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Dietary meat intake in relation to colorectal adenoma in asymptomatic women

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Abstract

Introduction—No previous study has concurrently assessed the association between meat intake, meat cooking methods and doneness levels, meat mutagens (heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons), heme iron, and nitrite from meat and colorectal adenoma in asymptomatic women undergoing colonoscopy.

Methods—Of 807 eligible women in a cross-sectional multi-center colonoscopy screening study, 158 prevalent colorectal adenoma cases and 649 controls satisfactorily completed validated food frequency and meat questionnaires. Using an established meat mutagen database and new iron and nitrite databases, we comprehensively investigated components of meat that may be involved in carcinogenesis. Using logistic regression we estimated odds ratios (OR) and 95% confidence intervals (CI) within quartiles of meat-related variables.

Results—Red meat was positively associated with colorectal adenoma (OR fourth versus first quartile = 2.02; 95% CI = 1.06–3.83; P trend = 0.38). Intake of pan fried meat (OR = 1.72; 95% CI = 0.96–3.07; P trend = 0.01) and the HCA: 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) (OR = 1.90; 95% CI = 1.05–3.42; P trend = 0.07) were also associated with increased risk of colorectal adenoma. The new databases yielded lower estimates of heme iron and nitrite than previous assessment methods, although the two methods were highly correlated for both exposures. Although not statistically significant, there were positive associations between iron and heme iron from meat and colorectal adenoma.

Conclusions—In asymptomatic women undergoing colonoscopy, colorectal adenomas were associated with high intake of red meat, pan fried meat, and the HCA MeIQx. Other meat-related exposures require further investigation.

Specific Author Contributions:

LMF performed and interpreted the statistical analyses and drafted the manuscript. AJC and RS participated in devising the hypothesis, interpreting the results, and edited the manuscript. BDC, AF, BIG, XM, STM, AS and PSS participated in interpreting the results and edited the manuscript. BDC, AF, AS, and PSS were also involved in the original design, conduct, and oversight of the CONCeRN study.

Potential Competing Interests: None

Introduction

Although much of the current epidemiologic research has found positive associations between both red meat and processed meat and colorectal cancer (1), the mechanisms to explain these associations remain largely unknown. In addition, the evidence for the role of meat in relation to colorectal adenomas, known precursors of colorectal cancer (2–4), has been mixed. There are a limited number of studies with full colonoscopy to verify adenoma status (5–7), as well as a lack of detail on meat intake and on the effect of different components of meat, including meat mutagens associated with cooking practices, heme iron and nitrite on colorectal adenoma development. Of these various components of meat, each has an independent and viable mechanism to impact carcinogenesis.

Meat mutagens, such as heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs), are formed in meats cooked well done at high temperatures (8–10). HCAs and PAHs produce intestinal tumors in rodents (11–13) and have been associated with an increased risk of colorectal adenoma in several epidemiologic studies (5,14–17).

Both non-heme iron and heme iron can induce oxidative DNA damage, by catalyzing the formation of reactive oxygen species (18,19). However, heme iron, which is found predominantly in red meat, may be more important in the carcinogenic process due to its greater bioavailability. Heme iron is associated with increased cytotoxicity of fecal water (20,21) and the promotion of chemically-induced colorectal cancer in rats (22). Human studies have also found a positive association between heme iron intake and endogenous formation of *N*-nitroso compounds (NOCs) (23,24), some of the most powerful chemical carcinogens (25).

Epidemiologic studies of dietary iron or serum iron indices in relation to colorectal adenoma have produced contradictory results (26–29), perhaps due to the inability to assess heme iron intake separately from total iron from meat. All previous analyses of heme iron have relied on two methods to estimate intake based on standard proportions of total iron from meat (30,31). Using these approximations for heme iron intake, one study of colorectal adenoma found no evidence of an association (29) and studies of colorectal cancer observed weak positive associations (31–33) or no association (34). However, research indicates that heme iron in meat can be partially converted to non-heme iron depending on the type and duration of the cooking method employed (35–37). A new heme iron database being developed at the National Cancer Institute (NCI), to be used in conjunction with a detailed meat-cooking module, allows for this consideration.

More recently, research has begun to focus on exposure to nitrite and NOCs related to the intake of processed meat. The addition of nitrite to processed meat can lead to the formation of NOCs, which cause tumors in both the colon and rectum of numerous animal species (38). Limited epidemiological research indicates *N*-nitrosodimethylamine intake may be associated with colorectal cancer (39) and combined nitrate and nitrite intake from meat may be associated with colorectal adenoma (40).

We examined the relationship between dietary meat intake and colorectal adenoma in asymptomatic women enrolled in a colonoscopy screening study by exploring several meat-related exposures that may impact carcinogenesis. This is the first study to assess the association between meat intake, method of meat cooking and doneness levels, meat mutagens, heme iron, and nitrite from meat and colorectal adenoma in asymptomatic women undergoing screening colonoscopy. Furthermore, this is the first study to utilize a heme iron database that estimates heme iron intake based on laboratory measures of various meats prepared according to different cooking methods and doneness levels (41), which may allow for a better quantification of heme iron intake. This is only the second study to examine nitrite intake in relation to colorectal adenoma with a database based on measured values of this compound in

processed meats. We hypothesized that women with high intakes of red meat, well done meat, pan fried or grilled meat, meat mutagens, heme iron, and nitrite would have an increased risk of colorectal adenoma compared to those with low intakes.

