A prospective study of meat, cooking methods, meat mutagens, heme iron, and lung cancer risks[1–3]

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ABSTRACT

Background: Red and processed meat consumption may play a role in lung cancer pathogenesis because of these meats' fat and carcinogen content.

Objective: We prospectively investigated whether meat type, cooking method, doneness level, and intake of specific meat mutagens and heme iron are associated with lung carcinoma.

Design: Men (n = 278,380) and women (n = 189,596) from the National Institutes of Health–AARP Diet and Health Study with no history of cancer at baseline were monitored for 8 y. Diet was assessed with a 124-item food-frequency questionnaire. A meat-cooking module was used to estimate the intake of individual heterocyclic amines, benzo(a)pyrene, and heme iron. Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% CIs.

Results: In a comparison of quintiles 5 with 1 (Q5vsQ1), a high intake of red meat was associated with an increased risk of lung carcinoma in both men (HR_{Q5vsQ1}: 1.22; 95% CI: 1.09, 1.38; P for trend = 0.005) and women (HR_{Q5vsQ1}: 1.13; 95% CI: 0.97, 1.32; P for trend = 0.05). A high intake of processed meat increased the risk only in men (HR_{Q5vsQ1}: 1.23; 95% CI: 1.10, 1.37; P for trend = 0.003). In an analysis stratified by smoking status, we observed a tendency for an increased risk with red meat intake in never smoking men and women; however, the risks were not statistically significant. In a comparison of tertiles 3 and 1 (T3vsT1), the risk of lung carcinoma was associated with intake of well-/very-well-done meat (HR_{T3vsT1}: 1.20; 95% CI: 1.07, 1.35; P for trend = 0.002) and the intake of 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (HR_{Q5vsQ1}: 1.20; 95% CI: 1.04, 1.38; P for trend = 0.04) in men. Heme iron intake increased the risk of lung carcinoma in both men (HR_{Q5vsQ1}: 1.25; 95% CI: 1.07, 1.45; P for trend = 0.02) and women (HR_{Q5vsQ1}: 1.18; 95% CI: 0.99, 1.42; P for trend = 0.002).

Conclusion: We observed a moderate association between meat consumption and lung carcinoma, which might be explained by heme iron intake, high-temperature cooking, and associated mutagens. *Am J Clin Nutr* 2009;89:1884–94.

INTRODUCTION

Lung cancer is the leading cause of cancer death worldwide (1). Smoking is by far the most important risk factor for lung cancer, to which 85% of all cases can be attributed (2); however, diet may also play a role.

A recent notable review of the evidence on diet and cancer concluded that fruit and foods containing carotenoids are probable protective factors for lung cancer, and there is limited suggestive evidence that nonstarchy vegetables and foods containing selenium and quercetin may be protective. Meat and fat, however, may be risk factors for lung cancer (2).

Red and processed meat intakes have been hypothesized to play a role in carcinogenesis because of these meats' fat content, the carcinogens produced during high-temperature cooking (3–6) and preservation (7, 8), and the endogenous formation of mutagens from heme present in meat (9). Many case-control (6, 10–21) and cohort (22–26) studies have investigated the association between meat intake and lung cancer, with inconclusive findings. However, most previous studies were based on limited dietary data. Detailed information on meat cooking was available in only one case-control study (6) and in no cohort studies. Such data are essential to assess the carcinogenic potential of different types of meat and to elucidate possible mechanisms.

In a recent analysis of multiple cancer sites in ≈0.5 million participants of the National Institutes of Health (NIH)–AARP Diet and Health Study, Cross et al (27) found an elevated risk of lung cancer for the highest compared with the lowest quintile of red (1.20; 95% CI: 1.10, 1.31) and processed meat (1.16; 95% CI: 1.06, 1.26) intakes. In the present study, we extended the analysis using detailed dietary data on meat cooking methods and doneness level to further investigate the association between

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meat and lung cancer. The detailed questionnaire enabled us to assess intakes of different types of meat, heme iron, and meat mutagens, including heterocyclic amines (HCAs) and the polycyclic aromatic hydrocarbon (PAH) benzo(a)pyrene (B(a)P), and an overall meat-mutagenic activity index. The large sample size allowed us to study the effect of meat by smoking strata and histologic subtypes of lung cancer.

SUBJECTS AND METHODS

Study population

The NIH-AARP Diet and Health Study is a prospective cohort study of men and women aged 50–71 y from 8 states in the United States (California, Florida, Louisiana, New Jersey, North Carolina, Michigan, Georgia, and Pennsylvania). Recruitment began in 1995 when a self-administered baseline questionnaire, including questions on demographic characteristics, personal and family medical history, diet, and other lifestyle factors, was mailed to 3.5 million members of the AARP. The questionnaire was returned by 617,119 members, of whom 567,169 completed the questionnaire satisfactorily. Further details of the recruitment and the study design are reported elsewhere (28). The NIH-AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the US National Cancer Institute, and written informed consent was obtained from all participants by means of completing the baseline questionnaire.

Cohort follow-up and case ascertainment

Cohort members were followed annually for change of address by using the US Postal Service and the Maximum Change of Address database (MaxCoA; maintained by Anchor Computer). Additional information on change of address was received directly from participants who reported address changes when responding to a study mailing, such as follow-up questionnaires or newsletters. Follow-up was calculated from baseline (1995–1996) until censoring at the end of 2003 or when the participant moved out of one of the study areas, had a cancer diagnosis, or died, whichever came first. In addition, we expanded our cancer registry ascertainment area by 3 states (Arizona, Nevada, and Texas) to capture cancer cases occurring among participants who moved to those states during follow-up. Approximately 4% of participants were lost to follow-up. Vital status was ascertained by annual linkage to the US Social Security Administration Death Master File and follow-up searches of the National Death Index (NDI). Cancer cases were identified by linkage to 11 state cancer registries and the NDI Plus. The state cancer registry databases are estimated to be $\geq$90% complete within 2 y of cancer incidence (29). For this analysis, we included all incident cases of primary epithelial lung and bronchial carcinoma [International Classification of Diseases (ICD) codes 34.0 to 34.9] (30). By histologic subtype, the cases were grouped as small cell (8002, 8041, 8042, 8043, 8044, and 8045), adenocarcinoma (bronchoalveolar: 8250, 8251, 8253, and 8254; and other: 8140, 8200, 8231, 8255, 8260, 8290, 8310, 8323, 8430, 8480, 8481, 8490, 8550, and 8574), squamous (8050, 8070, 8071, 8072, 8073, 8074, 8075, and 8084), undifferentiated/large cell (8012, 8014, 8020, 8021, 8022, 8031, and 8032), other or not otherwise specified carcinoma (NOS) (8010, 8011, 8033, 8046, 8123, 8560, and 8562), sarcoma (8800, 8801, 8830, 8890, 8972, 8980, 9120), neuroendocrine (8246), and carcinoid (8240, 8244, and 8249) tumors. We excluded a total of 659 cases of sarcoma and neuroendocrine and carcinoid tumors, because of their potentially different etiologies.

