Meat and Meat-Mutagen Intake and Pancreatic Cancer Risk in the NIH-AARP Cohort

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Abstract

Meat intake, particularly red meat, has been positively associated with pancreatic cancer in some epidemiologic studies. Detailed meat-cooking methods and related mutagens formed in meat cooked at high temperatures have not been evaluated prospectively as risk factors for this malignancy. We investigated the association between meat, meat-cooking methods, meat-mutagen intake, and exocrine pancreatic cancer in the NIH-American Association of Retired Persons (NIH-AARP) Diet and Health Study cohort of 537,302 individuals, aged 50 to 71 years, with complete baseline dietary data (1995-1996) ascertained from a food frequency questionnaire. A meat-cooking module was completed by 332,913 individuals 6 months after baseline. During 5 years of follow-up, 836 incident pancreatic cancer cases (555 men, 281 women) were identified. Four hundred and fifty-nine cases had complete meat module data. We used Cox proportional hazard models to calculate hazard ratios (HR) and 95% confidence intervals (CI). Total, red, and high-temperature cooked meat intake was positively associated with pancreatic cancer among men (fifth versus first quintile: HR, 1.41, 95% CI, 1.08-1.83, *P* trend = 0.001; HR, 1.42, 95% CI, 1.05-1.91, *P* trend = 0.01; and HR, 1.52, 95% CI, 1.12-2.06, *P* trend = 0.005, respectively), but not women. Men showed significant 50% increased risks for the highest tertile of grilled/barbecued and broiled meat and significant doubling of risk for the highest quintile of overall meat-mutagenic activity (*P* trends < 0.01). The fifth quintile of the heterocyclic amine, 2-amino-3,4,8-trimethylimidazo[4,5-*f*]quinoxaline intake showed a significant 29% (*P* trend = 0.006) increased risk in men and women combined. These findings support the hypothesis that meat intake, particularly meat cooked at high temperatures and associated mutagens, may play a role in pancreatic cancer development. (Cancer Epidemiol Biomarkers Prev 2007;16(12):2664–75)

Introduction

Pancreatic cancer ranks fourth for cancer mortality for men and women in the United States and has a 5-year survival of <5% (1). The incidence of pancreatic cancer is higher in men compared with women and in blacks compared with whites (1). Of the few potentially modifiable risk factors that have been identified, cigarette smoking, history of diabetes mellitus, and obesity (1) seem to be among the most consistent, but the effect of dietary factors is unclear.

The association between meat intake and pancreatic cancer has been examined in both case control (2-22) and cohort (23-32) studies with positive (2-7, 9-12, 22-27), inverse (13-15, 28), and null (4, 5, 8, 14-21, 29, 32) associations reported for both study designs. The inconsistent results among case-control studies may partly be due to retrospective ascertainment of diet, which, given the rapid fatality of pancreatic cancer, may be fraught with biases, such as recall and proxy, and reverse causation. Furthermore, some of the cohort studies have <100 cases (23, 25) and may have limited power to observe associations. In addition, dietary assessment tools used to ascertain meat consumption have often lacked detailed questions about meat, meat-cooking methods, and doneness level, with only two case-control studies examining meat mutagens and pancreatic cancer risk (12, 22). These methodologic hindrances could lead to misclassification of the mutagenic potential of meat exposure and, hence, inaccurate risk estimates.

Biologically plausible pancreatic carcinogens that can be present in meats include heterocyclic amines (HCA), polycyclic aromatic hydrocarbons (PAH), and N-nitroso compounds (NOC). Formation of HCAs and PAHs depends on meat-cooking methods, temperature, and degree of doneness (33). Well-done grilled/barbecued and pan-fried meat contain high concentrations of these compounds, whereas stewed and microwaved meats do not (33). NOCs may be found in preserved, cured, and

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smoked meat, or endogenous formation may occur from the reaction of nitrosating agents, including nitrite in preserved meat, with amines or amides facilitated by gastrointestinal bacteria (34). Endogenous NOC formation seems to be dose-dependently related to red meat intake (34). Dietary fat and iron, both found in meat, may also be relevant to pancreatic carcinogenesis (26, 30, 34).

We conducted an analysis in a large cohort, the NIH-American Association of Retired Persons (NIH-AARP) Diet and Health Study, to investigate the association between meat intake, meat-cooking methods, and doneness, as well as meat-derived HCAs and benzo(*a*)pyrene [B(a)P], a marker of PAHs, and exocrine pancreatic cancer. In addition, we examined a meat-derived mutagenic activity index (revertants per gram of daily meat intake), a biological measure quantified using the Ames test (35), that integrates all classes of meat-related mutagens, both those that are known (e.g., HCA) and unknown (33), as a risk factor for pancreatic cancer. Our meat exposures were based on a unique meat questionnaire and mutagen database (33). Detailed meat-cooking methods and related meat mutagens have not been evaluated prospectively as risk factors for this malignancy. Given the size of the NIH-AARP cohort, we also have a large number of pancreatic cancer cases, which enabled us to examine sex-specific associations.

Materials and Methods

Study Population. The NIH-AARP Diet and Health Study is a large prospective study of AARP members established in 1995 to 1996. Details of the study's design have been described elsewhere (36). AARP members (617,119) aged 50 and 71 years, who resided in six U.S. states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, GA, and Detroit, MI) were mailed and returned a self-administered questionnaires eliciting information on demographic characteristics, dietary intake, and numerous health-related behaviors. The questionnaire was satisfactorily completed by 567,169 subjects (36). The study was approved by the National Cancer Institute Special Studies Institutional Review Board, and consent was implicit for all the participants who returned the questionnaires.

We excluded subjects with duplicate representation (n = 179), who moved out of the eight areas included in our study before returning the baseline questionnaire (n = 321), died before study entry (n = 261), or withdrew (n = 1). We further excluded subjects who had questionnaires completed by proxy respondents (n = 15,760), prevalent cancers as determined by the cancer registry data (n = 8,552) and with extreme energy intake outside the normal distribution of the cohort by sex, defined as more than two interquartile ranges above the 75th or below the 25th percentile on the logarithmic scale (n = 4,793). Our final analytic cohort consisted of 537,302 individuals (316,763 men, 220,539 women).

Dietary Assessment and Meat Variables. At baseline, study subjects completed a self-administered food frequency questionnaire (FFQ) that was a grid-based version of the National Cancer Institute instrument the Diet History Questionnaire and included questions on diet, demographic factors, medical history, and health-related behaviors (36). The questionnaire assessed the usual frequency of consumption and portion size of 124 food items and 21 questions on low-fat, high-fiber foods and food preparation over the previous 12 months (36). Among 1,415 persons who participated in a diet calibration sub-study within the NIH-AARP Study cohort, the de-attenuated correlations between red meat intake from the FFQ and two 24-h dietary recalls (administered an average of 25 days apart) were 0.62 and 0.70 for men and women, respectively (36).

Six months after the baseline questionnaire was sent, baseline respondents were sent a second FFQ that included a meat-cooking module (36) that 332,913 subjects completed (response rate = 63%). The meat-cooking module queried consumption of hamburgers, steak, bacon and chicken, usual cooking method (pan-fried; grilled or barbecued; oven-broiled; other such as sautéed, baked, or microwaved), and level of doneness on the outside (not browned, lightly browned, well-browned, black, or charred) and inside (for red meat: raw; rare to medium-rare or red-deep pink; medium to medium well or light pink; well-done or gray-brown with juice; very well-done or gray-brown dry; and for chicken: just until done or still juicy; well-done or somewhat dry; very well-done or very dry; ref. 33). A formal validation study for the meat-mutagen data has not been conducted within the NIH-AARP study cohort. The validity of the meat intake, meat-cooking methods, and doneness, as well as meat-derived mutagens, however, was assessed in a U.S. population of 165 healthy subjects who completed an FFQ that included the meat module and three sets of four nonconsecutive day diaries (37). Correlations were computed for intake between the two methods of dietary assessment (37). The relative validity of the meat module was similar to that of other nutrients and food quantified in FFQs (38, 39). For example, the de-attenuated correlations were 0.60 and 0.36 for 2-amino-3,4,8-trimethylimidazo[4,5-*f*]quinoxaline (DiMeIQx) and 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP), respectively (37).