Materials and methods

The CONCeRN Study

The CONCeRN (*CO*lorectal *Neoplasia* screening with *CO*lonoscopy in asymptomatic women at *R*egional *N*avy/army medical centers) study, previously described in detail (42), is a multi-center screening study designed to determine the relative benefits of colonoscopy versus sigmoidoscopy for colorectal cancer screening in asymptomatic, average-risk women. From January 1, 2000 to December 31, 2002, women were invited to participate in an etiologic component of the CONCeRN study involving additional biospecimen and questionnaire data collection. Prior to colonoscopy, participants returned two self-administered questionnaires they had received in the mail: a risk factor questionnaire (RFQ) (e.g. family history, height, weight, etc.) and the NCI's diet history questionnaire (DHQ) (43).

Case Ascertainment

Any polyp found during colonoscopy was reviewed by an expert gastrointestinal pathologist, and participants were classified as cases of colorectal adenoma if they had a pathologically verified adenomatous (i.e. tubular, villous, or serrated) polyp of any size in the proximal or distal colon or rectum. The protocol was approved by the institutional review boards at the NCI and each participating medical center. All participants provided written informed consent.

Assessment of meat, meat mutagens, iron and heme iron from meat, and nitrite from meat

Estimates of meat intake (g/day) were based on responses to the DHQ that assessed usual intake (frequency and portion size) of 124 food items over the past year. The DHQ has been validated against four 24-hour dietary recalls and found to be comparable to other food frequency questionnaires (44). Nutrient intake was estimated using the Diet*Calc Analysis Program (version 1.4.3, 2005), based on nutrient content information from the U.S. Department of Agriculture (USDA) Survey Nutrient Database and the Nutrition Data Systems for Research from the University of Minnesota. Intake of red meat included bacon, beef, cheeseburgers, cold cuts, ham, hamburgers, hot dogs, liver, pork, sausage, veal, venison, and red meat from mixed dishes. White meat included chicken, fish, and turkey. Processed meat included bacon, cold cuts, ham, hot dogs, and sausage.

Usual meat cooking methods (e.g. baked, broiled, grilled, microwaved, pan fried) and doneness levels (e.g. rare, medium, well done, and very well done) were assessed in a detailed meat-cooking module administered as part of the RFQ. Using this information, along with the Computerized Heterocyclic Amines Resource for Research in Epidemiology of Disease (CHARRED) (<http://www.charred.cancer.gov>) software application, we generated estimates of three HCAs (ng/day): 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline (DiMeIQx), 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx), and 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), as well as benzo[*a*]pyrene (B[*a*]P), a marker of total PAH exposure. CHARRED computes estimates based on data from more than 120 categories of meat cooked by different methods and to varying doneness levels. CHARRED also estimates mutagenic activity (revertant colonies/day), a measure of total mutagenic potential incorporating all meat-related mutagens.

Cooking method, doneness level, and meat intake data were further utilized to estimate heme iron intake from meat using preliminary data from a NCI heme iron database based on measured values from meat samples cooked by different methods and to varying doneness levels (41).

Currently, the heme iron database includes data on bacon, chicken (not in mixed dishes), cold cuts, hamburgers, hot dogs (regular), pork chops, roast beef, sausage (regular), and steak cooked by a variety of cooking methods to a range of doneness levels. In addition, iron (heme and non-heme) from meat was estimated from nutrient content information from the USDA Survey Nutrient Database. Finally, we estimated exposure to nitrite from processed meat using a NCI database containing measured values of nitrite from 10 types of processed meat, representing 90% of the processed meat assessed in FFQs (40,41). The database does not take into account other dietary sources of nitrite.

Statistical analysis

The demographic characteristics and dietary covariates of those with and without colorectal adenoma were compared using the χ^2 test for categorical variables and the Wilcoxon rank sum test for continuous variables. The dietary variables were nutrient density adjusted; using residual energy adjustment (45) did not alter our findings. Quartile cut-points for dietary variables were based on intake in those without colorectal adenomas; setting the cut-points using all the data did not alter our results. To assess total iron intake from diet and supplements, we residually energy adjusted the dietary iron so that it could be combined with supplemental iron and remain on the same scale (g/day). Odds ratios (OR) and 95% confidence intervals (CI) were computed using unconditional logistic regression, with the first quartile as the referent group. Trend tests were calculated using the median intake values of each quartile. We also calculated ORs based on continuous measures of intake for each exposure. To further evaluate whether the associations between red meat intake and colorectal adenoma were linear, we created restricted cubic regression splines with varying knots (3, 4, and 5) located at set percentiles of intake (46). All reported P values are two sided and analyses were conducted using SAS software (SAS Institute, Cary, NC, Version 9).