Dietary assessment

A self-administered semiquantitative food-frequency questionnaire (FFQ) with 124 food items (31) was sent at baseline to assess the participants' usual diet over the previous 12 mo. The FFQ was calibrated in a substudy of 1415 participants by using 2 nonconsecutive 24-h dietary recalls (28). The correlations between red meat intake from the FFQ and the 24-h dietary recalls, adjusted for random within-person error, were 0.62 in men and 0.70 in women.

A second FFQ was mailed within 6 mo of the baseline questionnaire to all participants, of whom 332,913 responded. The second FFQ contained a meat-cooking module with detailed questions on cooking methods and the doneness level of certain meats (ie, hamburgers, steak, bacon, and chicken). We used the CHARRED-database (http://charred.cancer.gov/) along with the meat-cooking module to estimate the intake of HCAs—2-amino-3,4,8-trimethylimidazo[4,5-*f*]quinoxaline (DiMeIQx); 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (MeIQx); and 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP)—, the PAH [B(a)P], and the overall mutagenic activity (revertant colonies per gram of daily meat intake) (32). The CHARRED database was developed from laboratory analyzed values of HCAs, B(a)P, and overall mutagenic activity from $\approx$120 categories of meat samples prepared by different cooking methods with varying doneness levels (4, 5, 33, 34). Heme iron was estimated by using preliminary data from a National Cancer Institute database based on measured values from meat samples (33) for all meats with known cooking information from the meat-cooking module and from pork chops, sausages, and hotdogs. The relative validity of the meat cooking module at estimating the intake of HCAs was assessed in 165 healthy participants; the de-attenuated correlation coefficients were 0.60 and 0.36 for MeIQx and PhIP, respectively (35).

Statistical analysis

We excluded subjects with duplicate questionnaires ($n = 179$), those who moved out of the study areas or died before baseline ($n = 582$), those who withdrew from the study ($n = 6$), those who were proxy responders ($n = 15{,}760$), prevalent cases of any cancer except nonmelanoma skin cancer ($n = 51{,}193$), those who reported end-stage renal disease at baseline ($n = 997$), subjects who died before the questionnaire was received ($n = 3876$), those with zero person-years ($n = 11$), and those who provided no information on smoking ($n = 19{,}096$). We further excluded subjects with implausible energy intakes (beyond twice the interquartile range of sex-specific Box-Cox transformed intake) ($n = 3897$). The same exclusion criteria was applied for those at the upper end of the intake distribution for energy-adjusted saturated fat ($n = 491$), fruit ($n = 744$), and vegetable servings ($n = 1702$). In the analyses with meat as a continuous variable, we also excluded subjects at the upper end for red, white, processed, or unprocessed meat intake after Box-Cox transformation ($n = 2790$). Our final baseline cohort consisted of 278,380 men and 189,596 women.

Completed meat-cooking modules were available for 168,879 men and 121,493 women.

Sex-specific Cox proportional hazards regression models, with age as the underlying time metric, were used to estimate hazard ratios (HRs) and 95% CIs by sex. The baseline meat and meat mutagen variables were categorized into quintiles based on sex-specific cutoffs within the cohort, whereas meat intake by cooking methods was categorized into tertiles because of the smaller ranges of intake. After testing for an interaction between sex and red meat intake for all the covariates, we found several statistically significant interactions; therefore, all findings are presented by sex. The multivariable models were developed by individually entering potential confounders into a basic model with age, energy, and red and white meat. Variables remained in the model if they were established risk factors for lung cancer (race, education, and smoking) or if they changed the risk estimate by $\geq$10% or were considered potential risk factors for lung carcinoma (body mass index, physical activity, and fruit, vegetable, alcohol, and saturated fat intakes). Definition of the covariates are listed in the tables. All dietary variables, except alcohol, were energy adjusted by using the nutrient density method. Because of the high proportion of zero values for alcohol, we modeled alcohol intake using 2 variables: *1*) a binary variable that equalled 1 if alcohol intake was $<$0.09 g/d or equalled 0 otherwise and *2*) a continuous variable where a value of 0 was imputed in participants with alcohol intake $<$0.09 g/d. To test for heterogeneity, we used Cochran's Q statistics (36).

Smoking

The baseline questionnaire queried about whether participants had smoked $>$100 cigarettes during their life (ever smokers), about smoking intensity (cigarettes smoked per day), whether they were currently smoking, and years since smoking cessation for former smokers. Those who reported quitting within the past year were considered current smokers. In the main analyses, we used a 9-level smoking variable. We conducted a stratified analyses by smoking status, in which, because of few cases among never smokers, meat was examined as a continuous variable after ensuring the linearity of the relation between meat and lung carcinoma by a non-parametric method with restricted cubic splines (37). The HRs on the continuous scale were calculated for the increase in the risk of the 90th compared with the 10th percentile of meat intake. To test for interactions between meat intake and smoking status in the proportional hazards models, we fitted 3 models that included cross-product terms between red and processed meat intake and smoking, modeled with either the 9-level smoking status variable, the 5-level smoking status variable (never smokers, former smokers who quit $>$10 y ago, former smokers who quit 5–10 y ago, former smokers who quit 1–5 y ago, or former smokers who quit $<$1 y ago or were current smokers) additionally adjusted for the 6-level smoking intensity variable (1–10, 11–20, 21–30, 31–40, 41–50, or 51–60 cigarettes/d) or with the 6-level smoking intensity variable additionally adjusted for the 5-level smoking status variable. We used a likelihood ratio test to compare the proportional hazards models with and without cross-product terms, to test their significance.

Sensitivity analyses to further investigate the confounding effect of smoking included the use of a 31-level smoking variable constructed by combining smoking status, smoking intensity, and time since quitting smoking, as well as investigating these 3 smoking variables as separate covariates in the model. All analyses were conducted by using SAS version 9.1. The *P* values for the statistical tests were 2-tailed and were considered significant at a level of $<$0.05.

RESULTS

After up to 8 y of follow-up in our cohort of 278,380 men and 189,596 women, lung carcinoma was diagnosed in 4089 men and in 2272 women. Both men and women were more likely to be high consumers of red meat if they were white, were younger, were less educated, were less physically active, smoked, and had a higher BMI (**Table 1**). Furthermore, those eating more red meat were more likely to have a high intake of processed meat, saturated fat, and total energy, but were less likely to eat white meat, eat fruit and vegetables, drink alcohol, and take β-carotene supplements.

Men in the fifth quintile (Q5) of red and processed meat intake were more likely to develop lung carcinoma than were those in the first quintile (red meat: 1.22; 95% CI: 1.09, 1.38; *P* for trend = 0.005; processed meat: 1.23; 95% CI: 1.10, 1.37; *P* for trend = 0.003) (**Table 2**). Consumption of red meat in women was of borderline statistical significance with lung carcinoma risk (HR_{Q5vsQ1}: 1.13; 95% CI: 0.97, 1.32; *P* for trend = 0.05), whereas consumption of processed meat was not associated with risk (HR_{Q5vsQ1}: 1.00; 95% CI: 0.87, 1.15; *P* for trend = 0.58).

