Meat, Meat Cooking Methods and Preservation, and Risk for Colorectal Adenoma

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Abstract

Cooking meat at high temperatures produces heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs). Processed meats contain *N*-nitroso compounds. Meat intake may increase cancer risk as HCAs, PAHs, and *N*-nitroso compounds are carcinogenic in animal models. We investigated meat, processed meat, HCAs, and the PAH benzo(*a*)pyrene and the risk of colorectal adenoma in 3,696 left-sided (descending and sigmoid colon and rectum) adenoma cases and 34,817 endoscopy-negative controls. Dietary intake was assessed using a 137-item food frequency questionnaire, with additional questions on meats and meat cooking practices. The questionnaire was linked to a previously developed database to determine exposure to HCAs and PAHs. Intake of red meat, with known doneness/cooking methods, was associated with an increased risk of adenoma in the descending and sigmoid colon [odds ratio (OR), 1.26; 95% confidence interval (95% CI), 1.05-1.50 comparing extreme quintiles of intake] but not rectal adenoma. Well-done red meat was associated with increased risk of colorectal adenoma (OR, 1.21; 95% CI, 1.06-1.37). Increased risks for adenoma of the descending colon and sigmoid colon were observed for the two HCAs: 2-amino-3,8-dimethylimidazo[4,5]quinoxaline and 2-amino-1-methyl-6-phenylimidazo[4,5]pyridine (OR, 1.18; 95% CI, 1.01-1.38 and OR, 1.17, 95% CI, 1.01-1.35, respectively) as well as benzo(*a*)-pyrene (OR, 1.18; 95% CI, 1.02-1.35). Greater intake of bacon and sausage was associated with increased colorectal adenoma risk (OR, 1.14; 95% CI, 1.00-1.30); however, total intake of processed meat was not (OR, 1.04; 95% CI, 0.90-1.19). Our study of screening-detected colorectal adenomas shows that red meat and meat cooked at high temperatures are associated with an increased risk of colorectal adenoma. (Cancer Res 2005; 65(17): 8034-41)

Introduction

There is "probable" evidence of increased risk of colon and rectal cancers with high intake of red meat (1). Some epidemiologic studies of colorectal adenoma and cancer have found an increased risk with increased cooking time and temperature (2–7). A group of compounds known as heterocyclic amines (HCAs) are formed in meat cooked at high temperatures, e.g., frying and grilling (8–11). HCAs are potent mutagens and animal carcinogens (2, 12–15); however, the carcinogenic potential in humans has not been definitively established (1, 2). There were two early case-control studies to estimate HCA intake to examine the association between HCAs and colorectal neoplasia. A Swedish population-based case-control study of cancers of the colon, rectum, bladder, and kidney found no association with HCAs within the usual dietary range in this population (16). However, there was evidence that HCAs may be carcinogenic at the extreme high end of intake as all participants at this level of intake were cases (16). The second smaller study found a 2- to 3-fold increased risk of colorectal adenoma, comparing the fifth to the first quintile of three different HCAs: 2-amino-3,4,8-trimethylimidazo[4,5]quinoxaline (DiMeIQx), 2-amino-3,8-dimethylimidazo[4,5]quinoxaline (MeIQx), and 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP; ref. 17).

Polycyclic aromatic hydrocarbons (PAHs) are formed during grilling or barbecuing meat and in cured meats or smoked foods (18, 19). Benzo(*a*)pyrene is one of the most potent PAH carcinogens in animal studies (20). However, only one epidemiologic study has directly investigated the association between dietary intake of PAHs and colon cancer. This population-based case-control study did not show an association between benzo(*a*)pyrene and colon cancer (21).

We investigated the association between meat and meat-related mutagens in the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial. To investigate the role of meat, meat cooking practices, and meat mutagens, we included a meat cooking module in the food frequency questionnaire used in the PLCO trial. We studied colorectal adenomas because they are precursors of colorectal cancer (22), allowing for the evaluation of risk factors early in the colorectal neoplastic process among asymptomatic individuals. The large case number of this study enables us to examine risk by tumor site, number, and histologic characteristics.

Materials and Methods

The PLCO cancer screening trial. More than 75,000 participants were randomized to the screening arm of the PLCO trial (~50% men and 50% women) in a multisite study (Birmingham, AL; Denver, CO; Detroit, MI; Honolulu, HI; Marshfield, WI; Minneapolis, MN; Pittsburgh, PA; Salt Lake City, UT; St. Louis, MO; and Washington, DC). Between September 1993 and July 2001, 57,569 men and women ages 55 to 74 years were successfully screened by sigmoidoscopy (insertion to at least 50 cm, with >90% of mucosa visible, or suspect lesion found). Of these participants, 52,143 subjects (90.6%) completed dietary and risk factor questionnaires. For this analysis, we excluded 7,571 participants for self-reported history of cancer (except basal cell cancer; n = 2,363); history of ulcerative colitis (n = 652), Crohn's disease (n = 203), familial polyposis (n = 156), colorectal polyps

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(n = 3,664), or Gardner's syndrome (n = 124); extreme high or low dietary energy intake (lowest and highest 1% on gender-specific energy intake; n = 998); or missing >7 items in the food frequency questionnaire (n = 436). Some subjects had more than one cause for exclusion.

Our analysis included 3,696 cases of pathologically verified colorectal adenoma of the descending colon, sigmoid colon, or rectum, and 34,817 controls with no lesions suspicious for neoplasia on endoscopy of the descending colon, sigmoid colon, or rectum. Participants were not included in the analysis if they had only hyperplastic polyps (n = 1,499), benign lesions not further specified (n = 109), colorectal lesions of unknown location (n = 276), polyps of uncertain histology or cancer (n = 1,526), indeterminate screening results (n = 37), or positive screening but no follow-up endoscopy (n = 2,612, of which n = 1,839; 70.0% had a polyp <5 mm) as well as the 7,571 subjects excluded above. Written informed consent was obtained from each participant in the study. The study was done after approval by the institutional review board of the National Cancer Institute and the trial screening centers.