We compared previous methods of assessing heme iron and nitrite from meat to our measured values. For this, we calculated heme iron intake using a current method in the literature (40% of iron from the meats included in the NCI heme iron database) (30) and compared these to the estimates from the NCI heme iron database. In addition, we calculated heme iron as 40% of iron for all meats. For nitrite, we compared the measured values to average values from the historical literature (40). We computed Pearson correlation coefficients, as well as weighted Kappa statistics (47,48) and percent agreement for agreement across quartiles to characterize descriptively the relationship between the different methods.

Multivariate models were adjusted for characteristics associated with colorectal adenomas in our dataset or associated with colorectal adenomas or colorectal cancer in the literature. The covariates were: age (continuous), education (high school or less, vocational/technical/business, 1–3 years or college/junior college, college graduate, graduate/professional degree), race (White, African-American, other), smoking status (never, former, current), highest level of physical activity (no moderate or vigorous activity, moderate activity, vigorous activity), body mass index (BMI) (continuous, kg/m²), study center (Bethesda, Portsmouth, San Diego, Washington D.C.), current hormone replacement therapy (HRT) use (yes, no), history of colorectal polyps or cancer in a primary relative (yes, no), regular non-steroidal anti-inflammatory drug (NSAID) use (defined as once a week for at least one month at any time prior to three months before colonoscopy; yes, no, don't know/missing), alcohol intake (<5 g/day, 5–14.9 g/day, ≥ 15 g/day), fiber (continuous, g/1,000 kcal), dietary calcium (continuous, mg/1,000 kcal), calcium from supplements (continuous, mg/day), and total caloric intake (continuous, kcal/day).

Results

A total of 910 women (92% participation) completed the RFQ and DHQ questionnaires and underwent colonoscopy. Participants were ineligible for this cross-sectional analysis if they had an incomplete colonoscopy ($n = 11$); missed more than seven items on the DHQ ($n = 77$); or were extreme outliers for reported total caloric intake (top and bottom 1% for intake, $n = 22$). After exclusions (some individuals met multiple criteria), there were 807 participants (158 with prevalent colorectal adenoma and 649 without).

Among the 158 women with prevalent colorectal adenoma, 37 (23.4%) had advanced adenomas, 89 (56.3%) had adenomas in the proximal colon, and 55 (34.8%) had adenomas in the distal colon (Table 1). Compared to participants without colorectal adenomas, cases were more likely to be older and to have a higher BMI. Cases had lower intake of dietary calcium and were less likely to report current use of HRT and regular use of NSAIDs.

Although we observed no association for total meat intake, there was a positive association between red meat intake and colorectal adenoma (OR for the fourth compared to the first quartile = 2.02; 95% CI = 1.06–3.83), with a possible threshold effect in the second quartile (Table 2, Figure 1). There were no statistically significant associations for white meat, processed meat, chicken, or fish.

Pan fried meat intake was positively associated with colorectal adenoma, with borderline statistical significance for the categorical data (OR for the fourth compared to the first quartile = 1.72; 95% CI = 0.96–3.07) and a statistically significant association for the continuous data (OR = 1.45 per additional 10g/1000kcal; 95% CI = 1.01–2.08) (Table 3). There was no evidence that grilled meat intake or meat doneness were associated with colorectal adenoma in this population.

Among the meat mutagens, there was a possible positive association between the HCA, MeIQx, and colorectal adenoma in the categorical data (OR for the fourth compared to the first quartile = 1.90; 95% CI = 1.05–3.42), as the P trend was borderline statistically significant (0.07) (Table 3). However, this relationship was statistically significant on the continuous scale (OR = 1.11 per additional 10ng/day, 95% CI = 1.03–1.21) (Table 3). There was no evidence that DiMeIQx, PhIP, B[a]P, or total mutagenic activity were associated with colorectal adenoma.

There were no statistically significant associations between total iron, dietary iron, or iron from supplements and colorectal adenoma (Table 4). However, there were positive associations between iron and heme iron from a subset of meats and colorectal adenoma, although these ORs did not reach statistical significance. There was no evidence of effect modification by alcohol status (< 5 g/day vs. ≥ 5 g/day) for the association between heme iron and colorectal adenoma (data not shown).

In our population, mean heme iron intake with the NCI heme iron database (mean = 0.16, standard deviation (SD) = 0.11 mg/1,000 kcal) was 88.9% of the amount estimated by calculating 40% of iron from the same meats for which we had measured values (mean = 0.18, SD = 0.12 mg/1,000 kcal). The Pearson correlation coefficient was 0.97 for comparing these two estimates of heme iron. When the heme iron estimates were categorized into quartiles there was high agreement (weighted Kappa = 0.85, 95% CI = 0.83–0.87; percent agreement = 81.5%, 95% CI = 78.8%–84.2%). Risk estimates (detailed data not shown) using 40% of iron from meat (limited to those in the heme iron database) to estimate heme iron intake were similar to those based on the NCI heme iron database (OR for the fourth compared to the first quartile = 1.71; 95% CI = 0.94–3.14, p-trend = 0.17). We also calculated heme iron as 40% of iron from all meats, not just those in the heme iron database, and saw no association with risk of colorectal

adenoma (OR for the fourth compared to the first quartile = 1.00; 95% CI = 0.55–1.82, p-trend = 0.76).

