Published in final edited form as:

Nutr Cancer. 2013 February ; 65(2): 202–226. doi:10.1080/01635581.2013.756534.

Meat-Related Compounds and Colorectal Cancer Risk by Anatomical Subsite

Paige E. Miller¹, Philip Lazarus^{2,3}, Samuel M. Lesko^{4,5}, Amanda J. Cross⁶, Rashmi Sinha⁶, Jason Laio^{3,4}, Jay Zhu³, Gregory Harper^{4,7}, Joshua E. Muscat^{3,4}, and Terry J. Hartman^{4,8}

¹Cancer Prevention Fellowship Program (corresponding author) National Cancer Institute National Institutes of Health 6120 Executive Boulevard, MSC 7105 Bethesda, MD 20892

²Department of Pharmacology Penn State College of Medicine 500 University Drive Hershey, PA 17033

³Department of Public Health Sciences Penn State College of Medicine 600 Centerview Drive Hershey, PA 17033

⁴Cancer Prevention and Control Program Penn State Cancer Institute 500 University Drive Hershey, PA 17033

⁵Northeast Regional Cancer Institute 334 Jefferson Avenue Scranton, PA 18510

⁶Division of Cancer Epidemiology and Genetics National Cancer Institute National Institutes of Health 6120 Executive Boulevard, MSC 7242 Bethesda, MD 20892

⁷Morgan Cancer Center 1240 S. Cedar Crest Blvd., Suite 408 Lehigh Valley Health Network Allentown, PA 18103

⁸Department of Nutritional Sciences Pennsylvania State University 104 Chandlee Laboratory The Pennsylvania State University University Park, PA 16802

Abstract

Since meat may be involved in the etiology of colorectal cancer, associations between meat-related compounds were examined to elucidate underlying mechanisms in a population-based case-control study. Participants (989 cases/1,033 healthy controls) completed a food frequency questionnaire with a meat-specific module. Multivariable logistic regression was used to examine associations between meat variables and colorectal cancer; polytomous logistic regression was used for subsite-specific analyses. The following significant positive associations were observed for meat-related compounds: 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline (DiMeIQx) and colorectal, distal colon, and rectal tumors; 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) and colorectal and colon cancer tumors; nitrites/nitrates and proximal colon cancer; 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) and rectal cancer; and benzo[a]pyrene and rectal cancer (P -trends < 0.05). For analyses by meat type, cooking method, and doneness preference, positive associations between red processed meat and proximal colon cancer and pan-fried red meat and colorectal cancer were found (P -trends < 0.05). Inverse associations were observed between unprocessed poultry and colorectal, colon, proximal colon, and rectal tumors; grilled/barbequed poultry and proximal colon cancer; and well-done/charred poultry and colorectal, colon, and proximal colon tumors (P -trends < 0.05). HCAs, PAHs, nitrites, and nitrates may be involved in colorectal cancer etiology. Further examination into the unexpected inverse associations between poultry and colorectal cancer is warranted.

Keywords

colorectal cancer; meat; heterocyclic amines; polycyclic aromatic hydrocarbons; *N*-nitroso compounds

INTRODUCTION

Colorectal cancer is the third most commonly diagnosed malignancy in developed countries (1), the second leading cause of cancer death among Americans (2), and the leading cause of cancer death among non-smokers in the U.S. (2). The five-year post-diagnosis survival rate is only 60% despite advancements in screening and treatment in the past few decades (2). Epidemiologic evidence indicates that a substantial proportion, ranging from 30 to 70 percent, of all colorectal cancer cases are attributable to diet (3-5), with red and processed meat intakes implicated as important dietary risk factors (6). The most recent consensus statement issued by the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) concluded that the evidence to support a positive association between intakes of red and processed meat and colorectal cancer was convincing (7), although the evidence for specific mechanisms explaining these associations remained inconclusive.

Several individual compounds have been suggested to explain the underlying mechanisms by which red and processed meat may increase the risk of colorectal cancer, including heme iron (8-9), heterocyclic amines (HCAs) (8, 10), polycyclic aromatic hydrocarbons (PAHs) (11), and nitrites and nitrates (8, 12). HCAs and PAHs are mutagenic compounds formed when muscle meat is cooked using high-temperature methods, such as grilling, barbequing, and pan-frying; both are known animal carcinogens (13-14). HCAs are formed when amino acids, sugars, and creatine react at high temperatures, especially those above 150 degrees Celsius. Cooking methods that result in the greatest amounts of HCAs include grilling and pan-frying (15). Meat that is cooked above an open flame, as with grilling and barbequing, results in fat and juices dripping onto the fire, yielding flames that contain PAHs. These PAHs then adhere to the surface of the meat (15). The smoking of meat, or other food preparation methods that expose meat to smoke or charring, also contributes to PAH formation. Sodium nitrites and nitrates are added to meat for preservation and curing purposes; these nitrites—and nitrates that are readily converted to nitrites by bacteria—react with amines or amides derived from protein, leading to the formation of *N*-nitroso compounds (NOCs), which are potent and organ-specific animal carcinogens (16).

A number of studies have examined relationships between red and processed meat intake and colorectal cancer, many of which have been summarized in at least one of four meta-analyses over the past decade (6, 17-19). Only recently have investigations started to examine the effects of exposure to meat-derived HCAs, PAHs, and nitrites and nitrates on colorectal cancer risk (8) since quantifying intake of these compounds requires more extensive assessment of meat intake, cooking habits, and the use of newly developed food-based mutagen databases. In addition, many previous investigations have not examined associations stratified by anatomical subsite, yet it is possible that risk factors differ between the proximal colon, distal colon, and rectum (19-21).

The present study examined associations between red meat, processed meat, and meat-derived HCAs, PAHs, nitrites, and nitrates and colorectal cancer in a population-based case-control study in central and northeast Pennsylvania. This study population is important as it is at particularly high risk for colorectal cancer compared to the U.S. as a whole (54.5 per

100,000 in Pennsylvania versus 48.8 per 100,000 in the U.S. at the start of this study in 2007).

MATERIALS AND METHODS

Study population

This study included incident colorectal cancer cases and healthy controls participating in a population-based case-control study in a contiguous 19-county area in central and northeast Pennsylvania. The study was designed to investigate risk factors for colorectal cancer among adult residents of this area. An evaluation of 24-hour dietary recall data from a similar central and northeast Pennsylvania study population (22) indicated that red and processed meat intake was higher in this population compared to a nationally representative sample [National Health and Nutrition Examination Survey (NHANES) 1999-2004] (23); thus, high red and processed meat intake was hypothesized to be a potentially important modifiable risk factor in this population.

All newly diagnosed cases, identified within 15 months of diagnosis, with histologically-confirmed colon or rectal cancers were identified between June 2007 and May 2011 from the Pennsylvania State Cancer Registry. Colorectal cancers were classified by anatomical site and histologic code of the International Classification of Diseases for Oncology (24), including codes C180 – C189, C199, C209, and C260. Cases were further classified by anatomical subsite: proximal colon (C180 – C184), distal colon (C185 – C187), and rectum (C199, C209). A letter introducing the study was sent to potential cases, followed by a telephone call from a study coordinator to further explain the study and answer questions. Controls residing in the same 19-county region were identified by random digit dialing (RDD), as described by Waksberg (25); both landlines and cell phones were in the RDD sample. Potential controls were screened to ensure they had no previous history of colorectal cancer and frequency-matched to cases by sex and race. Potential cases or controls were eligible for inclusion if they were fluent in English and > 18 years of age. Of those contacted, 57% of eligible cases and 51% of eligible controls participated in the study.

Written consent was obtained from consenting cases and controls, a personal interview was scheduled at the home of the participant, and a self-administered food frequency questionnaire (FFQ) was mailed with instructions to complete the FFQ before the interview. Data on sociodemographic factors, medical history, alcohol use, lifetime tobacco exposure, physical activity, height, weight, medication use, and other lifestyle-related factors were collected by trained interviewers during in-person interviews. The mean (SD) time interval between diagnosis and interview of cases were 14.2 (4.2) months; the median was 15.1 months. For health and lifestyle-related factors, such as weight, diet, and physical activity, data prior to diagnosis were collected for cases. The FFQ was reviewed for completeness by the interviewer during the in-person home interview. The institutional review boards at the Northeast Regional Cancer Institute, the Pennsylvania Department of Health, Penn State College of Medicine, and Lehigh Valley Hospital (Allentown, PA) approved this study.

For the present analysis, individuals who reported implausible energy intakes [< 500 kcal or $> 5,000$ kcal] (26-27)] ($n = 80$), who were < 35 years of age ($n = 12$), or who had missing data for a covariate in the logistic regression models ($n = 2$) were excluded. The resulting analytic sample included 2,022 participants (989 colorectal cancer cases and 1,033 controls). Of the 989 colorectal cancer cases, there were 693 cases with colon cancer (416 with proximal colon cancer, 253 with distal colon cancer, and 24 with cancer in overlapping colon sites or in the colon but not otherwise specified) and 289 cases with rectal cancer. The remaining seven colorectal cancer cases lacked anatomical subsite data.

Dietary assessment method

Participants completed a modified version of the Diet History Questionnaire (DHQ), a validated FFQ developed by the National Cancer Institute (NCI) (29). The reference period was the year prior to the interview for controls and the year prior to diagnosis for cases. The DHQ was modified for our study population based on previously collected 24-hour dietary recall data from a similar Pennsylvania study population (22). The DHQ included a detailed meat module (28) containing questions on preferred meat cooking methods and doneness levels for individual meat subtypes and modified to capture the distinct meat eating patterns of Pennsylvania residents in this catchment area. These modifications included the addition of processed meat items commonly consumed in this population, such as specific Italian cured meats and corned beef.

The DHQ and visual materials, which were designed to facilitate the recall of portion sizes and preferences for meat doneness levels, were mailed with instructions to complete the DHQ before the scheduled interview. The DHQ included questions about respondents' usual intake and portion size of 137 separate food and beverage items, 49 of which contained additional embedded questions. Thirty-two of the 137 items were related to meat consumption. Respondents selected from 10 frequency categories that ranged from never to two or more times per day for each food and from nine frequency categories that ranged from never to six or more times per day for each beverage. Three food- and beverage-specific portion size ranges were available for each question; photographs of portion sizes were also provided. The DHQ included questions that addressed variations in food type (e.g., regular vs. low-fat), seasonal intake, and added fats. Data pertaining to dietary supplement use were also collected with the DHQ.

Energy and nutrient intake values were calculated with Diet*Calc (version 1.4.3), nutrient analysis software developed by the NCI for use with this instrument and configured to accommodate our questionnaire modifications. Portion size and frequency of food intake data were used to calculate the average daily servings according to standard USDA serving sizes (29) for each food item consumed. The unprocessed red meat variable included the following beef and pork items: hamburgers, roast beef, pot roast, roast pork, steak, pork chops, pork or beef spare ribs, liver, and meat added to mixed dishes such as chili and spaghetti. The processed red meat category included bacon, sausage, cold cuts (ham, bologna, salami, pepperoni, beef luncheon meat, dried or chipped beef), beef jerky, corned beef, hot dogs, ham, and processed meat added to mixed dishes such as pizza. The unprocessed poultry category included all poultry items that were not smoked and/or processed, while the processed poultry category contained cold cuts, hot dogs, bacon, and sausages made of chicken or turkey as well as smoked turkey. Due to low consumption of fish in the study population and previous data indicating that grilled poultry may accumulate higher levels of certain HCAs compared to red meat (30) poultry was examined without fish.

Data on frequency of intake, portion sizes, and cooking and doneness preferences of meat items were used to generate estimated exposure to meat-derived mutagens with the NCI's Computerized Heterocyclic Amines Resource for Research in Epidemiology of Disease (CHARRED) software application (28). The CHARRED program estimated exposure [nanograms (ng)/day] to three HCAs (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)) and one PAH (benzo[a]pyrene). In addition, the CHARRED application generated total mutagenic activity (revertant colonies/day), a measure of overall mutagenic potential that accounts for differences in mutagenic activity between the various compounds. Frequency and portion size data were used to generate estimated processed meat-derived nitrate and nitrite intakes based on an NCI database (28). The database contained measured values from 10 commonly consumed meat items in the

U.S. that accounted for 90% of the processed meats consumed according to nationally representative survey data.

Statistical analysis

Dietary variables were adjusted for total energy intake by the nutrient density method (servings or grams per 1,000 kcal) (31), with the exception of folate, calcium, and vitamin D. Since these three micronutrients had both dietary and supplemental intakes, dietary intakes were energy-adjusted using the residual method (31) and then combined with supplemental intakes. Energy-adjusted intakes of meat variables were categorized into quintiles according to the distribution among the controls. Meat variables that had between 20 to 50 percent zero values (processed poultry, grilled/barbequed red meat, microwaved/baked meat, and rare/medium cooked red meat) were categorized into tertiles, with zero consumption as the referent group. Meat variables with greater than or equal to 50 percent zero values (grilled/barbequed poultry, pan-fried poultry, broiled red meat, broiled poultry, and rare/medium cooked poultry) were dichotomized, with zero consumption as the referent group.