We calculated meat intake in grams per day from the frequency and portion size information ascertained from the baseline FFQ. The total meat category included all types of beef, poultry, fish, pork, and processed meats. The red meat category included bacon, beef (including that added to complex food mixtures, such as pizza, chili, lasagna, stew), cold cuts, ham, hamburger, regular hotdogs, liver, pork, sausage, and steak. The white meat category included all forms of poultry (chicken, cold cuts, ground, turkey), fish (fresh, frozen, canned), and low-fat hotdogs and sausages, which are usually made from turkey. All types of cold cuts, bacon, ham, hotdogs, and sausages from red and white meats were included in the processed meat variable. Because the baseline questionnaire did not query cooking methods or doneness levels, we created a proxy variable for baseline meats generally cooked at high temperatures (e.g., fried or grilled), which included bacon, hamburger, steak, and sausage (40-42).

For meat intake estimated from the meat-cooking module, we calculated grams consumed per day and created meat variables according to cooking method and doneness level (raw/rare/medium and well/very well

done). In addition, we used the CHARRED database[7] to estimate daily intake of meat-mutagens, including the HCAs: DiMeIQx, 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (MeIQx), and PhIP, B(a)P, and an overall meat-mutagenic activity index (33). All meats queried on the meat-cooking module (i.e., hamburgers, steak, bacon, and chicken) were used to create these variables. Details about the methods used to create the CHARRED database are described elsewhere (33, 40-42). Briefly, the CHARRED database was developed using ~120 categories of meat samples prepared by different cooking methods with varying doneness levels and their composites analyzed for HCAs, B(a)P, and overall mutagenic activity (40-42). Mutagenic activity in meat was determined by the standard plate incorporation assay with *Salmonella typhimurium* strain TA98, measured as revertant colonies (i.e., Ames test; ref. 35).

Cohort Follow-up and Case Ascertainment. Cancer cases were identified by linking cohort members to state cancer registries and to the U.S. National Death Index between 1995 and 2000 and are estimated to be about 90% complete (43). Vital status of cohort participants was also ascertained by linkage to the Social Security Administration Death Master File. For this analysis, we included incident primary adenocarcinoma of the exocrine pancreas (ICD-O-3 code C250-C259). Eight hundred and thirty-six incident pancreatic cancer cases (555 men, 281 women) were identified, with 459 cases (291 men, 168 women) having complete meat-cooking module data. Our case definition excluded endocrine pancreatic tumors (histology type, 8150, 8151, 8153, 8155, 8240, 8246) because the etiology of these cancers is thought to be different.

Statistical Analysis. Generalized linear models were used to estimate the means within each red meat intake quintile for the continuous population characteristic variables shown in Table 1. For the categorical variables in Table 1, we show frequency proportions. Follow-up for this analysis was from the date of receipt of the baseline questionnaire through December 2000 or until death and represented up to 5 years of follow-up. Cox proportional hazard models, with age as the underlying time metric, was used to generate hazard ratios (HR) and 95% confidence intervals (95% CI). Entry time was defined as the subjects' age in days at return of the questionnaire, and exit time was defined as the subjects' age in days at cancer diagnosis or censoring. The meat and other dietary variables were energy adjusted using the density method, with energy included in the model, because most dietary variables were correlated with total energy (44). We created a compound smoking variable to control for confounding based on risk estimates from our data that integrated never, former including time since having quit smoking, and current smoking, as well as smoking dose (never, quit >10 years, quit 5 to 9 years ago; quit 1 to 4 years ago, quit <1 year ago, or current and smoked <20 or >20 cigarettes/day). The meat variables were categorized based on the cohort distribution and sex-specific distribution. Baseline meat and the meat module meat mutagens were categorized into quintiles. Cooking methods were categorized into tertiles due to the small intake range. Trend tests across categorical variables were calculated using a score variable based on the median values of each category. HRs for the baseline meat variables were additionally calculated among the subjects who completed the meat module to assess internal consistency with associations observed for the baseline cohort.

Our multivariable models were developed by individually entering potential confounding variables into the model. We show both a putative risk factor model and parsimonious best-fit model because important putative pancreatic risk factors [i.e., body mass index (BMI), diabetes, race] did not substantially influence our risk estimates. Variables remained in the model if they were associated with both the disease and exposure, changed the risk estimate 10%, or were putative risk factors for pancreatic cancer. Variables investigated and included in the multivariable model 1 were smoking, BMI (kg/m^2, <18.5, >18.5 and <25, >25 and <30, > 30 and <35, > 35, and missing), education (<11 years, 12 years or completed high school, post-high school or some college, college or postgraduate, and missing), race (Caucasian; Black; Hispanic; Asian, Pacific Islander, or American Indian/Alaskan Native; and missing), self-reported diabetes (yes, no), total caloric intake (kcal/day), and saturated fat intake (g/1,000 kcal/day). Only smoking history and energy-adjusted saturated fat intake (g/1,000 kcal/day) confounded the association between meat and pancreatic cancer and, based on changing the risk estimate 10% and evaluation of changes in −2 log likelihoods, were included in our most parsimonious model 2. Recreational (never/rarely, 1-3 per month; 1-2, 3-4, and >5 times per week, respectively; missing) or occupational (sedentary; sit/walk a fair amount; stand/walk a lot, no lifting; lift/carry light loads, climb stairs and hills; heavy labor; missing) physical activity; alcohol consumption (continuous); and energy-adjusted folate, protein, or total fat (continuous) intake were not confounders and, therefore, were not included in the final regression models. In addition, relevant meat groups and cooking methods were controlled simultaneously in our models (white and red; high-temperature and low-temperature cooked; processed and non-processed; rare/medium, well/very well-done, pan-fried; grilled/barbecued; oven-broiled; other such as sautéed, baked, or microwaved).

Interactions by sex and smoking status were evaluated by including cross-product terms in multivariable models for the meat quantile trend score variable with sex or smoking status (never or former smoker having quit >10 years ago and former having quit <10 years ago or current smoker) in full models and stratified analyses. The smoking interaction models were limited to subjects who had complete smoking data (baseline: men, 311,305, n = 547 cases; women, 216,742, n = 277 cases; meat module: men, 180,914, n = 288 cases; women, 131,681, n = 165 cases). The majority of subjects in our population were former smokers having quit >10 years ago, and a minority was current smokers. To provide an adequate number of cases in strata to evaluate smoking interactions by sex, for the recent smoker strata, we combined recent quitters (<10 years) with current smokers, and for

[7] http://charred.cancer.gov/

Table 1. Selected baseline characteristics of study participants by red meat category (n = 537,302)

Characteristics	Quintile of daily red meat (g/1,000 kcal)				
Men (n = 316,763)	≤19.0	>19.0 and ≤29.9	>29.9 and ≤40.5	>40.5 and ≤54.7	>54.7
Red meat (g/1,000 kcal)	12.0	24.7	35.1	46.7	66.9
Age (y)	62.8	62.7	62.4	62.1	61.5
BMI (kg/m^2)	26.1	26.9	27.3	27.7	28.4
Smoking history*					
Never (%)	34.1	30.4	28.9	27.6	25.6
Former smoker (%)	58.6	59.6	58.9	58.5	57.4
Quit ≥10 y ago (%)	47.9	47.0	45.6	44.3	41.8
Quit >1 or <10 y ago (%)	9.4	11.0	11.5	12.2	13.5
Current smoker or having quit <1 y ago (%)	6.8	9.9	12.2	14.2	17.4
Education, college graduate or postgraduate (%)	51.9	46.8	44.0	41.7	38.5
African American (%)	4.1	3.0	2.6	2.0	1.9
Non-Hispanic white (%)	89.2	92.3	93.4	94.3	94.0
Self-reported diabetes (%)	7.4	8.4	9.6	11.3	14.8
Heavy physical activity, ≥5 times per wk	29.3	22.7	19.9	18.2	16.0
Dietary intake					
Energy (kcal)	1,911	1,964	2,010	2,057	2,126
Total fat (g/1,000 kcal/day)	26.6	31.6	34.3	36.6	39.9
Saturated fat (g/1,000 kcal/day)	7.9	9.8	10.7	11.6	12.8
Alcohol (g/day)	20.6	19.3	16.7	14.8	12.2
Women (n = 220,539)	Quintile daily red meat (g/1,000 kcal)				
	≤13.0	>13.0 and ≤21.9	>21.9 and ≤31.1	>31.1 and ≤43.7	>43.7
Red meat (g/1,000 kcal)	7.8	17.5	26.3	36.5	54.7
Age (y)	62.2	62.2	62.1	61.8	61.4
BMI (kg/m^2)	25.4	26.4	26.9	27.4	28.2
Smoking history*					
Never (%)	46.2	45.1	44.4	43.1	41.1
Former smoker (%)	43.7	41.5	39.8	38.5	36.9
Quit ≥10 y ago (%)	31.9	28.5	26.6	24.4	22.5
Quit >1 or <10 y ago (%)	10.3	11.1	11.3	11.9	11.9
Current smoker or having quit <1 y ago (%)	9.8	13.6	16.1	18.9	22.8
Education, college graduate or postgraduate (%)	38.4	31.9	29.0	26.6	23.5
African American (%)	7.8	6.0	5.2	4.2	3.9
Non-Hispanic white (%)	85.6	89.1	90.5	91.6	91.5
Self-reported diabetes (%)	5.3	6.0	7.0	8.3	11.2
Heavy physical activity, ≥5 times per wk	23.9	17.5	15.0	12.9	11.3
Dietary intake					
Energy (kcal/day)	1,528	1,529	1,557	1,601	1,639
Total fat (g/1,000 kcal/day)	27.0	31.0	33.6	35.9	39.2
Saturated fat (g/1,000 kcal/day)	8.1	9.5	10.4	11.2	12.4
Alcohol (g/day)	5.5	6.4	6.3	5.9	5.3