In the analyses by histologic subtype, the risk of squamous cell carcinoma was increased in men in the highest quintile of red (1.34; 95% CI: 1.04, 1.73; *P* for trend = 0.02) and processed (1.39; 95% CI: 1.10, 1.75; *P* for trend = 0.01) meat intake (**Table 3**). In women, the most striking observation was an elevated risk of small cell carcinoma for those in the highest quintile of red meat intake (HR_{Q5vsQ1}: 1.74; 95% CI: 1.14, 2.66; *P* for trend = 0.03). Yet, *P* values for heterogeneity among histologic subtypes were not statistically significant for either men (red meat: $P = 0.52$; processed meat: $P = 0.57$) or women (red meat: $P = 0.11$; processed meat: $P = 0.16$).

In an analysis stratified by smoking, none of the risk estimates among never smoking men or women were statistically significant (**Table 4**). However, the HRs for red meat in never smoking men and women were of a similar magnitude compared with the estimates for the whole cohort (Table 2) (men: 1.19 compared with 1.22; women: 1.21 compared with 1.13, respectively). The observed risk associated with processed meat intake in never smoking men was, however, notably lower than in the non-stratified analysis (HR: 1.06 compared with 1.23). In men, processed meat was associated with a statistically significant elevated risk in current smokers (*P* for trend = 0.008) and in former smokers who quit 1–10 y ago (*P* for trend = 0.001), whereas red meat intake increased the risk in those who quit $>$10 y ago (*P* for trend = 0.003) (Table 4) and yielded borderline statistically significant risk estimate in current smokers (*P* for trend = 0.09). In women, none of the risk estimates were statistically significant.

In models that included interactions between red and processed meat intake and smoking, we found no statistically significant interaction between meat intake and smoking in a multivariable model with interaction terms by a 9-level smoking variable for either men (red meat: $P = 0.64$; processed meat: $P = 0.39$) or women (red meat: $P = 0.91$; processed meat: $P = 0.87$). Likewise, we found no statistically significant interaction in

TABLE 1
Baseline characteristics of the subjects by quintile (Q) of red meat intake[1]

	Men (n = 278,380)			Women (n = 189,596)		
Characteristics	Q1	Q3	Q5	Q1	Q3	Q5
Red meat intake (g/1000 kcal)[2]	≤19.2 (12.2)	>30.0 to ≤40.6 (35.2)	>54.7 (67.0)	≤13.3 (8.0)	>22.1 to ≤31.2 (26.5)	>43.8 (54.7)
Age (y)	62.6 ± 0.02[3]	62.2 ± 0.02	61.3 ± 0.02	62.1 ± 0.03	62.0 ± 0.03	61.3 ± 0.03
BMI (kg/m^2)	26.1 ± 0.02	27.3 ± 0.02	28.4 ± 0.02	25.4 ± 0.03	26.9 ± 0.03	28.2 ± 0.03
First-degree relative with cancer (%)	46.6	48.0	47.3	50.5	52.0	50.9
Race (%)						
Non-Hispanic white	89.6	93.4	94.1	85.9	90.5	91.7
Non-Hispanic black	3.8	2.5	1.9	7.9	5.3	3.9
Education, college graduate or postgraduate (%)	52.4	44.2	38.8	38.4	29.1	23.5
Physical activity, ≥5 times/wk (%)	29.4	19.9	16.1	23.7	15.0	11.3
Smoking (%)						
Never smokers	35.3	30.0	26.6	48.1	46.1	42.7
Quit > 10 y ago	48.3	45.9	41.9	31.6	26.3	22.3
Quit 5–9 y ago	6.3	7.6	8.4	6.7	6.9	7.0
Quit 1–4 y ago	3.2	3.9	5.1	3.6	4.4	4.8
Quit <1 y ago, ≤20 cigarettes/d	0.8	1.0	1.0	1.3	1.4	1.7
Quit <1 y ago, >20 cigarettes/d	0.4	0.8	1.1	0.3	0.5	0.8
Current, ≤20 cigarettes/d	3.8	6.5	8.3	6.7	10.8	14.2
Current, >20–40 cigarettes/d	1.7	3.8	6.6	1.7	3.4	6.2
Current, >40 cigarettes/d	0.2	0.5	1.0	0.1	0.3	0.5
Married (%)	81.9	86.6	85.6	37.0	45.4	50.9
Menopausal hormonal users (%)				45.3	45.1	42.3
Dietary intake						
Energy intake (kcal/d)	1918 ± 3.6	2010 ± 3.5	2129 ± 3.7	1531 ± 3.3	1560 ± 3.3	1637 ± 3.6
White meat intake (g/1000 kcal)	35.9 ± 0.1	30.7 ± 0.1	31.1 ± 0.1	37.9 ± 0.2	35.1 ± 0.1	35.3 ± 0.1
Processed meat intake (g/1000 kcal)	5.6 ± 0.03	11.2 ± 0.03	20.2 ± 0.06	3.6 ± 0.03	7.6 ± 0.03	14.6 ± 0.06
Vegetables (servings/1000 kcal)	1.2 ± 0.003	1.0 ± 0.002	1.0 ± 0.002	1.5 ± 0.004	1.3 ± 0.003	1.2 ± 0.003
Fruit (servings/1000 kcal)	1.5 ± 0.004	1.0 ± 0.003	0.7 ± 0.002	1.8 ± 0.005	1.3 ± 0.004	0.9 ± 0.003
Saturated fat (g/1000 kcal)	7.9 ± 0.01	10.7 ± 0.01	12.8 ± 0.01	8.1 ± 0.02	10.4 ± 0.01	12.4 ± 0.01
Alcohol (g/d)	21.0 ± 0.2	16.7 ± 0.1	12.2 ± 0.1	5.6 ± 0.1	6.3 ± 0.1	5.2 ± 0.1
β-Carotene supplements (μg/d)	889.3 ± 5.7	639.4 ± 4.6	537.4 ± 4.1	914.1 ± 6.5	710.3 ± 5.5	588.5 ± 4.9

[1] P for trend < 0.0001 for all variables except a first-degree relative with cancer across quintiles of red meat intake (men: $P = 0.005$; women: $P = 0.187$) estimated by the Cochran-Armitage tests for categorical variables and the t test for slope in generalized linear models for continuous variables.
[2] All values are ranges; medians in parentheses.
[3] Mean ± SE (all such values).

a multivariable model with interaction terms by smoking status adjusted for smoking intensity in men (red meat: $P = 0.35$; processed meat: $P = 0.60$) and women (red meat: $P = 0.82$; processed meat: $P = 0.65$) or in a model with interaction terms by smoking intensity adjusted for smoking status in men (red meat: $P = 0.56$; processed meat: $P = 0.72$) and women (red meat: $P = 0.99$; processed meat: $P = 0.94$).