Intake of nitrite from meat was not associated with colorectal adenoma (Table 5). Although highly correlated (Pearson correlation = 0.97), intake of nitrite estimated by the NCI database was 70.4% of the estimated intake from previously published values. When the measured and published nitrite values were categorized into quartiles, the weighted Kappa statistic was 0.88 (95% CI = 0.84–0.90) and percent agreement was 84.4% (81.9%–86.9%).

Discussion

This is the first study to concurrently assess the association of meat intake, meat cooking methods and doneness levels, meat mutagens, heme iron and nitrite with prevalent colorectal adenomas in asymptomatic women undergoing colonoscopy. It is the first study to utilize a new NCI heme iron database to quantify heme iron intake based on laboratory measured meat samples. In our study, we found an increased risk of colorectal adenoma for women who consumed the highest amounts of red meat, pan fried meat, and the HCA MeIQx. Although there was no association for total iron, dietary iron, iron from supplements, or nitrite, there were positive associations between iron and heme iron from meat and colorectal adenoma although these associations did not reach statistical significance.

Our findings for red meat and pan fried meat agree with several previous studies that have observed positive associations between red meat and meat cooked at high temperatures and colorectal adenoma (5,14,49–52). The motive for studying pan fried meat is based on the hypothesis that formation of HCAs during such high temperature cooking methods will increase the risk of neoplasia; therefore, it is particularly interesting that we also observed a positive association with MeIQx, which has been associated with increased risk of colorectal adenoma in previous studies (14,15). Unlike some previous studies, we did not observe an elevated risk for grilled meat (17,50) or for well/very well done meat (14,50,51).

Although some studies have linked high intake of processed meat intake to an increased risk of colorectal adenoma (40,51), we did not observe such an association in our study population, which had a relatively low intake of processed meat and thus low levels of nitrite from meat. The one previous study that utilized the NCI nitrite database found a two-fold increased risk of colorectal adenoma for those in the highest quartile of nitrate and nitrite intake compared to the lowest quartile; however, the range of intake of processed meat was higher in the previous study compared to ours (40). Consequently, our study may have lacked statistical power to assess the association of nitrite with colorectal adenoma.

Our null findings for dietary iron are similar to those reported by three previous studies of colorectal adenoma (27–29). Several cohort studies have examined the association between dietary iron (34,53) or iron stores (34,53–55) and colorectal cancer, but results have been inconclusive. Nelson et al., evaluated 33 case-control studies and concluded that higher dietary iron and iron stores were associated with an increased risk of colorectal cancer (56). However, results from a recent nested case-control study among male smokers found inverse associations between several serum iron indices and colon cancer, but not rectal cancer (57). The inconsistency in the literature might be due to the different study populations, as well as the different sources and types of iron evaluated in these studies. Future research may also need to consider role of individual variation in genes related to iron absorption and metabolism in colorectal neoplasia. Finally, the role of iron in colorectal carcinogenesis is most likely very complex, as excess exposure to iron could be at the systemic level through excess iron absorption or directly through the lumen due to the passage of excess dietary iron through the gastrointestinal tract.

Our findings do not show a clear association between iron and heme iron from meat and colorectal adenoma in women, although there was a suggestion of an increased risk. This is the first study to assess heme iron intake using a database based on laboratory measured values of heme iron in various meats cooked by different methods and to varying degrees of doneness. Previous studies of colorectal cancer that have attempted to evaluate heme iron intake using a proportion of total iron (32,33) or by employing a methodology that accounts for varying levels of heme iron by meat type (31,34), have yielded inconsistent results. In this study, heme iron intake estimated as 40% of iron from those meats in the heme iron database was highly correlated with the heme iron database values and most individuals were classified in the same quartile of intake. However, had we only assessed heme iron as 40% of iron from all meats, as done in previous research, the risk estimate would have been completely null.

Our current findings on heme iron may be somewhat limited as this population of women had a higher consumption of white meat as compared to red meat and a narrow range of cooking methods and doneness levels. In addition, heme iron intake is most likely underestimated in this population as the heme database only accounted for 57.3% of the red meat intake in our population and we may have lacked the power to observe a statistically significant association for a low range of intake. In light of the inconsistent findings for heme iron, additional studies are necessary. The NCI heme iron database should also be investigated in other larger populations to further evaluate current estimation methods of exposure to heme iron.

The strengths of our study include colonoscopy confirmed colorectal adenoma status for all participants, detailed exposure assessment of meat intake, cooking methods and doneness levels, analysis of multiple potential mechanisms, and a high participation rate. This dataset provided a unique opportunity to comprehensively examine a wide range of meat-related exposures among asymptomatic women with little risk of dietary changes due to disease status. Participants also completed questionnaires prior to colonoscopy eliminating recall bias. Limitations of this study include the cross-sectional rather than longitudinal design, as well as the evaluation of usual dietary intake only during the year prior to colonoscopy, which may not be the time period most relevant to the development of colorectal adenoma. Although this study utilized comprehensive methods of assessment for meat, meat cooking methods, and doneness levels, the possibility of some degree of measurement error remains. As in any observational study, it is possible that the observed association is due to unmeasured or residual confounding, although this study did assess all known potential confounders. We also were not able to evaluate genetic variation that may be involved in colorectal carcinogenesis. Finally, the generalizability of these results is limited to predominantly Caucasian and highly educated women.