Characteristics of cases and controls were compared using *t* tests for continuous variables and χ^2 tests for categorical variables. Non-normally distributed dietary intake variables were logarithmically transformed to normalize their distributions. Odds ratios (ORs) and 95% confidence intervals (CIs) for associations between meat exposures and total colorectal cancer were estimated from unconditional logistic regression models. Likelihood ratio tests were used to evaluate the fit of each model. Linear trend tests were calculated using the median intake values for each quintile. Associations between meat exposures and anatomical subsites were investigated through the use of polytomous logistic regression, which allowed for an assessment of effect heterogeneity across subsites (total colon v. rectum and proximal colon v. distal colon). Heterogeneity also was examined between early (carcinoma-in-situ or localized) and late stage (regional or distant) cancer cases.

All logistic regression models controlled for age (years), total energy intake (kcal/day), and sex. The following variables were evaluated for confounding in the multivariable models: alcohol intake (g/day); educational attainment (< high school, high school/some college, and college graduate/advanced degree); BMI (kg/m²); smoking status (never, current, or past smoker); fruit and vegetable intake (servings/1,000 kcal); dairy intake (servings/1,000 kcal); whole grain intake (servings/1,000 kcal); saturated fat intake (g/1,000 kcal); fiber intake (g/1,000 kcal); total folate intake (dietary folate equivalents (DFE)/ 1,000 kcal); total calcium intake (mg/day); total vitamin D intake (mcg/day); family history of colorectal cancer in a first-degree relative (yes, no); regular nonsteroidal anti-inflammatory drug (NSAID) use (yes, no); multivitamin/mineral use; calcium supplement use; vitamin D supplement use; and physical activity (< 1 hour and > 1 hour/week of vigorous activity). NSAID use was defined as ever having been a regular user (> 3/week for at least 1 year prior to the interview for controls or diagnosis for cases). Supplement use was defined as > 1 time/week for at least 1 year prior to the interview for controls or diagnosis for cases. The category of calcium supplements included individual calcium and calcium plus vitamin D combination supplements; similarly, the category of vitamin D supplements included individual vitamin D and calcium plus vitamin D combination supplements. In addition, multivariable models investigating any category of red meat intake adjusted for all white meat intake and vice versa. According to a 10% change-in-estimate criterion (32), BMI, fruit and vegetable intake, and past regular NSAID use were important covariates in our analyses; thus, these variables along with age, total energy intake, and sex were included in the final multivariable logistic regression models. The possibility of effect modification with meat-derived compounds was examined by creating cross-product terms of meat variables and potential modifiers. Likelihood ratio tests were used to evaluate the fit of a multiplicative

interaction term in each model. Reported *P* values are 2-sided and *P* < 0.05 was considered significant for all tests. All statistical analyses were performed with SAS (version 9.2, SAS Institute, Inc., Cary, North Carolina).

RESULTS

Table 1 shows the characteristics of the study population. Compared to controls, cases were significantly younger, more likely to be obese (BMI > 30 kg/m²), and more likely to have a family history of colorectal cancer. Controls were significantly more likely to be physically active, to be past regular users of NSAIDs, and to have a college or advanced degree. Racial distribution, sex, multivitamin use, calcium supplement use, and vitamin D supplement use did not differ significantly between cases and controls. There were no differences in ever having regularly smoked between cases and controls, although cases were significantly more likely to have quit smoking. Table 1 also summarizes dietary intakes of cases and controls. Controls reported greater consumption of fruits and vegetables, dietary fiber, total calcium intake, total vitamin D intake, and alcohol compared to cases.

Associations between intakes of red meat and poultry and colorectal cancer are shown in Table 2. Although significant positive associations were observed between processed red meat and total colorectal, colon, rectal, and proximal colon cancers in the simple logistic regression models (i.e., models adjusting only for age, sex, and energy intake) when comparing the highest to the lowest quintile, these associations were attenuated and no longer remained statistically significant after further adjustment for BMI, fruit and vegetable intake, NSAID use, and total poultry intake. The linear trend for increasing proximal colon cancer risk with greater intakes of red processed meat remained significant in the fully adjusted multivariable model (*P*-trend = 0.044). Greater intakes of unprocessed poultry were inversely associated with total colorectal (OR = 0.62, 95% CI = 0.46, 0.84, *P*-trend = 0.003), total colon (OR = 0.68, 95% CI = 0.48, 0.95, *P*-trend = 0.023), proximal colon (OR = 0.56, 95% CI = 0.37, 0.85, *P*-trend = 0.003), and rectal (OR = 0.56, 95% CI = 0.35, 0.90, *P*-trend = 0.022) tumors when comparing the top to the bottom quintiles. There was no statistical evidence of heterogeneity between anatomical subsites (*P*-heterogeneity > 0.05 for all comparisons).

The ORs and 95% CIs for colorectal cancer and meat-related compounds are shown in Table 3. In the multivariable models, a significant elevated risk for proximal colon cancer was observed when comparing the highest to the lowest levels of nitrites plus nitrate intake (OR = 1.57, 95% CI = 1.06-2.34, *P*-trend = 0.023). Greater intakes of DiMeIQx were positively associated with total colorectal (OR = 1.36, 95% CI = 1.02, 1.82, *P*-trend = 0.027), distal colon (OR = 1.66, 95% CI = 1.06, 2.59, *P*-trend = 0.020), and rectal tumors (OR = 1.54, 95% CI = 1.02, 2.33, *P*-trend = 0.010). Significant positive associations were observed between MeIQx intake and colorectal (*P*-trend = 0.047) and distal colon cancers (*P*-trend = 0.005), whereas both PhIP intake and benzo[a]pyrene intake were positively associated with rectal cancer (*P*-trends = 0.023 and 0.027, respectively).

Table 4 presents the ORs and 95% CIs for colorectal cancer and red meat by cooking method and doneness level. Greater intakes of pan-fried red meat significantly increased risk for total colorectal cancer, as well as all subsite-specific cancers, in the simple models when comparing the top to the bottom category of intake, but these associations were not significant after full multivariable adjustment. The linear trend for increasing risk of colorectal cancer with greater intakes of pan-fried red meat was significant (*P*-trend = 0.044). Risk estimates for proximal colon cancer were significantly different than those for distal colon cancer when comparing the highest to the lowest tertile of red meat cooked rare/

medium (OR = 1.19, 95% CI = 0.88, 1.63; OR = 0.78, 95% CI = 0.54, 1.10, respectively; P -heterogeneity = 0.004), although associations did not reach significance for either subsite.

The ORs and 95% CIs for colorectal cancer and poultry by cooking method and doneness level are shown in Table 5. Associations between grilled or barbequed poultry and proximal vs. distal colon tumors were statistically different (P -heterogeneity = 0.017); an inverse association was observed between any consumption of grilled or barbequed poultry and proximal colon cancer (OR = 0.70, 95% CI = 0.53, 0.94, P -trend = 0.017), whereas a non-significant positive association was observed between grilled or barbequed poultry and distal colon cancer (OR = 1.22, 95% CI = 0.91, 1.66, P -trend = 0.188). Statistical heterogeneity in risk estimates for proximal vs. distal colon cancers with any consumption of poultry cooked rare/medium also was observed (P -heterogeneity = 0.026), with non-significant inverse associations found for proximal colon cancer (OR = 0.87, 95% CI = 0.65, 1.17, P -trend = 0.349) and non-significant positive associations found for distal colon cancer (OR = 1.32, 95% CI = 0.96, 1.81, P -trend = 0.084). Intakes of poultry cooked well-done/charred were inversely associated with total colorectal (OR = 0.72, 95% CI = 0.53, 0.97, P -trend = 0.014) and colon tumors (OR = 0.69, 95% CI = 0.49, 0.98, P -trend = 0.014) were observed when comparing the top to the bottom quintile. The linear trend for decreasing risk of proximal colon cancer with increasing consumption of poultry cooked well-done/charred (P -trend = 0.015) also was found.

DISCUSSION

In this large, population-based, case-control study in a high-risk population in northeast Pennsylvania, greater intakes of red processed meat and meat-derived nitrites plus nitrates were associated with elevated risk of proximal colon cancer. Significant positive associations were observed between MeIQx intake and total colorectal and distal colon cancer risk; DiMeIQx intake and total colorectal, distal colon, and rectal cancer risk; PhIP intake and rectal cancer risk; and benzo[a]pyrene intake and rectal cancer risk. These findings suggest that previously observed associations between red and processed meat and colorectal cancer risk (6, 8, 17-19) could be due, at least in part, to compounds that arise from cooking meat well-done at high temperatures, cooking meat over a direct flame, or preserving and curing meat with nitrites and nitrates (15). Given the large sample size, the detailed meat exposure data collected, the wide variation in reported meat consumption, and the greater average intake of meat compared to a nationally representative sample (23), this study was well-designed to investigate these associations. In addition, our large number of cases allowed for the examination of associations between meat variables and anatomical subsites, which is important in light of suggestive biologic (20, 33) and epidemiologic evidence (21) that risk factors may differ by subsite.

Four meta-analyses examining associations between red and processed meat and colorectal cancer have been conducted in the past decade (6, 17-19). Of the three meta-analyses that provided risk estimates separately for colon and rectal tumors (6, 18-19), one reported that red meat was more strongly associated with rectal compared to colon cancer (18), but no differential associations between colon and rectal cancer were found with processed meat. Larsson et al. (18) summarized the results from three prospective cohort studies (34-36) that stratified by anatomical subsite within the colon and found suggestive evidence of heterogeneity for processed meat intake between proximal and distal colon tumors (P -heterogeneity = 0.06). These authors reported a significant positive association between processed meat and distal colon cancer (OR for the highest vs. the lowest intake category = 1.41, 95% CI = 1.09-1.84) but not proximal colon cancer. Results from a recent U.S. prospective cohort study (8) among more than 300,000 men and women (2,179 colorectal cancer cases) residing in eight states suggested that both red and processed meat

consumption were slightly greater risk factors for rectal cancer than colon cancer, although the differences between tumor sites were not statistically significant. Our study found a positive association between processed meat and proximal colon cancer risk, but no significant associations with distal colon or rectal cancer risk. One possible explanation for these differences across studies is that the meat categories have included different combinations of red and white meat items with variable levels of HCAs, PAHs, nitrites, and nitrates (37). Other potential factors include insufficient sample sizes to stratify by subsite and a lack of detailed meat exposure data required to explore HCA, PAH, nitrite, and nitrate intakes in past studies.

Since bacterial content, rates of xenobiotic metabolism, transit time, morphology, enzymatic expression, and the level of pro-carcinogenic DNA-adducts differ between the proximal colon, distal colon, and rectum (33, 38-39), the degree of susceptibility to the effects of potential carcinogens may vary between sites (33). It is possible that the proximal colon may be more susceptible to the harmful effects of nitrites whereas the distal colon and rectum may be more susceptible to the negative effects of HCAs and PAHs. Greater bacterial decarboxylation of amino acids into nitrosatable amines and amides, as well as reduction of nitrates to nitrites, occurs in the proximal colon due to the larger number of bacteria present (40-41). The reaction of nitrites with amines and amides results in the formation of NOCs, which have been shown to induce tumors at a variety of sites in over 40 unique animal species, including higher primates (16). In our analyses, greater HCA and PAH intakes were more consistently associated with tumors of the distal colon and rectum compared to the proximal colon in multivariable analyses. Findings from our investigation are consistent with an earlier report by Le Marchand and colleagues (42), who found that total HCA intake was positively associated with rectal cancer, but not colon cancer, among men and women in a multi-ethnic U.S. population-based case-control study. On the contrary, Augustsson et al. (43) examined associations between HCAs and colorectal cancer stratified by tumor site in a Swedish population-based case-control study, but found no evidence of an association between meat-related compounds and colon or rectal cancer. The inconsistent results across studies may be attributable to differences in study populations; for example, consumption patterns, meat cooking methods, meat doneness preferences, and thus meat-related compound exposure likely vary between populations.

