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Are meat and heme iron intake associated with pancreatic cancer? Results from the NIH-AARP Diet and Health Cohort

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Abstract

Several studies on pancreatic cancer have reported significant positive associations for intake of red meat but null associations for heme iron. We assessed total, red, white, and processed meat intake, meat cooking methods and doneness, and heme iron and mutagen intake in relation to pancreatic cancer in the NIH-AARP Diet and Health Study cohort. 322,846 participants (187,265 men; 135,581 women) successfully completed and returned the food frequency questionnaire between 1995–1996. After a mean follow-up of 9.2 years (up to 10.17 years), 1,417 individuals (895 men, 522 women) developed exocrine pancreatic cancer. Cox proportional hazard models were used to calculate hazard ratios (HR) and 95% confidence intervals (CI), and trends were calculated using the median value of each quantile. Models incorporated age as the time metric and were adjusted for smoking history, BMI, self-reported diabetes, and energy-adjusted saturated fat. Pancreatic cancer risk significantly increased with intake of total meat (Q5 vs. Q1 HR=1.20, 95% CI 1.02–1.42, p-trend=0.03), red meat (HR=1.22, 95% CI 1.01–1.48, p-trend=0.02), high-temperature cooked meat (HR=1.21, 95% CI 1.00–1.45, p-trend=0.02), grilled/barbequed meat (HR=1.24, 95% CI 1.03–1.50, p-trend=0.007), well/very well done meat (HR=1.32, 95% CI 1.10–1.58, p-trend = 0.005), and heme iron from red meat (Q4 vs. Q1 HR=1.21, 95% CI 1.01–1.45, p-trend=0.04). When stratified by sex, these associations remained significant in men but not women except for white meat intake in women (HR = 1.33, 95% CI 1.02–1.74, p-trend = 0.04). Additional studies should confirm our findings that consuming heme iron from red meat increases pancreatic cancer risk.

Keywords

pancreatic cancer; heme iron; meat

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INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer-related mortality in men and women of all ages in the United States (1). It is rapidly fatal and has a 5-year survival rate of <7% (1). Cigarette smoking, history of diabetes mellitus, and overweight and obesity are consistent potentially modifiable risk factors for pancreatic cancer (2). The association between diet and pancreatic cancer risk is unclear mostly because of inconsistent study findings.

In 2012, a panel from the World Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR) concluded that the evidence that red and processed meats contribute to pancreatic cancer was suggestive. Dose-response meta-analyses of eight prospective cohort studies revealed that higher intake of red meat was positively, but insignificantly, associated with pancreatic cancer risk with some heterogeneity between studies (3). In addition, two meta-analyses on 5 case-control studies and 11 prospective cohort studies similarly found significant positive associations for red meat which were stronger in case-control studies and among men, respectively (4, 5). Processed meat was also positively associated with pancreatic cancer; however, the association was only significant in men (3, 5). Further, these associations could potentially be explained by other factors in meat particularly confounded by compounds that are generated with meat cooking methods and doneness levels (6–10).

Our prior examination of the NIH-AARP Diet and Health Study cohort revealed significant positive associations between total, red, and high-temperature cooked meats and pancreatic cancer in men but not women (8). The study also noted that associated meat mutagens specifically, overall mutagenic activity in men and the heterocyclic amine (HCA) 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline (DiMeIQx) in both men and women may contribute to pancreatic carcinogenesis. Therefore, we examined the association between meat, meat cooking methods, and compounds in meat in the large NIH-AARP Diet and Health Study cohort. In contrast to our previous examination of these hypotheses, the present study has longer follow-up time (6 additional years) and more than three times as many pancreatic cancer cases (n > 1400 cases) with meat cooking methods and related mutagens. The greater number of cases increases the power of our study and also enables us to look at interactions by other exposures. In addition to the meat mutagens, our current study also examines heme iron intake as a risk factor for pancreatic cancer.

SUBJECTS AND METHODS

Study Population

The NIH-AARP Diet and Health Study is a large prospective study of AARP members established in 1995–1996 (8, 11). In total, 567,169 AARP members aged 50–71 years living in six US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and in two metropolitan areas (Atlanta, GA and Detroit, MI) successfully completed and returned the self-administered questionnaires (8, 11) that assessed demographic characteristics, dietary intake over the previous year, and health-related factors (8). Six months after this baseline questionnaire was sent, participants who responded to the baseline questionnaire received a second risk factor questionnaire (RFQ) eliciting information on meat cooking methods (8, 11, 12). In total, 332,913 participants completed and returned the second questionnaire (8). Informed consent was obtained from all study participants and the study was approved by the National Cancer Institute Special Studies Institutional Review Board (8).

For the present study, we only included participants who completed the meat module portion of the second questionnaire. We excluded subjects who had questionnaires filled out by proxy respondents (n=6,959), who had prevalent cancers as determined by the cancer registry data (n=2,361) and whose energy consumption lay outside the normal sex-specific distribution for energy intake by two interquartile ranges above the 75^{th} or below the 25^{th} percentile on the logarithmic scale (n=2,701; ref. 8). We also excluded those with ≤0 years of follow-up (n=38). Our final analytic cohort consisted of 322,846 individuals (187,265 men, 135,581 women; ref. 8).

Cohort Follow-up and Case Ascertainment

Pancreatic cancer cases were ascertained by linking cohort members to state cancer registries where the study participants reside, as well as Arizona, Texas and Nevada and to the U.S. National Death Index from 1995 to 2006 (8, 12, 13). Vital status of cohort participants was also ascertained by linkage to the Social Security Administration Death Master File. We included incident adenocarcinoma of the exocrine pancreas as the primary outcome in our analysis [*International Classification of Disease for Oncology, Third Edition* (code C250-C259); ref. 8, 12]. Our case definition excluded pancreatic endocrine tumors, sarcomas, and lymphomas (histology types, 8150, 8151, 8153, 8155, 8240) as the etiologies may differ (8, 12).

Dietary Assessment and Meat Variable

The baseline questionnaire gathered information on demographic characteristics, medical history, and health-related behaviors and also contained a grid based food frequency questionnaire (FFQ) that assessed the frequency and portion size of 124 food items consumed over the past year (8, 11). These line items were constructed using over 5,000 individual food codes found in the United States Department of Agriculture (USDA)'s Continuing Survey of Food Intake by Individuals database (14). Intake of total, red, white, processed, and high-temperature cooked meats, heme iron, as well as energy and other nutrients was determined from the baseline FFQ. While the specific items in each category have been described in detail elsewhere (8), a few categories have been altered. We included all forms of poultry products in the white meat category. Processed meat from red meat and poultry contributed to the processed meat category. The validity of both questionnaires was discussed in an earlier study (8).

The RFQ included a meat module that elicited meat-cooking methods (barbequed/grilled, pan-fried, oven-broiled, and microwaved) and doneness levels (rare/medium and well/very well done; ref. 8, 15, 16). Meat samples cooked by different methods and to varying levels of doneness were analyzed for levels of HCAs, polycyclic aromatic hydrocarbons (PAHs), and overall mutagenicity. Overall mutagenic activity was quantified using the Ames assay

(8, 9, 15, 17). These meat mutagens were entered into the CHARRED database (8, 15, 18–21). The RFQ was linked to the CHARRED database to estimate the daily intake of meat-mutagens including HCAs DiMeIQx, 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx), 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), and benzo(a)pyrene (BaP), a marker for PAHs (8, 15, 18–21).

Statistical Analysis

We used generalized linear models to calculate the means within each total meat intake quintile for the continuous variables and frequency proportions for the categorical variables in Table 1.

Person-years were determined by the date of receipt of the RFQ and date of pancreatic cancer diagnosis, death, emigration out of the registry area, or December 2006, whichever occurred first (8, 13, 16).

Cox proportional hazard models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CI). Trends were estimated using the median value of each quantile. As the dietary variables were correlated with energy, we adjusted for energy using the density method. The distribution of the meat related variables differed by sex (e.g. men consumed higher levels of red meat, women consumed higher levels of white meat); therefore, the quintiles for the meat related variables were based on the distribution of each variable in the cohort by sex. For foods that were consumed by less than 20% of the cohort (pan-fried, oven-broiled, and microwaved meats, DiMeIQx), sex specific categories were created using zero intake as the referent and remaining subjects categorized as quartiles or tertiles. Subjects were merged in sex-specific quantile categories for sex-combined risk estimates. Relevant meat groups were controlled simultaneously in our models (red and white; processed and non-processed; high- and low-temperature cooked; barbequed/grilled, pan-fried, oven-broiled, and microwaved; rare/medium and well/very well done).