This is the first study to assess meat intake and the currently hypothesized potentially carcinogenic components of meat in relation to colorectal adenoma in a population of asymptomatic women undergoing screening colonoscopy. In this population, there was an increased risk of colorectal adenoma with high intake of red meat, pan fried meat, and, the HCA MeIQx. Future research on meat and colorectal neoplasia should focus on assessing all meat-related exposures to enhance our understanding of the mechanisms for the role of meat in cancer. Given our small sample size, evaluation of heme iron and nitrite from meat in large, prospective cohort studies is needed to clarify the role of these exposures in carcinogenesis.

Study Highlights

1. What is current knowledge
 - a. Red and processed meat positively associated with colorectal neoplasia

- b.** Mechanisms are not well understood
 - c.** Possible meat-related exposures implicated include: meat mutagens, heme iron, nitrite
 - d.** No study has analyzed these exposures simultaneously
 - e.** Prior research has estimated heme iron intake by applying a standard factor to total iron from meat
- 2.** What is new here
- a.** This is the first study of asymptomatic women with full colonoscopy and concurrent assessment of multiple components of meat intake, including meat cooking methods, doneness levels, meat mutagens, nitrite, and heme iron
 - b.** Estimated heme iron and nitrite using databases based on measured values
 - c.** Increased risk of adenoma with high intake of red meat, pan fried meat, and the heterocyclic amine MeIQx
 - d.** Possible association between iron and heme iron from meat and colorectal adenoma

Abbreviations

B[a]P	benzo[a]pyrene
BMI	body mass index
CHARRED	Computerized Heterocyclic Amines Resource for Research in Epidemiology of Disease
CONCeRN	COlorectal Neoplasia screening with Colonoscopy in asymptomatic women at Regional Navy/army medical centers
CI	confidence interval
DHQ	diet history questionnaire
DiMeIQx	2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline
HCAs	heterocyclic amines
MeIQx	2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline
NCI	National Cancer Institute
NOCs	N-nitroso compounds
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
PAHs	polycyclic aromatic hydrocarbons
PhIP	2-amino-1-methyl-6-phenyl-imidazo[4,5-b]pyridine
RFQ	risk factor questionnaire
SD	standard deviation
USDA	U.S. Department of Agriculture

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Figure 1. Odds ratios* for colorectal adenoma risk in relation to red meat intake (g/1000 kcal) in the CONCeRN study (test for curvature p-value = 0.09)

*Odds ratios (1.00 indicated by solid horizontal black line) are modeled on a continuous basis using a four knot cubic regression spline. Odds ratios are indicated by the solid red line and 95% confidence intervals by dashed blue lines. The referent (solid vertical black line) is an intake of 9.4 g/1000kcal of red meat (median of the first quartile), with knots placed at the 5th, 25th, 75th, and 95th percentiles of the distribution of red meat intake. The odds ratios were adjusted for age (continuous), education (high school or less, vocational/technical/business, 1–3 years or college/junior college, college graduate, graduate/professional degree), race (White, African-American, other), smoking status (never, former, current), physical activity (no moderate or vigorous activity, moderate, vigorous), BMI (continuous, kg/m²), study center (Bethesda, Portsmouth, San Diego, Washington D.C.), current HRT use (yes, no), family history of colorectal polyps or cancer (yes, no), regular NSAID use (defined as once a week for at least one month at any time prior to three months before colonoscopy; yes, no, don't know/missing), alcohol intake (<5 g/day, 5–14.9 g/day, ≥15 g/day), fiber (continuous, g/1,000 kcal), dietary calcium (continuous, g/1,000 kcal), calcium from supplements (continuous, g/day), and total caloric intake (continuous, kcal/day).

Table 1

Characteristics of asymptomatic women in the CONCeRN study (N=807).