Unexpectedly, greater intakes of unprocessed poultry were associated with a reduced risk for total colorectal, total colon, proximal colon, and rectal tumors. Several past prospective cohort studies have reported similar inverse associations between poultry and colorectal cancer (8, 35-36, 44), although a number of others have reported either null (34, 45-47) or positive associations (48-50). One reason for these findings could be that poultry, compared to red meat, contains lower amounts of heme, and heme stimulates the production of endogenous NOCs in the gastrointestinal tract (51). Another potential explanation for the inverse association between poultry and colorectal cancer in our study population is that individuals who consumed more poultry also consumed more fruits, vegetables, legumes, low-fat dairy, and whole grains and less red and processed meat. This overall dietary pattern was found to be protective against colorectal cancer, as described in an earlier publication from this study (52). In addition, a recent review of the epidemiological literature (53) found that a dietary pattern similar to the protective pattern in our study, commonly termed “prudent” or “high fruits and vegetables” (54-55), has been shown to be inversely associated with colorectal cancer incidence in the majority of studies investigated. Therefore, multicollinearity—or the high degree of intercorrelation among certain dietary intake variables—may have limited our efforts to isolate the independent effect of poultry. A third possible explanation is that those who consumed an overall healthier dietary pattern were more likely to engage in other healthy lifestyle behaviors and adhere to health behavior recommendations; this clustering of health behaviors has been described previously (56).

For example, individuals in our study with higher red processed meat intake were more likely to have a higher BMI ($P < 0.001$) and less likely to engage in at least one hour of vigorous physical activity ($P < 0.001$). Although these potential confounders were investigated in our analysis, residual or unknown confounding remains possible. Given the absence of an underlying biological mechanism to explain how poultry may be protective against colorectal cancer incidence, our findings with poultry and colorectal cancer risk should be interpreted cautiously.

Associations between meat cooking method and doneness preferences, surrogate measures of different compounds formed during the cooking process, and colorectal cancer differed between red meat and poultry in the present study. Most associations between cooking methods and doneness preferences for red meat and colorectal cancer were null, with the exception of pan-fried red meat, which increased colorectal cancer risk. On the other hand, several statistically significant inverse associations were observed between cooking methods and doneness preferences for poultry and colorectal cancer risk, including associations between grilled/barbequed poultry and proximal colon cancer and well-done/charred poultry and total colorectal, total colon, and proximal colon tumors. These inverse associations were surprising since HCAs and PAHs are found in higher concentrations in poultry that is grilled/barbequed and cooked well/charred compared to poultry cooked by methods that do not require open flames (e.g., baking and microwaving) and poultry not exposed to prolonged cooking times at high-temperatures (30). However, further investigation revealed that 83% of the poultry consumed was cooked well-done/charred; thus, well-done/charred poultry is likely reflecting total poultry intake since it also was found to be inversely associated with colorectal cancer. Due to the high percentage of zero values (70%), grilled/barbequed poultry was dichotomized (any vs. no consumption), which did not allow for comparisons of very high intakes to low or zero intakes. Overall, the analysis by cooking method and doneness preference should be interpreted with caution as these are surrogate measures, whereas the CHARRED program (28), which generates values for HCA and PAH intakes, was designed to capture variability in HCA and PAH levels as it accounts for a number of factors, such as the specific type of meat, doneness levels, cooking methods, and processing methods.

An important strength of the present study was the dietary assessment method, which included a validated cooked and processed meat module (57) that was modified to reflect the distinct meat consumption patterns observed in an earlier Pennsylvania study population (e.g., comparatively high intakes of cured meat items) (22). This meat module, which was linked to a database of HCAs and PAHs, was embedded within a validated comprehensive FFQ (58). Recently estimated values of processed meat-derived nitrites and nitrates (28) also were incorporated into a database that was linked to the FFQ. The use of these databases allowed for the examination of specific mechanisms underlying previously observed associations between meat and colorectal cancer (6, 17-19). In addition, participants were provided with colored photographs of six meat items often cooked by high-temperature methods to reduce misclassification of reported cooking and doneness preferences (59). Another notable strength was the representativeness according to the distribution of stage among enrolled cases, which was comparable to the stage distribution among all invasive colorectal cancer cases reported to the Pennsylvania cancer registry for the 18 counties in the present study. Lastly, our study was conducted in an important population that suffers from a higher risk for colorectal cancer compared to the United States as a whole.

Several limitations of the present study also should be considered. Measurement error associated with FFQs may lead to non-differential misclassification of respondents into dietary exposure categories, thereby attenuating risk estimates. The case-control design used in this study is susceptible to recall bias since cases may have reported past meat

consumption differently than controls if meat intake was preconceived to be a risk factor for colorectal cancer. Although the potential for recall bias is a concern for both cases and controls, it is likely a larger concern for cases given the mean time interval (14.2 months) between diagnosis and interview, in addition to the reference period (one year before diagnosis). Recall bias also may have arisen if cases had reported past diet differentially depending on stage of diagnosis; however, there was no evidence of such bias in analyses stratified by stage. The relatively low participation rates in the present study (57% of eligible cases and 51% of eligible controls), as well as the lack of information regarding those who did not respond, may have introduced selection bias into the study, especially if those who refused to participate had different dietary intakes than those who agreed to participate. Another potential source of selection bias was the lack of frequency-matching based on phone use (i.e., landline only, cell phone only, or both) since it is possible that phone use patterns differed between cases and controls. Another limitation is that respondents reported diet for the past year (prior to diagnosis for cases), but long-term dietary exposure is likely important in the development of cancer. Dietary habits have been shown to be relatively stable over time (60) suggesting that a food frequency questionnaire administered at one time point may reliably rank individuals according to long-term dietary intakes. Potential confounders were considered and included in our multivariable models, yet residual or unknown confounding remains possible.

The degree to which greater consumption of specific meat compounds elevates the risk of colorectal cancer is likely affected by genetic variability in the expression and activity of the enzymes responsible for their activation and detoxification. Findings from several studies that have investigated interactions between meat compounds, genetic polymorphisms, and colorectal polyps (61), adenomas (12, 62), or cancer (63-64) have been inconsistent, which may be due to insufficient statistical power to examine these diet-gene interactions. Further investigation of potential interactions between multiple genetic polymorphisms and meat exposures in relation to colorectal cancer risk is warranted. In addition, HCA and PAH formation has been shown to be affected by several factors, including using marinades, increasing the distance between the meat and flame, lessening the cooking time if high-temperature methods are used, and pre-cooking meat by microwaving before grilling or barbecuing. These factors were not captured in our study but should be addressed in future studies.

In summary, our findings suggest there is value in collecting detailed meat cooking and consumption data to allow for the study of specific mechanisms involved in colon and rectal carcinogenesis. Results from the present study support the hypothesis that increased exposure to HCAs, PAHs, nitrites, and nitrates is a plausible mechanism by which red and processed meat may increase colorectal cancer risk. The unexpected finding of a protective effect of fresh poultry should be interpreted with extreme caution as residual confounding, multicollinearity, and health behavior clustering are likely playing key roles in these observed inverse associations. Lastly, our study found that associations between meat-derived compounds and colorectal cancer may differ by subsite, which highlights the need for additional studies that examine dietary risk factors for rectal, proximal, and distal colon cancers as separate endpoints.

Acknowledgments

This research was supported by the Pennsylvania Department of Health Grant #4100038714. The authors would like to thank the dedicated staff of this study: Karen Ryzcak [Northeast Regional Cancer Institute (NRCI)], Gladys Escobar [Penn State Cancer Institute (PSCI)], Tammy Ryder (PSCI), Christine Christ (PSCI), Anne Greetcher (PSCI), Wendy Stanton (NRCI), Kimberlee Welsh (NRCI), Pauline Kozik (NRCI), Margaret Fox-Dougherty (NRCI), Nancy Ziegler (NRCI), Stefanie Crouse (NRCI), Judith Rose (NRCI), Nicholas Kelly (NRCI), and Corey

Lazarus (PSCI). We also would like to acknowledge the many residents of Pennsylvania for their generous participation in our study.

REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, et al. Global cancer statistics. *CA Cancer J Clin*. 2011; 61:69–90. [PubMed: 21296855]
2. American Cancer Society. Cancer facts and figures 2009. American Cancer Society; Atlanta, GA: 2009.
3. Willett WC. Diet, nutrition, and avoidable cancer. *Environ Health Perspect*. 1995; 103(Suppl 8): 165–170. [PubMed: 8741778]
4. Boutron MC, Wilpart M, Faivre J. Diet and colorectal cancer. *Eur J Cancer Prev*. 1991; 1(Suppl 2): 13–20. [PubMed: 1842726]
5. Potter JD. Nutrition and colorectal cancer. *Cancer Causes Control*. 1996; 7:127–146. [PubMed: 8850441]
6. World Cancer Research Fund. American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. American Institute for Cancer Research; Washington DC: 2007.
7. World Cancer Research Fund. American Institute for Cancer Research: Continuous Update Project Summary. Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective. World Cancer Research Fund/American Institute for Cancer Research; Washington, DC: 2011.
8. Cross AJ, Ferrucci LM, Risch A, Graubard BI, Ward MH, et al. A large prospective study of meat consumption and colorectal cancer risk: an investigation of potential mechanisms underlying this association. *Cancer Res*. 2010; 70:2406–2414. [PubMed: 20215514]
9. Bastide NM, Pierre FH, Corpet DE. Heme iron from meat and risk of colorectal cancer: a meta-analysis and a review of the mechanisms involved. *Cancer Prev Res (Phila)*. 2011; 4:177–184. [PubMed: 21209396]
10. Zheng W, Lee SA. Well-done meat intake, heterocyclic amine exposure, and cancer risk. *Nutr Cancer*. 2009; 61:437–446. [PubMed: 19838915]
11. Sinha R, Peters U, Cross AJ, Kulldorff M, Weissfeld JL, et al. Meat, meat cooking methods and preservation, and risk for colorectal adenoma. *Cancer Res*. 2005; 65:8034–8041. [PubMed: 16140978]
12. Ward MH, Cross AJ, Divan H, Kulldorff M, Nowell-Kadlubar S, et al. Processed meat intake, CYP2A6 activity and risk of colorectal adenoma. *Carcinogenesis*. 2007; 28:1210–1216. [PubMed: 17277235]
13. Turteltaub KW, Dingley KH, Curtis KD, Malfatti MA, Turesky RJ, et al. Macromolecular adduct formation and metabolism of heterocyclic amines in humans and rodents at low doses. *Cancer Lett*. 1999; 143:149–155. [PubMed: 10503895]
14. Ito N, Hasegawa R, Imaida K, Tamano S, Hagiwara A, et al. Carcinogenicity of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) in the rat. *Mutat Res*. 1997; 376:107–114. [PubMed: 9202745]
15. Cross AJ, Sinha R. Meat-related mutagens/carcinogens in the etiology of colorectal cancer. *Environ Mol Mutagen*. 2004; 44:44–55. [PubMed: 15199546]
16. Tricker AR, Preussmann R. Carcinogenic N-nitrosamines in the diet: occurrence, formation, mechanisms and carcinogenic potential. *Mutat Res*. 1991; 259:277–289. [PubMed: 2017213]
17. Sandhu MS, White IR, McPherson K. Systematic review of the prospective cohort studies on meat consumption and colorectal cancer risk: a meta-analytical approach. *Cancer Epidemiol Biomarkers Prev*. 2001; 10:439–446. [PubMed: 11352852]
18. Larsson SC, Wolk A. Meat consumption and risk of colorectal cancer: a meta-analysis of prospective studies. *Int J Cancer*. 2006; 119:2657–2664. [PubMed: 16991129]
19. Norat T, Lukanova A, Ferrari P, Riboli E. Meat consumption and colorectal cancer risk: dose-response meta-analysis of epidemiological studies. *Int J Cancer*. 2002; 98:241–256. [PubMed: 11857415]