Our crude models included age at study entry, energy (kcal) and sex (in sex combined models). Additional variables were included in our models if they were confounders that altered the risk estimate ≥10% or were putative risk factors for pancreatic cancer. Variables tested as potential confounders included smoking history, BMI, self-reported diabetes, saturated fat intake, and alcohol use. Smoking was a confounder in most of the models and saturated fat in our model for total meat. Our final model included age, smoking (never, quit ≥10 y ago, quit 5–9 y ago, quit 1–4 y ago, quit <1 y ago or current and smokes ≤20 cigarettes/day, quit <1 y ago or current and smokes >20 cigarettes/day, and missing), BMI (kg/m^2, <18.5, ≥18.5 and <25, ≥25 and <30, ≥30 and <35, ≥35, and missing), self-reported diabetes (yes, no), and energy-adjusted saturated fat (continuous) as well as sex (in sex combined models). The meat mutagens, total heme iron, heme iron from red meat, and advanced glycation end-products were all correlated with each other as they are all present in meat and mutual adjustment of all attenuated associations; therefore we show associations without mutual adjustment. We evaluated interactions by sex, diabetes, BMI and smoking status (never, former, and current) on the association between meat exposure and pancreatic cancer by including cross-product terms for the meat trend variable with the respective effect modifier in the multivariable model. Significant interactions were further stratified.

We additionally performed sensitivity analyses of the baseline FFQ meat variables (total, red, white, and high-temperature cooked meats, and heme iron) on the full baseline cohort to assess internal consistency with associations observed for the RFQ cohort. Statistical Analysis Systems (SAS) software was used to perform all statistical analyses, and P values for all tests were 2-tailed (8, 12).

RESULTS

During follow-up up to 10.17 years (median 10.07 y, 2,974,128 person-years of observation), 1,417 individuals (895 men, 522 women) in the risk factor cohort developed exocrine pancreatic cancer (12). The characteristics of our study population according to total meat intake quintile are shown in Table 1. Men and women with higher total meat intake were more likely to be younger, current smokers, of higher BMI, less physically active, and diabetic; they also consumed more red and white meat, total and saturated fat, and heme iron but less alcohol (12). A greater proportion of men consumed more red than white meat while women consumed more white than red meat.

In men and women combined, total, red, and high-temperature cooked meat intake were significantly associated with pancreatic cancer with significant trends across quintiles (Table 2, Q5 vs. Q1 HR=1.20, 95% CI 1.02–1.42, p-trend=0.03; HR=1.22, 95% CI 1.01–1.48, p-trend=0.02; HR=1.21, 95% CI 1.00–1.45, p-trend=0.02, respectively). These associations tended to be stronger in men than in women; however, the interaction by sex was only significant for red meat (p-interaction=0.03; Q5 vs. Q1 men HR=1.36, 95% CI 1.07–1.73, p-trend=0.004; women HR=1.01, 95% CI 0.74–1.38, p-trend=0.91). White meat intake showed a significant positive association in women (Q5 vs. Q1 HR = 1.33, 95% CI 1.02–1.74, p-trend = 0.04) but not in men (HR = 1.05, 95% CI 0.85–1.30, p-trend = 0.63, p-interaction=0.26). Men and women consuming moderate amounts of processed meat (quintiles 2–4 compared to quintile 1) had significantly elevated risk for pancreatic cancer, although extreme intake was not associated. We also conducted substitution model analyses to examine the associations of sub-groups of meat while holding total meat constant and observed associations similar to those obtained by the partition method. For example, holding total meat constant the association between red meat and pancreatic cancer still remained significant. Therefore, our associations were robust with both the partition and substitution methods.

Certain meat preparation methods were associated with pancreatic cancer (Table 3). In sex combined models, those consuming the most barbequed meat compared to the least had a significant 24% (95% CI 1.03–1.50) increased pancreatic cancer risk with significant trends across the quintiles (p-trend = 0.007). In sex-stratified analysis, men in the highest quintile of barbequed meat intake and quartile of broiled meat intake had a 33% (95% CI 1.05–1.68) and 34% (95% CI 1.09–1.64) greater risk, respectively, than those with the lowest intake. This risk increased across the quintiles and quartile (p-trends = 0.004 and 0.01), respectively. There was a borderline non-significant interaction for broiled meat by sex (p-interaction = 0.07). Consumption of pan-fried and microwaved meats was not associated with pancreatic cancer. With regards to doneness levels, well/very-well done meat was associated with a significantly elevated risk for pancreatic cancer in sex combined and stratified models (Q5 vs. Q1 men and women HR=1.32, 95% CI 1.10–1.58, p-trend = 0.005; men HR=1.33, 95% CI 1.05–1.67, p-trend=0.01). Rare/medium done cooked meat showed non-significant positive associations with a significant trend in sex combined models (p-trend=0.03).

Heme iron showed borderline non-significant positive associations with pancreatic cancer in men and sex combined models (Table 4). In multivariable models, before energy-adjusting for saturated fats, the association between heme iron and pancreatic cancer was significant (Q5 vs. Q1 HR=1.21, 95% CI 1.00–1.45, p-trend=0.03). This association was significant in men (Q5 vs. Q1 HR=1.31, 95% CI 1.04–1.65, p-trend=0.02) but not in women (Q5 vs. Q1 HR=1.05, 95% CI 0.79–1.42, p-trend=0.83). Consumption of heme iron from red meat was significantly associated with pancreatic cancer in sex combined models and among men (Q4 vs. Q1 men and women HR=1.21, 95% CI 1.01–1.45, p-trend=0.04; men HR=1.34, 95% CI 1.06–1.69, p-trend=0.02). Overall mutagenic activity intake was significantly associated with increased pancreatic cancer in men (Q5 vs. Q1 HR=1.30, 95% CI 1.04–1.63, p-trend=0.13). None of the other meat mutagens showed significant associations with pancreatic cancer.

There was a significant interaction for total meat intake by smoking status in men (p-interaction = 0.01) such that in stratified and joint effects models positive associations were present among former and current smokers but not never smokers (Table 5). BMI and diabetes did not significantly modify any of the associations. None of the risk estimates for the various meat exposures significantly changed in lag analyses excluding the first two years of follow-up.

DISCUSSION

In this large prospective cohort of AARP members (8), there were significant associations overall between intake of total, red, high-temperature cooked, grilled/barbequed, and well/very well done meats, heme iron from red meat and pancreatic cancer. When analyses were stratified by sex, white meat was the only dietary exposure that was significantly associated with increased risk for pancreatic cancer in women. Consumption of total, red, high-temperature cooked, grilled/barbequed, oven-broiled, and well/very well done meats and heme iron from red meat appreciably was associated with elevated risk more strongly in men compared to that in women, although the interaction by sex was only significant for red meat. None of the meat mutagens were appreciably associated with pancreatic cancer, although a significant threshold association was observed for overall mutagenic activity in men only. Smoking tended to modify the association for total meat such that the positive association was strongest among former smokers, particularly among men. In the joint analysis, associations were significant in former and current smokers, but not in never smokers. To the best of our knowledge, this is the largest prospective study to examine meat cooking methods, related mutagens, and heme iron in relation to pancreatic cancer.

Our results add to the evidence that meat intake may play a role in pancreatic cancer development (3). The WCRF/AICR’s Continuous Update Project concluded that there was suggestive evidence that red and processed meat increased the risk for pancreatic cancer.

The panel found a positive, borderline non-significant, association between red meat intake and pancreatic cancer (per 100 g compared to 20 g RR=1.19, 95% CI 0.98–1.86), and in the meta-analysis the increased risk was most apparent in men (RR=1.43, 95% CI 1.10–1.86) but not women (RR=1.06, 95% CI 0.86–1.30). Previous cohort studies have found significant findings in men (8, 22) but not in women (23). Two meta-analyses on 10 (4) and 11 (5) prospective studies found no significant relation between red meat intake and pancreatic cancer. However, both meta-analyses reported a significant P-heterogeneity among the cohort studies due to differing red meat definitions. Overall the WCRF showed a borderline significant increased risk for processed meat (per 50 g/day increase, RR=1.17, 95% CI 1.01–1.34) which was significant in men (per 50 g/day increase, RR=1.21, 95% CI 1.01–1.45) but not women (per 50 g/day increase, RR=1.09, 95% CI 0.69–1.73) (3). A meta-analysis on 11 prospective studies also found a significant association between consumption of processed meat and pancreatic cancer (5). In the present analysis, we observed significant positive associations at intermediate quantiles of processed meat intake for both men and women but no associations comparing intake extremes. We also observed significant positive associations with a significant trend across quintiles for white meat intake among women. To the best of our knowledge, no studies have found a significant positive association between pancreatic cancer and white meat consumption. A large meta-analysis on poultry consumption and pancreatic cancer found a non-significant inverse association (combined OR=0.84, 95% CI 0.68–1.06) in four case control studies and a non-significant association (total RR=1.02 95% CI 0.84–1.24) in six cohort studies (4). The positive associations that we observe for red, processed, and white meat intake were independent of saturated fat intake and other potential confounders. The present results contrast earlier analyses conducted in NIH-AARP with less follow-up time and fewer cancer cases. Previously, we observed positive associations for total meat for sexes combined and red meat among men but no associations for processed meat or poultry (8). The positive association for total meat seen in the highest quintile may be explained by high red meat intake among these individuals.