Characteristic	With Adenoma N = 158 n (%), mean $\pm$ SD	Without Adenoma N = 649 n (%), mean $\pm$ SD	P-value *
Age (years)	60.2 $\pm$ 9.0	57.2 $\pm$ 7.6	<0.01
Study Center			0.10
Bethesda	95 (60.1)	420 (64.7)	
Portsmouth	20 (12.7)	66 (10.2)	
San Diego	25 (15.8)	122 (18.8)	
Washington D.C.	18 (11.4)	41 (6.3)	
Race			0.06
White	115 (72.8)	525 (80.9)	
African-American	21 (13.3)	54 (8.3)	
Other	22 (13.9)	70 (10.8)	
Education, Graduate or professional degree	34 (21.5)	164 (25.3)	0.06
Body mass index (kg/m ²)	27.6 $\pm$ 5.8	26.7 $\pm$ 5.7	0.03
Physical activity, vigorous	53 (33.5)	239 (36.8)	0.46
Smoking status			0.16
Never	82 (51.9)	387 (59.6)	
Former	64 (40.5)	229 (35.3)	
Current	12 (7.6)	33 (5.1)	
Alcohol (g/day)	6.0 $\pm$ 9.6	7.1 $\pm$ 13.3	0.14
Current use of hormone replacement therapy	86 (54.4)	422 (65.0)	0.01
Positive family history of colorectal cancer or polyps	37 (23.4)	148 (22.8)	0.87
Regular use of non-steroidal anti-inflammatory drugs	58 (36.7)	334 (51.5)	<0.01
Total energy intake (kcal/day)	1471 $\pm$ 554	1556 $\pm$ 601	0.17
Dietary folate (mcg/day)	349.1 $\pm$ 158.5	365.0 $\pm$ 166.8	0.23
Supplemental folate (mcg/day)	233.3 $\pm$ 185.8	233.1 $\pm$ 187.9	0.88
Dietary calcium (mg/day)	599.1 $\pm$ 279.3	679.3 $\pm$ 339.2	0.01
Supplemental calcium (mg/day)	404.5 $\pm$ 397.3	430.0 $\pm$ 396.7	0.23
Fiber (g/day)	16.1 $\pm$ 8.7	17.3 $\pm$ 8.6	0.09
Fruit (g/day)	274.6 $\pm$ 336.9	280.7 $\pm$ 232.1	0.44
Vegetables (g/day)	274.9 $\pm$ 184.2	295.9 $\pm$ 238.4	0.53
Adenoma Characteristics			
Advanced ^a	37 (23.4)	-	
Proximal ^b	89 (56.3)	-	
Distal ^b	55 (34.8)	-	

* χ^2 test for categorical variables and Wilcoxon rank sum test for continuous variables.^a Advanced adenomas met one of the following histologic criteria: greater than 10mm in diameter, villous, tubulovillous, high-grade dysplasia, or cancer (invasive or in situ).

^b Proximal adenomas were those in the cecum, ascending colon, hepatic flexure, transverse colon, or splenic flexure. Distal adenomas were those in the descending colon, sigmoid colon, or rectum. 14 cases had both proximal and distal adenomas and are not classified here.

Table 2

Multivariate ORs* for colorectal adenoma risk associated with intake of meat (g/1,000 kcal).

Characteristic	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P Trend ^a	Continuous (per 10 g)
Total meat						
Median (Cut-points)	34.2 (≤44.4)	53.6 (>44.4–64.2)	77.9 (>64.2–90.8)	111.1 (>90.8)		
Cases/Controls	36/161	37/158	51/159	31/158		
OR (95% CI)	1.00	1.08 (0.62–1.89)	1.79 (1.05–3.07)	0.99 (0.55–1.81)	0.75	1.00 (0.95–1.06)
Red meat						
Median (Cut-points)	9.4 (≤15.0)	18.7 (>15.0–24.0)	28.7 (>24.0–35.6)	45.1 (>35.8)		
Cases/Controls	22/160	54/160	39/158	40/158		
OR (95% CI)	1.00	2.97 (1.64–5.37)	2.05 (1.10–3.84)	2.02 (1.06–3.83)	0.38	1.07 (0.95–1.21)
White meat						
Median (Cut-points)	13.3 (≤22.1)	27.9 (>22.1–36.9)	44.6 (>36.9–59.1)	80.2 (>59.1)		
Cases/Controls	43/159	45/161	29/156	38/160		
OR (95% CI)	1.00	1.06 (0.63–1.78)	0.81 (0.46–1.43)	0.98 (0.57–1.70)	0.89	0.99 (0.93–1.05)
Processed meat^b						
Median (Cut-points)	1.5 (≤2.6)	3.9 (>2.6–5.1)	6.7 (>5.1–9.7)	15.7 (>9.7)		
Cases/Controls	36/160	37/161	41/160	41/155		
OR (95% CI)	1.00	1.09 (0.62–1.92)	0.99 (0.56–1.74)	1.05 (0.59–1.85)	0.84	0.98 (0.78–1.23)
Chicken						
Median (Cut-points)	5.4 (≤9.8)	15.3 (>9.8–20.9)	27.8 (>20.9–39.6)	59.5 (>39.6)		
Cases/Controls	40/158	42/159	36/158	37/161		
OR (95% CI)	1.00	1.20 (0.69–2.08)	1.19 (0.67–2.10)	1.11 (0.62–1.98)	0.84	1.01 (0.93–1.08)
Fish						
Median (Cut-points)	3.0 (≤4.5)	6.3 (>4.5–8.7)	11.4 (>8.7–15.5)	24.5 (>15.5)		
Cases/Controls	46/161	36/160	35/157	38/158		
OR (95% CI)	1.00	0.74 (0.43–1.26)	0.86 (0.50–1.49)	1.15 (0.67–1.99)	0.44	1.00 (0.86–1.16)

* OR adjusted for age (continuous), education (high school or less, vocational/technical/business, 1–3 years or college/junior college, college graduate, graduate/professional degree), race (White, African-American, other), smoking status (never, former, current), physical activity (no moderate or vigorous activity, moderate, vigorous), BMI (continuous, kg/m²), study center (Bethesda, Portsmouth, San Diego, Washington D.C.), current HRT use (yes, no), family history of colorectal polyps or cancer (yes, no), regular NSAID use (defined as once a week for at least one month at any time prior to three months before colonoscopy; yes, no, don't know/missing), alcohol intake (<5 g/day, 5–14.9 g/day, ≥15 g/day), fiber (continuous, g/1,000 kcal), dietary calcium (continuous, g/1,000 kcal), calcium from supplements (continuous, g/day), and total caloric intake (continuous, kcal/day).