20. Minoo P, Zlobec I, Peterson M, Terracciano L, Lugli A. Characterization of rectal, proximal and distal colon cancers based on clinicopathological, molecular and protein profiles. *Int J Oncol*. 2010; 37:707–718. [PubMed: 20664940]
21. Wei EK, Giovannucci E, Wu K, Rosner B, Fuchs CS, et al. Comparison of risk factors for colon and rectal cancer. *Int J Cancer*. 2004; 108:433–442. [PubMed: 14648711]
22. Bailey RL, Miller PE, Mitchell DC, Hartman TJ, Lawrence FR, et al. Dietary screening tool identifies nutritional risk in older adults. *Am J Clin Nutr*. 2009; 90:177–183. [PubMed: 19458013]
23. Wang Y, Beydoun MA. Meat consumption is associated with obesity and central obesity among US adults. *Int J Obes (Lond)*. 2009; 33:621–628. [PubMed: 19308071]
24. World Health Organization (WHO). Report of a joint WHO/FAO expert consultation. WHO; Geneva: 2003. Diet, nutrition and the prevention of chronic disease.
25. Waksberg J. Sampling methods for random digit dialing. *Journal of the American Statistical Association*. 1978; 73:40–46.
26. Harnack L, Nicodemus K, Jacobs DR Jr, Folsom AR. An evaluation of the Dietary Guidelines for Americans in relation to cancer occurrence. *Am J Clin Nutr*. 2002; 76:889–896. [PubMed: 12324305]
27. Chiu BC, Gapstur SM. Changes in diet during adult life and risk of colorectal adenomas. *Nutr Cancer*. 2004; 49:49–58. [PubMed: 15456635]
28. Sinha R, Cross A, Curtin J, Zimmerman T, McNutt S, et al. Development of a food frequency questionnaire module and databases for compounds in cooked and processed meats. *Mol Nutr Food Res*. 2005; 49:648–655. [PubMed: 15986387]
29. Friday, JE.; Bowman, SA. MyPyramid Equivalents Database for USDA Survey Food Codes, 1994–2002 Version 1.0 [Internet]. U.S. Department of Agriculture, Agricultural Research Service, Community Nutrition Research Group; Beltsville (MD): 2006. Available from: <http://www.ars.usda.gov/>
30. Sinha R, Rothman N, Brown ED, Salmon CP, Knize MG, et al. High concentrations of the carcinogen 2-amino-1-methyl-6-phenylimidazo-[4,5-b]pyridine (PhIP) occur in chicken but are dependent on the cooking method. *Cancer Res*. 1995; 55:4516–4519. [PubMed: 7553619]
31. Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. *Am J Clin Nutr*. 1997; 65:1220S–8S. discussion 9S–31S. [PubMed: 9094926]
32. Greenland, S.; Rothman, KJ. Introduction to stratified analysis. In: Rothman, KJ.; Greenland, S.; Lash, TL., editors. *Modern Epidemiology*. 3rd ed. Lippincott Williams & Wilkins; Philadelphia, PA: 2008.
33. Iacopetta B. Are there two sides to colorectal cancer? *Int J Cancer*. 2002; 101:403–408. [PubMed: 12216066]
34. Norat T, Bingham S, Ferrari P, Slimani N, Jenab M, et al. Meat, fish, and colorectal cancer risk: the European Prospective Investigation into cancer and nutrition. *J Natl Cancer Inst*. 2005; 97:906–916. [PubMed: 15956652]
35. Larsson SC, Rafter J, Holmberg L, Bergkvist L, Wolk A. Red meat consumption and risk of cancers of the proximal colon, distal colon and rectum: the Swedish Mammography Cohort. *Int J Cancer*. 2005; 113:829–834. [PubMed: 15499619]
36. Chao A, Thun MJ, Connell CJ, McCullough ML, Jacobs EJ, et al. Meat consumption and risk of colorectal cancer. *JAMA*. 2005; 293:172–182. [PubMed: 15644544]
37. Sinha R, Rothman N, Salmon CP, Knize MG, Brown ED, et al. Heterocyclic amine content in beef cooked by different methods to varying degrees of doneness and gravy made from meat drippings. *Food Chem Toxicol*. 1998; 36:279–287. [PubMed: 9651044]
38. Povey AC, Hall CN, Badawi AF, Cooper DP, O'Connor PJ. Elevated levels of the pro-carcinogenic adduct, O(6)-methylguanine, in normal DNA from the cancer prone regions of the large bowel. *Gut*. 2000; 47:362–365. [PubMed: 10940272]
39. Bleday R, Braidt J, Ruoff K, Shellito PC, Ackroyd FW. Quantitative cultures of the mucosal-associated bacteria in the mechanically prepared colon and rectum. *Dis Colon Rectum*. 1993; 36:844–849. [PubMed: 8375226]

40. Bingham SA, Pignatelli B, Pollock JR, Ellul A, Malaveille C, et al. Does increased endogenous formation of N-nitroso compounds in the human colon explain the association between red meat and colon cancer? *Carcinogenesis*. 1996; 17:515–523. [PubMed: 8631138]
41. Gervaz P, Bucher P, Morel P. Two colons-two cancers: paradigm shift and clinical implications. *J Surg Oncol*. 2004; 88:261–266. [PubMed: 15565587]
42. Le Marchand L, Hankin JH, Pierce LM, Sinha R, Nerurkar PV, et al. Well-done red meat, metabolic phenotypes and colorectal cancer in Hawaii. *Mutat Res*. 2002; 506-507:205–214. [PubMed: 12351160]
43. Augustsson K, Skog K, Jagerstad M, Dickman PW, Steineck G. Dietary heterocyclic amines and cancer of the colon, rectum, bladder, and kidney: a population-based study. *Lancet*. 1999; 353:703–707. [PubMed: 10073512]
44. English DR, MacInnis RJ, Hodge AM, Hopper JL, Haydon AM, et al. Red meat, chicken, and fish consumption and risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev*. 2004; 13:1509–1514. [PubMed: 15342453]
45. Flood A, Velie EM, Sinha R, Chatterjee N, Lacey JV Jr. et al. Meat, fat, and their subtypes as risk factors for colorectal cancer in a prospective cohort of women. *Am J Epidemiol*. 2003; 158:59–68. [PubMed: 12835287]
46. Lee SA, Shu XO, Yang G, Li H, Gao YT, et al. Animal origin foods and colorectal cancer risk: a report from the Shanghai Women's Health Study. *Nutr Cancer*. 2009; 61:194–205. [PubMed: 19235035]
47. Wu K, Giovannucci E, Byrne C, Platz EA, Fuchs C, et al. Meat mutagens and risk of distal colon adenoma in a cohort of U.S. men. *Cancer Epidemiol Biomarkers Prev*. 2006; 15:1120–1125. [PubMed: 16775169]
48. Oba S, Shimizu N, Nagata C, Shimizu H, Kametani M, et al. The relationship between the consumption of meat, fat, and coffee and the risk of colon cancer: a prospective study in Japan. *Cancer Lett*. 2006; 244:260–267. [PubMed: 16519996]
49. Sato Y, Nakaya N, Kuriyama S, Nishino Y, Tsubono Y, et al. Meat consumption and risk of colorectal cancer in Japan: the Miyagi Cohort Study. *Eur J Cancer Prev*. 2006; 15:211–218. [PubMed: 16679863]
50. Jarvinen R, Knekt P, Hakulinen T, Rissanen H, Heliovaara M. Dietary fat, cholesterol and colorectal cancer in a prospective study. *Br J Cancer*. 2001; 85:357–361. [PubMed: 11487265]
51. Bingham SA, Hughes R, Cross AJ. Effect of white versus red meat on endogenous N-nitrosation in the human colon and further evidence of a dose response. *J Nutr*. 2002; 132:3522S–3525S. [PubMed: 12421881]
52. Miller PE, Lazarus P, Lesko SM, Muscat JE, Harper G, et al. Diet index-based and empirically derived dietary patterns are associated with colorectal cancer risk. *J Nutr*. 2010; 140:1267–1273. [PubMed: 20444952]
53. Miller PE, Lesko SM, Muscat JE, Lazarus P, Hartman TJ. Dietary patterns and colorectal adenoma and cancer risk: a review of the epidemiological evidence. *Nutr Cancer*. 2010; 62:413–424. [PubMed: 20432162]
54. Tseng M, DeVillis R. Correlates of the “western” and “prudent” diet patterns in the us. *Ann Epidemiol*. 2000; 10:481–482. [PubMed: 11018432]
55. Fung T, Hu FB, Fuchs C, Giovannucci E, Hunter DJ, et al. Major dietary patterns and the risk of colorectal cancer in women. *Arch Intern Med*. 2003; 163:309–314. [PubMed: 12578511]
56. Reedy J, Haines PS, Campbell MK. The influence of health behavior clusters on dietary change. *Prev Med*. 2005; 41:268–275. [PubMed: 15917021]
57. Cantwell M, Mittl B, Curtin J, Carroll R, Potischman N, et al. Relative validity of a food frequency questionnaire with a meat-cooking and heterocyclic amine module. *Cancer Epidemiol Biomarkers Prev*. 2004; 13:293–298. [PubMed: 14973110]
58. Thompson FE, Subar AF, Brown CC, Smith AF, Sharbaugh CO, et al. Cognitive research enhances accuracy of food frequency questionnaire reports: results of an experimental validation study. *J Am Diet Assoc*. 2002; 102:212–225. [PubMed: 11846115]

59. Keating GA, Sinha R, Layton D, Salmon CP, Knize MG, et al. Comparison of heterocyclic amine levels in home-cooked meats with exposure indicators (United States). *Cancer Causes Control*. 2000; 11:731–739. [PubMed: 11065010]
60. Goldbohm RA, van 't Veer P, van den Brandt PA, van 't Hof MA, Brants HA, et al. Reproducibility of a food frequency questionnaire and stability of dietary habits determined from five annually repeated measurements. *Eur J Clin Nutr*. 1995; 49:420–429. [PubMed: 7656885]
61. Shin A, Shrubsole MJ, Rice JM, Cai Q, Doll MA, et al. Meat intake, heterocyclic amine exposure, and metabolizing enzyme polymorphisms in relation to colorectal polyp risk. *Cancer Epidemiol Biomarkers Prev*. 2008; 17:320–329. [PubMed: 18268115]
62. Ishibe N, Sinha R, Hein DW, Kulldorff M, Strickland P, et al. Genetic polymorphisms in heterocyclic amine metabolism and risk of colorectal adenomas. *Pharmacogenetics*. 2002; 12:145–150. [PubMed: 11875368]
63. Butler LM, Duguay Y, Millikan RC, Sinha R, Gagne JF, et al. Joint effects between UDP-glucuronosyltransferase 1A7 genotype and dietary carcinogen exposure on risk of colon cancer. *Cancer Epidemiol Biomarkers Prev*. 2005; 14:1626–1632. [PubMed: 16030093]
64. Nothlings U, Yamamoto JF, Wilkens LR, Murphy SP, Park SY, et al. Meat and heterocyclic amine intake, smoking, NAT1 and NAT2 polymorphisms, and colorectal cancer risk in the multiethnic cohort study. *Cancer Epidemiol Biomarkers Prev*. 2009; 18:2098–2106. [PubMed: 19549810]

Table 1

Frequency or mean (SD) of selected characteristics and dietary intakes among colorectal cancer cases and controls (n = 2,022)

Characteristic	Cases ^a (n = 989)		Controls ^a (n = 1,033)		P-Value ^b
	No	%	No	%	
Male (%)	493	49.9	516	50.0	0.963
Race (% non-white)	33	3.3	23	2.2	0.128
Education (%)					
< High school	110	11.1	47	4.6	<0.001
High school/some college	644	65.3	633	61.3	
College graduate/advanced degree	233	23.6	352	34.1	
BMI (%) ^c					
<25	91	21.9	213	29.3	<0.001
25-29.9	139	33.5	264	36.4	
30	185	44.6	249	34.3	
Smoking status (%)					
Never	459	46.4	484	46.9	0.030
Former	426	43.1	404	39.1	
Current	104	10.5	145	14.0	
Past regular NSAID use (% yes) ^d	466	47.1	571	55.3	<0.001
Vigorous physical activity (% > 1 hour/week)	264	26.7	392	38.0	<0.001
Family history of colorectal cancer (% yes)	173	17.5	125	12.1	<0.001
Stage (%)					
Early stage	400	40.4	--	--	--
Late stage	481	48.6	--	--	
Unknown	108	10.9	--	--	
Multivitamin/mineral use (% yes) ^e	409	41.4	445	43.1	0.433
Supplemental calcium use (% yes) ^e	204	20.6	246	23.8	0.085
Supplemental vitamin D use (% yes) ^e	99	10.0	108	10.5	0.742
	Mean (SD)		Mean (SD)		

Characteristic	Cases ^a (n = 989)	Controls ^a (n = 1,033)	P-Value ^b
Age (yr)	61.4 (11.1)	66.5 (12.1)	<0.001
<i>Dietary intakes^f</i>			
Total energy intake (kcal/day)	1,870 (871)	1,781 (762)	0.116
Alcohol (g/day)	9.3 (30.5)	9.7 (25.2)	<0.001
Fruits and vegetables (servings/1,000 kcal)	3.1 (1.8)	3.4 (1.9)	<0.001
Dairy products (servings/1,000 kcal)	0.87 (0.56)	0.83 (0.50)	0.231
Whole grains (servings/1,000 kcal)	0.62 (0.58)	0.67 (0.63)	0.086
Saturated fat (g/1,000 kcal)	12.8 (3.4)	12.7 (3.5)	0.241
Fiber (g/1,000 kcal)	9.2 (3.5)	9.9 (3.5)	<0.001
Total folate (dietary folate equivalents)	808 (377)	832 (381)	0.109
Total calcium (mg)	934 (430)	1,012 (489)	<0.001
Total vitamin D (mcg)	10.5 (7.4)	11.4 (8.3)	0.023

Abbreviations are as follows: BMI, body mass index (kg/m²); NSAID, nonsteroidal anti-inflammatory drug

^aNumbers were smaller for some risk factors due to missing data.

