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Meat Intake and Meat Preparation in Relation to Risk of Postmenopausal Breast Cancer in the NIH-AARP Diet and Health Study

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Abstract

A number of studies have reported that intake of red meat or meat cooked at high temperatures is associated with increased risk of breast cancer, but other studies have shown no association. We assessed the association between meat, meat-cooking methods, meat-mutagen intake and postmenopausal breast cancer in the NIH-AARP Diet and Health Study cohort of 120,755 postmenopausal women who completed a food frequency questionnaire at baseline (1995-1996) as well as a detailed meat-cooking module within 6 months following baseline. During 8 years of follow-up, 3,818 cases of invasive breast cancer were identified in this cohort. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI). After adjusting for covariates, intake of total meat, red meat, meat cooked at high temperatures, and meat mutagens showed no association with breast cancer risk. This large prospective study with detailed information on meat preparation methods provides no support for a role of meat mutagens in the development of postmenopausal breast cancer.

High temperature cooking of meat such as grilling/barbecuing and pan-frying especially to a high degree of doneness produces high concentrations of heterocyclic amines (HCAs), such as 2-amino-3,4,8-trimethylimidazo[4,5-*f*]quinoxaline (DiMeIQx), 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (MeIQx), and 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) and polycyclic aromatic hydrocarbons (PAHs), such as benzo[a]pyrene (B[a]P), compared to stewing or microwaving of meats (1, 2). The amounts of these compounds that are produced vary depending on the cooking method, temperature, duration of cooking, and type of meat (1, 3).

Both HCAs and PAHs can induce mammary tumors in laboratory animals (4, 5). However, epidemiologic studies examining both meat preparation methods and estimated intake of HCAs in relation to breast cancer risk have yielded inconsistent results, with some showing a positive association with degree of doneness or estimated intake of mutagens/carcinogens (6-10) and others showing no evidence of an association (11-13). Some of these studies had limited information on methods of cooking different types of meat, degree of doneness, and estimation of mutagenic compounds (6, 11, 12). Additionally, case-control studies may be subject to recall and selection bias (6, 9-11, 13).

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In view of the inconsistent results of previous studies, we used detailed data on meat intake, meat preparation methods, and estimated intake of meat-mutagens as measured in the NIH-AARP Diet and Health Study to determine whether these factors influenced the risk of breast cancer in postmenopausal women.

Materials and Methods

Study Population

The NIH-AARP Diet and Health Study is a large cohort study of AARP (formerly known as the American Association of Retired Persons) members initiated in 1995-1996. Details of the study's design have been described previously (14). AARP members (617,119) between 50 and 71 years old and residing in six U.S. states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, GA, and Detroit, MI) were mailed self-administered questionnaires covering demographic characteristics, food intake, and other health-related behaviors. The questionnaires were satisfactorily completed by 567,169 subjects, of whom 226,733 were women (14). The study was approved by the National Cancer Institute Special Studies Institutional Review Board, and consent was implicit for all participants who returned the questionnaire.

We excluded subjects who had questionnaires completed by proxy respondents, who had prevalent cancers, or who died before study entry (n = 26,410). Women who reported that they were still menstruating and were not taking hormones were classified as premenopausal. Women who reported that their periods had stopped due to natural menopause, surgery, radiation, or chemotherapy; women who had had both ovaries or their uterus removed; and women older than 57 years were classified as postmenopausal. Based on this definition, the study population was restricted to 186,361 postmenopausal women by excluding women who were pre-menopausal or with uncertain menstrual status (n = 13,895). Further exclusions based on the availability of detailed meat preparation data are described below.

Dietary Assessment and Meat Variables

At baseline, study subjects completed a self-administered food frequency questionnaire (FFQ) that assessed the usual frequency of consumption and portion size of 124 food items (14). A diet calibration sub-study within the NIH-AARP Study cohort showed good correlations between red meat intake from the FFQ and two 24-h dietary recalls (14).