Exposure assessment. At the initial screening, participants completed a baseline questionnaire that included information on age, ethnicity, education, occupation, current and past smoking behavior, history of cancer and other diseases, use of selected drugs, and previous screening examinations. Usual diet over the past 12 months before enrollment was assessed using a food frequency questionnaire with 137 individual food items, 77 of which queried about usual portion size.[5] Eighty-nine percent of the subjects filled out the food frequency questionnaire before or the same day of sigmoidoscopy screening. Information on the frequency of consumption and portion size of meat was obtained for various meat groups (Appendix 1). For hamburger and steak, information on cooking method and doneness level were obtained; the doneness was determined as rare, medium-rare, medium, medium-well, well-done, or very well-done. For pork chops/ham steaks, sausage/hotdogs, and bacon, doneness was defined as just until done, well-done/crisp, and very well-done/charred.

We calculated the amount of meat consumed (g/d) from frequency of consumption and portion size information in the food frequency questionnaire. We created a category for meats with known doneness levels; these are the meats generally cooked by high-temperature cooking techniques (steak, hamburger, bacon, sausage, and pork chops). For these meats with information on the degree to which they were cooked, we calculated grams of meat consumed according to doneness level and created two different categories: well-done and medium/rare (Appendix 1). A variable was created for red meat by cooking techniques (bake/roast, pan-fry, grill/barbecue, microwave, oven-broil, and other methods). HCAs (MeIQx, DiMeIQx, and PhIP), benzo(a)pyrene, and mutagenic activity (which is a measure of total mutagenic potential and, therefore, incorporates all meat-related mutagens) were estimated using the frequency and portion size data from the food frequency questionnaire. We used the software application known as the Computerized Heterocyclic Amines Resource for Research in Epidemiology of Disease, CHARRED[6], to generate estimates of HCA and benzo(a)pyrene intake. The CHARRED application consists of HCA and PAH data generated from ~120 categories of meat. Multiple meat samples prepared by different cooking methods to varied doneness levels were cooked and their composites were analyzed for HCAs and PAHs. The details on the meat samples are provided in the published reports (9–11).

Statistical analysis. The data was analyzed in quintiles generated from the distribution among the controls. Prevalence odds ratios (OR) and 95% confidence intervals (95% CI) were computed using unconditional logistic regression, using the first quintile as the reference group. Trend tests were calculated using the median intake values of each quintile. The strength of association was determined for all meat and subgroups of meat, specific HCAs, and mutagenic activity. To account for potential confounders, based on *a priori* hypotheses for colorectal adenoma and cancer risk factors, we calculated a multivariate model controlling for age, gender, screening center, and energy intake (kcal/d), ethnicity (American Indian/Alaskan Native, Asian, Hispanic, non-Hispanic Black, non-Hispanic White, or Pacific Islander), educational attainment (<8 years school, 8-11 years school, 12 years school/high school equivalent, post–high school other than college, some college, college graduate, or postgraduate), tobacco use (never, smoked cigar or pipe, quit smoking 20+ years, and smoked ≤1 pack/d, quit 20+ years and smoked >1 pack/d, quit <20 years and smoked ≤1 pack/d, quit <20 years and smoked >1 pack/d, or unknown), alcohol use (<1, ≥1-15, >15-30, or >30 g/d), use of aspirin and ibuprofen separately (no regular use, <2, 2-3, 4, 8, 12-16, 30, or 60 per month), vigorous physical activity (none, <1, 1, 2, 3, or 4+ h/wk), body mass index (BMI; calculated as kg/m^2), total folate intake (μg/d), calcium intake (mg/d), and dietary fiber intake (g/d).

Results

Participants in the highest quintile of meat intake, compared with those in the lowest quintile, were younger and more likely to be male (Table 1). High meat consumers also had a higher BMI, exercised less, smoked more, drank more alcohol, and reported a diet high in total calories and total and saturated fat compared with low meat consumers.

The ORs for all adenomas adjusted for only age, gender, and study site fifth versus first quintiles were as follows: total meat, 1.15 (95% CI, 1.3-1.29); red meat, 1.38 (95% CI, 1.22-1.55); white meat, 0.88 (95% CI, 0.79-0.99); red meat normally cooked at high temperatures, 1.51 (95% CI, 1.31-1.73); well-done red meat, 1.44 (95% CI, 1.27-1.62); grilled red meat, 1.19 (95% CI, 1.06-1.32); pan-fried red meat, 1.34 (95% CI, 1.19-1.51); broiled red meat, 1.07 (95% CI, 0.98-1.17); total processed meat, 1.26 (95% CI, 1.11-1.44); and bacon and sausage, 1.32 (95% CI, 1.16-1.50). In a fully adjusted model for all adenomas combined, there was no association with red meat intake, but we observed an increased risk associated with well-done red meat (Table 2). For processed meats, we found an increased risk of adenoma associated with bacon and sausage intake, although no association was found for all processed meats combined (Table 2).

Stratified analyses by adenoma subtype showed increased risks for nonadvanced adenoma with a high intake of bacon and sausage and with well-done red meat intake (Table 2).

For adenoma of the descending and sigmoid colon, elevated risks were found with high consumption of red meat with known doneness level, well-done red meat, bacon, and sausage (Table 2). In contrast, rectal cancer was not associated with any of the meat variables. Risk for single adenomas was positively associated with bacon and sausage consumption and well-done red meat (Table 2); however, none of the meat variables were associated with multiple adenomas.