^bP-values for differences in means were calculated with t tests and differences in proportions were calculated with χ^2 tests.

^cWeight (kg)/height (m)².

^dNSAID use is defined as ever having been a regular user (3 time/week for at least 1 year prior to the interview for controls and diagnosis for cases).

^eSupplement use was defined as use 1 time/week for at least 1 year prior to the interview for controls and diagnosis for cases.

^fDietary intakes of folate, vitamin D, and calcium were energy-adjusted by the residual method and then combined with supplemental intake; other dietary variables without supplemental intakes were energy-adjusted by the nutrient density method.

Table 2

Odds ratios (ORs) and 95% confidence intervals (CIs) for colorectal cancer according to category of red meat and poultry intakes

	Q1 ^b	Quintile of intake ^d								P-Trend	P-heterogeneity between subtypes ^e	
		Q2		Q3		Q4		Q5				
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI			
Red meat (unprocessed), g/1,000 kcal												
Total colorectal cancer												
No. of cases	184	217		184		231		173				
Age-, sex-, and energy-adjusted	1	1.31	0.99, 1.75	1.15	0.86, 1.53	1.48	1.11, 1.97	1.14	0.85, 1.54	0.478	—	
Multivariable ^d	1	1.24	0.92, 1.67	1.05	0.78, 1.43	1.38	1.03, 1.86	1.02	0.75, 1.40	0.975	—	
Colon cancer ^e												
No. of cases	139	146		127		162		119				
Age-, sex-, and energy-adjusted	1	1.18	0.86, 1.62	1.09	0.79, 1.50	1.44	1.05, 1.97	1.11	0.80, 1.54	0.437	—	
Multivariable	1	1.12	0.81, 1.55	1.00	0.72, 1.40	1.34	0.97, 1.86	1.00	0.71, 1.40	0.865	—	
Rectal cancer												
No. of cases	42	71		55		67		54				
Age-, sex-, and energy-adjusted	1	1.83	1.19, 2.83	1.41	0.90, 2.21	1.72	1.11, 2.67	1.37	0.87, 2.16	0.608	0.493	
Multivariable	1	1.72	1.10, 2.68	1.28	0.81, 2.03	1.61	1.02, 2.52	1.21	0.76, 1.94	0.997	0.544	
Proximal colon cancer ^f												
No. of cases	78	93		89		94		62				
Age-, sex-, and energy-adjusted	1	1.42	0.97, 2.07	1.47	1.01, 2.16	1.63	1.11, 2.38	1.16	0.77, 1.74	0.637	—	
Multivariable	1	1.38	0.94, 2.03	1.41	0.95, 2.08	1.58	1.07, 2.33	1.09	0.72, 1.65	0.888	—	
Distal colon cancer												
No. of cases	54	50		32		66		51				
Age-, sex-, and energy-adjusted	1	0.96	0.62, 1.48	0.63	0.39, 1.02	1.28	0.84, 1.94	0.99	0.64, 1.54	0.514	0.547	
Multivariable	1	0.89	0.57, 1.39	0.56	0.34, 0.92	1.15	0.75, 1.77	0.86	0.55, 1.35	0.944	0.457	
Red meat (processed), g/1,000 kcal												
Red meat (processed), g/1,000 kcalTotal colorectal cancer												
No. of cases	170	181		195		218		225				
Age-, sex-, and energy-adjusted	1	1.12	0.83, 1.50	1.26	0.94, 1.69	1.37	1.02, 1.83	1.49	1.11, 2.00	0.007	—	

	Quintile of intake ^a										P-heterogeneity between subsites ^c
	Q1 ^b	Q2		Q3		Q4		Q5		P-Trend	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI		
Multivariable	1	0.99	0.73, 1.34	1.09	0.81, 1.49	1.18	0.87, 1.61	1.18	0.87, 1.62	0.223	—
Total colon cancer											
No. of cases	125		120		142		149		157		
Age-, sex-, and energy-adjusted	1	1.01	0.73, 1.41	1.28	0.93, 1.76	1.31	0.95, 1.81	1.48	1.07, 2.05	0.009	—
Multivariable	1	0.91	0.65, 1.28	1.13	0.81, 1.57	1.15	0.82, 1.61	1.21	0.86, 1.70	0.157	—
Total rectal cancer											
No. of cases	42		59		53		68		67		
Age-, sex-, and energy-adjusted	1	1.48	0.95, 2.30	1.33	0.85, 2.10	1.61	1.03, 2.49	1.62	1.04, 2.53	0.089	0.685
Multivariable	1	1.28	0.81, 2.01	1.12	0.70, 1.79	1.35	0.86, 2.13	1.22	0.77, 1.95	0.613	0.919
Proximal colon cancer											
No. of cases	83		70		85		74		104		
Age-, sex-, and energy-adjusted	1	0.89	0.60, 1.31	1.18	0.81, 1.72	1.01	0.68, 1.49	1.62	1.11, 2.35	0.003	—
Multivariable	1	0.80	0.54, 1.19	1.06	0.72, 1.57	0.90	0.60, 1.34	1.33	0.89, 1.97	0.044	—
Distal colon cancer											
No. of cases	36		46		51		72		48		
Age-, sex-, and energy-adjusted	1	1.29	0.80, 2.09	1.46	0.91, 2.34	1.96	1.25, 3.08	1.34	0.83, 2.18	0.347	0.461
Multivariable	1	1.16	0.71, 1.89	1.27	0.79, 2.07	1.72	1.08, 2.74	1.09	0.66, 1.81	0.920	0.603
Poultry (unprocessed), g/1,000 kcal											
Poultry (unprocessed), g/1,000 kcalTotal colorectal cancer											
No. of cases	301		211		188		160		129		
Age-, sex-, and energy-adjusted	1	0.76	0.58, 0.99	0.72	0.55, 0.94	0.62	0.47, 0.82	0.56	0.42, 0.75	<0.001	—
Multivariable	1	0.77	0.59, 1.02	0.79	0.59, 1.04	0.63	0.47, 0.85	0.62	0.46, 0.84	0.003	—
Total colon cancer											
No. of cases	217		148		128		105		95		
Age-, sex-, and energy-adjusted	1	0.76	0.56, 1.01	0.71	0.53, 0.96	0.59	0.43, 0.81	0.62	0.45, 0.86	0.004	—
Multivariable	1	0.77	0.57, 1.04	0.77	0.56, 1.05	0.60	0.44, 0.84	0.68	0.48, 0.95	0.023	—
Total rectal cancer											
No. of cases	79		61		60		55		34		

	Quintile of intake ^a								P-Trend	P-heterogeneity between subsites ^c	
	Q1 ^b	Q2	Q3	Q4	Q5						
		OR	95% CI	OR	95% CI	OR	95% CI				
Age-, sex-, and energy-adjusted	1	0.80	0.54, 1.18	0.81	0.54, 1.19	0.73	0.49, 1.08	0.49	0.31, 0.77	0.003	0.255
Multivariable	1	0.83	0.56, 1.24	0.91	0.60, 1.37	0.77	0.51, 1.18	0.56	0.35, 0.90	0.022	0.379
Proximal colon cancer											
No. of cases	138	99		71		62		46			
Age-, sex-, and energy-adjusted	1	0.81	0.58, 1.14	0.65	0.45, 0.93	0.58	0.40, 0.84	0.51	0.34, 0.77	<0.001	—
Multivariable	1	0.83	0.59, 1.16	0.70	0.48, 1.01	0.59	0.40, 0.87	0.56	0.37, 0.85	0.003	—
Distal colon cancer											
No. of cases	70	45		54		40		44			
Age-, sex-, and energy-adjusted	1	0.68	0.44, 1.03	0.85	0.56, 1.27	0.63	0.40, 0.97	0.75	0.49, 1.17	0.310	0.108
Multivariable	1	0.67	0.44, 1.04	0.89	0.58, 1.36	0.62	0.39, 0.98	0.80	0.51, 1.26	0.469	0.209
Poultry (processed), g/1,000 kcal ^g											
Total colorectal cancer											
No. of cases	316	337		336							
Age-, sex-, and energy-adjusted	1	0.87	0.70, 1.09	0.90	0.72, 1.12					0.603	—
Multivariable	1	0.88	0.70, 1.11	0.94	0.75, 1.19					0.938	—
Total colon cancer											
No. of cases	219	233		241							
Age-, sex-, and energy-adjusted	1	0.89	0.70, 1.14	0.96	0.75, 1.23					0.926	—
Multivariable	1	0.90	0.70, 1.16	0.99	0.77, 1.28					0.580	—
Total rectal cancer											
No. of cases	95	102		92							
Age-, sex-, and energy-adjusted	1	0.83	0.60, 1.15	0.76	0.54, 1.05					0.160	0.139
Multivariable	1	0.85	0.61, 1.18	0.82	0.58, 1.14					0.752	0.199
Proximal colon cancer											
No. of cases	133	145		138							
Age-, sex-, and energy-adjusted	1	0.96	0.71, 1.28	0.95	0.70, 1.28					0.801	—
Multivariable	1	0.97	0.72, 1.30	0.96	0.70, 1.30					0.829	—
Distal colon cancer											

	Quintile of intake ^a										P-Trend	P-heterogeneity between subsites ^c
	Q1 ^b	Q2		Q3		Q4		Q5				
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI			
No. of cases	78	76		99								
Age-, sex-, and energy-adjusted	1	0.77	0.54, 1.10	1.01	0.72, 1.42					0.409	0.955	
Multivariable	1	0.78	0.54, 1.11	1.07	0.76, 1.52					0.245	0.873	

^a Quintiles of intake were as follows: unprocessed red meat (g/1,000 kcal), quintile 1 (< 8.7), quintile 2 (8.7-14.5), quintile 3 (14.6-22.6), quintile 4 (22.7-35.6), quintile 5 (> 35.6); processed red meat (g/1,000 kcal), quintile 1 (< 2.8), quintile 2 (2.8-5.5), quintile 3 (5.6-9.4), quintile 4 (9.5-17.6), quintile 5 (> 17.6); unprocessed poultry (g/1000 kcal), quintile 1 (< 4.5), quintile 2 (4.5-9.0), quintile 3 (9.1-14.9), quintile 4 (15.0-26.2), quintile 5 (> 26.2); processed poultry (g/1000 kcal), tertile 1 (0), tertile 2 (0.1-0.9), tertile 3(> 1.0).

^b Referent quintile.

^c Effect heterogeneity was evaluated between colon and rectal cancer and proximal and distal colon cancer.

^d ORs were adjusted for age, sex, body mass index, past regular NSAID use, and intakes of total energy and fruits and vegetables. Unprocessed and processed red meat both were adjusted for total poultry intake; unprocessed and processed poultry both adjusted for total red meat.

^e 7 cases lacked anatomical subsite information.

^f 24 cases had colon cancer in overlapping sites or not otherwise specified colon sites.

^g Processed poultry was categorized into tertiles, with zero consumption as the referent group, due to smaller intake ranges and more than 20 percent zero values.