NOTE: Generalized linear models were used to estimate mean values for the continuous variables and frequencies for dichotomous proportions within each red meat intake quintile.
*11,065 (3.5%) men and 6,756 (3.1%) women have missing smoking history data.

the nonsmoker strata, we combined groups of never and former smoker having quit >10 years ago. Former smoking having quit >10 years was not significantly associated with pancreatic cancer in our cohort. All statistical analysis was done using Statistical Analysis Systems (SAS, Inc.) software, and the P values for statistical tests were two tailed.

Results

For both men and women (Table 1), BMI; energy and total and saturated fat intake; and the proportion of subjects who quit smoking during the past 10 years, currently smoking, were non-Hispanic white ethnicity, or had a history of diabetes mellitus were directly related to greater red meat intake. In contrast, age; alcohol consumption; and the proportion of subjects who were never smokers, former smokers, and quit >10 years ago, being a college graduate or having postgraduate education, being African American, or with heavy physical activity >5 times per week were inversely associated with red meat intake.

We discuss the results from the most parsimonious multivariable models because they did not differ substantially from the models that adjusted for all putative pancreatic cancer risk factors (Table 2). High total meat intake was associated with a 26% (95% CI, 1.02-1.56; P trend = 0.004) increased pancreatic cancer risk for men and women combined in adjusted models. Compared with the lowest quintile, the highest quintiles of total, red, and high-temperature cooked meats showed significant 41%, 42%, and 52% increased pancreatic cancer risk in men, respectively, with trends across

Table 2. HRs and 95% CI for baseline meat intake (*n* = 836 cases; 555 male and 281 female cases)

Variable	Quintile of daily meat intake (g/1,000 kcal)					*P* trend*
	1	2	3	4	5	
Total meat						
Men	≤43.9	>43.9 and ≤59.1	>59.1 and ≤73.6	>73.6 and ≤93.3	>93.3	
Cases/person-years	102/281,153	96/281,929	101/282,193	119/282,062	137/281,979	
Age-adjusted HR (95% CI) †	1.00 (reference)	0.97 (0.73-1.28)	1.04 (0.79-1.38)	1.28 (0.99-1.67)	1.57 (1.21-2.03)	<0.0001
Multivariable 1 HR (95% CI) ‡	1.00 (reference)	0.92 (0.69-1.21)	0.97 (0.73-1.28)	1.16 (0.88-1.52)	1.35 (1.03-1.76)	0.004
Multivariable 2 HR (95% CI)§	1.00 (reference)	0.92 (0.70-1.22)	0.98 (0.74-1.29)	1.18 (0.91-1.55)	1.41 (1.08-1.83)	0.001
Women	≤38.2	>38.2 and ≤53.7	>53.7 and ≤68.9	>68.9 and ≤89.1	>89.1	
Cases/person-years	61/197,422	51/198,018	56/197,889	54/198,203	59/197,894	
Age-adjusted HR (95% CI) †	1.00 (reference)	0.85 (0.58-1.23)	0.95 (0.66-1.37)	0.93 (0.65-1.35)	1.06 (0.74-1.52)	0.56
Multivariable 1 HR (95% CI) ‡	1.00 (reference)	0.81 (0.56-1.18)	0.90 (0.63-1.30)	0.87 (0.60-1.26)	0.97 (0.68-1.40)	0.91
Multivariable 2 HR (95% CI)§	1.00 (reference)	0.82 (0.57-1.20)	0.92 (0.64-1.33)	0.90 (0.62-1.30)	1.02 (0.71-1.46)	0.72
Men and women combined‖	≤41.4	>41.5 and ≤56.9	>56.9 and ≤71.8	>71.8 and ≤91.7	>91.7	
Cases/person-years	160/478,996	148/479,891	154/479,985	175/480,185	199/479,684	
Multivariable 2 HR (95% CI)§	1.00 (reference)	0.89 (0.71-1.11)	0.93 (0.74-1.16)	1.07 (0.86-1.33)	1.26 (1.02-1.56)	0.004
Red meat						
Men	≤19.0	>19.0 and ≤29.9	>29.9 and ≤40.5	>40.5 and ≤54.7	>54.7	
Cases/person-years	89/282,269	108/282,172	97/281,797	114/281,838	147/281,239	
Age-adjusted HR (95% CI) †	1.00 (reference)	1.23 (0.93-1.63)	1.14 (0.85-1.52)	1.37 (1.04-1.81)	1.87 (1.43-2.44)	<0.0001
Multivariable 1 HR (95% CI) ‡	1.00 (reference)	1.10 (0.83-1.47)	0.96 (0.71-1.30)	1.09 (0.81-1.47)	1.36 (1.00-1.84)	0.03
Multivariable 2 HR (95% CI)§	1.00 (reference)	1.11 (0.83-1.48)	0.97 (0.72-1.32)	1.12 (0.83-1.50)	1.42 (1.05-1.91)	0.01
Women	≤13.0	>13.0 and 21.9	>21.9 and ≤31.1	>31.1 and ≤43.7	>43.7	
Cases/person-years	60/198,061	52/198,166	59/198,099	63/197,674	47/197,426	
Age-adjusted HR (95% CI) †	1.00 (reference)	0.87 (0.60-1.25)	0.99 (0.69-1.43)	1.09 (0.76-1.56)	0.85 (0.58-1.25)	0.71
Multivariable 1 HR (95% CI) ‡	1.00 (reference)	0.80 (0.55-1.16)	0.87 (0.60-1.27)	0.91 (0.62-1.33)	0.66 (0.43-1.01)	0.12
Multivariable 2 HR (95% CI)§	1.00 (reference)	0.81 (0.55-1.17)	0.89 (0.61-1.29)	0.93 (0.64-1.36)	0.69 (0.45-1.05)	0.17
Men and women combined‖	≤16.1	>16.1 and ≤26.3	>26.3 and ≤36.6	>36.6 and ≤50.5	>50.5	
Cases/person-years	147/481,053	157/480,605	154/479,753	180/479,119	198/478,213	
Multivariable 2 HR (95% CI)§	1.00 (reference)	0.96 (0.76-1.21)	0.89 (0.71-1.13)	1.00 (0.79-1.27)	1.06 (0.83-1.35)	0.39
White meat						
Men	≤13.7	>13.7 and ≤21.8	>21.8 and ≤31.3	>31.3 and ≤46.2	>46.2	
Cases/person-years	114/280,417	121/281,337	98/282,250	119/282,377	103/282,935	
Age-adjusted HR (95% CI) †	1.00 (reference)	1.05 (0.81-1.36)	0.86 (0.65-1.12)	1.07 (0.83-1.38)	1.00 (0.76-1.30)	0.92
Multivariable 1 HR (95% CI) ‡	1.00 (reference)	1.12 (0.86-1.44)	0.93 (0.71-1.23)	1.20 (0.92-1.55)	1.11 (0.85-1.47)	0.36
Multivariable 2 HR (95% CI)§	1.00 (reference)	1.12 (0.86-1.44)	0.94 (0.71-1.23)	1.21 (0.93-1.57)	1.14 (0.87-1.50)	0.35
Women	≤15.0	>15.0 and ≤24.2	>24.2 and ≤35.0	>35.0 and ≤52.3	>52.3	
Cases/person-years	51/196,961	67/198,015	47/197,954	53/198,039	63/198,456	
Age-adjusted HR (95% CI) †	1.00 (reference)	1.32 (0.91-1.90)	0.94 (0.63-1.40)	1.08 (0.73-1.59)	1.30 (0.90-1.89)	0.32
Multivariable 1 HR (95% CI) ‡	1.00 (reference)	1.35 (0.93-1.95)	0.98 (0.66-1.47)	1.15 (0.78-1.69)	1.37 (0.94-1.99)	0.27
Multivariable 2 HR (95% CI)§	1.00 (reference)	1.36 (0.94-1.97)	0.99 (0.67-1.48)	1.17 (0.79-1.72)	1.41 (0.97-2.05)	0.15
Men and women combined‖	≤14.2	>14.2 and ≤22.7	>22.7 and ≤32.8	>32.8 and ≤48.7	>48.7	
Cases/person-years	168/477,253	182/479,212	153/480,191	173/480,506	160/481,579	
Multivariable 2 HR (95% CI)§	1.00 (reference)	1.14 (0.92-1.40)	1.00 (0.80-1.25)	1.20 (0.97-1.49)	1.20 (0.96-1.49)	0.10
Processed meat						
Men	≤4.0	>4.0 and ≤7.2	>7.2 and ≤11.4	>11.4 and ≤18.2	>18.4	
Cases/person-years	89/281,920	112/282,237	106/281,893	131/281,944	117/281,321	
Age-adjusted HR (95% CI) †	1.00 (reference)	1.26 (0.95-1.67)	1.18 (0.89-1.58)	1.43 (1.09-1.89)	1.29 (0.97-1.71)	0.13
Multivariable 1 HR (95% CI) ‡	1.00 (reference)	1.14 (0.86-1.52)	1.02 (0.76-1.37)	1.19 (0.90-1.59)	1.01 (0.76-1.36)	0.81
Multivariable 2 HR (95% CI)§	1.00 (reference)	1.15 (0.87-1.53)	1.04 (0.78-1.39)	1.23 (0.93-1.63)	1.07 (0.80-1.43)	0.84
Women	≤2.2	>2.2 and ≤4.4	>4.4 and ≤7.3	>7.3 and ≤12.5	>12.5	
Cases/person-years	52/198,031	52/198,156	73/197,968	59/197,975	45/197,296	
Age-adjusted HR (95% CI) †	1.00 (reference)	1.02 (0.69-1.50)	1.44 (1.00-2.07)	1.16 (0.79-1.70)	0.86 (0.57-1.30)	0.24
Multivariable 1 HR (95% CI) ‡	1.00 (reference)	0.96 (0.65-1.41)	1.31 (0.91-1.90)	1.02 (0.69-1.52)	0.73 (0.48-1.12)	0.05
Multivariable 2 HR (95% CI)§	1.00 (reference)	0.97 (0.66-1.44)	1.35 (0.93-1.95)	1.07 (0.72-1.58)	0.78 (0.48-1.12)	0.09
Men and women combined‖	≤3.0	>3.0 and ≤5.9	>5.9 and ≤9.6	>9.6 and ≤16.0	>16.0	
Cases/person-years	135/480,678	171/480,466	171/480,044	189/479,434	170/478,120	
Multivariable 2 HR (95% CI)§	1.00 (reference)	1.16 (0.92-1.46)	1.09 (0.86-1.38)	1.13 (0.90-1.43)	0.97 (0.76-1.23)	0.26
Meat cooked at high temperatures						
Men	≤5.7	>5.7 and ≤10.4	>10.4 and ≤15.8	>15.8 and ≤24.0	>24.0	
Cases/person-years	82/282,441	93/282,186	119/281,747	122/281,565	139/281,377	
Age-adjusted HR (95% CI) †	1.00 (reference)	1.17 (0.87-1.58)	1.55 (1.16-2.06)	1.62 (1.22-2.16)	1.94 (1.47-2.57)	<0.0001
Multivariable 1 HR (95% CI) ‡	1.00 (reference)	1.07 (0.79-1.44)	1.33 (0.99-1.79)	1.34 (0.99-1.80)	1.49 (1.10-2.03)	0.008
Multivariable 2 HR (95% CI)§	1.00 (reference)	1.07 (0.79-1.45)	1.34 (1.00-1.80)	1.35 (1.00-1.82)	1.52 (1.12-2.06)	0.005
Women	≤3.5	>3.5 and ≤7.0	>7.0 and ≤11.2	>11.2 and ≤18.0	>18.0	
Cases/person-years	62/197,991	54/198,277	65/198,031	43/197,843	57/197,283	
Age-adjusted HR (95% CI) †	1.00 (reference)	0.88 (0.61-1.28)	1.09 (0.77-1.55)	0.74 (0.50-1.10)	1.03 (0.71-1.49)	0.90
Multivariable 1 HR (95% CI) ‡	1.00 (reference)	0.82 (0.56-1.19)	0.97 (0.68-1.40)	0.63 (0.42-0.96)	0.83 (0.56-1.25)	0.29