For advanced adenoma, we observed a significant association with intake of red meat with known doneness/cooking methods (Table 2), although none of the specific cooking techniques explored (for example grilling, pan frying, oven broiling) were associated with an elevated risk of colorectal adenoma. The ORs for a fully adjusted model comparing fifth to the first quintiles for cooking methods were as follows: grilled meat, 0.99 (95% CI, 0.80-1.23); broiled red meat, 0.92 (95% CI, 0.78-1.09); pan-fried red meat, 0.95 (95% CI, 0.74-1.22).

The ORs for all adenomas adjusted for age, gender, and study site fifth versus first quintiles for the meat mutagens were as follows: DiMeIQx, 1.18 (95% CI, 1.06-1.32); MeIQx, 1.33 (95% CI, 1.18-49); PhIP, 1.23 (95% CI,1.09-1.38); mutagenicity, 1.25 (95% CI, 1.12-1.41); benzo(a)pyrene, 1.23 (95% CI, 1.10-1.38). However, in a fully adjusted model, total mutagenicity, DiMeIQx, and MeIQx intake were not associated with colorectal adenoma risk when all adenomas were combined. However, PhIP and benzo(a)pyrene resulted in a marginally elevated risk for colorectal adenoma (Table 3). In addition, MeIQx, PhIP, benzo(a)pyrene, and overall

[5] http://dcp.nci.nih.gov/plco/diet
[6] http://charred.cancer.gov/

Table 1. Distribution of study characteristics overall by first and fifth quintiles of total meat consumption

Characteristics	Overall (n = 38,513)	By total meat intake	
		Lowest quintile (n = 7,625)	Highest quintile (n = 7,870)
Age (y)	62.8	63.5	61.8
Female (%)	47.6	70.4	20.9
Ethnicity (%)			
Non-Hispanic White	90.00	88.89	89.02
Non-Hispanic Black	3.80	3.53	4.37
Hispanic	1.46	1.76	1.65
Asian	3.91	5.11	3.74
Pacific Island	0.50	0.33	0.80
American Indian, Alaskan native	0.21	0.25	0.23
Not answered	0.13	0.13	0.19
Some college level education (%)	70.8	68.8	70.8
BMI (kg/m^2)	27.3	25.9	28.8
Vigorous physical activity (%)			
>1 h/wk	67.98	70.56	64.21
≤1 h/wk	31.70	29.03	35.51
Not answered or multiple answers	0.32	0.41	0.28
Regular use of nonsteroidal anti-inflammatory drugs (%)			
Yes	59.35	56.17	62.01
No	40.0	43.10	37.24
Not answered	0.65	0.73	0.75
Smoking status (%)			
Never	45.13	55.46	34.45
Current cigarette smoker	8.09	5.91	10.65
Ex-cigarette smoker	42.32	36.24	47.88
Never cigarettes, but pipe and cigar	4.32	2.26	6.87
Not answered	0.14	0.13	0.15
Alcohol (g/d)	10.7	5.9	16.3
Total caloric intake (kcal/d)	2,057	1,459	2,912
Red meat (g/d)	77.8	25.1	164.7
White meat (g/d)	53.7	20.1	105.3
Total fat (g/d)	67.6	41.5	105.9
Saturated fat (g/d)	22.9	14.1	35.9
Folate (μg/d)	378.0	318.4	463.0
Calcium (mg/d)	961.0	780.6	1,214.0
Fiber (g/d)	23.4	19.9	28.7

mutagenicity were associated with an increased risk of nonadvanced colorectal adenoma (Table 3). For adenoma of the descending and sigmoid colon, elevated risks were found with high intake of MeIQx, PhIP, and benzo(a)pyrene (Table 3). In contrast, rectal cancer was not associated with any of the HCA or benzo(a)pyrene variables.

Risk for single adenomas was positively associated with MeIQx, PhIP, and benzo(a)pyrene intake (Table 3). However, none of the meat mutagen variables were associated with multiple adenomas.

Discussion

In this large study population, with detailed information on meat intake and meat cooking techniques, we found increased risks for adenoma of the descending and sigmoid colon associated with high intake of red meat, bacon, and sausage; well-done red meat; as well as HCAs and benzo(a)pyrene. These associations were strongest for subjects with single adenomas and adenomas with less advanced features; increased risks ranged from 13% to 27%, comparing participants in the lowest quintile with the highest quintile of meat or meat mutagen consumption.

Red meat was associated with increased risk in two meta-analyses of meat intake and colorectal cancer (23, 24). Data from 13 prospective studies showed increased risks of 12% to 17% associated with increases in consumption of red meat of 100 g/d, which is similar to the difference in red meat intake between the first to the fifth quintile in our study (23). Norat et al. (24) included both cohort (n = 14) and case-control studies (n = 34) and reported a significant increase in risk of 35% in the highest quintile of red meat consumption compared with the lowest quintile. In this analysis, we did not find an association between total red meat consumption and colorectal adenoma. However, red meat with doneness/cooking methods (steak, hamburger, pork chops, bacon, and sausage) were associated with an elevated risk of colon, but not rectal adenoma, and advanced adenoma.