Table 3

Odds ratios and 95% confidence intervals (CIs) of colorectal cancer, by quintile of meat-related compounds

	Q1 ^b	Quintile of intake ^d								P-trend	P-heterogeneity between subsites ^c
		Q2		Q3		Q4		Q5			
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI		
Nitrites plus nitrates (µg/1,000 kcal)											
Total colorectal cancer											
No. of cases	182		177		194		211		225		
Age-, sex-, and energy-adjusted	1	1.06	0.79, 1.41	1.19	0.89, 1.59	1.23	0.92, 1.65	1.44	1.07, 1.93	0.008	—
Multivariable ^d	1	0.98	0.72, 1.32	1.07	0.79, 1.45	1.09	0.80, 1.47	1.19	0.87, 1.61	0.189	—
Total colon cancer ^e											
No. of cases	126		124		140		146		157		
Age-, sex-, and energy-adjusted	1	1.09	0.79, 1.51	1.27	0.92, 1.75	1.28	0.93, 1.77	1.53	1.11, 2.12	0.008	—
Multivariable	1	1.02	0.73, 1.42	1.15	0.83, 1.61	1.14	0.82, 1.60	1.28	0.92, 1.80	0.115	—
Rectal cancer											
No. of cases	53		52		54		63		67		
Age-, sex-, and energy-adjusted	1	1.04	0.68, 1.60	1.10	0.71, 1.69	1.17	0.77, 1.79	1.32	0.86, 2.02	0.152	0.482
Multivariable	1	0.95	0.61, 1.48	0.96	0.62, 1.50	1.02	0.66, 1.58	1.04	0.67, 1.62	0.722	0.363
Proximal colon cancer ^f											
No. of cases	77		75		86		76		102		
Age-, sex-, and energy-adjusted	1	1.11	0.75, 1.64	1.35	0.92, 1.98	1.16	0.78, 1.72	1.81	1.24, 2.66	0.002	—
Multivariable	1	1.05	0.71, 1.56	1.25	0.85, 1.86	1.06	0.71, 1.58	1.57	1.06, 2.34	0.023	—
Distal colon cancer											
No. of cases	43		45		50		64		51		
Age-, sex-, and energy-adjusted	1	1.08	0.68, 1.72	1.19	0.76, 1.89	1.46	0.94, 2.27	1.21	0.76, 1.92	0.339	0.101
Multivariable	1	0.99	0.62, 1.59	1.06	0.67, 1.70	1.28	0.81, 2.01	0.98	0.61, 1.58	0.952	0.076
DiMeIQx (ng/1,000 kcal)											
Total colorectal cancer											
No. of cases	181		185		203		183		237		181
Age-, sex-, and energy-adjusted	1	1.06	0.79, 1.42	1.15	0.86, 1.54	1.12	0.83, 1.48	1.48	1.12, 1.96	0.004	—

	Q1 ^b	Quintile of intake ^a								P-trend	P-heterogeneity between subsites ^c
		Q2		Q3		Q4		Q5			
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI		
Multivariable	1	1.04	0.77, 1.40	1.09	0.81, 1.47	1.03	0.77, 1.39	1.36	1.02, 1.82	0.027	—
Total colon cancer											
No. of cases	127		132		152		127		155		
Age-, sex-, and energy-adjusted	1	1.09	0.79, 1.51	1.25	0.91, 1.72	1.12	0.81, 1.55	1.43	1.04, 1.96	0.034	—
Multivariable	1	1.07	0.77, 1.49	1.19	0.86, 1.64	1.05	0.75, 1.46	1.32	0.95, 1.82	0.118	—
Rectal cancer											
No. of cases	51		52		49		56		81		
Age-, sex-, and energy-adjusted	1	1.04	0.67, 1.61	0.98	0.63, 1.52	1.16	0.76, 1.79	1.67	1.11, 2.51	0.003	0.591
Multivariable	1	1.01	0.65, 1.57	0.92	0.59, 1.44	1.08	0.70, 1.67	1.54	1.02, 2.33	0.010	0.637
Proximal colon cancer											
No. of cases	79		78		101		78		80		
Age-, sex-, and energy-adjusted	1	1.03	0.70, 1.52	1.35	0.93, 1.95	1.14	0.77, 1.67	1.30	0.84, 1.80	0.356	—
Multivariable	1	1.01	0.68, 1.49	1.28	0.88, 1.87	1.08	0.73, 1.59	1.14	0.77, 1.69	0.598	—
Distal colon cancer											
No. of cases	40		50		45		48		70		
Age-, sex-, and energy-adjusted	1	1.26	0.80, 2.00	1.13	0.71, 1.81	1.24	0.78, 1.97	1.82	1.18, 2.82	0.005	0.242
Multivariable	1	1.22	0.77, 1.94	1.07	0.66, 1.71	1.15	0.72, 1.84	1.66	1.06, 2.59	0.020	0.266
MeIQx (ng/1,000 kcal)											
Total colorectal cancer											
No. of cases	194		170		185		197		243		
Age-, sex-, and energy-adjusted	1	0.94	0.71, 1.26	1.03	0.77, 1.38	1.13	0.85, 1.51	1.40	1.06, 1.86	0.003	—
Multivariable	1	0.90	0.67, 1.22	0.96	0.71, 1.29	1.05	0.78, 1.41	1.22	0.91, 1.64	0.047	—
Total colon cancer											
No. of cases	142		115		139		126		171		
Age-, sex-, and energy-adjusted	1	0.89	0.64, 1.23	1.10	0.80, 1.50	1.02	0.74, 1.40	1.40	1.03, 1.91	0.007	—
Multivariable	1	0.85	0.61, 1.19	1.02	0.74, 1.41	0.95	0.68, 1.32	1.23	0.89, 1.69	0.068	—
Rectal cancer											
No. of cases	50		55		44		70		70		

	Q1 ^b	Quintile of intake ^a								P-trend	P-heterogeneity between subsites ^c
		Q2		Q3		Q4		Q5			
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI		
Age-, sex-, and energy-adjusted	1	1.15	0.75, 1.77	0.90	0.57, 1.42	1.47	0.97, 2.22	1.47	0.97, 2.22	0.029	0.969
Multivariable	1	1.09	0.70, 1.69	0.82	0.52, 1.30	1.34	0.87, 2.05	1.24	0.81, 1.91	0.172	0.906
Proximal colon cancer											
No. of cases	87		74		96		69		90		
Age-, sex-, and energy-adjusted	1	0.96	0.65, 1.40	1.29	0.89, 1.87	0.95	0.64, 1.40	1.25	0.87, 1.82	0.249	—
Multivariable	1	0.92	0.62, 1.36	1.21	0.83, 1.76	0.89	0.60, 1.32	1.11	0.76, 1.63	0.591	—
Distal colon cancer											
No. of cases	45		38		40		54		76		
Age-, sex-, and energy-adjusted	1	0.87	0.54, 1.40	0.92	0.58, 1.47	1.22	0.78, 1.91	1.74	2.14, 2.65	<0.001	0.332
Multivariable	1	0.83	0.51, 1.34	0.84	0.52, 1.35	1.13	0.72, 1.77	1.49	0.97, 2.30	0.005	0.373
PhIP (ng/1,000 kcal)											
Total colorectal cancer											
No. of cases	223		207		186		190		183		
Age-, sex-, and energy-adjusted	1	1.03	0.78, 1.36	0.95	0.72, 1.26	1.05	0.79, 1.39	1.15	0.86, 1.54	0.266	—
Multivariable	1	0.97	0.73, 1.29	0.87	0.65, 1.16	0.98	0.73, 1.31	1.06	0.79, 1.43	0.439	—
Total colon cancer											
No. of cases	163		154		135		131		110		
Age-, sex-, and energy-adjusted	1	1.07	0.79, 1.45	0.98	0.72, 1.34	1.05	0.77, 1.44	1.02	0.74, 1.42	0.944	—
Multivariable	1	1.01	0.74, 1.38	0.90	0.66, 1.24	0.98	0.71, 1.35	0.95	0.68, 1.33	0.830	—
Rectal cancer											
No. of cases	59		49		51		57		73		
Age-, sex-, and energy-adjusted	1	0.87	0.58, 1.36	0.91	0.59, 1.39	1.05	0.69, 1.59	1.44	0.96, 2.17	0.013	0.149
Multivariable	1	0.82	0.53, 1.26	0.81	0.53, 1.26	0.97	0.63, 1.49	1.33	0.88, 2.02	0.023	0.167
Proximal colon cancer											
No. of cases	99		102		78		87		50		
Age-, sex-, and energy-adjusted	1	1.20	0.84, 1.71	0.99	0.68, 1.43	1.28	0.89, 1.85	0.87	0.57, 1.31	0.425	—
Multivariable	1	1.15	0.80, 1.64	0.92	0.63, 1.35	1.21	0.83, 1.76	0.81	0.54, 1.24	0.313	—
Distal colon cancer											

	Q1 ^b	Quintile of intake ^a								P-trend	P-heterogeneity between subsites ^c
		Q2		Q3		Q4		Q5			
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI		
No. of cases	55		48		51		42		57		
Age-, sex-, and energy-adjusted	1	0.92	0.60, 1.43	0.97	0.63, 1.49	0.83	0.53, 1.31	1.21	0.79, 1.87	0.251	0.328
Multivariable	1	0.86	0.55, 1.34	0.88	0.57, 1.36	0.76	0.48, 1.21	1.11	0.72, 1.72	0.363	0.356
benzo[a]pyrene (ng/1,000 kcal)											
Total colorectal cancer											
No. of cases	264		219		152		184		170		
Age-, sex-, and energy-adjusted	1	0.94	0.72, 1.23	0.71	0.53, 0.95	0.92	0.69, 1.22	0.91	0.68, 1.21	0.926	—
Multivariable	1	0.95	0.72, 1.25	0.69	0.52, 0.93	0.92	0.69, 1.23	0.90	0.67, 1.21	0.906	—
Total colon cancer											
No. of cases	199		153		108		133		100		
Age-, sex-, and energy-adjusted	1	0.90	0.67, 1.21	0.69	0.51, 0.95	0.94	0.69, 1.27	0.78	0.56, 1.08	0.347	—
Multivariable	1	0.91	0.67, 1.23	0.67	0.49, 0.93	0.93	0.68, 1.27	0.77	0.55, 1.07	0.325	—
Rectal cancer											
No. of cases	63		64		43		50		69		
Age-, sex-, and energy-adjusted	1	1.07	0.71, 1.60	0.78	0.50, 1.21	0.92	0.60, 1.40	1.25	0.83, 1.89	0.143	0.031
Multivariable	1	1.09	0.72, 1.64	0.77	0.49, 1.20	0.92	0.60, 1.43	1.26	0.83, 1.91	0.145	0.027
Proximal colon cancer											
No. of cases	131		102		62		68		53		
Age-, sex-, and energy-adjusted	1	0.95	0.68, 1.33	0.63	0.43, 0.91	0.79	0.55, 1.14	0.72	0.48, 1.07	0.171	—
Multivariable	1	0.95	0.68, 1.34	0.61	0.42, 0.90	0.79	0.55, 1.15	0.71	0.48, 1.06	0.159	—
Distal colon cancer											
No. of cases	57		47		44		61		44		
Age-, sex-, and energy-adjusted	1	0.88	0.57, 1.37	0.87	0.56, 1.36	1.23	0.81, 1.86	0.90	0.57, 1.42	0.967	0.448
Multivariable	1	0.88	0.57, 1.37	0.84	0.54, 1.32	1.22	0.80, 1.87	0.89	0.56, 1.41	0.949	0.436
Total mutagenic activity (revertant colonies/1,000 kcal)											
Total colorectal cancer											
No. of cases	208		192		187		208		194		
Age-, sex-, and energy-adjusted	1	0.95	0.72, 1.27	1.00	0.75, 1.33	1.16	0.87, 1.54	1.16	0.87, 1.54	0.139	—

	Q1 ^b	Quintile of intake ^a								P-trend	P-heterogeneity between subsites ^c
		Q2		Q3		Q4		Q5			
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI		
Multivariable	1	0.91	0.68, 1.21	0.93	0.70, 1.25	1.06	0.79, 1.41	1.05	0.78, 1.41	0.433	—
Total colon cancer											
No. of cases	154		135		135		141		128		
Age-, sex-, and energy-adjusted	1	0.92	0.67, 1.25	1.00	0.73, 1.37	1.10	0.81, 1.51	1.10	0.80, 1.51	0.325	—
Multivariable	1	0.87	0.64, 1.20	0.95	0.69, 1.30	1.01	0.74, 1.39	0.99	0.72, 1.37	0.707	—
Rectal cancer											
No. of cases	52		55		52		65		65		
Age-, sex-, and energy-adjusted	1	1.07	0.70, 1.65	1.04	0.68, 1.61	1.34	0.88, 2.03	1.37	0.90, 2.09	0.078	0.361
Multivariable	1	1.01	0.65, 1.56	0.96	0.62, 1.50	1.22	0.79, 1.86	1.23	0.80, 1.89	0.210	0.410
Proximal colon cancer											
No. of cases	98		89		82		84		63		
Age-, sex-, and energy-adjusted	1	0.94	0.65, 1.35	0.99	0.69, 1.43	1.08	0.74, 1.56	0.91	0.62, 1.34	0.794	—
Multivariable	1	0.91	0.63, 1.31	0.94	0.65, 1.37	1.00	0.69, 1.45	0.83	0.56, 1.24	0.493	—
Distal colon cancer											
No. of cases	46		42		49		53		63		
Age-, sex-, and energy-adjusted	1	0.92	0.58, 1.46	1.10	0.70, 1.73	1.22	0.78, 1.91	0.91	0.61, 1.34	0.020	0.095
Multivariable	1	0.88	0.55, 1.40	1.03	0.65, 1.62	1.11	0.71, 1.74	1.34	0.86, 2.08	0.068	0.107

Abbreviations: DiMeIQx, 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline; MeIQx, 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine.

