 (168)	0.24 (254)	
NAT2*5	0.29 (125)	0.27 (167)		0.43 (245)	0.47 (491)	
NAT2*6	0.24 (104)	0.26 (160)		0.25 (141)	0.27 (279)	
NAT2*7	0.03 (11)	0.03 (18)		0.03 (15)	0.02 (21)	
NAT2*14	0.06 (26)	0.05 (33)		0.00 (1)	0.00 (1)	
Chi-square *P*-value		0.909			0.127[c]	
Genotype frequency (n)[d]						
NAT2-slow	0.39 (83)	0.39 (120)	1.0 (ref)	0.51 (144)	0.58 (305)	1.0 (ref)
NAT2-intermediate	0.47 (100)	0.45 (138)	0.9 (0.5, 1.5)	0.40 (114)	0.35 (182)	1.6 (0.9, 2.7)
NAT2-rapid	0.15 (32)	0.16 (49)	1.1 (0.7, 1.6)	0.09 (27)	0.07 (36)	1.3 (1.0, 1.8)
NAT2-rapid/intermediate	0.61 (132)	0.61 (187)	1.0 (0.7, 1.5)	0.49 (141)	0.42 (218)	1.4 (1.0, 1.8)
Chi-square *P*-value[e]		0.911			0.033	

[a] Adjusted for age, sex, and offsets.

[b] Allele frequency = number of alleles/number of chromosomes. N=number of chromosomes.

[c] Fisher's exact test was used because cell size was less than five counts.

[d] Genotype frequency = Number of participants with genotype/total number of participants. N=number of participants.

[e] Chi-square statistic compares case and control frequencies by slow and combined rapid/intermediate groups.

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Table 2

Odds ratios with meat-related intake, overall and stratified by NAT1 and NAT2 genotype, for colon cancer, among African Americans

		Daily well/very well-done red meat intake (tertile median, g)		
		4.2	**21.4**	**50.1**
	OR (95% CI)	1.0 (ref)[a]	1.0 (0.6, 1.7)	1.7 (0.9, 3.0)
	Cases/controls	43/80	60/112	114/123
NAT1				
Non*10	OR (95% CI)	1.0 (ref)[a]	0.6 (0.2, 1.8)	1.0 (0.3, 3.2)
	Cases/controls[b]	15/15	18/29	32/39
*10	OR (95% CI)	1.0 (ref)	1.1 (0.6, 2.1)	2.2 (1.0, 4.7)
	Cases/controls	26/61	38/77	79/78
	p-value = 0.08[e]			
NAT2				
Slow	OR (95% CI)	1.0 (ref)[a]	1.0 (0.4, 2.7)	1.2 (0.5, 3.3)
	Cases/controls[c]	15/29	25/37	43/54
Rapid/ intermediate	OR (95% CI)	1.0 (ref)	0.9 (0.5, 1.9)	2.0 (0.9, 4.3)
	Cases/controls	28/49	34/72	70/66
	p-value = 0.28[e]			
		Daily pan fried red meat intake (tertile median, g)		
		0.0	9.0	30.0
	OR (95% CI)	1.0 (ref)[a]	1.0 (0.6, 1.7)	1.4 (0.8, 2.4)
	Cases/controls	43/78	57/109	117/128
NAT1				
Non*10	OR (95% CI)	1.0 (ref)[a]	0.5 (0.2, 1.6)	0.9 (0.3, 2.7)
	Cases/controls[b]	14/15	18/32	33/36
*10	OR (95% CI)	1.0 (ref)	1.3 (0.7, 2.4)	1.5 (0.8, 3.0)
	Cases/controls	25/57	38/72	80/87
	p-value = 0.23[e]			
NAT2				
Slow	OR (95% CI)	1.0 (ref)[a]	1.1 (0.4, 2.6)	0.8 (0.4, 2.6)
	Cases/controls[c]	15/24	25/43	43/53
Rapid/ intermediate	OR (95% CI)	1.0 (ref)	1.2 (0.6, 2.3)	1.9 (0.9, 3.9)
	Cases/controls	27/53	31/62	74/72
	p-value = 0.28[e]			
		Daily pan fried chicken intake (tertile median, g)		
		0.0	4.2	14.6
	OR (95% CI)	1.0 (ref)[a]	1.2 (0.7, 2.0)	1.8 (1.2, 2.7)
	Cases/controls	97/179	40/57	80/79
NAT1				
Non*10	OR (95% CI)	1.0 (ref)[a]	1.0 (0.4, 3.0)	1.3 (0.5, 2.9)
	Cases/controls[b]	33/42	10/14	22/27
*10	OR (95% CI)	1.0 (ref)	1.4 (0.7, 2.6)	2.6 (1.5, 4.5)
	Cases/controls	59/129	28/41	56/46
	p-value = 0.07[e]			
NAT2				
Slow	OR (95% CI)	1.0 (ref)[a]	1.3 (0.6, 3.0)	2.7 (1.3, 5.8)
	Cases/controls[c]	33/69	18/26	32/25
Rapid/ intermediate	OR (95% CI)	1.0 (ref)	1.1 (0.5, 2.1)	1.4 (0.8, 2.4)
	Cases/controls	63/104	22/31	47/52
	p-value = 0.19[e]			
		Daily DiMeIQx intake (tertile median, ng)		
		0.3	2.2	7.6
	OR (95% CI)	1.0 (ref)[d]	1.8 (1.1, 3.0)	1.7 (1.0, 2.9)
	Cases/controls	36/92	80/105	101/118
NAT1				
Non*10	OR (95% CI)	1.0 (ref)[d]	0.9 (0.4, 2.5)	0.7 (0.3, 2.0)
	Cases/controls[b]	13/16	28/34	24/33
*10	OR (95% CI)	1.0 (ref)[d]	2.3 (1.2, 4.6)	2.3 (1.2, 4.6)
	Cases/controls	21/70	48/65	74/81