(*Continued on the following page*)

Table 2. HRs and 95% CI for baseline meat intake (*n* = 836 cases; 555 male and 281 female cases) (Cont'd)

Variable	Quintile of daily meat intake (g/1,000 kcal)					*P* trend*
	1	2	3	4	5	
Multivariable 2 HR (95% CI)§	1.00 (reference)	0.83 (0.57-1.20)	0.99 (0.69-1.42)	0.65 (0.43-0.98)	0.86 (0.58-1.28)	0.36
Men and women combined‖	≤4.6	>4.6 and ≤8.9	>8.9 and ≤13.8	>13.8 and ≤21.7	>21.7	
Cases/person-years	145/480,964	136/480,798	168/479,735	189/479,043	198/478,202	
Multivariable 2 HR (95% CI)§	1.00 (reference)	0.87 (0.68-1.10)	1.03 (0.82-1.30)	1.13 (0.89-1.42)	1.15 (0.90-1.47)	0.07

NOTE: Baseline cohort: *n* = 836 cases, *n* = 537,302 cohort subjects; 555 male cases, 316,763 male cohort subjects; 281 female cases; 220,539 female cohort subjects.

**P* trend calculated using median values for each quantile.

† Cox proportional hazard models used to calculate hazard ratios. All models should be considered adjusted for age because age is the time metric. All meats are adjusted for energy by the density method (g/1,000 kcal) with energy additionally in the model and relevant meat groups adjusted simultaneously for each other (i.e., white and red; processed and nonprocessed, high-temperature and low-temperature cooked).

‡ Models additionally adjusted for smoking (never, quit ≥10 y, quit 5 to 9 y ago; quit 1 to 4 y ago, quit <1 y ago or current and smoked ≤20 or >20 cigarettes/day; and missing), BMI (kg/m^2, <18.5, ≥18.5 and <25, ≥25 and <30, ≥30 and <35, ≥35, and missing), education (≤11 y, 12 y, or completed high school, post-high school or some college, college or postgraduate, and missing), race (Caucasian; Black; Hispanic; Asian, Pacific Islander or American Indian/Alaskan Native; and missing), self-reported diabetes (yes, no), and energy-adjusted saturated fat (continuous).

§ Most parsimonious model adjusted for smoking (never, quit ≥10 y, quit 5 to 9 y ago; quit 1 to 4 y ago, quit <1 y ago or current and smoked ≤20 or >20 cigarettes/day; and missing), and energy-adjusted saturated fat (continuous).

‖ Sex combined models additionally adjusted for sex. *P* value for interaction by sex: total meat = 0.08, red meat = 0.009, white meat = 0.89, processed meat = 0.21, and high-temperature cooked meat = 0.03.

quintiles (*P* trends < 0.01), but not in women. The interactions for red and high-temperature cooked meat by sex were significant (*P* interaction = 0.01 and 0.03, respectively); therefore, we show sex-stratified results. No significant associations were observed for white or processed meat; however, among women, higher white meat intake tended to be associated with greater risk (fifth compared with first quintile, HR, 1.41; 95% CI, 0.97-2.05; *P* trend = 0.15). Individual meat sources were not significantly associated with pancreatic cancer.

In sex-stratified analyses, men with the highest compared with those with the lowest intake of meat that was grilled/barbecued and oven broiled had significant 48% and 47% increased pancreatic cancer risk, respectively (Table 3). The interaction for grilled/barbecued cooked meat by sex was significant (*P* interaction = 0.01). No associations were observed for pan-fried or sautéed, baked, or microwaved meat among men or any of the meat-cooking methods among the women. Meat with known doneness levels were not significantly associated with pancreatic cancer except among men, where high intake of well/very well done meat showed a borderline significant 37% increased risk. The subset of subjects who completed the meat module showed similar patterns of pancreatic cancer risk for total, red, white, processed, and high-temperature cooked meat and sex interactions as that observed in the baseline cohort.

Among men, meat-mutagenic activity intake was significantly associated with pancreatic cancer, with the second to fifth quintiles having 1.8- to 2.3-fold risks compared with the lowest quintile (Table 4) and with a trend across quintiles (*P* trend = 0.001). DiMeIQx in both sexes and PhIP among men showed patterns of association for pancreatic cancer risk such that elevated risk is only observed in the highest compared with the lowest quintile. The highest DiMeIQx quintile showed positive associations for both sexes and a significant 29% increased pancreatic cancer risk with a trend (*P* trend = 0.006) among men and women combined. Compared with the lowest, the highest PhIP quintile showed a nonsignificant 38% increased pancreatic cancer risk among men. Significant associations were not observed for MeIQx or B(a)P in either men or women nor PhIP or mutagenic activity among women.