^aQuintiles of intake were as follows: nitrites plus nitrates ($\mu\text{g}/1,000\text{ kcal}$), quintile 1 (< 114.6), quintile 2 (114.6–197.0), quintile 3 (197.1–310.2), quintile 4 (310.3–496.6), quintile 5 (> 496.6); DiMeIQx (ng/1,000 kcal), quintile 1 (< 0.23), quintile 2 (0.23–0.67), quintile 3 (0.68–1.23), quintile 4 (1.24–2.20), quintile 5 (> 2.20); MeIQx (ng/1,000 kcal), quintile 1 (< 4.2), quintile 2 (4.2–8.3), quintile 3 (8.4–14.2), quintile 4 (14.3–23.8), quintile 5 (> 23.8); PhIP (ng/1,000 kcal), quintile 1 (< 7.2), quintile 2 (7.2–17.4), quintile 3 (17.5–33.7), quintile 4 (33.8–68.3), quintile 5 (> 68.3); benzo[a]pyrene (ng/1,000 kcal), quintile 1 (< 0.32), quintile 2 (0.32–2.2), quintile 3 (2.3–6.6), quintile 4 (6.7–19.0), quintile 5 (> 19.0); total mutagenic activity (revertant colonies/1,000 kcal), quintile 1 (< 665), quintile 2 (665–1,344), quintile 3 (1,345–2,310), quintile 4 (2,311–3,995), quintile 5 ($> 3,995$).

^bReferent quintile.

^cEffect heterogeneity was evaluated between colon and rectal cancer and proximal and distal colon cancer.

^dORs were adjusted for age, sex, total energy intake, body mass index, past regular NSAID use, and fruit and vegetable consumption.

^e7 cases lacked anatomic subsite information.

^f24 cases had colon cancer in overlapping sites or not otherwise specified colon sites.

Table 4

Odds ratios (ORs) and 95% confidence intervals (CIs) for colorectal cancer and red meat by cooking method and doneness level

	Q1 ^b	Quintile of intake ^d								P-Trend	P-heterogeneity between subsites ^c	
		Q2		Q3		Q4		Q5				
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI			
Grilled/barbequed, g/1,000 kcal												
Total colorectal cancer												
No. of cases	285		352		352							
Age-, sex-, and energy-adjusted	1	0.80	0.64, 1.01	0.94	0.74, 1.19					0.702		
Multivariable ^d	1	0.84	0.66, 1.06	0.94	0.74, 1.20					0.808		
Colon cancer ^e												
No. of cases	205		257		231							
Age-, sex-, and energy-adjusted	1	0.82	0.64, 1.06	0.91	0.70, 1.18					0.954		
Multivariable	1	0.85	0.66, 1.10	0.91	0.70, 1.19					0.858		
Rectal cancer												
No. of cases	77		93		119							
Age-, sex-, and energy-adjusted	1	0.77	0.54, 1.08	1.03	0.73, 1.44					0.287	0.472	
Multivariable	1	0.81	0.57, 1.15	1.05	0.74, 1.48					0.320	0.439	
Proximal colon cancer ^f												
No. of cases	126		162		128							
Age-, sex-, and energy-adjusted	1	0.85	0.63, 1.14	0.91	0.66, 1.24					0.866		
Multivariable	1	0.89	0.66, 1.20	0.93	0.67, 1.27					0.873		
Distal colon cancer												
No. of cases	67		93		93							
Age-, sex-, and energy-adjusted	1	0.88	0.62, 1.25	0.92	0.64, 1.32					0.888	0.843	
Multivariable	1	0.90	0.63, 1.29	0.90	0.63, 1.31					0.750	0.940	
Pan-fried, g/1,000 kcal												
Total colorectal cancer												
No. of cases	178		181		183		188		259			
Age-, sex-, and energy-adjusted	1	1.08	0.81, 1.45	1.17	0.87, 1.56	1.14	0.85, 1.52	1.64	1.24, 2.18	<0.001		—

	Q1 ^b	Quintile of intake ^a								P-Trend	P-heterogeneity between subsites ^c
		Q2		Q3		Q4		Q5			
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI		
Multivariable	1	0.97	0.71, 1.31	0.99	0.73, 1.34	0.93	0.69, 1.26	1.26	0.93, 1.70	0.044	—
Total colon cancer											
No. of cases	133		134		118		130		178		
Age-, sex-, and energy-adjusted	1	1.09	0.79, 1.50	1.01	0.73, 1.40	1.06	0.77, 1.46	1.57	1.15, 2.14	0.001	—
Multivariable	1	0.99	0.71, 1.37	0.87	0.62, 1.22	0.88	0.63, 1.23	1.23	0.89, 1.71	0.072	—
Total rectal cancer											
No. of cases	45		44		63		58		79		
Age-, sex-, and energy-adjusted	1	1.00	0.63, 1.59	1.52	0.98, 2.34	1.33	0.86, 2.06	1.80	1.18, 2.74	0.003	0.640
Multivariable	1	0.87	0.54, 1.39	1.23	0.79, 1.93	1.05	0.66, 1.65	1.31	0.84, 2.04	0.129	0.933
Proximal colon cancer											
No. of cases	84		86		71		71		104		
Age-, sex-, and energy-adjusted	1	1.15	0.79, 1.67	0.98	0.66, 1.44	0.94	0.64, 1.38	1.55	1.07, 2.23	0.015	—
Multivariable	1	1.05	0.72, 1.55	0.85	0.53, 1.37	0.80	0.54, 1.20	1.25	0.85, 1.83	0.162	—
Distal colon cancer											
No. of cases	45		41		45		53		69		
Age-, sex-, and energy-adjusted	1	0.94	0.59, 1.49	1.06	0.67, 1.68	1.19	0.76, 1.86	1.58	1.03, 2.43	0.007	0.806
Multivariable	1	0.85	0.53, 1.37	0.91	0.57, 1.46	0.99	0.62, 1.56	1.25	0.85, 1.83	0.104	0.777
Microwaved/baked, g/1,000 kcal ^g											
Total colorectal cancer											
No. of cases	213		194		196		204		182		
Age-, sex-, and energy-adjusted	1	0.93	0.70, 1.23	0.97	0.73, 1.28	1.03	0.78, 1.36	0.90	0.68, 1.20	0.633	—
Multivariable	1	0.89	0.67, 1.20	0.93	0.69, 1.24	0.97	0.72, 1.30	0.87	0.65, 1.17	0.533	—
Total colon cancer											
No. of cases	155		132		136		140		130		
Age-, sex-, and energy-adjusted	1	0.86	0.63, 1.18	0.93	0.68, 1.27	0.99	0.73, 1.36	0.91	0.66, 1.25	0.852	—
Multivariable	1	0.83	0.60, 1.15	0.99	0.65, 1.22	0.93	0.68, 1.29	0.87	0.63, 1.21	0.709	—
Total rectal cancer											
No. of cases	56		61		59		62		51		

	Q1 ^b	Quintile of intake ^a								P-Trend	P-heterogeneity between subsites ^c
		Q2		Q3		Q4		Q5			
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI		
Age-, sex-, and energy-adjusted	1	1.12	0.74, 1.70	1.09	0.72, 1.66	1.15	0.76, 1.74	0.91	0.59, 1.40	0.524	0.868
Multivariable	1	1.07	0.70, 1.64	1.05	0.68, 1.60	1.08	0.71, 1.65	0.88	0.57, 1.38	0.483	0.968
Proximal colon cancer											
No. of cases	86		85		84		92		69		
Age-, sex-, and energy-adjusted	1	1.01	0.70, 1.47	1.08	0.74, 1.57	1.25	0.86, 1.80	0.91	0.61, 1.34	0.752	—
Multivariable	1	1.00	0.68, 1.46	1.05	0.72, 1.54	1.21	0.83, 1.76	0.91	0.61, 1.35	0.761	—
Distal colon cancer											
No. of cases	62		43		47		46		55		
Age-, sex-, and energy-adjusted	1	0.69	0.45, 1.07	0.76	0.49, 1.16	0.75	0.49, 1.16	0.88	0.58, 1.33	0.976	0.894
Multivariable	1	0.65	0.42, 1.01	0.71	0.46, 1.10	0.69	0.45, 1.07	0.82	0.53, 1.25	0.771	0.827
Broiled, g/1,000 kcal											
Total colorectal cancer											
No. of cases	727		262								
Age-, sex-, and energy-adjusted	1	0.97	0.79, 1.19							0.771	—
Multivariable	1	0.99	0.80, 1.22							0.891	—
Total colon cancer											
No. of cases	507		186								
Age-, sex-, and energy-adjusted	1	0.98	0.78, 1.22							0.834	—
Multivariable	1	0.99	0.79, 1.25							0.951	—
Total rectal cancer											
No. of cases	216		73								
Age-, sex-, and energy-adjusted	1	0.94	0.70, 1.27							0.687	0.680
Multivariable	1	0.95	0.70, 1.30							0.755	0.670
Proximal colon cancer											
No. of cases	297		119								
Age-, sex-, and energy-adjusted	1	1.04	0.80, 1.36							0.750	—
Multivariable	1	0.95	0.69, 1.30							0.668	—
Distal colon cancer											

	Quintile of intake ^d										P-heterogeneity between subsites ^c	
	Q1 ^b	Q2		Q3		Q4		Q5		P-Trend		
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI			
No. of cases	189	64										
Age-, sex-, and energy-adjusted	1	0.93	0.68, 1.28							0.662	0.327	
Multivariable	1	0.95	0.70, 1.29							0.732	0.333	
Rare/medium, g/1,000 kcal												
Total colorectal cancer												
No. of cases	279	362										
Age-, sex-, and energy-adjusted	1	0.98	0.78, 1.23	1.04	0.82, 1.30					0.658	—	
Multivariable	1	0.94	0.75, 1.90	0.99	0.79, 1.26					0.844	—	
Total colon cancer												
No. of cases	196	257										
Age-, sex-, and energy-adjusted	1	0.98	0.76, 1.26	1.04	0.81, 1.34					0.649	—	
Multivariable	1	0.95	0.73, 1.22	1.00	0.77, 1.30					0.813	—	
Total rectal cancer												
No. of cases	81	101										
Age-, sex-, and energy-adjusted	1	0.96	0.69, 1.34	1.04	0.75, 1.45					0.676	0.953	
Multivariable	1	0.92	0.66, 1.29	1.00	0.72, 1.40					0.807	0.858	
Proximal colon cancer												
No. of cases	111	156										
Age-, sex-, and energy-adjusted	1	1.03	0.77, 1.40	1.22	0.90, 1.66					0.151	—	
Multivariable	1	1.00	0.74, 1.36	1.19	0.88, 1.63					0.183	—	
Distal colon cancer												
No. of cases	79	93										
Age-, sex-, and energy-adjusted	1	0.92	0.66, 1.29	0.81	0.57, 1.15					0.258	0.026	
Multivariable		0.89	0.63, 1.26	0.78	0.54, 1.10					0.179	0.021	
Well-done/charred, g/1,000 kcal												
Total colorectal cancer												
No. of cases	210	176										
Age-, sex-, and energy-adjusted	1	0.87	0.66, 1.16	1.04	0.78, 1.38	1.12	0.84, 1.48	1.08	0.81, 1.43	0.287	—	

	Q1 ^b	Quintile of intake ^d								P-Trend	P-heterogeneity between subsites ^c
		Q2		Q3		Q4		Q5			
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI		
Multivariable	1	0.77	0.57, 1.03	0.92	0.69, 1.24	1.01	0.75, 1.35	0.87	0.64, 1.16	0.857	—
Total colon cancer											
No. of cases	156		128		133		139		137		
Age-, sex-, and energy-adjusted	1	0.85	0.62, 1.17	0.96	0.70, 1.31	1.06	0.77, 1.44	1.02	0.74, 1.39	0.512	—
Multivariable	1	0.75	0.55, 1.04	0.86	0.63, 1.19	0.96	0.70, 1.32	0.83	0.60, 1.15	0.702	—
Total rectal cancer											
No. of cases	53		47		61		65		63		
Age-, sex-, and energy-adjusted	1	0.91	0.59, 1.41	1.23	0.81, 1.89	1.31	0.87, 1.99	1.24	0.81, 1.88	0.200	0.394
Multivariable	1	0.79	0.50, 1.23	1.07	0.70, 1.65	1.16	0.76, 1.78	0.96	0.62, 1.48	0.789	0.484
Proximal colon cancer											
No. of cases	103		77		76		85		75		
Age-, sex-, and energy-adjusted	1	0.76	0.53, 1.11	0.85	0.59, 1.24	1.02	0.71, 1.47	0.89	0.61, 1.29	0.953	—
Multivariable	1	0.68	0.46, 0.99	0.77	0.53, 1.30	0.94	0.65, 1.37	0.73	0.50, 1.08	0.483	—
Distal colon cancer											
No. of cases	45		45		55		51		57		
Age-, sex-, and energy-adjusted	1	1.02	0.64, 1.61	1.26	0.81, 1.96	1.20	0.76, 1.87	1.29	0.83, 2.00	0.257	0.085
Multivariable	1	0.88	0.55, 1.40	1.12	0.71, 1.76	1.07	0.68, 1.69	1.02	0.65, 1.61	0.815	0.095

^a Categories of red meat intake were as follows: grilled/barbequed (g/1,000 kcal), tertile 1 (0), tertile 2(0.01-4.35), tertile 3 (> 4.36); pan-fried (g/1,000 kcal), quintile 1 (< 0.36), quintile 2 (0.36-1.39), quintile 3 (1.40-3.33), quintile 4 (3.34-6.79), quintile 5 (> 6.79); microwaved/baked (g/1,000 kcal), quintile 1 (< 4.65), quintile 2 (4.65-7.56), quintile 3 (7.67-11.4), quintile 4 (11.5-18.6), quintile 5 (> 18.6); broiled (any versus no consumption); rare/medium (g/1000 kcal), tertile 1 (0), tertile 2 (0.01-4.08), tertile 3 (> 4.08); well-done/charred (g/1000 kcal), quintile 1 (< 0.89), quintile 2 (0.89-2.41), quintile 3 (2.42-4.70), quintile 4 (4.71-8.96), quintile 5 (> 8.96).