Of 168,879 men and 121,493 women who completed the meat cooking module, lung carcinoma was subsequently diagnosed in 2279 men and 1327 women. Analysis of meat intake by cooking method showed only a statistically significant elevated risk in women in the highest tertile (T3) of oven-broiled meat (**Table 5**). We observed a positive association for lung carcinoma and consumption of well-/very-well-done meat in men (HR_{T3vsT1}: 1.20; 95% CI: 1.07, 1.35; P for trend = 0.002) and of rare/medium done meat in women (HR_{T3vsT1}: 1.30; 95% CI: 1.11, 1.52; P for trend = 0.001). MeIQx intake in men was positively associated with lung carcinoma (HR_{Q5vsQ1}: 1.20; 95% CI: 1.04, 1.38; P for trend = 0.04) (**Table 6**). In women, we found no significant risk of any of the meat mutagens.

Intake of heme iron was dose-dependently positively associated with lung carcinoma in men (P for trend = 0.02) with an HR of 1.25 (95% CI:1.07,1.45) in those in the fifth quintile of heme iron intake (Table 6). We also observed a statistically significant trend in women (P for trend = 0.002) with an HR_{Q5} of 1.18 (95% CI: 0.99, 1.42). To investigate whether the balance between pro-oxidants and antioxidants in the diet modifies the effect of dietary heme iron on lung cancer risk, we compared participants with a high heme iron intake and a low intake of fruit and vegetables with those with a high heme iron intake and a high intake of fruit and vegetables in multivariable model; the models were additionally adjusted for vitamin C supplement intake because of its ability to enhance heme-iron absorption. Among participants with a high heme iron intake, we found a statistically significant increase in risk in men with a low intake compared with those with a high fruit and vegetable intake (HR: 1.68; 95% CI: 1.03, 2.75; P for trend = 0.04). In women, there was no evidence of an increased risk (HR: 0.75; 95% CI: 0.48, 1.18).

In additional sensitivity analyses (data not shown) by smoking status, the risk estimates remained virtually unchanged. We found no effect of menopausal hormone use on the associations between meat intake and lung carcinoma in women. Exclusion of lung carcinoma cases diagnosed within the first year of follow-up or

TABLE 2
Hazard ratios (HRs) and 95% CIs for lung carcinoma by quintile (Q) of baseline meat intake by sex (n = 278,380 men and n = 189,596 women)

	Baseline meat intake					
	Q1	Q2	Q3	Q4	Q5	P for trend
Men (cases = 4089)						
Red meat (g/1000 kcal)[1]	≤19.2 (12.2)	>19.2 to ≤30.0 (24.9)	>30.0 to ≤40.6 (35.2)	>40.6 to ≤54.7 (46.8)	>54.7 (67.0)	
Age- and energy-adjusted HR[2]	1	1.29 (1.16, 1.44)	1.51 (1.36, 1.67)	1.56 (1.41, 1.73)	1.91 (1.73, 2.12)	<0.001
Multivariable HR[3]	1	1.10 (0.98, 1.23)	1.18 (1.05, 1.31)	1.13 (1.00, 1.26)	1.22 (1.09, 1.38)	0.005
Processed meat (g/1000 kcal)[1]	≤4.0 (2.3)	>4.0 to ≤7.3 (5.6)	<7.3 to ≤11.4 (9.1)	<11.4 to ≤18.2 (14.2)	>18.2 (24.8)	
Age- and energy-adjusted HR[2]	1	1.40 (1.25, 1.55)	1.45 (1.30, 1.61)	1.54 (1.39, 1.72)	1.77 (1.60, 1.97)	<0.001
Multivariable HR[3]	1	1.17 (1.05, 1.31)	1.13 (1.01, 1.26)	1.16 (1.04, 1.29)	1.23 (1.10, 1.37)	0.003
Women (cases = 2272)						
Red meat (g/1000 kcal)[1]	≤13.3 (8.0)	>13.3 to ≤22.1 (17.8)	>22.1 to ≤31.2 (26.5)	>31.2 to ≤43.8 (36.7)	>43.8 (54.7)	
Age- and energy-adjusted HR[2]	1	1.24 (1.08, 1.43)	1.21 (1.05, 1.40)	1.53 (1.33, 1.76)	1.86 (1.62, 2.13)	<0.001
Multivariable HR[3]	1	1.05 (0.91, 1.21)	0.93 (0.80, 1.08)	1.05 (0.91, 1.22)	1.13 (0.97, 1.32)	0.05
Processed meat (g/1000 kcal)[1]	≤2.3 (1.2)	>2.3 to ≤4.5 (3.3)	<4.5 to ≤7.3 (5.8)	<7.3 to ≤12.5 (9.4)	>12.5 (18.3)	
Age- and energy-adjusted HR[2]	1	1.05 (0.91, 1.21)	1.33 (1.16, 1.53)	1.26 (1.10, 1.45)	1.43 (1.24, 1.63)	<0.001
Multivariable HR[3]	1	0.89 (0.77, 1.03)	1.05 (0.91, 1.20)	0.95 (0.82, 1.10)	1.00 (0.87, 1.15)	0.58

[1] All values are ranges; medians in parentheses.

[2] Cox proportional hazards regression model adjusted for age (time metric) and energy intake as a continuous variable. Meats were additionally adjusted for energy by the density method (g/1000 kcal), and the relevant meat groups were adjusted simultaneously for each other summing up to total meat (white and red; processed and nonprocessed).

[3] Cox proportional hazards regression model additionally adjusted for BMI (in kg/m^2; <18.5, ≥18.5 to <25, ≥25 to <30, ≥30 to <35, ≥35, and missing), smoking (never smoker; quit ≥10 y ago; quit 5–9 y ago; quit 1–4 y ago; quit <1 y ago, ≤20 cigarettes/d; quit <1 y ago, >20 cigarettes/d; current, ≤20 cigarettes/d; current, >20–40 cigarettes/d; and current, >40 cigarettes/d), race (white, black, or Hispanic/Asian/Pacific Islander/American Indian/Alaskan native/unknown), education (less than high school or unknown, high school graduate, some college, and college graduate), physical activity (never/rarely/missing, 1–3 times/mo, 1–2 times/wk, 3–4 times/wk, and ≥5 times/wk), and intake of alcohol, energy-adjusted vegetable and fruit servings, and saturated fat (as continuous variables).

participants who reported a history of emphysema did not change any of our findings.

DISCUSSION

In the present cohort, we observed a moderate positive association between meat consumption and lung carcinoma, which might be explained by heme iron and cooking-related mutagens in the meat. A high intake of red and processed meat increased the risk of lung carcinoma in men; in women, the risk with high red meat intake was less pronounced, and no risk was observed with processed meat intake. Other cohorts reported inconsistent findings for both red (22, 23, 26) and processed (22–26) meat intakes. It is difficult to compare the findings from different studies because these studies defined the meat groups differently, categorized meat intakes differently, did not all report sex-specific risk estimates, and investigated the mortality rather than the morbidity of lung carcinoma (23–25). Furthermore, small sample size (24), small numbers of cases (23–26), and the use of brief dietary questionnaires (23–25) may have underpowered these studies and affected the precision of risk estimates. Four of 5 cohorts (26–29) did not adjust for other possible dietary confounders.