Within six months following the initial questionnaire, baseline respondents were sent a second FFQ that included a meat-cooking module (14) that 332,913 men and women completed (response rate = 63%). The meat-cooking module queried consumption of hamburgers, steak, bacon, and chicken, usual cooking method (pan-fried; grilled or barbecued; oven-broiled; other such as sautéed, baked, or microwaved), and level of doneness on the outside (not browned, lightly browned, well-browned, black or charred) and inside (for red meat: raw; rare to medium-rare or red-deep pink; medium to medium well-done, or light pink; well-done or gray-brown with juice; very well-done or gray-brown dry; and for chicken: just until done or still juicy; well-done or somewhat dry; very well-done or very dry; ref. 15).

The validity of the meat intake, meat-cooking methods, degree of doneness, and meat-derived mutagens was assessed in a U.S. population of 165 healthy subjects who completed a FFQ that included the meat module and 3 sets of 4 non-consecutive day diaries (16). Correlations were calculated for intake between the two methods of dietary assessment (16). The relative validity of the meat module was similar to that of other nutrients and foods quantified in FFQs (17, 18). For example, the deattenuated correlations were 0.60 and 0.36

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for DiMeIQx and PhIP, respectively (16). Even though the validity of the total mutagenic activity was not directly addressed by Cantwell et al (16), the correlation between mutagenic activity was found to be highly correlated with HCAs (Spearman correlation: mutagenic activity and PhIP r=0.65; mutagenic activity and MeIQx r=0.71) (19).

A detailed description of the methods used in estimating intake of different types of meat, cooking practices, degree of doneness, and meat mutagens is given elsewhere (20). In brief, intake of total meat, red meat, white meat, processed meat, and meat cooked at high temperature were calculated in grams per day based on the frequency and portion size information in the baseline FFQ (1, 2, 21).

For meat intake estimated from the meat-cooking module, we calculated grams consumed per day and created meat variables according to cooking method and doneness level (raw/rare/medium and well/very well done). In addition, we used the CHARRED database* to estimate daily intake of meat-mutagens, including the HCAs DiMeIQx, MeIQx, and PhIP; the PAH B[a]P; and an overall meat-mutagenic activity index (15). All meats queried on the meat-cooking module (i.e., hamburgers, steak, bacon, and chicken) were used to create these variables. Details of the methods used to create the CHARRED database are described elsewhere (2, 3, 15, 21). Briefly, the CHARRED database was developed using ~120 categories of meat samples prepared by different cooking methods with varying doneness levels and their composites analyzed for HCAs, B[a]P, and overall mutagenic activity (2, 3, 21). Mutagenic activity in meat was determined by the standard plate incorporation assay with *Salmonella typhimurium* strain TA98, measured as revertant colonies (i.e., Ames assay, ref. 22).

Cohort Follow-up and Case Ascertainment

Cancer cases were identified by linking cohort members to state cancer registries and to the U.S. National Death Index between 1995 and 2003 and are estimated to identify 90% of all cancer cases in our cohort (23). Vital status of cohort participants was also ascertained by linkage to the Social Security Administration Death Master File. Person-years of follow-up for this analysis were calculated from the date of the baseline questionnaire scanning to the date of invasive breast cancer diagnosis or censoring at the date of other cancer diagnosis (except for nonmelanoma skin cancer), death, emigration out of the study area, or December 31, 2003, whichever occurred first. For this analysis, we included registry-confirmed incident primary invasive breast cancer (ICD-O-3 code C50.0-C50.9) occurring in postmenopausal women in the cohort. A total of 3,818 cases were identified among 120,755 women with complete information on the baseline questionnaire and complete meat-cooking module data.

Statistical Analysis

Generalized linear models were used to estimate the means of the baseline variables within each quintile of intake of red meat for continuous variables, whereas proportions were calculated for categorical variables in the total cohort (Table 1). Cox proportional hazards models, with person-years as the underlying time metric, were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI). Analyses using age as the underlying time metric gave similar results, and we present the results using person-years. The meat and other dietary variables were energy-adjusted using the density method, with energy included in the model, because most dietary variables were correlated with total energy intake (24). Models using unadjusted meat intake but with calories as a covariate were also fitted; these models gave similar results to the multivariable nutrient density method. The meat intake

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and meat mutagen variables were categorized into quintiles based on the cohort distribution among women. In additional analyses, we examined the association of deciles of meat intake with risk to take advantage of the full range of variation. Intake of meats prepared by different cooking methods were categorized into 4 groups consisting of a group with no intake (referent group) and tertiles of those with >0 intake. Tests for trend across categorical variables were calculated using the median value of each category. Models assessing specific meat groups and cooking methods simultaneously controlled for the remaining meat groups and cooking methods in order to account for total meat consumption (white and red; high-temperature and low-temperature cooked; processed and non-processed; rare/medium and well/very well-done; pan-fried; grilled/barbecued; oven-broiled; other, such as sautéed, baked, or microwaved).