Well-done meat, surface browning, and cooking methods have been used as surrogates for HCAs and PAHs in previous studies (4, 6, 7, 16, 17, 25, 26). Well-done red meat has previously been associated with a 29% increased risk per 10 g of meat consumed of colorectal adenoma (17) and over a 4-fold increased risk of colorectal cancer (27). In this study, we also found an increased risk for colorectal adenoma and adenomas with less advanced features associated with consumption of well-done red meat. The more modest risk associated with well-done red meat consumption in

Table 2. Meat intake and risk for colorectal adenoma

Meat type (quintiles)	All adenoma (n = 3,696)	Type		Site*		Number	
	OR (95% CI)†	Nonadvanced (n = 2,271)	Advanced (n = 1,425)	Colon (n = 2,474)	Rectum (n = 688)	Single (n = 2,796)	Multiple (n = 900)
		OR (95% CI)†		OR (95% CI)†		OR (95% CI)†	
Total meat (g/d)							
Q2 (63.9-92.4)	0.91 (0.81-1.03)	0.89 (0.76-1.03)	0.94 (0.79-1.13)	0.94 (0.81-1.08)	0.95 (0.73-1.24)	0.93 (0.81-1.06)	0.85 (0.67-1.07)
Q3 (92.4-126.2)	0.96 (0.85-1.08)	1.00 (0.86-1.15)	0.89 (0.74-1.07)	0.95 (0.83-1.10)	1.11 (0.86-1.44)	1.00 (0.88-1.14)	0.82 (0.65-1.04)
Q4 (126.2-182.7)	1.07 (0.94-1.20)	1.04 (0.89-1.21)	1.10 (0.91-1.33)	1.06 (0.91-1.22)	1.27 (0.97-1.66)	1.10 (0.96-1.26)	0.97 (0.76-1.23)
Q5 (182.7-1212.7)	1.05 (0.92-1.22)	1.11 (0.93-1.33)	0.97 (0.78-1.21)	1.09 (0.92-1.30)	1.14 (0.83-1.57)	1.12 (0.95-1.32)	0.88 (0.66-1.15)
P_{trend}	P = 0.09	P = 0.05	P = 0.78	P = 0.08	P = 0.28	P = 0.04	P = 0.79
Red meat (g/d)							
Q2 (29.2-48.7)	0.95 (0.85-1.08)	0.98 (0.85-1.15)	0.90 (0.75-1.09)	0.96 (0.83-1.10)	0.98 (0.74-1.28)	1.00 (0.87-1.14)	0.82 (0.64-1.04)
Q3 (48.7-72.8)	0.97 (0.86-1.10)	1.02 (0.88-1.19)	0.89 (0.74-1.08)	0.94 (0.81-1.08)	1.15 (0.88-1.50)	1.04 (0.90-1.19)	0.78 (0.62-1.00)
Q4 (72.8-113.8)	1.07 (0.94-1.21)	1.11 (0.95-1.30)	1.00 (0.83-1.22)	1.06 (0.91-1.24)	1.30 (0.98-1.71)	1.17 (1.01-1.35)	0.81 (0.63-1.03)
Q5 (113.8-845.4)	1.07 (0.92-1.24)	1.10 (0.91-1.31)	1.03 (0.82-1.29)	1.09 (0.92-1.30)	1.14 (0.82-1.59)	1.12 (0.95-1.32)	0.91 (0.69-1.20)
P_{trend}	P = 0.13	P = 0.23	P = 0.29	P = 0.09	P = 0.38	P = 0.10	P = 0.81
White meat (g/d)							
Q2 (20.3-33.2)	1.04 (0.93-1.16)	1.03 (0.90-1.19)	1.05 (0.88-1.24)	1.03 (0.90-1.18)	1.18 (0.93-1.51)	1.09 (0.96-1.24)	0.91 (0.74-1.12)
Q3 (33.2-48.8)	1.00 (0.90-1.12)	0.95 (0.82-1.10)	1.09 (0.92-1.30)	1.03 (0.90-1.18)	0.99 (0.77-1.28)	1.07 (0.94-1.21)	0.84 (0.68-1.04)
Q4 (48.8-75.6)	0.97 (0.86-1.09)	0.99 (0.86-1.14)	0.92 (0.77-1.12)	0.99 (0.86-1.13)	1.00 (0.77-1.29)	0.99 (0.87-1.13)	0.91 (0.74-1.13)
Q5 (75.6-822.9)	1.03 (0.91-1.16)	1.02 (0.88-1.19)	1.03 (0.85-1.24)	1.02 (0.88-1.18)	1.16 (0.89-1.52)	1.09 (0.95-1.26)	0.84 (0.67-1.06)
P_{trend}	P = 0.94	P = 0.81	P = 0.84	P = 0.97	P = 0.53	P = 0.51	P = 0.31
Red meat with known doneness level (g/d)							
Q2 (8.7-16.9)	1.03 (0.91-1.17)	0.93 (0.80-1.09)	1.20 (0.98-1.46)	1.12 (0.96-1.30)	0.84 (0.64-1.10)	0.98 (0.85-1.12)	1.22 (0.95-1.57)