In the present study we observe significant associations with higher intake of high temperature cooked, grilled/barbequed, and well/very well done meats with stronger associations among men although the interaction by sex was not significant. Three retrospective case-controls studies and two cohort studies have examined meat cooking methods, doneness levels, or mutagens and pancreatic cancer risk with most showing positive associations (6–10). Among prospective studies, in the PLCO cohort, well to very well done red and barbequed red meat were associated with significantly elevated pancreatic cancer risk, and in an earlier analysis in the NIH-AARP study grilled/barbequed and broiled meats were positively associated with pancreatic cancer but only among men (8). HCAs (DiMeIQx, MeIQx, and PhIP) and PAHs (BaP) present in barbequed and high temperature cooked meat could explain these associations and have been variably associated with pancreatic cancer (7–9). Experimental studies show that human and animal pancreatic tissues are susceptible to HCAs and PAHs (7). Animals exposed to HCAs are found to have higher levels of HCA-induced DNA adducts in their pancreas than any other organ. Specifically, PhIP DNA adducts have been detected more frequently in the pancreatic tissue of cancer patients than in non-cancer patients (8). PAHs and all HCAs other than DiMeIQx have been found to be carcinogenic in animals (7). In contrast to our previous study in NIH-AARP that showed significant elevated pancreatic cancer risks for DiMeIQx overall and PhIP in men (8), we do not observe any associations with these meat mutagens. It is possible that these previous associations were chance. Our present analysis has an additional 6 years of follow-up and over three times as many cases, therefore more power to observe associations if they exist. Recent literature suggests that advanced end glycation products (AGEs) may mediate the association between red meat cooked at high temperatures and pancreatic cancer in men (24). AGEs have been hypothesized to promote chronic inflammation and may be another mechanism in addition to mutagens that might explain the relationship between meat intake consumption and pancreatic cancer. Yet, biomarker studies of AGEs measured in the peripheral blood have been inconsistently associated with pancreatic cancer (24, 25).

Given the presence of heme iron in red meat and heme iron's role in promoting oxidative stress, heme iron has also been hypothesized as a dietary risk factor for pancreatic cancer (26). Heme iron may help catalyze the formation of N-nitroso compounds (NOCs) and malondialdehyde, both of which are carcinogens and promote DNA damage and inflammation (26, 27). Studies on colorectal carcinogenesis in mouse models suggest that heme iron also promotes epithelial cell proliferation by inducing lipid oxidation (28, 29). Heme iron from meat is more efficiency absorbed in the small intestine in comparison to non-heme iron from vegetable food sources. Though prediagnostic serum iron concentrations have been linked with pancreatic cancer (30), the results of a few case-control (31–36) and prospective cohort studies (37, 38, 39) assessing dietary intake of iron have been null (26). Neither a prospective study of male health professionals nor participants men or women in the Netherlands Cohort Study observed significant association between total or heme iron intake and pancreatic cancer (37). The European Prospective Investigation into Cancer and Nutrition Cohort (EPIC) did not show an association between heme-iron and pancreatic cancer overall; however heme iron was significantly associated with greater pancreatic cancer risk in both men and women with abdominal obesity (26). Further, non-significant positive associations for heme iron intake were observed in women, and were statistically significant among women who were current smokers (26).

We observed interactions by smoking status such that in joint effects models for men and women, associations between higher total meat intake and pancreatic cancer were strongest among former and current smokers. These interactions along with those observed in the EPIC study may suggest that the effects of smoking and meat consumption on pancreatic cancer may be synergistic particularly as smoking is a source of nitrosamines, and heme iron catalyzes NOC production. However, residual confounding from smoking should also be considered as an alternative explanation for these interactions. In contrast to the EPIC findings, however, we observed significant positive associations between heme iron from red meat in men but not women. Although speculative this sex-specific difference could possibly be explained by men having higher iron status in comparison to women. Men may have higher iron stores due to greater lifetime meat consumption as well as lack of menstrual blood loss (40).

An important strength of our study is its large prospective design with detailed information about diet being assessed prior to cancer diagnosis, thereby reducing the influence of reverse causation, and differential biases such as recall and selection (8, 26). We have a relatively large number of cancer cases compared to earlier reports, as well as a wide distribution of dietary intake (11). This increases the power of our study to observe associations if they exist, as well as enables us to stratify our analyses by sex and smoking status. Our meat exposures were also based on a unique meat questionnaire and mutagen and heme iron database (36). Our study also has limitations. As with other dietary intake studies, measurement error related to both dietary assessment and the meat-related nutrients and mutagens database is likely present and could result in inaccurate risk estimates. Dietary intake and other exposures were only assessed for the year before baseline. Repeated assessments would better reflect long-term exposure, as well as changes over time. There may be residual confounding from the exposures controlled in our models. Although we controlled for confounders and known risk factors for pancreatic cancer, other exposures correlated with meat intake could potentially explain our associations. Finally, our population is primarily Caucasian and may not be generalizable to other ethnic groups.

In conclusion, we observed that higher consumption of total, red, high-temperature cooked, grilled/barbequed, and well/very well done meats and heme iron from red meat was significantly associated with increased pancreatic cancer risk. Further research is required to confirm our study findings and possibly evaluate biomarkers of iron status in relation to pancreatic cancer.

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Abbreviations used

AARP	American Association of Retired Persons
BaP	benzo(a)pyrene
CI	confidence interval
DiMeIQx	2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline
FFQ	Food Frequency Questionnaire

HCAs	heterocyclic amines
HR	hazard ratio
MeIQx	2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline
NIH	National Institutes of Health
PAHs	polycyclic aromatic hydrocarbons
PhIP	2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine
RFQ	Risk Factor Questionnaire
SAS	Statistical Analysis Systems
WCFR/AICR	World Cancer Research Fund and American Institute for Cancer Research

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Novelty and impact of paper

To the best of our knowledge, this is the largest prospective study to examine meat cooking methods, related mutagens, and heme iron in relation to pancreatic cancer.

Table 1

Selected baseline characteristics of NIH-AARP Diet and Health Study cohort participants by total meat intake [1]

Characteristics	Quintile of daily total meat intake (g/1,000 kcal) in men				
Men (n=187,265)	**≤43.6**	**>43.6 and ≤58.5**	**>58.5 and ≤72.9**	**>72.9 and ≤92.3**	**>92.3**
Meat Intake (g/1,000 kcal)					
Total Meat	30.9	51.3	65.6	81.8	115.9
Red Meat	17.0	28.8	36.8	45.1	59.0
White Meat	13.9	22.5	28.8	36.7	56.9
Age (y)	63.2	63.0	62.7	62.2	61.6
Education, college graduate or postgraduate (%)	46.5	47.0	47.6	48.0	47.6
Race					
African American (%)	3.7	3.1	3.0	3.0	3.5
Non-Hispanic white (%)	90.8	93.0	93.3	93.5	92.5
Smoking history[2]					
Never (%)	30.4	29.5	29.7	29.6	29.0
Former smoker (%)	57.0	58.0	57.9	57.4	57.5
Current smoker (%)	8.9	9.0	9.1	9.6	10.0
BMI (kg/m^2)	26.2	26.7	27.1	27.5	28.1
<25 kg/m^2 (%)	39.5	33.4	30.2	27.0	22.12
25–<30 kg/m^2 (%)	44.9	48.3	49.2	49.3	49.0
≥30 kg/m^2 (%)	13.8	16.7	19.2	22.3	27.4
Heavy physical activity, ≥5 times/wk (%)	26.9	23.2	21.2	20.4	19.4
Self-reported diabetes (%)	6.6	7.8	9.2	11.2	14.2
Dietary Intake					
Energy (kcal)	2,032	1,985	1,987	2,004	2,024
Total fat (g/1,000 kcal/day)	28.5	32.5	34.0	35.4	37.3