Several possible mechanisms might explain the positive associations observed between meat intake and lung carcinoma. Grilling or barbecuing meat results in the formation of HCAs and PAHs, which are potent lung carcinogens (38, 39) that are also present in cured and smoked foods (7, 40). *N*-Nitroso compounds (NOCs), which are known carcinogens (41), are found in nitrite-preserved meat and are endogenously produced when red meat is consumed (42). Heme iron from red meat can act as a pro-oxidant and can catalyze lipid peroxidation and DNA damage in the tissues (43, 44), but may also induce endogenous NOC formation (9, 45). Observed increased risks with well-/very-well-done meat and MeIQx intakes in our men support the hypothesis that the mutagens formed in meat cooked at high temperatures may partly explain the association. The lack of effect by meat-cooking method and other meat mutagens might have been due to the narrow intake range of the investigated exposures; our cooking module included only meats commonly cooked at high temperatures (hamburgers, steak, bacon, and chicken). In a case-control study involving 1216 women using a dietary questionnaire similar to ours, Sinha et al (6) found a borderline statistically significant increase in the risk of lung cancer for MeIQx intake and well-done, fried, and broiled red meat intakes (46), whereas our women had an increased risk with intake of rare/medium cooked meat and no risk with any of the meat mutagens. However, compared with our study, Sinha et al (6, 46) reported higher intakes of the exposures. The increased risk with rare/medium cooked meat in our study might have been due to a chance or to multiple comparisons.

The intake of heme iron from meat was positively associated with lung carcinoma—an association that was stronger in men than in women. In addition, we found that men with a high intake of bioavailable heme iron and a low intake of antioxidants were at even higher risk. Redox-active iron has been detected in the epithelial lining fluid of the normal lung (47). Thus, it is plausible that an unbalanced diet may disrupt the balance between pro-oxidants and antioxidants in the lung tissue and trigger oxidative damage and carcinogenesis. Furthermore, in its nitrosylated form produced under alkaline conditions in the small bowel, heme iron can induce endogenous NOC formation (9, 45), and, once absorbed, these compounds can have a systematic effect as

TABLE 3
Hazard ratios (HRs) and 95% CIs for the fifth quintile (Q) of red and processed meat intake by histologic subtype of lung carcinoma by sex (n = 278,380 men and n = 189,596 women)

	Men			Women		
	No. of cases[1]	Q5 vs Q1	P for trend	No. of cases[1]	Q5 vs Q1	P for trend
Adenocarcinoma	1578			1004		
Red meat						
Age- and energy-adjusted HR[2]		1.61 (1.37, 1.88)	<0.001		1.42 (1.17, 1.73)	<0.001
Multivariable HR[3]		1.16 (0.96, 1.39)	0.21		0.98 (0.79, 1.23)	0.68
Processed meat						
Age- and energy-adjusted HR[2]		1.52 (1.29, 1.80)	<0.001		1.12 (0.92, 1.37)	0.096
Multivariable HR[3]		1.15 (0.97, 1.36)	0.42		0.89 (0.72, 1.09)	0.77
Small cell carcinoma	568			373		
Red meat						
Age- and energy-adjusted HR[2]		2.23 (1.68, 2.96)	<0.001		3.41 (2.32, 5.00)	<0.001
Multivariable HR[3]		1.13 (0.82, 1.57)	0.50		1.74 (1.14, 2.66)	0.03
Processed meat						
Age- and energy-adjusted HR[2]		2.10 (1.59, 2.79)	<0.001		2.11 (1.48, 3.01)	<0.001
Multivariable HR[3]		1.31 (0.98, 1.76)	0.07		1.24 (0.86, 1.78)	0.19
Squamous carcinoma	913			322		
Red meat						
Age- and energy-adjusted HR[2]		2.19 (1.76, 2.74)	<0.001		2.17 (1.52, 3.11)	<0.001
Multivariable HR[3]		1.34 (1.04, 1.73)	0.02		1.05 (0.71, 1.57)	0.60
Processed meat						
Age- and energy-adjusted HR[2]		2.13 (1.70, 2.66)	<0.001		1.83 (1.26, 2.65)	0.002
Multivariable HR[3]		1.39 (1.10, 1.75)	0.01		1.09 (0.74, 1.61)	0.66
Large cell carcinoma	254			136		
Red meat						
Age- and energy-adjusted HR[2]		2.49 (1.60, 3.88)	<0.001		2.08 (1.21, 3.58)	0.003
Multivariable HR[3]		1.57 (0.95, 2.58)	0.13		1.28 (0.69, 2.35)	0.25
Processed meat						
Age- and energy-adjusted HR[2]		1.64 (1.06, 2.53)	0.04		2.33 (1.28, 4.27)	0.03
Multivariable HR[3]		1.05 (0.67, 1.65)	0.95		1.64 (0.87, 3.06)	0.32

[1] Number of total carcinoma cases by histologic subtype.

[2] Cox proportional hazards regression model adjusted for age (time metric) and energy intake as a continuous variable. Meats were additionally adjusted for energy by the density method (g/1000 kcal), and the relevant meat groups were adjusted simultaneously for each other summing up to total meat (white and red; processed and nonprocessed).

[3] Cox proportional hazards regression model additionally adjusted for BMI (in kg/m^2; <18.5, ≥18.5 to <25, ≥25 to <30, ≥30 to <35, ≥35, and missing), smoking (never smoker; quit ≥10 y ago; quit 5–9 y ago; quit 1–4 y ago; quit <1 y ago, ≤20 cigarettes/d; quit <1 y ago, >20 cigarettes/d; current, ≤20 cigarettes/d; current, >20–40 cigarettes/d; and current, >40 cigarettes/d), race (white, black, or Hispanic/Asian/Pacific Islander/American Indian/Alaskan native/unknown), education (less than high school or unknown, high school graduate, some college, and college graduate), physical activity (never/rarely/missing, 1–3 times/mo, 1–2 times/wk, 3–4 times/wk, and ≥5 times/wk), and intake of alcohol, energy-adjusted vegetable and fruit servings, and saturated fat (as continuous variables).

tissue-specific carcinogens, directly or after metabolic activation (48).

The effect of meat consumption by histologic subtype of lung carcinoma was investigated in a few studies (13, 15, 20). One study detected an increased risk of nonadenocarcinoma cell tumors (22). In another study, risk was increased for all histologic types, but was strongest for adenocarcinoma (20), whereas 2 studies showed an increased risk of squamous cell carcinoma (15). We found no statistically significant difference in meat-associated risk between the different histologic subtypes of lung carcinoma.