The other meat variable pancreatic cancer associations (total, white, and processed meats; cooking methods; or meat-derived mutagens) were not significantly modified by sex. There were no significant interactions of any of the meat variables and pancreatic cancer by smoking status (*P* interaction >0.20), except men who were never or former smokers having quit >10 years, which showed a stronger significant positive PhIP association (fifth quintile, HR, 1.65; 95% CI, 1.07-2.52; *P* trend = 0.001; *P* interaction = 0.12, data not shown).

Discussion

In this large prospective cohort of AARP members, high total and red meat intake were significantly associated with increased pancreatic cancer risk among men, but not women. In particular, men showed increased risks with greater intake of high-temperature, grilled/barbecued, and broiled meat, as well as meat-derived overall mutagenic activity and PhIP. High intake of meat-derived DiMeIQx showed a modest increased risk with a significant trend across quintiles in men and women combined. The associations that we observe are independent of saturated fat intake, smoking, and other potential confounders.

Of the 10 cohort studies that have examined consumption of various meats in association with exocrine pancreatic cancer (23-32), five showed significant or borderline significant positive associations for total or red (beef, pork, or lamb) meat, with risks ranging from 1.4 to 3.0 (24-27). Some previous studies were limited by small case numbers (23, 25), lack of detailed meat intake data (23-25, 28, 29), or too narrow a range in meat intake (30) to observe associations. The red meat and pancreatic cancer association observed among the NIH-AARP Diet and Health Study men is similar to the results of two recent cohort studies (26, 27). An analysis in Swedish women (*n* = 172 cases) showed that high red meat intake, measured by the average intake at two time points

Table 3. HRs and 95% CI for meat-cooking methods and doneness levels (*n* = 459 cases; 291 male and 168 female cases)

Variable	Tertile of daily meat intake (g/1,000 kcal)			*P* trend*
	1	2	3	
Grilled or barbecued meat †				
Men	≤2.9	>2.9 and ≤10.2	>10.2	
Cases/person-years	88/274,824	91/275,288	112/275,338	
Age-adjusted HR (95% CI) ‡	1.00 (reference)	1.18 (0.87-1.59)	1.67 (1.23-2.27)	0.001
Multivariable 1 HR (95% CI)§	1.00 (reference)	1.10 (0.82-1.49)	1.46 (1.06-2.00)	0.02
Multivariable 2 HR (95% CI)‖	1.00 (reference)	1.12 (0.83-1.51)	1.48 (1.08-2.02)	0.01
Women	≤1.4	>1.4 and ≤6.1	>6.1	
Cases/person-years	73/201,499	44/201,833	51/201,731	
Age-adjusted HR (95% CI) ‡	1.00 (reference)	0.60 (0.41-0.88)	0.69 (0.46-1.02)	0.13
Multivariable 1 HR (95% CI)§	1.00 (reference)	0.59 (0.40-0.86)	0.65 (0.43-0.97)	0.09
Multivariable 2 HR (95% CI)‖	1.00 (reference)	0.59 (0.41-0.87)	0.67 (0.45-1.00)	0.11
Men and women combined¶	≤2.1	>2.1 and ≤8.4	>8.4	
Cases/person-years	162/476,600	126/477,040	171/476,873	
Multivariable 2 HR (95% CI)‖	1.00 (reference)	0.81 (0.64-1.03)	1.13 (0.88-1.44)	0.19
Pan-fried meat †				
Men	0	>0 and ≤0.5	>0.5	
Cases/person-years	101/286,998	86/263,938	104/274,513	
Age-adjusted HR (95% CI) ‡	1.00 (reference)	1.01 (0.75-1.37)	1.19 (0.90-1.59)	0.23
Multivariable 1 HR (95% CI)§	1.00 (reference)	0.97 (0.71-1.32)	0.96 (0.71-1.31)	0.76
Multivariable 2 HR (95% CI)‖	1.00 (reference)	0.97 (0.71-1.31)	0.98 (0.72-1.32)	0.76
Women	0	>0 and ≤0.4	>0.4	
Cases/person-years	68/242,316	39/161,346	61/201,402	
Age-adjusted HR (95% CI) ‡	1.00 (reference)	0.94 (0.63-1.40)	1.03 (0.72-1.48)	0.65
Multivariable 1 HR (95% CI)§	1.00 (reference)	0.91 (0.61-1.35)	0.91 (0.63-1.33)	0.86
Multivariable 2 HR (95% CI)‖	1.00 (reference)	0.91 (0.61-1.35)	0.92 (0.63-1.33)	0.89
Men and women combined¶	0	>0 and ≤0.5	>0.5	
Cases/person-years	169/529,314	117/425,445	173/475,755	
Multivariable 2 HR (95% CI)‖	1.00 (reference)	0.90 (0.70-1.14)	1.00 (0.80-1.27)	0.63
Oven-broiled meat †				
Men	0	>0 and ≤1.5	>1.5	
Cases/person-years	152/488,478	20/61,780	119/275,192	
Age-adjusted HR (95% CI) ‡	1.00 (reference)	1.12 (0.70-1.80)	1.53 (1.18-1.99)	0.002
Multivariable 1 HR (95% CI)§	1.00 (reference)	1.07 (0.67-1.72)	1.45 (1.12-1.89)	0.006
Multivariable 2 HR (95% CI)‖	1.00 (reference)	1.08 (0.67-1.73)	1.47 (1.13-1.92)	0.004
Women	0	>0 and ≤0.7	>0.7	
Cases/person-years	104/385,000	9/18,282	55/201,781	
Age-adjusted HR (95% CI) ‡	1.00 (reference)	1.66 (0.83-3.30)	0.85 (0.60-1.21)	0.35
Multivariable 1 HR (95% CI)§	1.00 (reference)	1.57 (0.79-3.13)	0.81 (0.57-1.15)	0.24
Multivariable 2 HR (95% CI)‖	1.00 (reference)	1.58 (0.79-3.14)	0.82 (0.58-1.17)	0.28
Men and women combined¶	0	>0 and ≤1.1	>1.1	
Cases/person-years	256/873,477	27/80,265	176/476,771	
Multivariable 2 HR (95% CI)‖	1.00 (reference)	1.12 (0.75-1.67)	1.21 (0.98-1.49)	0.07
Sautéed, baked or microwaved meat †				
Men	0	>0 and ≤1.2	>1.2	
Cases/person-years	141/418,526	50/131,647	100/275,276	
Age-adjusted HR (95% CI) ‡	1.00 (reference)	1.17 (0.83-1.65)	1.22 (0.93-1.61)	0.24
Multivariable 1 HR (95% CI)§	1.00 (reference)	1.09 (0.77-1.54)	1.16 (0.88-1.53)	0.36
Multivariable 2 HR (95% CI)‖	1.00 (reference)	1.10 (0.78-1.55)	1.16 (0.88-1.53)	0.35
Women	0	>0 and ≤4.0	>4.0	
Cases/person-years	57/203,377	58/199,799	53/201,887	
Age-adjusted HR (95% CI) ‡	1.00 (reference)	0.95 (0.65-1.38)	0.81 (0.54-1.21)	0.27
Multivariable 1 HR (95% CI)§	1.00 (reference)	0.90 (0.62-1.32)	0.79 (0.53-1.18)	0.27
Multivariable 2 HR (95% CI)‖	1.00 (reference)	0.91 (0.63-1.34)	0.81 (0.54-1.20)	0.31
Men and women combined¶	0	>0 and ≤2.3	>2.3	
Cases/person-years	198/621,903	113/331,095	148/477,515	
Multivariable 2 HR (95% CI)‖	1.00 (reference)	1.04 (0.82-1.33)	1.05 (0.83-1.31)	0.79
Rare/medium done cooked meat**				
Men	≤1.26	>1.26 and ≤9.1	>9.1	
Cases/person-years	94/275,342	84/275,052	113/275,055	
Age-adjusted HR (95% CI) ‡	1.00 (reference)	0.98 (0.72-1.33)	1.46 (1.07-1.99)	0.01
Multivariable 1 HR (95% CI)§	1.00 (reference)	0.95 (0.71-1.31)	1.32 (0.96-1.80)	0.06
Multivariable 2 HR (95% CI)‖	1.00 (reference)	0.94 (0.69-1.27)	1.30 (0.95-1.78)	0.07
Women	≤0.7	>0.7 and ≤7.0	>7.0	
Cases/person-years	61/201,899	58/201,743	49/201,421	
Age-adjusted HR (95% CI) ‡	1.00 (reference)	0.93 (0.64-1.35)	0.72 (0.47-1.11)	0.23