Q3 (16.9-28.4)	1.10 (0.97-1.25)	1.07 (0.91-1.25)	1.16 (0.94-1.43)	1.13 (0.97-1.33)	0.91 (0.68-1.20)	1.08 (0.94-1.25)	1.16 (0.88-1.51)
Q4 (28.4-48.2)	1.14 (1.00-1.31)	1.10 (0.93-1.30)	1.22 (0.99-1.52)	1.15 (0.97-1.35)	1.09 (0.81-1.45)	1.17 (1.01-1.37)	1.05 (0.80-1.39)
Q5 (48.2-510.7)	1.17 (1.00-1.35)	1.08 (0.90-1.31)	1.32 (1.04-1.67)	1.26 (1.05-1.50)	0.91 (0.66-1.27)	1.15 (0.97-1.36)	1.21 (0.90-1.62)
P_{trend}	P = 0.06	P = 0.24	P = 0.09	P = 0.04	P = 0.91	P = 0.06	P = 0.54
Red meat cooked rare/medium (g/d)							
Q2 (0.7-4.5)	1.02 (0.90-1.15)	1.01 (0.86-1.17)	1.04 (0.86-1.27)	1.02 (0.88-1.19)	0.98 (0.75-1.28)	1.09 (0.95-1.25)	0.79 (0.61-1.02)
Q3 (4.5-12.5)	1.06 (0.94-1.20)	1.06 (0.91-1.23)	1.06 (0.87-1.28)	1.06 (0.92-1.23)	0.94 (0.72-1.24)	1.03 (0.90-1.18)	1.15 (0.91-1.45)
Q4 (12.5-27.8)	1.08 (0.96-1.22)	1.07 (0.92-1.24)	1.11 (0.91-1.34)	1.08 (0.93-1.25)	1.12 (0.86-1.46)	1.14 (0.99-1.30)	0.93 (0.73-1.18)
Q5 (27.8-393.7)	1.12 (0.99-1.28)	1.10 (0.94-1.29)	1.17 (0.96-1.43)	1.13 (0.97-1.32)	1.06 (0.80-1.41)	1.13 (0.98-1.31)	1.09 (0.86-1.39)
P_{trend}	P = 0.06	P = 0.23	P = 0.10	P = 0.10	P = 0.46	P = 0.11	P = 0.28
Red meat cooked well-done (g/d)							
Q2 (2.8-5.9)	1.09 (0.97-1.23)	1.10 (0.95-1.28)	1.07 (0.89-1.29)	1.11 (0.96-1.28)	0.89 (0.69-1.15)	1.12 (0.98-1.28)	1.00 (0.79-1.26)
Q3 (5.9-10.7)	1.09 (0.97-1.23)	1.07 (0.92-1.24)	1.14 (0.95-1.37)	1.14 (0.99-1.32)	0.93 (0.72-1.20)	1.18 (1.04-1.35)	0.84 (0.66-1.07)
Q4 (10.7-20.1)	1.13 (1.00-1.28)	1.20 (1.03-1.39)	1.03 (0.85-1.25)	1.10 (0.95-1.28)	1.06 (0.82-1.37)	1.17 (1.02-1.34)	1.02 (0.80-1.28)
Q5 (20.1-510.7)	1.21 (1.06-1.37)	1.25 (1.07-1.47)	1.14 (0.93-1.40)	1.23 (1.05-1.44)	0.95 (0.71-1.26)	1.27 (1.10-1.47)	1.02 (0.79-1.31)
P_{trend}	P = 0.01	P = 0.01	P = 0.43	P = 0.04	P = 0.87	P = 0.01	P = 0.49
Processed meat (g/d)							
Q2 (3.8-7.9)	1.01 (0.90-1.15)	1.00 (0.86-1.17)	1.03 (0.85-1.25)	1.02 (0.88-1.18)	0.92 (0.71-1.20)	1.11 (0.96-1.27)	0.74 (0.58-0.96)
Q3 (7.9-14.3)	0.95 (0.84-1.08)	0.97 (0.83-1.14)	0.92 (0.75-1.13)	0.95 (0.81-1.10)	0.92 (0.70-1.20)	1.00 (0.87-1.16)	0.80 (0.62-1.03)
Q4 (14.3-26.8)	1.12 (0.98-1.27)	1.14 (0.97-1.34)	1.08 (0.88-1.32)	1.13 (0.96-1.32)	0.96 (0.72-1.27)	1.23 (1.06-1.42)	0.82 (0.63-1.05)
Q5 (26.8-367.1)	1.04 (0.90-1.19)	1.03 (0.86-1.23)	1.06 (0.85-1.32)	1.05 (0.89-1.25)	0.86 (0.63-1.17)	1.08 (0.92-1.27)	0.90 (0.69-1.17)
P_{trend}	P = 0.51	P = 0.71	P = 0.48	P = 0.46	P = 0.46	P = 0.66	P = 0.51
Bacon/sausage (g/d)							
Q2 (0.5-1.3)	1.08 (0.95-1.22)	1.01 (0.86-1.17)	1.21 (1.00-1.46)	1.16 (1.00-1.34)	0.76 (0.58-0.98)	1.07 (0.93-1.22)	1.12 (0.88-1.43)
Q3 (1.3-2.9)	1.02 (0.90-1.15)	0.99 (0.85-1.16)	1.06 (0.87-1.29)	1.08 (0.93-1.26)	0.83 (0.64-1.07)	1.05 (0.91-1.21)	0.92 (0.72-1.18)
Q4 (2.9-6.3)	1.01 (0.89-1.14)	0.96 (0.82-1.13)	1.10 (0.90-1.34)	1.09 (0.94-1.28)	0.72 (0.55-0.94)	1.07 (0.92-1.23)	0.84 (0.65-1.08)
Q5 (6.3-306.0)	1.14 (1.00-1.30)	1.15 (0.98-1.36)	1.13 (0.92-1.40)	1.20 (1.02-1.41)	0.86 (0.65-1.14)	1.15 (0.99-1.34)	1.11 (0.86-1.43)
P_{trend}	P = 0.03	P = 0.01	P = 0.56	P = 0.09	P = 0.75	P = 0.05	P = 0.22