		Daily well/very well-done red meat intake (tertile median, g)		
		4.2	**21.4**	**50.1**
	p-value = 0.06[e]			
NAT2				
Slow	OR (95% CI)	1.0 (ref)[d]	1.7 (0.7, 4.1)	1.9 (0.8, 4.7)
	Cases/controls[c]	14/32	29/43	40/45
Rapid/ intermediate	OR (95% CI)	1.0 (ref)[d]	1.8 (0.9, 3.5)	1.6 (0.8, 3.2)
	Cases/controls	22/56	50/61	60/70
	p-value = 0.63[e]			
		Daily MeIQx intake (tertile median, ng)		
		8.0	38.1	90.8
	OR (95% CI)	1.0 (ref)[d]	1.2 (0.7, 2.0)	1.3 (0.8, 2.3)
	Cases/controls	41/82	73/116	103/117
NAT1				
Non*10	OR (95% CI)	1.0 (ref)[d]	0.7 (0.3, 1.8)	0.6 (0.2, 1.7)
	Cases/controls[b]	15/16	26/34	24/33
*10	OR (95% CI)	1.0 (ref)[d]	1.2 (0.6, 2.4)	1.7 (0.8, 3.3)
	Cases/controls	24/59	43/78	76/79
	p-value = 0.09[e]			
NAT2				
Slow	OR (95% CI)	1.0 (ref)[d]	1.3 (0.5, 3.1)	1.2 (0.5, 3.0)
	Cases/controls[b]	14/27	29/45	40/48
Rapid/ intermediate	OR (95% CI)	1.0 (ref)[d]	1.1 (0.6, 2.0)	1.4 (0.7, 2.9)
	Cases/controls	27/52	42/69	63/66
	p-value = 0.65[e]			
		Daily PhIP intake (tertile median, ng)		
		3.7	42.4	148.2
	OR (95% CI)	1.0 (ref)[d]	1.8 (1.1, 2.8)	1.3 (0.8, 2.1)
	Cases/controls	59/121	73/84	85/110
NAT1				
Non*10	OR (95% CI)	1.0 (ref)[d]	0.9 (0.4, 2.2)	0.5 (0.2, 1.4)
	Cases/controls[b]	21/22	22/26	22/35
*10	OR (95% CI)	1.0 (ref)[d]	2.4 (1.3, 4.4)	1.8 (1.0, 3.3)
	Cases/controls	35/91	49/53	59/72
	p-value = 0.02[e]			
NAT2				
Slow	OR (95% CI)	1.0 (ref)[d]	1.0 (0.4, 2.1)	0.9 (0.4, 1.9)
	Cases/controls[c]	25/37	26/38	32/45
Rapid/ intermediate	OR (95% CI)	1.0 (ref)[d]	2.2 (1.2, 4.1)	1.5 (0.8, 2.8)
	Cases/controls	34/80	45/45	53/62
	p-value = 0.12[e]			

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

[b] Missing NAT1 data: N=9 cases and 16 controls.