(*Continued on the following page*)

Table 3. HRs and 95% CI for meat-cooking methods and doneness levels (*n* = 459 cases; 291 male and 168 female cases) (Cont'd)

Variable	Tertile of daily meat intake (g/1,000 kcal)			*P* trend*
	1	2	3	
Multivariable 1 HR (95% CI)§	1.00 (reference)	0.92 (0.63-1.34)	0.69 (0.45-1.07)	0.17
Multivariable 2 HR (95% CI)‖	1.00 (reference)	0.92 (0.64-1.33)	0.70 (0.45-1.08)	0.19
Men and women combined¶	≤1.0	>1.0 and ≤8.2	>8.2	
Cases/person-years	154/477,388	142/476,755	163/476, 370	
Multivariable 2 HR (95% CI)‖	1.00 (reference)	0.94 (0.74-1.19)	1.07 (0.83-1.38)	0.48
Well/very well-done cooked meat**				
Men	≤2.7	>2.7 and ≤9.7	>9.7	
Cases/person-years	84/274,926	100/275,178	107/275,346	
Age-adjusted HR (95% CI) ‡	1.00 (reference)	1.31 (0.97-1.77)	1.48 (1.08-2.03)	0.02
Multivariable 1 HR (95% CI)§	1.00 (reference)	1.22 (0.90-1.65)	1.33 (0.97-1.84)	0.09
Multivariable 2 HR (95% CI)‖	1.00 (reference)	1.24 (0.92-1.68)	1.37 (1.00-1.89)	0.06
Women	≤2.5	>2.5 and ≤9.4	>9.4	
Cases/person-years	60/201,446	48/201,527	60/202,091	
Age-adjusted HR (95% CI) ‡	1.00 (reference)	0.70 (0.47-1.05)	0.84 (0.56-1.26)	0.69
Multivariable 1 HR (95% CI)§	1.00 (reference)	0.67 (0.45-1.00)	0.80 (0.53-1.21)	0.58
Multivariable 2 HR (95% CI)‖	1.00 (reference)	0.68 (0.45-1.01)	0.82 (0.55-1.22)	0.68
Men and women combined¶	≤2.6	>2.6 and ≤9.6	>9.6	
Cases/person-years	142/476,386	150/476,706	167/477,421	
Multivariable 2 HR (95% CI)‖	1.00 (reference)	1.04 (0.82-1.32)	1.17 (0.91-1.51)	0.18

NOTE: Cohort that completed the meat-cooking module: *n* = 459 cases, *n* = 317,371 cohort subjects; 291 male cases, 183,650 male cohort subjects; 168 female cases; 133,721 female cohort subjects.

P trend calculated using median values for each quantile.

† Meat-cooking method.

‡ Cox proportional hazard models used to calculate hazard ratios. All models should be considered adjusted for age because age is the time metric. All nutrients are adjusted for energy by the density method with energy additionally in the model and relevant meat groups adjusted simultaneously for each other (i.e., rare/medium and well-done/very well-done, pan-fried, grilled/barbecued, oven broiled, and sautéed, baked, or microwaved).

§Models additionally adjusted for smoking (never, quit ≥10 y, quit 5 to 9 y ago; quit 1 to 4 y ago, quit <1 y ago or current and smoked ≤20 or >20 cigarettes/day; and missing), BMI (kg/m^2, <18.5, ≥18.5 and <25, ≥25 and <30, ≥30 and <35, ≥35, and missing), education (≤11 y, 12 y, or completed high school, post-high school or some college, college or postgraduate, and missing), race (Caucasian; Black; Hispanic; Asian, Pacific Islander, or American Indian/Alaskan Native; and missing), self-reported diabetes (yes, no), and energy-adjusted saturated fat (continuous).

‖Most parsimonious model adjusted for smoking (never, quit ≥10 y, quit 5 to 9 y ago; quit 1 to 4 y ago, quit <1 y ago or current and smoked ≤20 or >20 cigarettes/day; and missing), and energy-adjusted saturated fat (continuous).

¶Sex combined models additionally adjusted for sex. *P* value for interaction by sex: grilled or barbecued = 0.009, pan-fried = 0.94, oven-broiled = 0.17, sautéed, baked, or microwaved = 0.66, rare/medium = 0.11, and well/very well-done = 0.46.

**Meat doneness level.

(1987-1990 and 1997), was associated with a borderline significant 1.7-fold pancreatic cancer risk compared with those with low intake, and subjects reporting high red meat intake at both times, a significant 2.6-fold pancreatic cancer risk (27). The Multiethnic Cohort Study, which has a substantial number of pancreatic cancer cases (*n* = 482), reported significant 45% and 68% increased risks in the highest compared with the lowest intake of red and processed meat, respectively (26).

Meat-cooking methods and pancreatic cancer risk has been evaluated in one cohort study that reported no associations (30) and eight case-control studies (2, 3, 8, 9, 12, 13, 19, 22), five of which showed greater pancreatic cancer risk for fried or grilled/barbecued meats, with odds ratios ranging from 2.2 to 16.7 (3, 8, 9, 12, 22). Two recent pancreatic cancer case-control studies have employed a meat-cooking module and mutagen database similar to that used in our study. The first was a population-based case-control study (193 cases) that showed a significant 2-fold pancreatic cancer risk with higher consumption of grilled/barbecued red meat; however, other meat preparation methods did not have significant associations (12). This previous study also reported that the highest quintiles of meat-derived PhIP, DiMeIQx, B(a)P, and mutagenic activity intake were significantly associated with risks ranging from 1.8 to 2.4 (45). These associations, except that for B(a)P, are consistent with the associations that we observed for grilled/barbecued meat and meat-derived mutagenic activity and PhIP in men and for DiMeIQx in both sexes. The second study, a large hospital-based case control (*n* = 626 cases), similar to our study, showed an overall significant 52% increased pancreatic cancer risk for the highest compared with the lowest DiMeIQx intake quintile (*P* trend = 0.02); however, when 60th percentile mutagen intake based on the distribution of the controls was used as the cut-point for comparison, all meat mutagens except PhIP show significant elevated risks ranging from 1.4 to 1.5 (22). These studies show patterns of risk between the meat-related mutagens and pancreatic cancer, similar to the associations that we observe in the NIH-AARP Diet and Health Study for DiMeiQx in both sexes and PhIP among men, such that positive risk is only observed in the highest quintile of intake (22, 45). Most populations consume cooking-related meat mutagens at very low concentrations with skewed distributions such that few have high intake at which genotoxic and carcinogenic effects may occur and subsequent risk is observed. Biological thresholds are often observed with food-related genotoxic carcinogens (46), such that no adverse effect is observed unless an upper limit of exposure is exceeded (47). Our results, along with those

Table 4. HRs and 95% CI for meat mutagens and mutagenic activity index intake (*n* = 459 cases; 291 male and 168 female cases)