*Five hundred thirty-four adenoma cases could not be strictly classified as one of these two subsites.

†Models were adjusted for age, gender, screening center, energy intake (kcal/d, standard method for energy adjustment), ethnicity (American Indian/Alaskan Native, Asian, Hispanic, non-Hispanic Black, non-Hispanic White, or Pacific Islander), educational attainment (<8 years school, 8-11 years school, 12 years school/high school equivalent, post–high school other than college, some college, college graduate, or postgraduate), tobacco use (never, smoked cigar or pipe, quit smoking 20+ years and smoked ≤1 pack/d, quit 20+ years and smoked >1 pack/d, quit <20 years and smoked ≤1 pack/d, quit <20 years and smoked >1 pack/d, or unknown), alcohol use (<1, ≥1-15, >15-30, or >30 g/d), use of aspirin and ibuprofen separately (no regular use, <2, 2-3, 4, 8, 12-16, 30, or 60 per month), vigorous physical activity (none, <1, 1, 2, 3, or 4+ hours/wk), BMI (calculated as kg/m^2), total folate intake (μg/d), calcium intake (mg/d), and dietary fiber intake (g/d).

Table 3. Meat-cooking mutagens and risk for colorectal adenoma

Mutagen	All adenomas (n = 3,696)	Stage		Site*		Number of adenomas	
	OR (95% CI)†	Nonadvanced (n = 2,271)	Advanced (n = 1,425)	Colon (n = 2,474)	Rectum (n = 688)	Single (n = 2,796)	Multiple (n = 900)
		OR (95% CI)†		OR (95% CI)†		OR (95% CI)†	
Mutagenicity							
Q2 (1,091.0-2,419.5)	1.00 (0.88-1.12)	1.02 (0.88-1.19)	0.95 (0.79-1.14)	1.00 (0.87-1.16)	0.95 (0.73-1.22)	1.04 (0.91-1.19)	0.86 (0.67-1.09)
Q3 (2,419.8-4,507.8)	1.06 (0.95-1.20)	1.09 (0.94-1.27)	1.03 (0.85-1.23)	1.07 (0.93-1.24)	0.99 (0.77-1.28)	1.11 (0.98-1.27)	0.91 (0.72-1.16)
Q4 (4,509.8-9,352.9)	1.14 (1.01-1.28)	1.17 (1.01-1.37)	1.08 (0.90-1.30)	1.19 (1.03-1.38)	1.07 (0.82-1.39)	1.20 (1.05-1.37)	0.96 (0.76-1.22)
Q5 (9,354.8-502,928.3)	1.08 (0.95-1.22)	1.15 (0.99-1.35)	0.97 (0.80-1.18)	1.15 (0.99-1.33)	0.93 (0.71-1.23)	1.11 (0.97-1.28)	0.97 (0.76-1.23)
P_{trend}	P = 0.32	P = 0.10	P = 0.70	P = 0.09	P = 0.63	P = 0.37	P = 0.59
DiMeIQx (ng/d)							
Q2 (0.2-0.5)	1.01 (0.90-1.13)	1.05 (0.91-1.21)	0.95 (0.80-1.13)	1.01 (0.88-1.15)	0.88 (0.69-1.12)	1.00 (0.88-1.14)	1.04 (0.83-1.29)
Q3 (0.5-1.3)	0.98 (0.87-1.10)	1.06 (0.92-1.22)	0.86 (0.72-1.02)	1.04 (0.91-1.19)	0.81 (0.63-1.03)	1.03 (0.91-1.17)	0.81 (0.64-1.02)
Q4 (1.3-2.6)	1.10 (0.98-1.22)	1.18 (1.03-1.36)	0.98 (0.83-1.16)	1.11 (0.97-1.27)	1.01 (0.80-1.28)	1.10 (0.97-1.24)	1.08 (0.88-1.34)
Q5 (2.6-159.1)	1.05 (0.94-1.18)	1.11 (0.97-1.28)	0.97 (0.82-1.15)	1.11 (0.97-1.27)	0.88 (0.69-1.13)	1.08 (0.95-1.22)	0.99 (0.79-1.23)
P_{trend}	P = 0.24	P = 0.16	P = 0.80	P = 0.10	P = 0.73	P = 0.20	P = 0.82
MeIQx (ng/d)							
Q2 (7.0-14.3)	0.96 (0.85-1.08)	0.98 (0.84-1.13)	0.92 (0.77-1.11)	1.02 (0.88-1.17)	0.70 (0.54-0.90)	1.03 (0.90-1.17)	0.76 (0.59-0.96)
Q3 (14.3-25.4)	1.06 (0.95-1.19)	1.16 (1.01-1.35)	0.91 (0.76-1.10)	1.12 (0.98-1.30)	0.93 (0.73-1.19)	1.14 (0.99-1.30)	0.85 (0.67-1.07)
Q4 (25.4-46.3)	1.12 (1.00-1.26)	1.14 (0.98-1.33)	1.09 (0.91-1.31)	1.15 (1.00-1.33)	0.97 (0.76-1.25)	1.18 (1.03-1.35)	0.96 (0.77-1.21)
Q5 (46.3-1,230.8)	1.08 (0.95-1.23)	1.18 (1.01-1.38)	0.94 (0.77-1.14)	1.18 (1.01-1.38)	0.79 (0.60-1.04)	1.14 (0.99-1.32)	0.91 (0.71-1.16)
P_{trend}	P = 0.12	P = 0.03	P = 0.91	P = 0.03	P = 0.43	P = 0.12	P = 0.63
PhIP (ng/d)							
Q2 (16.8-40.0)	1.09 (0.97-1.23)	1.11 (0.95-1.28)	1.06 (0.89-1.28)	1.11 (0.96-1.29)	0.97 (0.75-1.25)	1.12 (0.98-1.28)	0.99 (0.78-1.26)
Q3 (40.1-86.1)	1.05 (0.93-1.18)	1.08 (0.93-1.25)	0.99 (0.82-1.19)	1.05 (0.91-1.22)	1.03 (0.80-1.33)	1.07 (0.93-1.22)	0.97 (0.77-1.22)
Q4 (86.1-222.0)	1.13 (1.00-1.28)	1.11 (0.95-1.29)	1.17 (0.97-1.40)	1.17 (1.01-1.35)	1.07 (0.83-1.38)	1.18 (1.03-1.35)	0.98 (0.77-1.24)
Q5 (222.1-13,334.8)	1.11 (0.98-1.25)	1.20 (1.04-1.40)	0.96 (0.79-1.16)	1.17 (1.01-1.35)	1.02 (0.79-1.33)	1.13 (0.98-1.29)	1.03 (0.81-1.31)
P_{trend}	P = 0.30	P = 0.03	P = 0.32	P = 0.11	P = 0.87	P = 0.37	P = 0.57
Benzo(a)pyrene (ng/d)							
Q2 (0.8-3.0)	1.13 (1.00-1.26)	1.13 (0.98-1.30)	1.13 (0.94-1.34)	1.09 (0.95-1.25)	1.19 (0.93-1.52)	1.16 (1.02-1.31)	1.03 (0.82-1.29)
Q3 (3.0-12.7)	1.10 (0.98-1.23)	1.10 (0.95-1.27)	1.09 (0.91-1.30)	1.12 (0.97-1.28)	1.04 (0.81-1.34)	1.09 (0.96-1.24)	1.11 (0.88-1.39)
Q4 (12.7-42.7)	1.00 (0.89-1.13)	1.01 (0.87-1.17)	0.99 (0.83-1.19)	1.03 (0.90-1.19)	0.87 (0.67-1.13)	1.02 (0.90-1.17)	0.93 (0.74-1.18)
Q5 (42.7-2,168.1)	1.15 (1.02-1.29)	1.18 (1.02-1.37)	1.08 (0.90-1.30)	1.18 (1.02-1.35)	1.12 (0.87-1.44)	1.17 (1.03-1.34)	1.06 (0.85-1.33)
P_{trend}	P = 0.16	P = 0.09	P = 0.90	P = 0.07	P = 0.73	P = 0.14	P = 0.79