Characteristics	Quintile of daily total meat intake (g/1,000 kcal) in men				
Men (n=187,265)	**≤43.6**	**>43.6 and ≤58.5**	**>58.5 and ≤72.9**	**>72.9 and ≤92.3**	**>92.3**
Saturated fat (g/1,000 kcal/day)	8.9	10.2	10.6	11.0	11.6
Heme iron (mg/1,000 kcal/day)	86.1	153.5	202.5	255.8	358.9
Advanced glycation end products	333.2	1274.6	1290.5	1444.8	1985.1
Alcohol intake (# drinks/day)	2.0	1.3	1.1	1.0	0.8
Alcohol intake ≥ 3 drinks/day (%)	15.9	12.3	10.8	9.2	6.8

Characteristics	Quintile of daily total teat intake (g/1,000 kcal) in women				
Women (n=135,581)	**≤38.0**	**>38.0 and ≤53.4**	**>53.4 and ≤68.4**	**>68.4 and ≤88.3**	**>88.3**
Meat Intake (g/1,000 kcal)					
Total Meat	25.7	45.9	60.7	77.5	113.7
Red Meat	12.6	22.6	29.4	35.7	45.0
White Meat	13.2	23.3	31.4	41.8	68.6
Age (y)	62.5	62.4	62.2	61.9	61.4
Education, college graduate or postgraduate (%)	33.2	30.6	31.1	32.1	31.8
Race					
African American (%)	2.7	2.2	2.0	2.0	2.2
Non-Hispanic white (%)	91.5	94.1	94.3	94.6	94.0
Smoking history[2]					
Never (%)	46.3	44.8	44.5	43.4	40.9
Former smoker (%)	38.5	38.4	39.1	39.8	41.8
Current smoker or having quit <1 y ago (%)	11.8	13.6	13.6	13.8	14.0
BMI (kg/m^2)	25.5	26.3	26.8	27.2	27.8
<25 kg/m^2 (%)	53.8	46.8	43.8	40.3	36.4
25–<30 kg/m^2 (%)	27.6	31.1	31.7	33.0	33.1
≥30 kg/m^2 (%)	15.2	19.3	21.9	24.3	27.8

Characteristics	Quintile of daily total teat intake (g/1,000 kcal) in women				
Women (n=135,581)	**≤38.0**	**>38.0 and ≤53.4**	**>53.4 and ≤68.4**	**>68.4 and ≤88.3**	**>88.3**
Heavy physical activity, ≥5 times/wk (%)	21.1	17.2	15.8	15.3	15.3
Self-reported diabetes (%)	4.8	5.7	6.5	7.8	10.0
Dietary Intake					
Energy (kcal)	1,553	1,557	1,563	1,573	1,567
Total fat (g/1,000 kcal/day)	28.9	32.1	33.7	34.8	36.1
Saturated fat (g/1,000 kcal/day)	9.1	10.0	10.4	10.7	10.9
Heme iron (mg/1,000 kcal/day)	59.5	114.6	154.5	196.5	270.7
Advanced glycation end products	372.7	1364.4	1382.8	1684.4	1698.5
Alcohol intake (drinks/day)	0.5	0.5	0.4	0.4	0.4
Alcohol intake ≥ 3 drinks/day (%)	3.4	3.4	3.0	2.4	1.7

[1] Generalized linear models were used to estimate mean values for the continuous variables and frequencies for dichotomous proportions within each total meat intake quintile.

[2] 6,599 (3.52%) men and 4,214 (3.11%) women having missing smoking history data. 2,878 (1.54%) men and 3,762 (2.77%) women have missing BMI data.

Table 2

Hazard ratios (HR) and 95% confidence intervals (CI) for baseline meat intake in the NIH-AARP Diet and Health Cohort[1]

Variable	Quintile of daily meat intake (g/1,000 kcal)					*P* trend[3]
	1	2	3	4	5	
Total meat						
Men and women combined[4]						
Cases/person-years	265/593,355	286/595,543	271/595,177	282/595,934	313/594,119	
Age-adjusted HR (95% CI)	1.00 (reference)	1.09 (0.92–1.29)	1.06 (0.89–1.25)	1.14 (0.96–1.34)	**1.32 (1.12–1.56)**	**0.0007**
Multivariable HR (95% CI)[2]	1.00 (reference)	1.05 (0.89–1.24)	1.01 (0.85–1.19)	1.06 (0.89–1.25)	**1.20 (1.02–1.42)**	**0.03**
Men						
Cases/person-years	162/340,658	188/342,044	173/342,094	165/342,570	207/341,577	
Age-adjusted HR (95% CI)	1.00 (reference)	1.18 (0.95–1.45)	1.11 (0.89–1.37)	1.09 (0.88–1.36)	**1.44 (1.17–1.77)**	**0.002**
Multivariable HR (95% CI)[2]	1.00 (reference)	1.12 (0.91–1.39)	1.04 (0.83–1.29)	1.00 (0.80–1.24)	**1.27 (1.02–1.57)**	0.08
Women						
Cases/person-years	103/252,697	98/253,499	98/253,082	117/253,369	106/252,543	
Age-adjusted HR (95% CI)	1.00 (reference)	0.96 (0.73–1.26)	0.98 (0.74–1.29)	1.20 (0.92–1.56)	1.14 (0.87–1.49)	0.13
Multivariable HR (95% CI)[2]	1.00 (reference)	0.93 (0.71–1.23)	0.95 (0.72–1.26)	1.15 (0.88–1.51)	1.08 (0.82–1.42)	0.27
Red Meat						
Men and women combined[4]						
Cases/person-years	243/598,789	268/596,590	284/595,847	306/593,567	316/589,339	
Age-adjusted HR (95% CI)	1.00 (reference)	1.11 (0.94–1.33)	**1.21 (1.02–1.44)**	**1.35 (1.14–1.60)**	**1.47 (1.24–1.74)**	**<0.0001**
Multivariable HR (95% CI)[2]	1.00 (reference)	1.06 (0.88–1.26)	1.11 (0.92–1.32)	1.18 (0.99–1.42)	**1.22 (1.01–1.48)**	**0.02**
Men						
Cases/person-years	148/344,177	159/342,803	180/342,009	191/341,440	217/338,513	
Age-adjusted HR (95% CI)	1.00 (reference)	1.09 (0.87–1.37)	**1.27 (1.02–1.58)**	**1.38 (1.11–1.71)**	**1.66 (1.34–2.05)**	**<0.0001**
Multivariable HR (95% CI)[2]	1.00 (reference)	1.02 (0.81–1.28)	1.14 (0.91–1.44)	1.20 (0.95–1.51)	**1.36 (1.07–1.73)**	**0.004**
Women						
Cases/person-years	95/254,612	109/253,788	104/253,838	115/252,127	99/250,826	
Age-adjusted HR (95% CI)	1.00 (reference)	1.16 (0.88–1.52)	1.12 (0.85–1.48)	1.29 (0.98–1.69)	1.16 (0.87–1.54)	0.3224