Variable	Quintile of daily meat mutagen intake					*P* trend*
	1	2	3	4	5	
Overall mutagenic activity (revertant colonies/1,000 kcal)						
Men	≤290	>490 and ≤1,013	>1,013 and ≤1,723	>1,723 and ≤3,077	>3,077	
Cases/person-years	31/165,002	61/165,036	59/165,077	65/165,001	75/165,335	
Age-adjusted HR (95% CI) †	1.00 (reference)	2.02 (1.31-3.11)	2.02 (1.31-3.12)	2.30 (1.50-3.53)	2.74 (1.80-4.17)	<0.0001
Multivariable 1 HR (95% CI) ‡	1.00 (reference)	1.78 (1.15-2.75)	1.72 (1.11-2.67)	1.89 (1.23-2.93)	2.20 (1.43-3.38)	0.003
Multivariable 2 HR (95% CI)§	1.00 (reference)	1.83 (1.18-2.82)	1.78 (1.15-2.76)	1.98 (1.28-3.05)	2.32 (1.52-3.56)	0.001
Women	≤260	>260 and ≤647	>647 and ≤1,239	>1,239 and ≤2,429	>2,429	
Cases/person-years	40/120,947	34/120,978	31/120,693	24/121,266	39/121,179	
Age-adjusted HR (95% CI) †	1.00 (reference)	0.87 (0.55-1.37)	0.81 (0.51-1.30)	0.64 (0.39-1.07)	1.08 (0.70-1.69)	0.52
Multivariable 1 HR (95% CI) ‡	1.00 (reference)	0.80 (0.50-1.27)	0.72 (0.45-1.16)	0.56 (0.33-0.94)	0.93 (0.59-1.48)	0.82
Multivariable 2 HR (95% CI)§	1.00 (reference)	0.81 (0.51-1.29)	0.74 (0.46-1.20)	0.58 (0.35-0.97)	0.99 (0.63-1.55)	0.69
Men and women combined‖	≤373	>373 and ≤850	>850 and ≤1,524	>1,524 and ≤2,818	>2,817	
Cases/person-years	75/286,140	81/285,998	94/285,927	98/286,095	111/286,353	
Multivariable 2 HR (95% CI)§	1.00 (reference)	0.99 (0.72-1.36)	1.14 (0.83-1.55)	1.20 (0.88-1.63)	1.39 (1.03-1.88)	0.01
DiMeIQx (ng/1,000 kcal)						
Men	0	>0 and ≤0.07	>0.07 and ≤0.40	>0.40 and ≤1.07	>1.07	
Cases/person-years	99/290,943	12/39,120	42/165,126	65/165,092	73/165,168	
Age-adjusted HR (95% CI) †	1.00 (reference)	0.88 (0.48-1.60)	0.73 (0.51-1.05)	1.17 (0.85-1.60)	1.36 (1.01-1.84)	0.006
Multivariable 1 HR (95% CI) ‡	1.00 (reference)	0.90 (0.49-1.64)	0.74 (0.51-1.05)	1.09 (0.80-1.50)	1.21 (0.89-1.64)	0.07
Multivariable 2 HR (95% CI)§	1.00 (reference)	0.89 (0.49-1.63)	0.74 (0.52-1.06)	1.12 (0.82-1.53)	1.25 (0.92-1.69)	0.04
Women	0	>0 and ≤0.05	>0.05 and ≤0.30	>0.30 and ≤0.83	>0.83	
Cases/person-years	62/226,766	5/15,147	30/121,086	27/120,907	44/121,158	
Age-adjusted HR (95% CI) †	1.00 (reference)	1.21 (0.49-3.00)	0.89 (0.57-1.37)	0.82 (0.52-1.29)	1.39 (0.94-2.04)	0.06
Multivariable 1 HR (95% CI) ‡	1.00 (reference)	1.10 (0.44-2.76)	0.88 (0.57-1.36)	0.79 (0.50-1.24)	1.30 (0.88-1.92)	0.12
Multivariable 2 HR (95% CI)§	1.00 (reference)	1.10 (0.44-2.74)	0.88 (0.57-1.36)	0.80 (0.51-1.26)	1.33 (0.90-1.96)	0.09
Men and women combined‖	0	>0 and ≤0.06	>0.06 and ≤0.35	>0.35 and ≤0.97	>0.97	
Cases/person-years	161/517,709	17/54,379	70/286,256	92/285,930	119/286,239	
Multivariable 2 HR (95% CI)§	1.00 (reference)	0.97 (0.59-1.60)	0.78 (0.59-1.04)	0.99 (0.77-1.28)	1.29 (1.01-1.64)	0.006
MeIQx (ng/1,000 kcal)						
Men	≤1.7	>1.7 and ≤4.2	>4.2 and ≤8.3	>8.3 and ≤16.5	>16.5	
Cases/person-years	45/165,040	49/165,268	57/165,262	69/165,005	71/164,874	
Age-adjusted HR (95% CI) †	1.00 (reference)	1.11 (0.74-1.67)	1.31 (0.89-1.94)	1.62 (1.11-2.36)	1.72 (1.18-2.49)	0.002
Multivariable 1 HR (95% CI) ‡	1.00 (reference)	1.03 (0.69-1.55)	1.13 (0.76-1.68)	1.33 (0.91-1.95)	1.28 (0.87-1.89)	0.17
Multivariable 2 HR (95% CI)§	1.00 (reference)	1.05 (0.70-1.58)	1.17 (0.79-1.73)	1.38 (0.94-2.02)	1.35 (0.92-2.02)	0.09
Women	≤1.1	>1.1 and ≤3.0	>3.0 and ≤6.2	>6.2 and ≤12.7	>12.7	
Cases/person-years	36/120,986	32/120,986	37/121,107	26/120,792	37/121,192	
Age-adjusted HR (95% CI) †	1.00 (reference)	0.91 (0.56-1.46)	1.06 (0.67-1.68)	0.76 (0.46-1.25)	1.10 (0.69-1.74)	0.64
Multivariable 1 HR (95% CI) ‡	1.00 (reference)	0.89 (0.55-1.43)	0.99 (0.62-1.57)	0.69 (0.41-1.15)	0.94 (0.58-1.52)	0.87
Multivariable 2 HR (95% CI)§	1.00 (reference)	0.89 (0.55-1.43)	1.01 (0.64-1.60)	0.71 (0.42-1.18)	0.98 (0.61-1.58)	1.00
Men and women combined‖	≤1.4	>1.4 and ≤3.7	>3.7 and ≤7.4	>7.4 and ≤14.9	>14.9	
Cases/person-years	82/286,082	78/286,411	88/286, 321	96/285, 830	115/285, 870	
Multivariable 2 HR (95% CI)§	1.00 (reference)	0.92 (0.68-1.26)	1.00 (0.74-1.36)	1.06 (0.79-1.44)	1.22 (0.91-1.64)	0.05
PhIP (ng/1,000 kcal)						
Men	≤8.8	>8.8 and ≤21.5	>21.5 and ≤40.5	>40.5 and ≤80.8	>80.8	
Cases/person-years	53/164,845	47/165,096	55/165,085	62/165,150	74/165,274	
Age-adjusted HR (95% CI) †	1.00 (reference)	0.91 (0.61-1.34)	1.10 (0.75-1.60)	1.27 (0.88-1.83)	1.56 (1.10-2.23)	0.001
Multivariable 1 HR (95% CI) ‡	1.00 (reference)	0.82 (0.55-1.22)	0.96 (0.66-1.41)	1.09 (0.75-1.58)	1.33 (0.93-1.90)	0.01
Multivariable 2 HR (95% CI)§	1.00 (reference)	0.84 (0.56-1.24)	0.99 (0.68-1.44)	1.12 (0.77-1.62)	1.38 (0.97-1.98)	0.007
Women	≤3.7	>3.7 and ≤11.6	>11.6 and ≤26.4	>26.4 and ≤61.5	>61.5	
Cases/person-years	45/120,859	30/121,028	35/120,910	23/120,946	35/121,320	
Age-adjusted HR (95% CI) †	1.00 (reference)	0.68 (0.43-1.08)	0.82 (0.53-1.28)	0.55 (0.34-0.92)	0.87 (0.56-1.36)	0.99
Multivariable 1 HR (95% CI) ‡	1.00 (reference)	0.65 (0.41-1.04)	0.77 (0.49-1.20)	0.51 (0.31-0.85)	0.81 (0.52-1.28)	0.86
Multivariable 2 HR (95% CI)§	1.00 (reference)	0.65 (0.41-1.04)	0.77 (0.49-1.20)	0.51 (0.31-0.85)	0.81 (0.52-1.28)	0.86
Men and women combined‖	≤5.9	>5.9 and ≤16.9	>16.9 and ≤34.7	>34.7 and ≤73.2	>73.2	
Cases/person-years	90/285,970	84/286,384	84/285,645	92/286,013	109/286,502	
Multivariable 2 HR (95% CI)§	1.00 (reference)	0.87 (0.64-1.17)	0.86 (0.64-1.16)	0.95 (0.71-1.28)	1.17 (0.88-1.56)	0.04
B(a)P (ng/1,000 kcal)						
Men	≤0.8	>0.8 and ≤4.6	>4.6 and ≤13.8	>13.8 and ≤30.7	>30.7	
Cases/person-years	62/164,578	63/165,067	54/165,331	42/165,202	70/165,272	
Age-adjusted HR (95% CI) †	1.00 (reference)	1.04 (0.73-1.48)	0.91 (0.63-1.31)	0.73 (0.49-1.08)	1.29 (0.92-1.82)	0.12
Multivariable 1 HR (95% CI) ‡	1.00 (reference)	1.04 (0.73-1.47)	0.93 (0.65-1.34)	0.70 (0.47-1.04)	1.15 (0.81-1.63)	0.47
Multivariable 2 HR (95% CI)§	1.00 (reference)	1.05 (0.74-1.50)	0.94 (0.66-1.36)	0.72 (0.48-1.06)	1.18 (0.84-1.67)	0.39

(*Continued on the following page*)

Table 4. HRs and 95% CI for meat mutagens and mutagenic activity index intake (*n* = 459 cases; 291 male and 168 female cases) (Cont'd)