In a stratified analysis by smoking, we observed a tendency for an increased risk with red meat intake in never smoking men and women; the risks, however, were not statistically significant. We observed somewhat stronger risks among former and current smokers compared with never smokers, which may also be explained by the synergistic effect of HCAs and NOCs present in meat as well as in tobacco smoke. Even though this inconsistency in our stratified analysis might have been due to few cases among the never smokers and even though none of the interaction models were statistically significant, the fact that the never smoking men had notably lower risk estimates for processed meat compared with all men, suggests that we still cannot entirely rule out the possibility of residual confounding despite the careful multivariate adjustment. We investigated the effect of smoking by different approaches, but we lacked information on lifetime smoking duration. Smoking duration is strongly associated with age in current smokers and with time of cessation in former smokers (49). It has been shown that, after control for age and smoking intensity, duration was no longer statistically significant in current smokers, possibly because of insufficient variation in smoking duration (49). Although the effect of duration may appear stronger in former smokers, control for time since cessation may account for this effect. Both information on

TABLE 4
Hazard ratios (HRs) and 95% CIs for the 90th compared with the 10th percentile of baseline red and processed meat intake in an analysis stratified by smoking in men (n = 278,380) and women (n = 189,596)

	Men	*P* for trend	Women	*P* for trend
Never smokers (no. of cases)	137		166	
Red meat				
Age- and energy-adjusted HR[1]	1.02 (0.66, 1.58)	0.92	1.12 (0.75, 1.67)	0.58
Multivariable HR[2]	1.19 (0.69, 2.06)	0.52	1.21 (0.76, 1.94)	0.44
Processed meat				
Age- and energy-adjusted HR[1]	1.03 (0.68, 1.56)	0.91	0.88 (0.62, 1.24)	0.46
Multivariable HR[2]	1.06 (0.69, 1.64)	0.79	0.89 (0.62, 1.29)	0.55
Former smokers, quit >10 y ago (no. of cases)	1299		387	
Red meat				
Age- and energy-adjusted HR[1]	1.35 (1.17, 1.56)	<0.0001	1.15 (0.88, 1.50)	0.29
Multivariable HR[2,3]	1.29 (1.09, 1.54)	0.003	1.31 (0.96, 1.79)	0.09
Processed meat				
Age- and energy-adjusted HR[1]	1.16 (1.02, 1.33)	0.03	0.98 (0.78, 1.22)	0.84
Multivariable HR[2,3]	1.07 (0.93, 1.24)	0.33	1.04 (0.82, 1.32)	0.74
Former smokers, quit 1–10 y ago (no. of cases)	952		475	
Red meat				
Age- and energy-adjusted HR[1]	1.26 (1.07, 1.48)	0.006	1.25 (0.99, 1.59)	0.06
Multivariable HR[2,3]	1.12 (0.92, 1.36)	0.24	1.14 (0.87, 1.50)	0.32
Processed meat				
Age- and energy-adjusted HR[1]	1.43 (1.22, 1.68)	<0.0001	1.17 (0.94, 1.45)	0.15
Multivariable HR[2,3]	1.31 (1.11, 1.55)	0.001	1.09 (0.87, 1.36)	0.46
Current smokers (no. of cases)	1832		1324	
Red meat				
Age- and energy-adjusted HR[1]	1.45 (1.29, 1.63)	<0.0001	1.41 (1.22, 1.62)	<0.0001
Multivariable HR[2,3]	1.13 (0.98, 1.29)	0.09	1.10 (0.94, 1.28)	0.26
Processed meat				
Age- and energy-adjusted HR[1]	1.37 (1.22, 1.53)	<0.0001	1.27 (1.11, 1.44)	0.0003
Multivariable HR[2,3]	1.18 (1.04, 1.33)	0.008	1.10 (0.96, 1.26)	0.17

[1] Cox proportional hazards regression model adjusted for age (time metric) and energy intake as a continuous variable. Meats were additionally adjusted for energy by the density method (g/1000 kcal), and the relevant meat groups were adjusted simultaneously for each other summing up to total meat (white and red; processed and nonprocessed).

[2] Cox proportional hazards regression model additionally adjusted for BMI (in kg/m^2; <18.5, ≥18.5 to <25, ≥25 to <30, ≥30 to <35, ≥35, and missing), smoking (never smoker; quit ≥10 y ago; quit 5–9 y ago; quit 1–4 y ago; quit <1 y ago, ≤20 cigarettes/d; quit <1 y ago, >20 cigarettes/d; current, ≤20 cigarettes/d; current, >20–40 cigarettes/d; and current, >40 cigarettes/d), race (white, black, or Hispanic/Asian/Pacific Islander/American Indian/Alaskan native/unknown), education (less than high school or unknown, high school graduate, some college, and college graduate), physical activity (never/rarely/missing, 1–3 times/mo, 1–2 times/wk, 3–4 times/wk, and ≥5 times/wk), and intake of alcohol, energy-adjusted vegetable and fruit servings, and saturated fat (as continuous variables).

[3] Cox proportional hazards regression model additionally adjusted for smoking intensity (1–10, 11–20, 21–30, 31–40, 41–50, and 51–60 cigarettes/d).

smoking intensity and time since cessation were modeled in our analyses.

The risk of lung carcinoma associated with processed meat intake, level of meat doneness, and meat mutagens differed between men and women. Although we observed no effect of menopausal hormone use in our analysis, the available evidence suggests that behavioral, biological, genetic, and hormonal differences between men and women may be responsible for the different susceptibilities to lung carcinoma risk (50), but what role these factors play in the association between diet and lung carcinoma pathogenesis is not clear. It is also possible that the smaller number of lung cancer cases, the narrower intake range in our women, and the tendency for women to underreport intakes (51, 52) may have obscured the associations.

Our study is the largest cohort study to date to investigate the association between lung carcinoma and meat intake. Its prospective design limited the effect of reverse causality and avoided the effect of recall or selection bias. The cohort had a wide distribution of intakes, which are expected to decrease the attenuation effect of measurement error (28). The FFQ was internally validated against two 24-h dietary recalls and exhibited reasonably high correlations for the meat estimates (28). The detailed information on meat cooking methods and doneness level and the meat mutagen database allowed us to investigate different possible mechanisms for the effect of meat on lung carcinoma.