Variable	Quintile of daily meat intake (g/1,000 kcal)					*P* trend[3]
	1	2	3	4	5	
Multivariable HR (95% CI) [2]	1.00 (reference)	1.11 (0.84–1.47)	1.05 (0.78–1.40)	1.17 (0.87–1.56)	1.01 (0.74–1.38)	0.91
White Meat						
Men and women combined[4]						
Cases/person-years	284/587,575	294/593,947	272/595,811	272/597,199	295/599,601	
Age-adjusted HR (95% CI)	1.00 (reference)	1.01 (0.86–1.19)	0.94 (0.79–1.11)	0.96 (0.81–1.13)	1.09 (0.93–1.29)	0.25
Multivariable HR (95% CI) [2]	1.00 (reference)	1.04 (0.88–1.23)	0.98 (0.83–1.16)	1.02 (0.86–1.20)	1.15 (0.98–1.36)	0.08
Men						
Cases/person-years	185/336,636	182/340,946	183/342,711	171/343,262	174/345,387	
Age-adjusted HR (95% CI)	1.00 (reference)	0.96 (0.78–1.17)	0.96 (0.78–1.18)	0.92 (0.75–1.14)	0.99 (0.81–1.22)	0.96
Multivariable HR (95% CI) [2]	1.00 (reference)	0.99 (0.81–1.22)	1.01 (0.82–1.24)	0.99 (0.80–1.22)	1.05 (0.85–1.30)	0.63
Women						
Cases/person-years	99/250,939	112/253,001	89/253,100	101/253,936	121/254,214	
Age-adjusted HR (95% CI)	1.00 (reference)	1.11 (0.85–1.46)	0.89 (0.67–1.19)	1.03 (0.78–1.36)	1.28 (0.98–1.67)	0.07
Multivariable HR (95% CI) [2]	1.00 (reference)	1.13 (0.86–1.49)	0.92 (0.69–1.23)	1.07 (0.81–1.42)	**1.33 (1.02–1.74)**	**0.04**
Processed Meat						
Men and women combined[4]						
Cases/person-years	228/597,449	308/597,036	301/595,084	313/593,677	267/590,886	
Age-adjusted HR (95% CI)	1.00 (reference)	**1.36 (1.14–1.62)**	**1.33 (1.12–1.59)**	**1.38 (1.15–1.64)**	1.17 (0.98–1.40)	0.73
Multivariable HR (95% CI) [2]	1.00 (reference)	**1.29 (1.08–1.53)**	**1.23 (1.02–1.46)**	**1.24 (1.04–1.49)**	1.02 (0.85–1.24)	0.23
Men						
Cases/person-years	141/343,575	200/342,861	181/341,653	200/341,213	173/339,640	
Age-adjusted HR (95% CI)	1.00 (reference)	**1.43 (1.15–1.77)**	**1.30 (1.04–1.62)**	**1.42 (1.14–1.77)**	1.23 (0.98–1.55)	0.49
Multivariable HR (95% CI) [2]	1.00 (reference)	**1.33 (1.07–1.66)**	1.17 (0.93–1.47)	**1.26 (1.00–1.58)**	1.05 (0.83–1.33)	0.44
Women						
Cases/person-years	87/253,874	108/254,176	120/253,431	113/252,464	94/251,246	
Age-adjusted HR (95% CI)	1.00 (reference)	1.25 (0.94–1.66)	**1.39 (1.05–1.84)**	1.30 (0.98–1.74)	1.06 (0.79–1.43)	0.60
Multivariable HR (95% CI) [2]	1.00 (reference)	1.22 (0.91–1.62)	**1.33 (1.00–1.76)**	1.23 (0.91–1.65)	0.98 (0.72–1.33)	0.25

Variable	Quintile of daily meat intake (g/1,000 kcal)					*P* trend[3]
	1	2	3	4	5	
Meat cooked at high temperatures						
Men and women combined[4]						
Cases/person-years	245/598,389	264/596,728	293/595,287	301/593,045	314/590,684	
Age-adjusted HR (95% CI)	1.00 (reference)	1.08 (0.91–1.29)	**1.23 (1.03–1.46)**	**1.29 (1.09–1.54)**	**1.43 (1.20–1.70)**	**<0.0001**
Multivariable HR (95% CI) [2]	1.00 (reference)	1.02 (0.86–1.22)	1.12 (0.94–1.34)	1.15 (0.96–1.37)	**1.21 (1.00–1.46)**	**0.02**
Men						
Cases/person-years	146/344,080	161/343,002	174/341,836	210/340,482	204/339,542	
Age-adjusted HR (95% CI)	1.00 (reference)	1.12 (0.89–1.40)	1.24 (0.99–1.55)	**1.54 (1.24–1.91)**	**1.58 (1.27–1.97)**	**<0.0001**
Multivariable HR (95% CI) [2]	1.00 (reference)	1.04 (0.83–1.31)	1.11 (0.88–1.40)	**1.33 (1.06–1.68)**	**1.30 (1.03–1.66)**	**0.009**
Women						
Cases/person-years	99/254,309	103/253,725	119/253,451	91/252,563	110/251,142	
Age-adjusted HR (95% CI)	1.00 (reference)	1.04 (0.78–1.37)	1.20 (0.92–1.57)	0.94 (0.70–1.26)	1.20 (0.91–1.59)	0.30
Multivariable HR (95% CI) [2]	1.00 (reference)	0.99 (0.75–1.32)	1.13 (0.86–1.49)	0.87 (0.64–1.17)	1.07 (0.79–1.45)	0.85

[1] Cohort that successfully completed the meat module on the RFQ: n=322,846 subjects (1,417 cases), 187,265 men (895 cases), and 135,581 women (522 cases).

[2] Cox proportional hazard models used to calculate hazard ratios with age as the time metric. All nutrients are adjusted for energy by the density method with energy also in the model. Models are 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 cigarettes/day, quit <1 y ago or current and smoked >20 cigarettes/day, and missing), BMI (kg/m^2, <18.5, ≥18.5 and <25, ≥25 and <30, ≥30 and <35, ≥35, and missing), self-reported diabetes (yes, no), and energy-adjusted saturated fat (continuous) P value for interaction by sex: total meat = 0.46, red meat = 0.03, white meat = 0.26, processed meat = 0.34, high temperature cooked meat = 0.12.

[3] P trend calculated using median values for each quintile

[4] Sex combined models additionally adjusted for sex.

Table 3

Hazard ratios and 95% confidence intervals (CI) for meat-cooking methods and doneness levels in the NIH-AARP Diet and Health Study [1]

	Quintile of daily meat intake (g/1,000 kcal)					
Variable	**1**	**2**	**3**	**4**	**5**	***P* trend[3]**
Grilled or barbecued meat						
Men and women combined[4]						
Cases/person-years	280/590,431	287/594,951	266/595,472	278/596,239	306/597,039	
Age-adjusted HR (95% CI)	1.00 (reference)	1.07 (0.90–1.26)	1.02 (0.85–1.21)	1.11 (0.93–1.33)	**1.32 (1.10–1.59)**	**0.0005**
Multivariable HR (95% CI)[2]	1.00 (reference)	1.07 (0.90–1.26)	0.99 (0.83–1.18)	1.07 (0.89–1.28)	**1.24 (1.03–1.50)**	**0.007**
Men						
Cases/person-years	178/338,896	165/341,761	170/342,324	179/342,876	203/343,086	
Age-adjusted HR (95% CI)	1.00 (reference)	0.99 (0.80–1.24)	1.06 (0.85–1.33)	1.18 (0.94–1.47)	**1.43 (1.14–1.80)**	**0.0002**
Multivariable HR (95% CI) [2]	1.00 (reference)	0.99 (0.80–1.23)	1.03 (0.83–1.29)	1.12 (0.89–1.41)	**1.33 (1.05–1.68)**	**0.004**
Women						
Cases/person-years	102/251,536	122/253,191	96/253,148	99/253,363	103/253,953	
Age-adjusted HR (95% CI)	1.00 (reference)	1.18 (0.90–1.54)	0.94 (0.70–1.25)	1.00 (0.74–1.34)	1.12 (0.82–1.53)	0.57
Multivariable HR (95% CI) [2]	1.00 (reference)	1.18 (0.90–1.55)	0.93 (0.70–1.24)	0.98 (0.72–1.31)	1.09 (0.80–1.49)	0.71
Pan-fried meat **(quartiles)**						
Men and women combined[4]						
Cases/person-years	526/1,102,279	207/472,711	215/469,921	233/465,750	236/463,472	
Age-adjusted HR (95% CI)	1.00 (reference)	0.98 (0.83–1.15)	1.01 (0.86–1.19)	1.08 (0.92–1.27)	1.14 (0.96–1.34)	0.10
Multivariable HR (95% CI) [2]	1.00 (reference)	0.98 (0.83–1.16)	0.98 (0.83–1.16)	1.01 (0.86–1.19)	1.02 (0.86–1.21)	0.71
Men						
Cases/person-years	319/594,905	124/281,626	135/279,941	161/277,080	156/275,390	
Age-adjusted HR (95% CI)	1.00 (reference)	0.90 (0.73–1.11)	0.97 (0.78–1.19)	1.14 (0.94–1.39)	1.18 (0.96–1.44)	0.06
Multivariable HR (95% CI) [2]	1.00 (reference)	0.91 (0.73–1.13)	0.93 (0.75–1.15)	1.05 (0.86–1.29)	1.04 (0.84–1.29)	0.51
Women						
Cases/person-years	207/507,374	83/191,085	80/189,980	72/186,670	80/188,082	
Age-adjusted HR (95% CI)	1.00 (reference)	1.12 (0.86–1.45)	1.11 (0.85–1.44)	0.98 (0.74–1.28)	1.07 (0.81–1.40)	0.86