^aP trend calculated using the median of each quartile.

^bIncludes bacon, sausage, hot dogs, ham, and cold cuts.

Table 3

Multivariate ORs* for colorectal adenoma risk associated with intake of meat cooking (g/1000 kcal), doneness levels (g/1000 kcal), and meat mutagens (ng/day).

Characteristic	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P Trend ^c	Continuous (per 10 unit)
Grilled meat						
Median (Cut-points)	0.1 (≤0.8)	1.8 (>0.8–3.1)	5.1 (>3.1–8.1)	15.0 (>8.1)		
Cases/Controls	33/160	50/157	35/161	37/158		
OR (95% CI)	1.00	1.85 (1.07–3.21)	1.21 (0.67–2.20)	1.40 (0.75–2.60)	0.88	0.89 (0.70–1.12)
Pan fried meat						
Median (Cut-points)	0.0 (≤0.3)	0.7 (>0.3–1.2)	2.1 (>1.2–3.4)	5.3 (>3.4)		
Cases/Controls	31/162	27/157	34/160	63/157		
OR (95% CI)	1.00	0.88 (0.47–1.63)	1.00 (0.55–1.82)	1.72 (0.96–3.07)	0.01	1.45 (1.01–2.08)
Well/Very well meat						
Median (Cut-points)	0.0 (≤0.3)	0.8 (>0.3–1.7)	3.0 (>1.7–5.3)	11.4 (>5.3)		
Cases/Controls	33/162	45/159	39/156	38/159		
OR (95% CI)	1.00	1.39 (0.80–2.41)	1.21 (0.68–2.15)	1.00 (0.56–1.82)	0.74	0.80 (0.60–1.05)
DiMeIQx						
Median (Cut-points)	0.0 (≤0.1)	0.2 (>0.1–0.4)	0.6 (>0.4–1.1)	2.1 (>1.1)		
Cases/Controls	35/162	34/159	46/158	40/156		
OR (95% CI)	1.00	1.04 (0.59–1.82)	1.41 (0.82–2.41)	1.21 (0.69–2.13)	0.60	2.00 (0.61–6.58)
MeIQx						
Median (Cut-points)	1.9 (≤3.7)	5.8 (>3.7–8.5)	12.2 (>8.5–18.2)	27.9 (>18.2)		
Cases/Controls	30/162	37/160	40/159	48/155		
OR (95% CI)	1.00	1.43 (0.81–2.54)	1.81 (1.01–3.24)	1.90 (1.05–3.42)	0.07	1.11 (1.03–1.21)
PhIP						
Median (Cut-points)	4.5 (≤9.0)	16.2 (>9.0–25.9)	44.5 (>25.9–68.1)	139.1 (>68.1)		
Cases/Controls	35/160	33/158	44/158	43/160		
OR (95% CI)	1.00	1.16 (0.66–2.05)	1.53 (0.89–2.62)	1.49 (0.85–2.62)	0.22	1.01 (0.98–1.03) ^b
B[a]P						
Median (Cut-points)	0.4 (≤1.6)	4.2 (>1.6–6.8)	13.4 (>6.8–22.2)	47.1 (>22.2)		
Cases/Controls	41/161	34/157	41/159	39/159		

Characteristic	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P Trend ^a	Continuous (per 10 unit)
OR (95% CI)	1.00	0.83 (0.48–1.42)	1.15 (0.68–1.94)	1.16 (0.67–2.00)	0.40	1.01 (0.91–1.11) ^b
Mutagenic activity (revertant colonies/day)						
Median (Cut-points)	260 (≤ 568)	841 (>568–1308)	2030 (> 1308–3162)	5654 (>3162)		
Cases/Controls	31/163	38/157	43/159	43/157		
OR (95% CI)	1.00	1.67 (0.94–2.95)	1.84 (1.04–3.26)	1.69 (0.94–3.04)	0.32	1.04 (0.99–1.08) ^c

* OR adjusted for age (continuous), education (high school or less, vocational/technical/business, 1–3 years or college/junior college, college graduate, graduate/professional degree), race (White, African-American, other), smoking status (never, former, current), physical activity (no moderate or vigorous activity, moderate, vigorous), BMI (continuous, kg/m²), study center (Bethesda, Portsmouth, San Diego, Washington D.C.), current HRT use (yes, no), family history of colorectal polyps or cancer (yes, no), regular NSAID use (defined as once a week for at least one month at any time prior to three months before colonoscopy; yes, no, don't know/missing), alcohol intake (<5 g/day, 5–14.9 g/day, ≥15 g/day), fiber (continuous, g/1,000 kcal), dietary calcium (continuous, g/1,000 kcal), calcium from supplements (continuous, g/day), and total caloric intake (continuous, kcal/day).

^a P trend calculated using the median of each quartile.

^b Per 20 ng/day.