Limitations of this study include the lack of information on B(a)P exposure from other dietary sources as well as the amount of NOCs present in meat, which may be very important to elucidating the meat–lung carcinoma hypothesis. FFQs are known to have substantial measurement error that can lead to bias in estimated diet-disease risks and, in multivariable models, can lead to distorted CIs. The NIH-AARP Diet and Health Study includes a calibration substudy to be used for measurement error correction (28). However, although methods exist for measurement error correction for foods or nutrients that are consumed daily, such

TABLE 5

Hazard ratios (HRs) and 95% CIs for lung carcinoma by tertile (T) of meat intake cooked by different methods and by level of doneness in participants who completed the meat-cooking module ($n = 168{,}879$ men and $n = 121{,}493$ women)[1]

	Dietary intake							
	Men (no. of cases = 2279)				Women (no. of cases = 1327)			
	T1	T2	T3	*P* for trend	T1	T2	T3	*P* for trend
Meat-cooking methods								
Grilled/barbecued (g/1000 kcal)[1]	≤2.9 (0.5)	>2.9 to ≤10.2 (5.9)	>10.2 (17.5)		≤1.4 (0)	>1.4 to ≤6.1 (3.2)	>6.1 (11.9)	
Age- and energy-adjusted HR[2]	1	1.10 (0.99, 1.22)	1.15 (1.03, 1.29)	0.02	1	1.04 (0.91, 1.18)	1.13 (0.98, 1.31)	0.11
Multivariate HR[3]	1	1.09 (0.98, 1.21)	1.09 (0.97, 1.22)	0.17	1	0.98 (0.86, 1.12)	1.01 (0.87, 1.17)	0.90
Pan-fried (g/1000 kcal)[1]	0	>0 to ≤0.52 (0.16)	>0.52 (2.41)		0	>0 to ≤0.4 (0.1)	>0.4 (2.2)	
Age- and energy-adjusted HR[2]	1	1.06 (0.95, 1.18)	1.46 (1.31, 1.61)	<0.0001	1	0.98 (0.85, 1.14)	1.44 (1.27, 1.64)	<0.001
Multivariate HR[3]	1	1.00 (0.90, 1.13)	1.06 (0.95, 1.18)	0.33	1	0.96 (0.83, 1.11)	1.10 (0.96, 1.26)	0.07
Oven-broiled (g/1000 kcal)[1]	0	>0 to ≤1.48 (0.78)	>1.49 (6.50)		0	>0 to ≤0.7 (0.4)	>0.7 (5.0)	
Age- and energy-adjusted HR[2]	1	0.85 (0.72, 1.02)	1.03 (0.94, 1.13)	0.53	1	1.20 (0.87, 1.64)	1.24 (1.10, 1.40)	0.001
Multivariate HR[3]	1	0.83 (0.70, 0.99)	1.04 (0.94, 1.15)	0.34	1	1.24 (0.90, 1.70)	1.14 (1.01, 1.29)	0.04
Sautéed/microwaved/baked (g/1000 kcal)[1]	0	>0 to ≤1.18 (0.44)	>1.18 (4.94)		0	>0 to ≤4.1 (1.2)	>4.1 (10.2)	
Age- and energy-adjusted HR[2]	1	1.18 (1.05, 1.33)	1.06 (0.96, 1.17)	0.62	1	1.06 (0.92, 1.21)	1.00 (0.87, 1.15)	0.70
Multivariate HR[3]	1	1.11 (0.98, 1.25)	1.07 (0.96, 1.18)	0.31	1	0.99 (0.86, 1.14)	1.03 (0.89, 1.19)	0.60
Level of doneness								
Rare/medium done (g/1000 kcal)[1]	≤1.3 (0)	>1.3 to ≤9.1 (4.5)	>9.1 (16.8)		≤0.7 (0)	>0.7 to ≤6.9 (3.1)	>6.9 (14.4)	
Age- and energy-adjusted HR[2]	1	1.05 (0.95, 1.17)	1.12 (1.00, 1.26)	0.13	1	1.22 (1.06, 1.40)	1.51 (1.30, 1.76)	<0.001
Multivariate HR[3]	1	1.02 (0.92, 1.14)	1.05 (0.94, 1.19)	0.40	1	1.13 (0.97, 1.30)	1.30 (1.11, 1.52)	0.001
Well-/very-well-done (g/1000 kcal)[1]	≤2.7 (0.5)	>2.7 to ≤9.7 (5.6)	>9.7 (16.3)		≤2.5 (0.4)	>2.5 to ≤9.4 (5.3)	>9.4 (16.0)	
Age- and energy-adjusted HR[2]	1	1.13 (1.02, 1.26)	1.27 (1.13, 1.42)	0.0002	1	1.00 (0.87, 1.15)	0.98 (0.85, 1.14)	0.58
Multivariate HR[3]	1	1.07 (0.96, 1.19)	1.20 (1.07, 1.35)	0.002	1	0.92 (0.80, 1.05)	0.93 (0.80, 1.08)	0.43

[1] All values are ranges; medians in parentheses.

[2] Cox proportional hazards regression model adjusted for age (time metric) and energy intake as a continuous variable. Meats were additionally adjusted for energy by the density method (g/1000 kcal), and the relevant meat groups were adjusted simultaneously for each other summing up to total meat (in models by cooking method: grilled/barbecued, pan-fried, oven-broiled, and sautéed/baked/microwaved; in models by doneness level: rare/medium and well-/very-well-done cooked meat).

[3] Cox proportional hazards regression model additionally adjusted for BMI (in kg/m^2; <18.5, ≥18.5 to <25, ≥25 to <30, ≥30 to <35, ≥35, and missing), smoking (never smoker; quit ≥10 y ago; quit 5–9 y ago; quit 1–4 y ago; quit <1 y ago, ≤20 cigarettes/d; quit <1 y ago, >20 cigarettes/d; current, ≤20 cigarettes/d; current, >20–40 cigarettes/d; and current, >40 cigarettes/d), race (white, black, or Hispanic/Asian/Pacific Islander/American Indian/Alaskan native/unknown), education (less than high school or unknown, high school graduate, some college, and college graduate), physical activity (never/rarely/missing, 1–3 times/mo, 1–2 times/wk, 3–4 times/wk, and ≥5 times/wk), and intake of alcohol, energy-adjusted vegetable and fruit servings, and saturated fat (as continuous variables).

TABLE 6
Hazard ratios (HRs) and 95% CIs for lung carcinoma by quintile (Q) of intake of meat mutagens and heme iron in participants who completed the meat-cooking module (n = 168,879 men and n = 121,493 women)[1]