Variable	Quintile of daily meat intake (g/1,000 kcal)					P trend[3]
	1	2	3	4	5	
Multivariable HR (95% CI) [2]	1.00 (reference)	1.13 (0.87–1.46)	1.08 (0.83–1.41)	0.92 (0.70–1.22)	0.99 (0.74–1.31)	0.74
Oven-broiled meat **(tertiles)**						
Men and women combined[4]						
Cases/person-years	838/1,818,804	205/384,723	170/385,123	204/385,483	--	
Age-adjusted HR (95% CI)	1.00 (reference)	1.15 (0.99–1.35)	0.96 (0.81–1.14)	**1.19 (1.01–1.41)**	--	0.09
Multivariable HR (95% CI) [2]	1.00 (reference)	1.13 (0.96–1.32)	0.93 (0.78–1.11)	1.15 (0.97–1.36)	--	0.16
Men						
Cases/person-years	507/1,013,280	132/231,299	107/232,031	149/232,331	--	
Age-adjusted HR (95% CI)	1.00 (reference)	1.18 (0.97–1.44)	0.96 (0.77–1.19)	**1.39 (1.14–1.70)**	--	**0.006**
Multivariable HR (95% CI) [2]	1.00 (reference)	1.15 (0.94–1.40)	0.93 (0.75–1.16)	**1.34 (1.09–1.64)**	--	**0.01**
Women						
Cases/person-years	331/805,524	73/153,423	63/153,091	55/153,152	--	
Age-adjusted HR (95% CI)	1.00 (reference)	1.10 (0.85–1.43)	0.96 (0.73–1.27)	0.86 (0.63–1.17)	--	0.35
Multivariable HR (95% CI) [2]	1.00 (reference)	1.08 (0.83–1.40)	0.93 (0.71–1.24)	0.84 (0.61–1.14)	--	0.28
Sautéed, baked or microwaved meat **(quartiles)**						
Men and women combined[4]						
Cases/person-years	589/1,291,368	208/420,332	215/419,049	194/420,675	211/422,710	
Age-adjusted HR (95% CI)	1.00 (reference)	1.12 (0.94–1.32)	1.17 (0.99–1.37)	1.06 (0.89–1.25)	**1.18 (1.00–1.40)**	0.10
Multivariable HR (95% CI) [2]	1.00 (reference)	1.09 (0.92–1.29)	1.13 (0.96–1.33)	1.03 (0.87–1.23)	1.17 (0.99–1.39)	0.08
Men						
Cases/person-years	430/865,872	119/210,873	130/209,788	106/210,391	110/212,018	
Age-adjusted HR (95% CI)	1.00 (reference)	1.13 (0.91–1.40)	**1.28 (1.04–1.56)**	1.06 (0.85–1.33)	1.13 (0.91–1.42)	0.46
Multivariable HR (95% CI) [2]	1.00 (reference)	1.10 (0.89–1.37)	**1.22 (1.00–1.50)**	1.03 (0.83–1.29)	1.12 (0.90–1.40)	0.45
Women						
Cases/person-years	159/425,495	89/209,458	85/209,261	88/210,284	101/210,692	
Age-adjusted HR (95% CI)	1.00 (reference)	1.09 (0.84–1.43)	0.98 (0.75–1.30)	1.01 (0.77–1.33)	1.18 (0.90–1.55)	0.21
Multivariable HR (95% CI) [2]	1.00 (reference)	1.07 (0.82–1.41)	0.97 (0.73–1.27)	1.00 (0.76–1.32)	1.19 (0.91–1.55)	0.17

Variable	Quintile of daily meat intake (g/1,000 kcal)					*P* trend[3]
	1	2	3	4	5	
Rare/medium done cooked meat						
Men and women combined[4]						
Cases/person-years	374/793,313	237/544,683	271/545,249	265/544,831	270/546,056	
Age-adjusted HR (95% CI)	1.00 (reference)	0.95 (0.80–1.12)	1.11 (0.94–1.30)	1.12 (0.95–1.33)	**1.21 (1.01–1.44)**	**0.01**
Multivariable HR (95% CI) [2]	1.00 (reference)	0.96 (0.81–1.13)	1.10 (0.94–1.29)	1.11 (0.94–1.31)	1.17 (0.99–1.40)	**0.03**
Men						
Cases/person-years	227/439,578	154/316,768	168/317,124	168/317,341	178/318,132	
Age-adjusted HR (95% CI)	1.00 (reference)	1.00 (0.81–1.23)	1.12 (0.91–1.38)	1.16 (0.94–1.44)	**1.31 (1.05–1.63)**	**0.01**
Multivariable HR (95% CI) [2]	1.00 (reference)	1.01 (0.82–1.24)	1.10 (0.90–1.36)	1.13 (0.91–1.40)	1.23 (0.99–1.54)	**0.05**
Women						
Cases/person-years	147/353,736	83/227,915	103/228,125	97/227,490	92/227,924	
Age-adjusted HR (95% CI)	1.00 (reference)	0.88 (0.67–1.15)	1.09 (0.84–1.42)	1.05 (0.80–1.39)	1.04 (0.77–1.40)	0.37
Multivariable HR (95% CI) [2]	1.00 (reference)	0.89 (0.67–1.16)	1.11 (0.85–1.43)	1.08 (0.82–1.41)	1.07 (0.80–1.42)	0.35
Well/very well-done cooked meat						
Men and women combined[4]						
Cases/person-years	254/595,971	302/593,133	264/593,450	277/595,427	320/596,152	
Age-adjusted HR (95% CI)	1.00 (reference)	**1.20 (1.01–1.43)**	1.07 (0.90–1.29)	1.14 (0.95–1.37)	**1.37 (1.14–1.65)**	**0.003**
Multivariable HR (95% CI) [2]	1.00 (reference)	1.16 (0.97–1.37)	1.03 (0.86–1.23)	1.11 (0.92–1.33)	**1.32 (1.10–1.58)**	**0.005**
Men						
Cases/person-years	159/342,670	180/340,844	165/341,142	191/342,311	200/341,975	
Age-adjusted HR (95% CI)	1.00 (reference)	1.16 (0.93–1.44)	1.10 (0.87–1.38)	**1.30 (1.04–1.63)**	**1.42 (1.13–1.79)**	**0.003**
Multivariable HR (95% CI) [2]	1.00 (reference)	1.11 (0.89–1.37)	1.04 (0.82–1.30)	1.23 (0.98–1.55)	**1.33 (1.05–1.67)**	**0.01**
Women						
Cases/person-years	95/253,300	122/252,289	99/252,308	86/253,115	120/254,178	
Age-adjusted HR (95% CI)	1.00 (reference)	1.26 (0.96–1.66)	1.03 (0.76–1.38)	0.89 (0.65–1.22)	1.27 (0.94–1.73)	0.29
Multivariable HR (95% CI) [2]	1.00 (reference)	1.23 (0.94–1.62)	1.02 (0.76–1.37)	0.90 (0.66–1.23)	1.30 (0.97–1.75)	0.23

[1] Cohort that successfully completed the meat module questions on the RFQ: n=322,846 subjects (1,417 cases), 187,265 men (895 cases), and 135,581 women (522 cases).

[2]Cox proportional hazard models used to calculate hazard ratios with age as the time metric. All nutrients are adjusted for energy by the density method with energy also in the model. Models are 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 cigarettes/day, quit <1 y ago or current and smoked >20 cigarettes/day, and missing), BMI (kg/m^2, <18.5, ≥18.5 and <25, ≥25 and <30, ≥30 and <35, ≥35, and missing), self-reported diabetes (yes, no), and energy-adjusted saturated fat (continuous). P value for interaction by sex: grilled/barbequed meat = 0.31, pan-fried meat = 0.45, broiled meat = 0.07, microwaved meat = 0.23, rare/medium done cooked meat = 0.66, well/very well-done cooked meat = 0.54.

[3]P trend calculated using median values for each quintile

[4]Sex combined models additionally adjusted for sex.