Variable	Quintile of daily meat mutagen intake					*P* trend*
	1	2	3	4	5	
Women	≤0.4	>0.4 and ≤2.2	>2.2 and ≤6.9	>6.9 and ≤18.9	>18.9	
Cases/person-years	35/120,726	40/120,891	36/121,158	28/121,093	29/121,195	
Age-adjusted HR (95% CI) †	1.00 (reference)	1.16 (0.74-1.83)	1.06 (0.67-1.69)	0.85 (0.52-1.40)	0.94 (0.57-1.54)	0.46
Multivariable 1 HR (95% CI) ‡	1.00 (reference)	1.12 (0.71-1.76)	1.07 (0.67-1.70)	0.84 (0.51-1.38)	0.89 (0.54-1.47)	0.37
Multivariable 2 HR (95% CI)§	1.00 (reference)	1.14 (0.72-1.79)	1.08 (0.68-1.72)	0.85 (0.52-1.41)	0.92 (0.56-1.51)	0.42
Men and women combined‖	≤0.6	>0.6 and ≤3.3	>3.3 and ≤10.6	>10.6 and ≤25.9	>25.9	
Cases/person-years	100/285,569	103/286,024	86/286,316	70/286,382	100/286,222	
Multivariable 2 HR (95% CI)§	1.00 (reference)	1.02 (0.78-1.35)	0.91 (0.68-1.21)	0.72 (0.53-0.98)	1.01 (0.76-1.34)	0.97

NOTE: Cohort that completed the meat-cooking module: *n* = 459 cases, *n* = 317,371 cohort subjects; 291 male cases, 183,650 male cohort subjects; 168 female cases; 133,721 female cohort subjects.

**P* trend calculated using median values for each quantile.

† Cox proportional hazard models used to calculate hazard ratios. All models should be considered adjusted for age because age is the time metric. All nutrients are adjusted for energy by the density method with energy additionally in the model.

‡ Models additionally adjusted for smoking (never, quit ≥10 y, quit 5 to 9 y ago; quit 1 to 4 y ago, quit <1 y ago or current and smoked ≤20 or >20 cigarettes/day; and missing), BMI (kg/m^2, <18.5, ≥18.5 and <25, ≥25 and <30, ≥30 and <35, ≥35, and missing), education (≤11 y, 12 y, or completed high school, post-high school or some college, college or postgraduate, and missing), race (Caucasian; Black; Hispanic; Asian, Pacific Islander, or American Indian/Alaskan Native; and missing), self-reported diabetes (yes, no), and energy-adjusted saturated fat (continuous).

§ Most parsimonious model adjusted for smoking (never, quit ≥10 y, quit 5 to 9 y ago; quit 1 to 4 y ago, quit <1 y ago or current and smoked ≤20 or >20 cigarettes/day; and missing), and energy-adjusted saturated fat (continuous).

‖ Sex combined models additionally adjusted for sex. *P* value for interaction by sex: mutagenic activity = 0.11, DiMeIQx = 0.60, MeIQx = 0.34, PhIP = 0.19, and B(a)P = 0.58.

reported earlier (22, 45), support the notion that meat-related mutagens are consumed in small quantities, and associations with cancer are observed only at high intake.

The strong, 2-fold, positive association we observed with overall meat-derived mutagenic activity suggests that the integration of all classes of meat-related mutagens is a more comprehensive exposure measurement of meat-derived mutagens compared with individual HCA and B(a)P and/or that mutagens not yet identified beyond the HCAs and B(a)P may contribute to pancreatic carcinogenesis. Among men, the positive associations that we observe for grilled/barbecued and broiled meat are consistent with the weaker but significant associations observed for DiMeiQx and PhIP. In our population, the top meat sources for DiMeIQx are well/very well-done barbecued hamburgers and chicken and, for PhIP, are medium-cooked barbecued steaks, well and very-well-done barbecued red meat, and well-done barbecued and broiled chicken. Our findings are further supported by rodent studies that have shown DiMeIQx (48) and PhIP (49-51) to enhance pancreatic carcinogenesis. PhIP DNA adducts are formed at high levels in the pancreas of animals (52, 53) and have been detected with higher intensity in pancreatic tissue of cancer patients compared with noncancer controls (54, 55). Polymorphisms in genes that are involved in HCA metabolism have also been associated with pancreatic cancer (56, 57).

We did not observe a positive association between processed meat and pancreatic cancer, which is consistent with the null results from most cohort studies (25, 27, 30, 31) and inverse association for sausage intake in a cohort of Swedish twins (28); however, it contrasts with the positive association for processed meat in the Multiethnic Cohort (26). NOCs found in processed meat are carcinogens in animals and have been suggested to be carcinogenic in humans (58). To address this concern, the U.S. Department of Agriculture does not permit meats to contain detectable amounts of NOCs and regulates the amount of nitrite added to meat (58). Since the 1970s, the amount of nitrite found in meat has been reduced by more than 80% (58). In addition, ascorbate or erythorbate is required as an additive to bacon to inhibit NOC formation (58). Other antioxidants such as BHT (butylated hydroxytoluene) and BHA (butylated hydroxyanisole) are often added to sausages and dried meats to prevent rancidity (58). The later compounds seem to be anticarcinogenic in animal models for pancreatic cancer (59). These preventive measures may have contributed to the lack of a positive association between processed meat and pancreatic cancer. Five of nine case-control studies (3, 4, 7-10, 13, 15, 18), however, some conducted before the impact of NOC meat regulations, showed significant positive associations for processed or smoked meats and pancreatic cancer (3, 4, 7, 9, 10). Meats preserved at home by individuals could contain high NOC levels and possibly contribute to excess pancreatic cancer risk in some populations. In addition, the cooking methods for the processed meats were not evaluated in some studies that observe positive associations (4, 7, 10, 26), and mutagens other than NOC could explain the positive associations.

We are uncertain why many of our results seem different in men compared with women. Given that a smaller number of women developed pancreatic cancer in our cohort (*n* = 281 from baseline and *n* = 168 with meat-cooking module data), we may not have the power to observe significant associations. In addition, compared with men, women in our cohort report less absolute meat intake, particularly red meat, and report more white meat and sautéed, baked, or microwaved prepared meat intake. Meats that are sautéed, baked, or microwaved do not contain HCAs or PAHs (33). Hence, relative to men, most women in our cohort are consuming less meat and

meat-related mutagens at levels below which associations may be evident. This could account for the observed sex differences in pancreatic cancer risk. Another speculative, biologically plausible explanation for our observed sex differences is heme iron, the type of iron abundant in red meat, that could enhance the growth of pancreatic cancer tumors. Heme iron is well absorbed and is less affected by factors that inhibit non–theme iron absorption. Due to normal iron loss during menstruation, women do not accrue as high iron stores during a lifetime as men. Higher free iron serum levels and percent transferrin saturation were significantly associated with pancreatic cancer in one prospective study (60). Finally, it is also plausible that susceptibility to meat mutagens may vary by gender; however, sex-related differences in pancreatic cancer incidence and risk are thought to be related to differences in exposure and diagnosis (1). Other epidemiologic meat studies that have examined sex-specific pancreatic cancer risks have not shown clear sex differences (4, 7, 8, 15, 21, 25, 27, 29-31).

The strength of our study is its large prospective nature with diet being assessed before cancer diagnosis, thereby reducing biases and the influence of reverse causality. However, our cohort does have a relatively short follow-up (5 years), and the pancreatic cancer risks we observe with meat intake may become stronger with extended follow-up. Our study is internally valid as the cases arose from the cohort that includes the noncases and, therefore, does not have control selection bias. It also has a larger number of cases compared with most previous studies, as well as a wide distribution of dietary intake (36), providing power to detect differences in the meat-related risk factors. The meat-cooking module used in our study was specifically developed to assess meat-cooking methods and doneness levels and linked to a database of meat-cooking–related mutagens. The NIH-AARP Diet and Health Study cohort includes both sexes and never, former, and current smokers; therefore, results may be generalizable to many older adults. As with all dietary intake studies, measurement error related to both the dietary assessment techniques and the meat-mutagen database is likely present and could cause inaccurate risk estimates. In addition, few in our population, particularly female participants, have meat-mutagen intake at high levels, such that associations can be observed for pancreatic cancer.

In conclusion, our findings support the hypothesis that meat intake, particularly red meat, meat that is cooked at high temperatures, and meat-associated HCAs, DiMeiQx, and PhIP, and overall mutagenic activity may play a role in exocrine pancreatic cancer development. Further research is needed to confirm our results, particularly pertaining to meat-related mutagens and pancreatic cancer risk in other populations with extended follow-up.

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