	Dietary intake							
	Men (no. of cases = 2279)				Women (no. of cases = 1327)			
	Q1	Q3	Q5	P for trend	Q1	Q3	Q5	P for trend
Meat mutagens								
Overall mutagenic activity (revertant colonies/1000 kcal)[2]	≤491 (240)	>1016 to ≤1726 (1331)	>3082 (4622)		≤261 (109)	>649 to ≤1244 (909)	>2432 (3908)	
Age- and energy-adjusted HR[3]	1	1.25 (1.09, 1.43)	1.36 (1.18, 1.55)	0.0004	1	1.36 (1.15, 1.62)	1.32 (1.10, 1.57)	0.02
Multivariable HR[4]	1	1.07 (0.93, 1.23)	1.09 (0.95, 1.25)	0.52	1	1.08 (0.90, 1.28)	1.02 (0.85, 1.22)	0.78
MeIQx (ng/1000 kcal)[2]	≤1.7 (0.7)	>4.2 to ≤8.3 (6.0)	>16.5 (26.5)		≤1.1 (0.4)	>3.0 to ≤6.2 (4.4)	>12.7 (21.1)	
Age- and energy-adjusted HR[3]	1	1.36 (1.18, 1.56)	1.69 (1.48, 1.93)	<0.0001	1	1.11 (0.93, 1.32)	1.29 (1.09, 1.53)	0.001
Multivariable HR[4]	1	1.15 (1.00, 1.32)	1.20 (1.04, 1.38)	0.04	1	0.97 (0.81, 1.15)	0.95 (0.80, 1.13)	0.66
DiMeIQx (ng/1000 kcal)[2]	0	>0.07 to ≤0.40 (0.22)	>1.07 (1.85)		0	>0.05 to ≤0.30 (0.15)	>0.83 (1.58)	
Age- and energy-adjusted HR[3]	1	1.01 (0.90, 1.13)	1.21 (1.08, 1.36)	0.0002	1	0.95 (0.82, 1.10)	1.00 (0.86, 1.16)	0.93
Multivariable HR[4]	1	0.98 (0.87, 1.10)	1.06 (0.94, 1.19)	0.25	1	0.96 (0.83, 1.11)	0.91 (0.78, 1.06)	0.19
PhIP (ng/1000 kcal)[2]	≤8.8 (3.7)	>21.5 to ≤40.5 (29.8)	>80.7 (131.7)		≤3.8 (0.5)	>11.7 to ≤26.4 (17.7)	>61.5 (110.4)	
Age- and energy-adjusted HR[3]	1	1.23 (1.08, 1.40)	1.24 (1.09, 1.42)	0.009	1	1.19 (1.00, 1.42)	1.26 (1.06, 1.50)	0.02
Multivariable HR[4]	1	1.12 (0.98, 1.28)	1.11 (0.97, 1.27)	0.22	1	0.99 (0.83, 1.18)	1.03 (0.86, 1.23)	0.53
B(a)P (ng/1000 kcal)[2]	≤0.8 (0.3)	>4.6 to ≤13.9 (8.6)	>30.7 (50.6)		≤0.4 (0.1)	>2.2 to ≤7.0 (4.1)	>18.9 (33.1)	
Age- and energy-adjusted HR[3]	1	0.96 (0.84, 1.09)	1.11 (0.98, 1.26)	0.03	1	0.80 (0.67, 0.95)	1.06 (0.90, 1.25)	0.30
Multivariable HR[4]	1	1.07 (0.94, 1.22)	1.09 (0.95, 1.24)	0.37	1	0.85 (0.71, 1.01)	0.96 (0.81, 1.13)	0.83
Heme iron								
Heme iron (μg/1000 kcal)[2]	≤90.2 (58.1)	>143.8 to ≤201.0 (171.1)	>285.2 (366.7)		≤63.2 (39.1)	>104.0 to ≤149.4 (125.2)	>217.2 (282.0)	
Age- and energy-adjusted HR[3]	1	1.44 (1.25, 1.65)	1.67 (1.46, 1.92)	<0.001	1	1.11 (0.93, 1.34)	1.75 (1.48, 2.07)	<0.001
Multivariable HR[4]	1	1.22 (1.06, 1.41)	1.25 (1.07, 1.45)	0.02	1	0.90 (0.74, 1.08)	1.18 (0.99, 1.42)	0.002

[1] MeIQx, 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline; DiMeIQx, 2-amino-3,4,8-trimethylimidazo[4,5-*f*]quinoxaline; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine; B(a)P, benzo(a)pyrene.
[2] All values are ranges; medians in parentheses.
[3] Cox proportional hazards regression model adjusted for age (time metric) and energy intake as a continuous variable.
[4] Cox proportional hazards regression model additionally adjusted for BMI (in kg/m^2; <18.5, ≥18.5 to <25, ≥25 to <30, ≥30 to <35, ≥35, and missing), smoking (never smoker; quit ≥10 y ago; quit 5–9 y ago; quit 1–4 y ago; quit <1 y ago, ≤20 cigarettes/d; quit <1 y ago, >20 cigarettes/d; current, ≤20 cigarettes/d; current, >20–40 cigarettes/d; and current, >40 cigarettes/d), race (white, black, or Hispanic/Asian/Pacific Islander/American Indian/Alaskan native/unknown), education (less than high school or unknown, high school graduate, some college, and college graduate), physical activity (never/rarely/missing, 1–3 times/mo, 1–2 times/wk, 3–4 times/wk, and ≥5 times/wk), and intake of alcohol, energy-adjusted vegetable and fruit servings, and saturated fat (as continuous variables).

methods are not currently available for episodically consumed foods, such as red or processed meat. The measurement error related to the meat mutagen database also likely caused further attenuation of the risk estimates. We lacked information on passive smoking, smoking duration, and age of smoking initiation, which might have limited our ability to fully control for this powerful confounder. Although we carefully explored the effect of smoking in many ways, the stratified analysis suggests that we cannot entirely rule out residual confounding by smoking.

In conclusion, consumption of a diet high in red or processed meat was moderately positively associated with lung carcinoma in men, whereas the association in women was weaker and apparent only for red meat intake. High-temperature cooking and associated mutagens and heme iron from meat may explain the role of meat in lung carcinoma pathogenesis.

Cancer incidence data from the Atlanta metropolitan area were collected by the Georgia Center for Cancer Statistics, Department of Epidemiology, Rollins School of Public Health, Emory University. Cancer incidence data from California were collected by the California Department of Health Services, Cancer Surveillance Section. Cancer incidence data from the Detroit metropolitan area were collected by the Michigan Cancer Surveillance Program, Community Health Administration, State of Michigan. The Florida cancer incidence data used in this report were collected by the Florida Cancer Data System under contract to the Department of Health (DOH). The views expressed herein are solely those of the authors and do not necessarily reflect those of the contractor or the DOH. Cancer incidence data from Louisiana were collected by the Louisiana Tumor Registry, Louisiana State University Medical Center in New Orleans. Cancer incidence data from New Jersey were collected by the New Jersey State Cancer Registry, Cancer Epidemiology Services, New Jersey State Department of Health and Senior Services. Cancer incidence data from North Carolina were collected by the North Carolina Central Cancer Registry. Cancer incidence data from Pennsylvania were supplied by the Division of Health Statistics and Research, Pennsylvania Department of Health, Harrisburg, Pennsylvania. The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations or conclusions. Cancer incidence data from Arizona were collected by the Arizona Cancer Registry, Division of Public Health Services, Arizona Department of Health Services. Cancer incidence data from Texas were collected by the Texas Cancer Registry, Cancer Epidemiology and Surveillance Branch, Texas Department of State Health Services. Cancer incidence data from Nevada were collected by the Nevada Central Cancer Registry, Center for Health Data and Research, Bureau of Health Planning and Statistics, State Health Division, State of Nevada Department of Health and Human Services. We are indebted to the participants in the NIH-AARP Diet and Health Study for their outstanding cooperation. We also thank Sigurd Hermansen and Kerry Grace Morrissey from Westat for study outcomes ascertainment and management and Leslie Carroll at Information Management Services for data support and analysis.

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