*Five hundred thirty-four adenoma cases could not be strictly classified as one of these two subsites.
†Models were adjusted for age, gender, screening center, energy intake (kcal/d, standard method for energy adjustment), ethnicity (American Indian/Alaskan Native, Asian, Hispanic, non-Hispanic Black, non-Hispanic White, or Pacific Islander), educational attainment (<8 years school, 8-11 years school, 12 years school/high school equivalent, post–high school other than college, some college, college graduate, or postgraduate), tobacco use (never, smoked cigar or pipe, quit smoking 20+ years and smoked ≤1 pack/d, quit 20+ years and smoked >1 pack/d, quit <20 years and smoked ≤1 pack/d, quit <20 years and smoked >1 pack/d, or unknown), alcohol use (<1, ≥1-15, >15-30, or >30 g/d), use of aspirin and ibuprofen separately (no regular use, <2, 2-3, 4, 8, 12-16, 30, or 60 per month), vigorous physical activity (none, <1, 1, 2, 3, or 4+ h/wk), BMI (calculated as kg/m^2), total folate intake (μg/d), calcium intake (mg/d), and dietary fiber intake (g/d).

this study is not inconsequential given the high prevalence of colorectal adenomas and the possibility of modifying the exposure.

In meta-analyses, Sandhu et al. (23) found that an increase of 25 g/d of processed meat was associated with a 49% increased risk of colorectal cancer, whereas Norat et al. (24) calculated a 31% increased risk of colorectal cancer comparing the highest quintile of processed meat intake to the lowest. Although processed meat has quite consistently been found to increase the risk of colorectal cancer, the particular meat items and their components have not been widely studied. We found consistently increased risks for colorectal adenoma, nonadvanced adenoma, and single adenoma, ranging from 14% to 20% in the fifth quintile, for bacon and sausage intake. Processed meat contains many different types of meat, but interestingly bacon and sausage, for which we find positive associations with colorectal adenoma, are also known to contain HCAs upon cooking (10, 11). It is important that further studies investigate processed meats in more detail to determine which specific meats are important and therefore elucidate the associated mechanism linking processed meat to colorectal neoplasia.

This study did not find an association between any of the specific cooking methods and colorectal adenoma risk. Although high-temperature cooking methods lead to the formation of HCAs and PAHs, the level to which these compounds are formed is also dependent on the degree of doneness of the meat. Despite finding an

association between benzo(*a*)pyrene intake and colorectal adenoma, there is no association between grilled meat, which produces benzo(*a*)pyrene, and colorectal adenoma. Unfortunately, we were not able to investigate the combination of grilled meat cooked well-done because the range and frequency of consumption was too low.

Meat cooking method and doneness level are used to estimate exposure to mutagens, such as HCAs and PAHs, found in cooked meat. In contrast to two studies of colorectal neoplasia that found an increased risk associated with high-temperature cooking methods (4, 17), we did not observe such associations. The estimated intake of HCAs in this study are similar to previously published data; median values of DiMeIQx, MeIQx, and PhIP in this study were 0.8, 19, and 55 ng/d, respectively, compared with 0.7, 12, and 38, respectively, from a previously published study (28). We found a weak to modest increased risk for nonadvanced adenoma and colon adenoma with MeIQx and PhIP intake. These findings are consistent with other studies reporting associations between high levels of HCAs and increased risk for colorectal adenoma (28), although the risk magnitude is smaller in this current study compared with previous findings but the confidence interval is very tight. Therefore, we have more confidence in the actual risk estimate from this large study compared with the previously published small case-control studies.

The associations found in this study are stronger for well-done meat, which is used as a surrogate for HCA and PAH formation than for individual HCAs or benzo(*a*)pyrene. HCAs and benzo(*a*)pyrene are present in a variety of meats, not only well-done meat; therefore, if the level of consumption of well-done meat is small, then meats consumed more frequently but containing a smaller concentration of HCAs and benzo(*a*)pyrene may actually be contributing more to daily exposure. By calculating individual HCA and benzo(*a*)pyrene variables, the variability in meat types, cooking method, doneness level, and frequency of consumption all factors are taken into account.

Given the large number of participants with adenomas, we had the opportunity to examine different subtypes of adenomas. Red meat, processed meats, HCAs, and benzo(*a*)pyrene were all associated with an increased risk for descending and sigmoid colon adenoma but not rectal adenoma. The lack of association with rectal neoplasia has previously been reported. Wei et al. (29) found that intake of beef, pork, or lamb as a main dish and processed meat was only associated with colon but not rectal cancer risk, thus supporting the notion that the etiology of these two subsites may differ. Location-specific differentials in adenoma risk may reflect differences in local bowel milieu, including fecal water content and gut flora. However, the difference in colon versus rectum may be due to chance alone as we carried out multiple numbers of comparisons in the analyses.