^c Per 1000 revertant colonies/day.

Table 4

Multivariate ORs* for colorectal adenoma risk associated with intake of total iron (mg/day), dietary iron (mg/1000 kcal), iron from meat (mg/1000 kcal), heme iron from meat (mg/1000 kcal), and supplemental iron (mg/day).

Characteristic	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P Trend ^a	Continuous (per 10 unit)
Total iron^b						
Median (Cut-points)	10.8 (≤ 12.6)	15.0 (>12.6–22.9)	28.3 (>22.9–30.2)	33.4 (>30.2)		
Cases/Controls	47/161	43/158	29/158	36/159		
OR (95% CI) ^c	1.00	1.21 (0.66–1.92)	0.73 (0.42–1.27)	0.91 (0.52–1.59)	0.34	0.96 (0.79–1.17)
Dietary iron						
Median (Cut-points)	6.3 (≤ 7.0)	7.5 (>7.0–8.1)	8.8 (>8.1–9.7)	10.9 (>9.7)		
Cases/Controls	36/159	43/161	41/157	35/159		
OR (95% CI)	1.00	1.30 (0.76–2.22)	1.55 (0.87–2.75)	1.11 (0.57–2.16)	0.77	1.29 (0.50–3.34)
Iron from meat^d						
Median (Cut-points)	0.16 (≤ 0.23)	0.31 (>0.23–0.38)	0.47 (>0.38–0.58)	0.78 (>0.58)		
Cases/Controls	26/163	47/162	41/162	44/162		
OR (95% CI)	1.00	1.67 (0.94–2.96)	1.75 (0.97–3.15)	1.71 (0.94–3.14)	0.17	1.06 (0.87–1.28) ^e
Heme iron from meat						
Median (Cut-points)	0.05 (≤ 0.09)	0.11 (>0.09–0.14)	0.17 (>0.14–0.21)	0.28 (>0.21)		
Cases/Controls	30/160	46/162	39/158	40/156		
OR (95% CI)	1.00	1.53 (0.88–2.66)	1.50 (0.84–2.66)	1.50 (0.83–2.73)	0.32	1.06 (0.89–1.27) ^f
Supplemental iron^g						
Cut-points	0.0	0.3–12.9	18.0–39.4			
Cases/Controls	76/247	22/130	57/259			
OR (95% CI)	1.00	0.72 (0.41–1.26)	0.82 (0.54–1.25)		0.34	0.94 (0.76–1.15)

* OR adjusted for age (continuous), education (high school or less, vocational/technical/business, 1–3 years or college/junior college, college graduate, graduate/professional degree), race (White, African-American, other), smoking status (never, former, current), physical activity (no moderate or vigorous activity, moderate, vigorous), BMI (continuous, kg/m²), study center (Bethesda, Portsmouth, San Diego, Washington D.C.), current HRT use (yes, no), family history of colorectal polyps or cancer (yes, no), regular NSAID use (defined as once a week for at least one month at any time prior to three months before colonoscopy; yes, no, don't know/missing), alcohol intake (<5 g/day, 5–14.9 g/day, ≥15 g/day), fiber (continuous, g/1,000 kcal), dietary calcium (continuous, g/1,000 kcal), calcium from supplements (continuous, g/day), and total caloric intake (continuous, kcal/day).

^aP trend calculated using the median of each quartile.

^b Dietary iron (residual energy adjusted) plus iron from supplements.

^c Nutrients in this model were residual energy adjusted.

^d Limited to only those meats in the heme iron database.

^e Per 0.30 mg/1000 kcal.

^f Per 0.10 mg/1000 kcal.

^g Due to the small number of people taking supplements containing iron, iron from supplements was broken into three levels.

Table 5

Multivariate ORs* for adenoma risk associated with intake of nitrite from meat (mg/day).

Characteristic	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P Trend ^a	Continuous (per mg)
Nitrite						
Median (Cut-points)	0.02 (≤ 0.03)	0.04 ($>0.03-0.06$)	0.08 ($>0.06-0.12$)	0.22 (>0.12)		
Cases/Controls	40/161	43/161	34/158	38/156		
OR (95% CI)	1.00	1.14 (0.67-1.93)	0.91 (0.52-1.59)	1.05 (0.59-1.86)	0.99	0.73 (0.15-3.58)

* OR adjusted for age (continuous), education (high school or less, vocational/technical/business, 1-3 years or college/junior college, college graduate, graduate/professional degree), race (White, African-American, other), smoking status (never, former, current), physical activity (no moderate or vigorous activity, moderate, vigorous), BMI (continuous, kg/m²), study center (Bethesda, Portsmouth, San Diego, Washington D.C.), current HRT use (yes, no), family history of colorectal polyps or cancer (yes, no), regular NSAID use (defined as once a week for at least one month at any time prior to three months before colonoscopy; yes, no, don't know/missing), alcohol intake (<5 g/day, 5-14.9 g/day, ≥ 15 g/day), fiber (continuous, g/1,000 kcal), dietary calcium (continuous, g/1,000 kcal), calcium from supplements (continuous, g/day), and total caloric intake (continuous, kcal/day).

^a P trend calculated using the median of each quartile.