^b Referent quintile.

^c Effect heterogeneity was evaluated between colon and rectal cancer and proximal and distal colon cancer.

^d ORs were adjusted for age, sex, total energy intake, body mass index, past regular NSAID use, and fruit and vegetable consumption. Red meat and poultry were mutually adjusted for each other.

^e 7 cases lacked anatomical subsite information.

^f 24 cases had colon cancer in overlapping sites or not otherwise specified colon sites.

^g Microwaved/baked and rare/medium red meat were categorized into tertiles, with zero consumption as the referent group, due to smaller intake ranges and more than 20 percent zero values. Broiled red meat was a dichotomous variable (any or no consumption) due to more than 50 percent zero values.

Table 5

Odds ratios and 95% confidence intervals (CIs) for colorectal cancer and poultry by cooking method and doneness level

	Quintile of intake ^a								P-Trend	P-heterogeneity between subsites ^c
	Q1 ^b	Q2		Q3		Q4		Q5		
		OR	95% CI	OR	95% CI	OR	95% CI			
Grilled/barbequed, g/1,000 kcal										
Total colorectal cancer										
No. of cases	716		273							
Age-, sex-, and energy-adjusted	1	0.93	0.76, 1.23						0.442	—
Multivariable ^d	1	0.98	0.80, 1.20						0.524	—
Colon cancer ^e										
No. of cases	518		175							
Age-, sex-, and energy-adjusted	1	0.86	0.69, 1.08						0.196	—
Multivariable	1	0.91	0.72, 1.15						0.424	—
Rectal cancer										
No. of cases	193		96							
Age-, sex-, and energy-adjusted	1	1.07	0.81, 1.42						0.636	0.218
Multivariable	1	1.15	0.86, 1.54						0.338	0.175
Proximal colon cancer ^f										
No. of cases	334		82							
Age-, sex-, and energy-adjusted	1	0.67	0.50, 0.89						0.005	—
Multivariable	1	0.70	0.53, 0.94						0.017	—
Distal colon cancer										
No. of cases	166		87							
Age-, sex-, and energy-adjusted	1	1.15	0.86, 1.55						0.344	0.005
Multivariable	1	1.22	0.91, 1.66						0.188	0.004
Pan-fried, g/1,000 kcal										
Total colorectal cancer										
No. of cases	504		485							
Age-, sex-, and energy-adjusted	1	1.03	0.86, 1.23						0.758	—

	Quintile of intake ^a										P-heterogeneity between subsites ^c
	Q1 ^b	Q2		Q3		Q4		Q5		P-Trend	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI		
Multivariable	1	0.97	0.80, 1.16							0.702	—
Total colon cancer											
No. of cases	359		334								
Age-, sex-, and energy-adjusted	1	1.00	0.82, 1.23							0.970	—
Multivariable	1	0.94	0.77, 1.16							0.574	—
Total rectal cancer											
No. of cases	144		145								
Age-, sex-, and energy-adjusted	1	1.05	0.81, 1.37							0.717	0.946
Multivariable	1	0.97	0.74, 1.27							0.836	0.940
Proximal colon cancer											
No. of cases	229		187								
Age-, sex-, and energy-adjusted	1	0.87	0.69, 1.11							0.263	—
Multivariable	1	0.81	0.64, 1.04							0.095	—
Distal colon cancer											
No. of cases	113		140								
Age-, sex-, and energy-adjusted	1	1.31	0.99, 1.72							0.061	0.066
Multivariable	1	1.23	0.93, 1.63							0.148	0.053
Microwaved/baked, g/1,000 kcal ^g											
Total colorectal cancer											
No. of cases	213		237		207		170		162		
Age-, sex-, and energy-adjusted	1	1.18	0.90, 1.56	1.03	0.78, 1.36	0.88	0.66, 1.17	0.89	0.66, 1.19	0.093	—
Multivariable	1	1.12	0.85, 1.49	1.00	0.75, 1.33	0.89	0.66, 1.19	0.85	0.63, 1.15	0.097	—
Total colon cancer											
No. of cases	157		174		143		104		115		
Age-, sex-, and energy-adjusted	1	1.19	0.88, 1.60	0.97	0.71, 1.32	0.74	0.53, 1.02	0.88	0.64, 1.22	0.098	—
Multivariable	1	1.14	0.84, 1.54	0.94	0.69, 1.29	0.74	0.53, 1.04	0.85	0.61, 1.19	0.097	—
Total rectal cancer											
No. of cases	55		61		62		64		47		

Quintile of intake ^d												P-heterogeneity between subsites ^e
Q1 ^b	Q2		Q3		Q4		Q5		P-Trend			
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI				
Age-, sex-, and energy-adjusted	1	1.16	0.77, 1.76	1.15	0.76, 1.75	1.23	0.81, 1.87	0.93	0.60, 1.45	0.481	0.868	
Multivariable	1	1.09	0.71, 1.67	1.11	0.73, 1.70	1.26	0.82, 1.92	0.89	0.57, 1.40	0.476	0.862	
Proximal colon cancer												
No. of cases	103		99		89		61		64			
Age-, sex-, and energy-adjusted	1	1.03	0.73, 1.47	0.92	0.64, 1.32	0.67	0.45, 0.99	0.77	0.52, 1.13	0.063	—	
Multivariable	1	0.98	0.68, 1.39	0.89	0.62, 1.28	0.66	0.45, 0.99	0.75	0.50, 1.11	0.074	—	
Distal colon cancer												
No. of cases	49		68		52		39		45			
Age-, sex-, and energy-adjusted	1	1.46	0.96, 2.22	1.11	0.72, 1.73	0.86	0.54, 1.38	1.04	0.66, 1.65	0.373	0.230	
Multivariable	1	1.43	0.93, 2.18	1.08	0.69, 1.69	0.88	0.55, 1.41	0.99	0.62, 1.57	0.300	0.229	
Broiled, g/1,000 kcal												
Total colorectal cancer												
No. of cases	841		148									
Age-, sex-, and energy-adjusted	1	0.95	0.74, 1.23							0.702	—	
Multivariable	1	0.97	0.75, 1.25							0.805	—	
Total colon cancer												
No. of cases	591		102									
Age-, sex-, and energy-adjusted	1	0.91	0.69, 1.21							0.530	—	
Multivariable	1	0.93	0.69, 1.23							0.593	—	
Total rectal cancer												
No. of cases	245		44									
Age-, sex-, and energy-adjusted	1	0.99	0.69, 1.43							0.958	0.674	
Multivariable	1	1.01	0.70, 1.47							0.943	0.608	
Proximal colon cancer												
No. of cases	349		67									
Age-, sex-, and energy-adjusted	1	1.00	0.72, 1.40							0.979	—	
Multivariable	1	1.02	0.73, 1.43							0.899	—	
Distal colon cancer												

Quintile of intake ^d												P-heterogeneity between subsites ^c
Q1 ^b	Q2		Q3		Q4		Q5		P-Trend			
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI				
No. of cases	222	31										
Age-, sex-, and energy-adjusted	1	0.76	0.50, 1.15							0.188	0.201	
Multivariable	1	0.76	0.50, 1.16							0.198	0.158	
Rare/medium, g/1,000 kcal												
Total colorectal cancer												
No. of cases	771	262										
Age-, sex-, and energy-adjusted	1	0.92	0.74, 1.13							0.413	—	
Multivariable	1	0.99	0.78, 1.23							0.923	—	
Total colon cancer												
No. of cases	532	161										
Age-, sex-, and energy-adjusted	1	0.96	0.76, 1.22							0.759	—	
Multivariable	1	1.04	0.82, 1.32							0.776	—	
Total rectal cancer												
No. of cases	227	62										
Age-, sex-, and energy-adjusted	1	0.84	0.61, 1.15							0.265	0.309	
Multivariable	1	0.91	0.66, 1.26							0.563	0.369	
Proximal colon cancer												
No. of cases	331	85										
Age-, sex-, and energy-adjusted	1	0.81	0.61, 1.09							0.161	—	
Multivariable	1	0.87	0.65, 1.17							0.349	—	
Distal colon cancer												
No. of cases	181	72										
Age-, sex-, and energy-adjusted	1	1.23	0.90, 1.67							0.194	0.019	
Multivariable	1	1.32	0.96, 1.81							0.084	0.026	
Well-done/charred, g/1,000 kcal												
Total colorectal cancer												
No. of cases	230	255			197		173		134			
Age-, sex-, and energy-adjusted	1	1.05	0.80, 1.37	0.86	0.65, 1.13	0.79	0.59, 1.04	0.69	0.51, 0.93	0.003	—	

	Quintile of intake ^a										P-Trend	P-heterogeneity between subsites ^c
	Q1 ^b	Q2		Q3		Q4		Q5				
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI			
Multivariable	1	0.99	0.75, 1.31	0.85	0.64, 1.14	0.79	0.59, 1.05	0.72	0.53, 0.97	0.014	—	
Total colon cancer												
No. of cases	167		185		136		114		91			
Age-, sex-, and energy-adjusted	1	1.02	0.76, 1.37	0.81	0.60, 1.10	0.73	0.53, 1.00	0.68	0.49, 0.94	0.004	—	
Multivariable	1	0.97	0.72, 1.32	0.81	0.59, 1.10	0.72	0.52, 1.00	0.69	0.49, 0.98	0.014	—	
Total rectal cancer												
No. of cases	60		68		59		59		43			
Age-, sex-, and energy-adjusted	1	1.13	0.75, 1.68	0.98	0.65, 1.50	0.98	0.65, 1.47	0.77	0.50, 1.20	0.139	0.573	
Multivariable	1	1.06	0.70, 1.59	0.98	0.64, 1.49	1.00	0.66, 1.52	0.82	0.52, 1.29	0.326	0.505	
Proximal colon cancer												
No. of cases	92		123		84		72		45			
Age-, sex-, and energy-adjusted	1	1.22	0.86, 1.73	0.93	0.64, 1.34	0.86	0.59, 1.26	0.64	0.42, 0.98	0.006	—	
Multivariable	1	0.74	0.49, 1.12	0.69	0.45, 1.06	0.56	0.36, 0.87	0.67	0.43, 1.05	0.015	—	
Distal colon cancer												
No. of cases	69		55		49		39		41			
Age-, sex-, and energy-adjusted	1	0.77	0.51, 1.15	0.71	0.47, 1.07	0.58	0.37, 0.89	0.66	0.43, 1.02	0.069	0.950	
Multivariable	1	0.74	0.49, 1.12	0.69	0.45, 1.06	0.56	0.36, 0.87	0.67	0.43, 1.05	0.105	0.993	

^aCategories of poultry intake were as follows: grilled/barbequed (any vs. no consumption); pan-fried (any vs. no consumption); microwaved/baked (g/1,000 kcal), quintile 1 (<0.25), quintile 2 (0.25-2.35), quintile 3 (2.36-6.22), quintile 4 (6.23-14.1), quintile 5 (> 14.1); broiled (any vs. no consumption); rare/medium (any vs. no consumption); well-done/charred (g/1,000 kcal), quintile 1 (< 0.94), quintile 2 (0.94-4.78), quintile 3 (4.78-10.5), quintile 4 (10.6-20.3), quintile 5 (> 20.3).

^bReferent quintile.

^cEffect heterogeneity was evaluated between colon and rectal cancer and proximal and distal colon cancer.

^dORs were adjusted for age, sex, body mass index, past regular NSAID use, and intakes of fruits and vegetables, total energy, and red meat.

^e7 cases lacked anatomical subsite information.

^f24 cases had colon cancer in overlapping sites or not otherwise specified colon sites.

^gGrilled/barbequed, pan-fried, broiled, and rare/medium poultry were dichotomous variables (any or no consumption) due to more than 50 percent zero values in each category of poultry.