[c] Missing NAT2 data: N=2 cases and 8 controls.

[d] Adjusted for age, race, sex, energy-adjusted fat intake, dietary fiber intake, total energy, and offsets.

[e] Likelihood ratio test p-value to assess interaction.

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Table 3

Odds ratios with meat-related intake, overall and stratified by NAT1 and NAT2 genotype, for colon cancer, among whites

		Daily well/very well-done red meat intake (tertile median, g)		
		4.7	**21.2**	**44.8**
	OR (95% CI)	1.0 (ref)[a]	1.2 (0.8, 1.8)	1.5 (0.9, 2.3)
	Cases/controls	81/192	97/181	112/161
NAT1				
Non*10	OR (95% CI)	1.0 (ref)[a]	1.2 (0.7, 2.0)	1.9 (1.1, 3.4)
	Cases/controls[b]	46/123	62/131	78/106
*10	OR (95% CI)	1.0 (ref)[a]	1.4 (0.7, 2.8)	0.8 (0.4, 2.0)
	Cases/controls	32/64	35/49	29/55
	p-value = 0.02[e]			
NAT2				
Slow	OR (95% CI)	1.0 (ref)[a]	1.0 (0.6, 1.9)	1.2 (0.6, 2.3)
	Cases/controls[c]	43/114	50/104	51/87
Rapid/ intermediate	OR (95% CI)	1.0 (ref)[a]	1.2 (0.7, 2.2)	1.6 (0.8, 3.3)
	Cases/controls	38/73	46/74	57/71
	p-value = 0.46[e]			
		Daily pan fried red meat intake (tertile median, g)		
		0.0	9.0	30.0
	OR (95% CI)	1.0 (ref)[a]	1.4 (0.9, 2.0)	2.0 (1.3, 3.1)
	Cases/controls	75/199	92/174	123/161
NAT1				
Non*10	OR (95% CI)	1.0 (ref)[a]	1.3 (0.8, 2.2)	2.2 (1.3, 3.8)
	Cases/controls[b]	46/131	59/124	81/105
*10	OR (95% CI)	1.0 (ref)[a]	1.6 (0.8, 3.3)	1.5 (0.7, 3.3)
	Cases/controls	26/62	33/50	37/56
	p-value = 0.13[e]			
NAT2				
Slow	OR (95% CI)	1.0 (ref)[a]	1.2 (0.7, 2.0)	2.0 (1.1, 3.7)
	Cases/controls[c]	37/113	42/102	65/90
Rapid/ intermediate	OR (95% CI)	1.0 (ref)[a]	1.4 (0.8, 2.5)	1.6 (0.8, 3.0)
	Cases/controls	38/79	48/69	55/70
	p-value = 0.27[e]			
		Daily pan fried chicken intake (tertile median, g)		
		0.0	4.2	10.9
	OR (95% CI)	1.0 (ref)[a]	0.9 (0.6, 1.3)	0.9 (0.5, 1.4)
	Cases/controls	208/385	47/85	35/64
NAT1				
Non*10	OR (95% CI)	1.0 (ref)[a]	0.9 (0.5, 1.5)	0.7 (0.4, 1.3)
	Cases/controls[b]	136/261	31/58	19/41
*10	OR (95% CI)	1.0 (ref)[a]	0.8 (0.4, 1.7)	1.0 (0.5, 2.2)
	Cases/controls	69/119	13/26	14/23
	p-value = 0.42[e]			
NAT2				
Slow	OR (95% CI)	1.0 (ref)[a]	0.9 (0.5, 1.6)	1.0 (0.5, 1.9)
	Cases/controls[c]	103/222	22/47	19/36
Rapid/ intermediate	OR (95% CI)	1.0 (ref)[a]	0.9 (0.5, 1.7)	0.7 (0.4, 1.4)
	Cases/controls	102/154	23/36	16/28
	p-value = 0.50[e]			
		Daily DiMeIQx intake (tertile median, ng)		
		0.2	2.4	7.2
	OR (95% CI)	1.0 (ref)[d]	1.1 (0.8, 1.6)	1.2 (0.8, 1.8)
	Cases/controls	82/183	99/183	109/168
NAT1				
Non*10	OR (95% CI)	1.0 (ref)[d]	0.9 (0.6, 1.5)	1.2 (0.7, 1.9)
	Cases/controls[b]	53/120	61/128	72/112
*10	OR (95% CI)	1.0 (ref)[d]	1.6 (0.8, 3.2)	1.0 (0.5, 2.2)