Table 4

Hazard ratios and 95% confidence intervals (CI) for heme iron and meat mutagen intake in the NIH-AARP Diet and Health Study [1]

Variable	Quintile of heme intake (mg/1,000 kcal) or daily meat mutagen intake (ng/1,000 kcal) 1	2	3	4	5	*P* trend[3]
Heme iron intake (mg/1,000 kcal)						
Men and women combined[4]						
Cases/person-years	241/296,684	274/596,346	302/596,125	301/593,768	299/591,211	
Age-adjusted HR (95% CI)	1.00 (reference)	1.14 (0.96–1.35)	**1.28 (1.08–1.52)**	**1.32 (1.11–1.56)**	**1.38 (1.17–1.64)**	**<0.0001**
Multivariable HR (95% CI) [2]	1.00 (reference)	1.07 (0.90–1.28)	1.18 (0.99–1.40)	1.17 (0.98–1.39)	1.17 (0.97–1.41)	0.08
Men						
Cases/person-years	146/342,879	166/342,461	193/342,647	192/341,077	198/339,879	
Age-adjusted HR (95% CI)	1.00 (reference)	1.14 (0.91–1.43)	**1.36 (1.10–1.69)**	**1.39 (1.12–1.73)**	**1.52 (1.22–1.88)**	**<0.0001**
Multivariable HR (95% CI) [2]	1.00 (reference)	1.06 (0.85–1.33)	1.22 (0.98–1.53)	1.21 (0.96–1.51)	1.24 (0.98–1.57)	0.07
Women						
Cases/person-years	95/253,805	108/253,884	109/253,478	109/252,690	101/251,332	
Age-adjusted HR (95% CI)	1.00 (reference)	1.13 (0.86–1.49)	1.16 (0.88–1.53)	1.20 (0.91–1.58)	1.18 (0.89–1.56)	0.28
Multivariable HR (95% CI) [2]	1.00 (reference)	1.09 (0.83–1.44)	1.10 (0.83–1.46)	1.11 (0.84–1.48)	1.06 (0.78–1.43)	0.82
Heme from red meat (mg/1,000 kcal)						
Men and women combined[4]						
Cases/person-years	238/597,849	282/596,472	278/595,592	312/593,486	307/590,734	
Age-adjusted HR (95% CI)	1.00 (reference)	**1.19 (1.00–1.41)**	**1.20 (1.01–1.42)**	**1.38 (1.16–1.63)**	**1.43 (1.20–1.70)**	**<0.0001**
Multivariable HR (95% CI) [2]	1.00 (reference)	1.12 (0.94–1.33)	1.09 (0.91–1.30)	**1.21 (1.01–1.45)**	1.20 (0.99–1.44)	**0.04**
Men						
Cases/person-years	140/343,676	173/342,480	176/342,084	204/341,016	202/339,687	
Age-adjusted HR (95% CI)	1.00 (reference)	**1.25 (1.00–1.56)**	**1.30 (1.04–1.63)**	**1.55 (1.25–1.92)**	**1.62 (1.30–2.01)**	**<0.0001**
Multivariable HR (95% CI) [2]	1.00 (reference)	1.16 (0.93–1.46)	1.17 (0.93–1.47)	**1.34 (1.06–1.69)**	**1.32 (1.04–1.69)**	**0.02**
Women						
Cases/person-years	98/254,173	109/253,993	102/253,508	108/252,470	105/251,047	
Age-adjusted HR (95% CI)	1.00 (reference)	1.10 (0.84–1.45)	1.04 (0.79–1.38)	1.13 (0.86–1.49)	1.16 (0.88–1.53)	0.30

Variable	Quintile of heme intake (mg/1,000 kcal) or daily meat mutagen intake (ng/1,000 kcal)					*P* trend[3]
	1	2	3	4	5	
Multivariable HR (95% CI) [2]	1.00 (reference)	1.06 (0.80–1.39)	0.97 (0.73–1.30)	1.03 (0.77–1.38)	1.02 (0.75–1.38)	0.94
Overall mutagenic activity (revertant colonies/1,000 kcal)						
Men and women combined[4]						
Cases/person-years	258/595,113	297/593,480	290/593,917	281/594,746	291/596,878	
Age-adjusted HR (95% CI)	1.00 (reference)	**1.18 (1.00–1.39)**	**1.18 (1.00–1.40)**	1.18 (0.99–1.39)	**1.26 (1.06–1.49)**	**0.03**
Multivariable HR (95% CI) [2]	1.00 (reference)	1.11 (0.94–1.31)	1.09 (0.92–1.29)	1.07 (0.90–1.27)	1.13 (0.95–1.34)	0.28
Men						
Cases/person-years	143/341,599	197/340,877	175/341,981	190/341,495	190/342,990	
Age-adjusted HR (95% CI)	1.00 (reference)	**1.41 (1.13–1.75)**	**1.28 (1.03–1.60)**	**1.43 (1.15–1.77)**	**1.47 (1.18–1.83)**	**0.008**
Multivariable HR (95% CI) [2]	1.00 (reference)	**1.32 (1.06–1.64)**	1.17 (0.94–1.47)	**1.28 (1.03–1.60)**	**1.30 (1.04–1.63)**	0.13
Women						
Cases/person-years	115/253,513	100/252,603	115/251,937	91/253,251	101/253,887	
Age-adjusted HR (95% CI)	1.00 (reference)	0.89 (0.68–1.17)	1.06 (0.82–1.37)	0.86 (0.65–1.13)	0.99 (0.75–1.29)	0.98
Multivariable HR (95% CI) [2]	1.00 (reference)	0.85 (0.65–1.12)	1.00 (0.76–1.30)	0.80 (0.60–1.06)	0.92 (0.70–1.21)	0.71
DiMeIQx** (ng/1,000 kcal) (**quartiles**)						
Men and women combined[4]						
Cases/person-years	494/1,076,064	217/475,182	218/474,216	240/474,017	244/474,653	
Age-adjusted HR (95% CI)	1.00 (reference)	0.95 (0.81–1.12)	0.98 (0.83–1.14)	1.10 (0.95–1.29)	1.16 (0.99–1.35)	**0.02**
Multivariable HR (95% CI) [2]	1.00 (reference)	0.97 (0.82–1.13)	0.96 (0.82–1.13)	1.06 (0.91–1.24)	1.09 (0.94–1.27)	0.13
Men						
Cases/person-years	306/602,034	134/277,205	132/276,672	158/276,640	165/276,392	
Age-adjusted HR (95% CI)	1.00 (reference)	0.93 (0.76–1.13)	0.93 (0.75–1.12)	1.14 (0.94–1.38)	**1.22 (1.01–1.48)**	**0.007**
Multivariable HR (95% CI) [2]	1.00 (reference)	0.94 (0.77–1.16)	0.91 (0.74–1.12)	1.09 (0.90–1.33)	1.14 (0.95–1.38)	0.07
Women						
Cases/person-years	192/474,030	83/197,978	86/197,544	82/197,377	79/198,261	
Age-adjusted HR (95% CI)	1.00 (reference)	1.01 (0.78–1.30)	1.06 (0.83–1.37)	1.04 (0.81–1.35)	1.04 (0.80–1.35)	0.80
Multivariable HR (95% CI) [2]	1.00 (reference)	1.01 (0.78–1.31)	1.05 (0.81–1.36)	1.02 (0.78–1.32)	1.00 (0.77–1.31)	0.99

Variable	Quintile of heme intake (mg/1,000 kcal) or daily meat mutagen intake (ng/1,000 kcal)					*P* trend[3]
	1	2	3	4	5	
MeIQx (ng/1,000 kcal)						
Men and women combined[4]						
Cases/person-years	266/595,605	269/595,642	287/595,857	309/593,701	286/592,328	
Age-adjusted HR (95% CI)	1.00 (reference)	1.03 (0.87–1.22)	1.11 (0.94–1.31)	**1.22 (1.04–1.44)**	**1.16 (0.98–1.37)**	**0.04**
Multivariable HR (95% CI) [2]	1.00 (reference)	1.00 (0.84–1.18)	1.04 (0.88–1.24)	1.12 (0.95–1.32)	1.02 (0.86–1.21)	0.73
Men						
Cases/person-years	162/342,183	162/343,158	181/342,592	205/341,273	185/339,735	
Age-adjusted HR (95% CI)	1.00 (reference)	1.02 (0.82–1.26)	1.15 (0.93–1.42)	**1.32 (1.08–1.63)**	**1.23 (1.00–1.52)**	**0.03**
Multivariable HR (95% CI) [2]	1.00 (reference)	0.98 (0.79–1.22)	1.06 (0.86–1.32)	1.19 (0.96–1.47)	1.05 (0.84–1.31)	0.54
Women						
Cases/person-years	104/253,421	107/253,483	106/253,365	104/252,428	101/252,593	
Age-adjusted HR (95% CI)	1.00 (reference)	1.06 (0.81–1.38)	1.06 (0.81–1.38)	1.06 (0.81–1.39)	1.05 (0.80–1.38)	0.84
Multivariable HR (95% CI) [2]	1.00 (reference)	1.04 (0.79–1.36)	1.02 (0.78–1.34)	1.01 (0.76–1.33)	0.97 (0.73–1.29)	0.69
PhIP (ng/1,000 kcal)						
Men and women combined[4]						
Cases/person-years	282/592,538	286/594,293	289/594,297	268/595,216	292/597,790	
Age-adjusted HR (95% CI)	1.00 (reference)	1.03 (0.88–1.22)	1.08 (0.91–1.27)	1.02 (0.86–1.21)	1.14 (0.97–1.35)	0.10
Multivariable HR (95% CI) [2]	1.00 (reference)	0.99 (0.84–1.16)	1.01 (0.85–1.19)	0.95 (0.80–1.12)	1.06 (0.89–1.25)	0.39
Men						
Cases/person-years	164/340,098	185/341,296	187/341,818	160/342,443	199/343,287	
Age-adjusted HR (95% CI)	1.00 (reference)	1.14 (0.93–1.41)	1.19 (0.96–1.46)	1.03 (0.83–1.29)	**1.32 (1.07–1.62)**	**0.03**
Multivariable HR (95% CI) [2]	1.00 (reference)	1.08 (0.87–1.34)	1.10 (0.89–1.36)	0.94 (0.76–1.18)	1.20 (0.97–1.48)	0.16
Women						
Cases/person-years	118/252,440	101/252,996	102/252,479	108/252,772	93/254,504	
Age-adjusted HR (95% CI)	1.00 (reference)	0.88 (0.68–1.15)	0.92 (0.71–1.20)	1.01 (0.78–1.31)	0.90 (0.68–1.18)	0.72
Multivariable HR (95% CI) [2]	1.00 (reference)	0.85 (0.65–1.11)	0.88 (0.67–1.15)	0.95 (0.73–1.24)	0.85 (0.64–1.12)	0.52