Our data suggest stronger associations between red meat intake and meat-related mutagens with single and nonadvanced adenoma. However, this finding is not totally consistent given that we also found a positive association between red meat with known doneness level and advanced adenoma. This study was able to analyze meat and meat-related mutagens in very specific individual analyses; therefore, consideration must be given to the possibility that some of the findings may have arisen due to chance as a result of multiple comparisons.

Conducting this detailed analysis on meat and meat cooking methods in the PLCO trial enabled us to study subjects who had undergone a standardized screening program. This cohort contained a very large number of well-characterized colorectal adenoma cases, providing us with sufficient power to investigate the role of meat and meat mutagens as risk factors for colorectal adenoma in relation to various end points, including adenoma location and number. Importantly, this study included detailed questions on meat and meat cooking methods in the dietary questionnaire for comprehensive assessment of meat cooking patterns, which were linked to a specific database of meat-related mutagens. Despite these dietary assessment methods for meat and HCAs being the most comprehensive methods available, it is still likely that there is a degree of measurement error associated with them. This measurement error can lead to attenuated risk estimates; therefore, the actual risks may be higher.

This study was of cross-sectional design, which could have resulted in dietary recall bias, although most participants (89%) filled out the food frequency questionnaire before or on the same day of sigmoidoscopy screening, thus before diagnosis. This potential bias was investigated and no appreciable differences were noted in risk estimates for meat intake among participants who completed the dietary exam before, on the day of, or subsequent to the day of the sigmoidoscopy screening exam, suggesting that the time when the questionnaire was filled out did not affect the meat adenoma associations.

In conclusion, we found an increased risk for colorectal adenoma associated with well-done red meat, bacon, and sausage and meat-related mutagens in one of the largest studies of meat and meat cooking methods conducted to date. We found differential effect by the characteristics of the adenomas. A higher intake of well-done red meat, bacon and sausage, MeIQx, PhIP, and benzo(*a*)pyrene were associated with an increased risk of adenoma of the colon, nonadvanced adenoma, and single adenomas.

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Appendix A. Meat groups

Meat groups	Types of meats* included in the different meat groups
All meat	Bacon, ham, beef stew 24%, fried fish, fried chicken, hamburgers, hotdogs, lasagna 9%, liver, cold cuts, meatloaf, fish, chicken, pork roast, pork chops, beef roast, sausage, shellfish, pasta 9%, steak, tuna

(*Continued on the following page*)

Appendix A. Meat groups (Cont'd)

Meat groups	Types of meats* included in the different meat groups
Red meat	Bacon, ham, beef stew 24%, hamburgers, hotdogs, lasagna 9%, liver, cold cuts, meatloaf, pork roast, pork chops, beef roast, sausage, pasta 9%, steak
White meat	Fried chicken, other chicken, fried fish, tuna, shellfish, fish (not fried)
Red meat without doneness	Ham, beef stew 24%, hotdogs, lasagna 9%, liver, cold cuts, meatloaf, pork roast, beef roast, pasta 9%, steak
Red meat with doneness/cooking methods	Hamburgers, steak, sausage, bacon, pork chops
Doneness†	
Red meat rare/medium	Hamburgers rare, hamburgers medium, steak rare, steak medium, sausage just, bacon just
Red meat well-done	Hamburgers well-done, steak well-done, pork chops well-done and ham steaks, hotdog or sausage well-done, and bacon well-done/crisp and breakfast sausage
Cooking methods†	
Red meat grilled	Grilled hamburgers, steak, and pork chops
Red meat not grilled	Hamburgers, steak, sausage, bacon, pork chops not grilled
Red meat broiled	Broiled hamburgers, steak, pork chops
Red meat not broiled	Hamburgers, steak, broiled, sausage, bacon, and pork chops not broiled
Red meat fried	Pan-fried hamburgers, steak, sausage, bacon, pork chops
Red meat not pan-fried	Hamburger, steak, pork chop not pan-fried
Red processed meat	Ham, hotdogs, cold cuts, bacon, sausage, liver
Red not processed meat	Beef stew 24%,‡ lasagna 9%, pasta 9%, meatloaf, pork roast, beef roast, hamburger, pork, steak

*Questions on meat intake were obtained for hamburger/cheeseburger; beef meatloaf/burritos/tacos; steaks; roast beef; beef stew/potpie; hotdogs; lunch meats such as bologna/salami/processed ham; pork chops; pork roast; baked/cured ham; fried chicken; other chicken (roasted/stewed/broiled); liver; fried fish; Tuna/tuna salad/tuna casserole; shellfish (shrimp/crab/lobster); other fish (broiled/baked); bacon; sausage; and gravies made with meat drippings.
†For steaks and hamburger patties, we obtained information on cooking methods (pan-fried, oven broiled, and grilled/barbecued) and the typical level of doneness (rare, medium rare, medium, medium well, well, and very well-done). For pork chops we obtained information on cooking methods (baked, grilled/barbecued, fried, broiled), whereas for bacon and sausage we inquired about the doneness level (just until done, well-done or crisp, charred). Cooking methods (roasted/baked, grilled/barbecues, broiled, stewed/boiled) were obtained for chicken that was not fried.
‡The percentage of meat in mixed-meat dishes, such as lasagna, stew, and pasta, were obtained from the U.S. Department of Agriculture who use national survey data to estimate amount of individual food items in mixed foods.

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Meat, Meat Cooking Methods and Preservation, and Risk for Colorectal Adenoma

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