		Daily well/very well-done red meat intake (tertile median, g)		
		4.7	**21.2**	**44.8**
	Cases/controls	27/59	37/53	32/56
	p-value = 0.09[e]			
NAT2				
Slow	OR (95% CI)	1.0 (ref)[d]	1.0 (0.6, 1.7)	1.1 (0.6, 1.8)
	Cases/controls[c]	45/109	49/107	50/89
Rapid/ intermediate	OR (95% CI)	1.0 (ref)[d]	1.2 (0.7, 2.1)	1.2 (0.6, 2.1)
	Cases/controls	37/69	49/72	55/77
	p-value = 0.89[e]			
		Daily MeIQx intake (tertile median, ng)		
		9.6	36.3	96.6
	OR (95% CI)	1.0 (ref)[d]	1.2 (0.8, 1.8)	1.4 (0.9, 2.2)
	Cases/controls	78/193	98/180	114/161
NAT1				
Non*10	OR (95% CI)	1.0 (ref)[d]	1.3 (0.8, 2.0)	1.9 (1.1, 3.1)
	Cases/controls[b]	46/129	65/130	75/101
*10	OR (95% CI)	1.0 (ref)[d]	1.3 (0.7, 2.6)	0.8 (0.4, 1.7)
	Cases/controls	29/59	33/49	34/60
	p-value = 0.03[e]			
NAT2				
Slow	OR (95% CI)	1.0 (ref)[d]	1.3 (0.7, 2.1)	1.5 (0.8, 2.7)
	Cases/controls[c]	39/117	51/105	54/83
Rapid/ intermediate	OR (95% CI)	1.0 (ref)[d]	1.0 (0.6, 1.8)	1.1 (0.6, 2.0)
	Cases/controls	39/70	46/72	56/76
	p-value = 0.31[e]			
		Daily PhIP intake (tertile median, ng)		
		2.5	45.6	137.3
	OR (95% CI)	1.0 (ref)[d]	0.8 (0.5, 1.2)	1.3 (0.9, 2.0)
	Cases/controls	70/151	89/208	131/175
NAT1				
Non*10	OR (95% CI)	1.0 (ref)[d]	0.8 (0.5, 1.3)	1.4 (0.9, 2.3)
	Cases/controls[b]	47/106	51/136	88/118
*10	OR (95% CI)	1.0 (ref)[d]	1.0 (0.5, 2.1)	1.2 (0.5, 2.5)
	Cases/controls	21/42	37/69	38/57
	p-value = 0.14[e]			
NAT2				
Slow	OR (95% CI)	1.0 (ref)[d]	0.5 (0.3, 0.9)	1.1 (0.6, 2.0)
	Cases/controls[c]	41/86	37/122	66/97
Rapid/ intermediate	OR (95% CI)	1.0 (ref)[d]	1.1 (0.6, 2.1)	1.5 (0.8, 2.9)
	Cases/controls	29/60	50/84	62/74
	p-value = 0.08[e]			

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

[b] Missing NAT1 data: N=8 cases and 6 controls.

[c] Missing NAT2 data: N=5 cases and 11 controls.

[d] Adjusted for age, race, sex, energy-adjusted fat intake, dietary fiber intake, total energy, and offsets.

[e] Likelihood ratio test p-value to assess interaction.

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