Variable	Quintile of heme intake (mg/1,000 kcal) or daily meat mutagen intake (ng/1,000 kcal) 1	2	3	4	5	*P* trend[3]
BaP (ng/1,000 kcal)						
Men and women combined[4]						
Cases/person-years	308/590,261	282/593,461	282/595,836	260/597,161	285/597,413	
Age-adjusted HR (95% CI)	1.00 (reference)	0.93 (0.79–1.09)	0.94 (0.80–1.11)	0.89 (0.76–1.05)	1.04 (0.88–1.22)	0.37
Multivariable HR (95% CI) [2]	1.00 (reference)	0.92 (0.78–1.08)	0.95 (0.81–1.12)	0.88 (0.74–1.04)	0.98 (0.83–1.16)	0.86
Men						
Cases/person-years	199/338,320	178/341,441	172/342,464	162/343,290	184/343,427	
Age-adjusted HR (95% CI)	1.00 (reference)	0.90 (0.74–1.11)	0.89 (0.72–1.09)	0.85 (0.69–1.05)	1.02 (0.83–1.25)	0.46
Multivariable HR (95% CI) [2]	1.00 (reference)	0.90 (0.74–1.11)	0.90 (0.73–1.11)	0.84 (0.68–1.03)	0.95 (0.78–1.17)	0.94
Women						
Cases/person-years	109/251,941	104/252,020	110/253,372	98/253,871	101/253,986	
Age-adjusted HR (95% CI)	1.00 (reference)	0.98 (0.75–1.28)	1.04 (0.80–1.36)	0.97 (0.74–1.27)	1.07 (0.81–1.40)	0.27
Multivariable HR (95% CI) [2]	1.00 (reference)	0.96 (0.73–1.25)	1.05 (0.80–1.37)	0.96 (0.73–1.26)	1.04 (0.79–1.37)	0.74

[1]Cohort that successfully completed the meat module questions on the RFQ: n=322,846 subjects (1,417 cases), 187,265 men (895 cases), and 135,581 women (522 cases).

[2]Cox proportional hazard models used to calculate hazard ratios. All nutrients are adjusted for energy by the density method with energy also in the model. Models are 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 cigarettes/day, quit <1 y ago or current and smoked >20 cigarettes/day, and missing), BMI (kg/m^2, <18.5, ≥18.5 and <25, ≥25 and <30, ≥30 and <35, ≥35, and missing), self-reported diabetes (yes, no), and energy-adjusted saturated fat (continuous). P value for interaction by sex: heme iron = 0.17, heme iron from red meat = 0.11, overall mutagenic activity = 0.15, DiMeIQx = 0.25, MeIQx = 0.32, PhIP = 0.12, BaP = 0.96

[3]P trend calculated using median values for each quintile

[4]Sex combined models additionally adjusted for sex.

Table 5

Multivariable adjusted hazard ratios (HR) and 95% confidence intervals (CI) for total meat intake by smoking and joint effects in the NIH-AARP Diet and Health Study [1,2]

Smoking status		Quintile of daily meat intake (g/1,000 kcal)					*P* trend[3]
		1	2	3	4	5	
Men and Women Combined[4]	Stratified by smoking						
	Never (n=411)	1.00 (reference)	0.96 (0.72–1.29)	0.79 (0.58–1.08)	0.94 (0.69–1.27)	0.90 (0.66–1.23)	0.53
	Former (n=736)	1.00 (reference)	1.19 (0.93–1.52)	1.20 (0.94–1.53)	1.22 (0.95–1.56)	**1.45 (1.14–1.83)**	**0.004**
	Current (n=224)	1.00 (reference)	0.80 (0.52–1.24)	0.94 (0.61–1.43)	0.89 (0.58–1.36)	1.15 (0.76–1.73)	0.33
	Joint Effects						
	Never	1.00 (reference)	0.97 (0.72–1.29)	0.79 (0.58–1.08)	0.94 (0.69–1.26)	0.90 (0.66–1.22)	
	Former	1.58 (0.99–2.53)	**1.90 (1.20–3.01)**	**1.91 (1.20–3.03)**	**1.94 (1.22–3.09)**	**2.32 (1.46–3.67)**	
	Current	**2.43 (1.64–3.60)**	**1.94 (1.29–2.92)**	**2.26 (1.53–3.35)**	**2.14 (1.44–3.17)**	**2.77 (1.91–4.01)**	
Men	Stratified by smoking						
	Never (n=215)	1.00 (reference)	0.91 (0.61–1.35)	0.69 (0.45–1.06)	0.75 (0.49–1.14)	0.75 (0.49–1.15)	0.14
	Former (n=522)	1.00 (reference)	1.25 (0.94–1.66)	1.19 (0.89–1.59)	1.10 (0.81–1.49)	**1.44 (1.08–1.92)**	**0.04**
	Current (n=127)	1.00 (reference)	0.98 (0.53–1.79)	1.12 (0.62–2.03)	1.11 (0.61–2.01)	1.55 (0.88–2.73)	0.08
	Joint Effects						
	Never	1.00 (reference)	0.94 (0.63–1.39)	0.72 (0.47–1.10)	0.79 (0.52–1.20)	0.81 (0.53–1.23)	
	Former	1.73 (0.96–3.11)	**2.14 (1.20–3.84)**	**2.04 (1.14–3.67)**	**1.89 (1.05–3.41)**	**2.47 (1.38–4.42)**	
	Current	**2.38 (1.41–4.03)**	**2.20 (1.29–3.75)**	**2.50 (1.50–4.18)**	**2.42 (1.46–4.02)**	**3.33 (2.10–5.28)**	
Women	Stratified by smoking						
	Never (n=196)	1.00 (reference)	1.03 (0.67–1.59)	0.92 (0.58–1.45)	1.18 (0.77–1.83)	1.09 (0.69–1.72)	0.57
	Former (n=214)	1.00 (reference)	1.04 (0.65–1.68)	1.21 (0.77–1.92)	1.50 (0.96–2.33)	1.45 (0.93–2.27)	**0.03**
	Current (n=97)	1.00 (reference)	0.66 (0.35–1.24)	0.79 (0.43–1.44)	0.71 (0.38–1.33)	0.81 (0.44–1.50)	0.67
	Joint Effects						
	Never	1.00 (reference)	1.01 (0.65–1.55)	0.89 (0.57–1.39)	1.13 (0.74–1.73)	1.02 (0.65–1.61)	
	Former	1.10 (0.49–2.45)	1.16 (0.52–2.58)	1.36 (0.62–3.00)	1.68 (0.77–3.67)	1.63 (0.75–3.55)	
	Current	**1.94 (1.02–3.66)**	1.32 (0.67–2.59)	1.58 (0.83–3.03)	1.44 (0.74–2.79)	1.65 (0.86–3.17)	

[1]Cohort that successfully completed the meat module and smoking questions on the RFQ: n=312,033 subjects (1,371 cases), 180,666 men (864 cases), and 131,367 women (507 cases).

[2]Cox proportional hazard models used to calculate hazard ratios with age as the time metric. All nutrients are adjusted for energy by the density method with energy also in the model. Models are 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 cigarettes/day, quit <1 y ago or current and smoked >20 cigarettes/day, and missing), BMI (kg/m^2, <18.5, ≥18.5 and <25, ≥25 and <30, ≥30 and <35, ≥35, and missing), self-reported diabetes (yes, no), and energy-adjusted saturated fat (continuous). P value for interaction by smoking: men and women combined = 0.07, men = 0.01, women = 0.99.

[3]P trend calculated using median values for each quintile

[4]Sex combined models additionally adjusted for sex.