Our multivariable models were constructed by individually adding potential confounding variables into the model. Variables were retained in the model if they were associated with both the disease and exposure, or changed the risk estimate by >10%. Although total energy intake (kcal) did not meet these criteria, it was included on a priori grounds. The following variables were included in the fully-adjusted model: age, body mass index (kg/m^2); height (inches); age at first menstrual period; age at first live birth; age at menopause; number of breast biopsies; family history of breast cancer; menopausal hormone therapy; education; race; total energy intake; saturated fat; alcohol intake; physical activity; and smoking.

Additional analyses were carried out stratifying by hormone receptor status, which was available for only a minority of breast cancer cases (estrogen receptor status on 47%; progesterone receptor status on 45%) Of cases with known hormone receptor status, 39% were estrogen receptor (ER) positive, 8% were ER negative, 32% were progesterone receptor (PR) positive and 13% were PR negative.

We further examined the association of the major meat variables with breast cancer within strata of potential effect modifiers, including body mass index, parity, menopausal hormone therapy, smoking, alcohol consumption, vegetable intake, fruit intake, and physical activity. Tests for interaction were based on the likelihood ratio tests comparing models with and without the product terms representing the variables of interest. All statistical significance tests were two-sided. All analyses were performed using SAS version 9 (SAS Institute Cary, NC, USA).

Results

Mean body mass index, use of oral contraceptives, mean energy intake, and saturated fat intake increased with increasing red meat intake (Table 1). In contrast, the proportions of women with higher education, who were African-American, nulliparous, over age 30 at first birth, never smokers, current users of menopausal hormone therapy, who engaged in physical activity 5+ times per week, and who were 50 or older at onset of menopause decreased with increasing meat intake.

In the age-adjusted models for intake of total meat, red meat, and meat cooked at high temperatures there were slight elevations in the HR, some of which reached statistical significance; however, there was no trend with increasing intake (Table 2). In the multivariable models, intake of total meat, red meat, white meat, processed meat, and meat cooked at high temperatures were not associated with breast cancer risk. Deciles of these meat variables also showed no elevation in the hazard ratios, which were all close to 1.0 (data not shown). Furthermore, omitting saturated fat as a covariate did not alter the risk estimates (data not shown). When cases diagnosed during the first 3 years of follow-up were excluded, the results were unchanged (data not shown).

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Breast cancer risk was not associated with high-temperature cooking methods or level of doneness (Table 3). The age-adjusted HR for intake of rare-/medium-done meat was statistically elevated, but there was no association in the fully-adjusted model.

Neither the age-adjusted nor the fully-adjusted models showed any suggestion of an association between any of the five indicators of mutagenic activity (overall mutagenic activity, DiMeIQx, MeIQx, PhIP, or B[a]P) and breast cancer risk (Table 4). Deciles of these indicators also showed no association.

No significant associations were seen by hormone receptor status (ER positive, ER negative, PR positive, PR negative) for intake of total meat, red meat, meat cooked at high temperatures, or 5 indicators of mutagenic activity (data not shown).

None of the meat or meat mutagen variables were associated with breast cancer within strata of age, body mass index, parity, alcohol consumption, smoking, menopausal hormone therapy, or intake of fruits and vegetables (data not shown), and there were no significant interactions between the meat variables (intake of total meat, red meat, high-temperature meat, and well-done meat) and these factors.

Discussion

This large prospective cohort of AARP members provides no support for the hypothesis that intake of meat, meat cooked at high temperatures, well-done meat, or estimated intake of mutagens/carcinogens from meat are associated with increased risk of postmenopausal breast cancer. Furthermore, our results do not indicate that consumption of meat or meat cooked at high temperatures affected breast cancer risk in subgroups, such as obese or nulliparous women, consumers of alcohol, smokers, users of menopausal hormone therapy, or women with low physical activity or with a low intake of fruits or vegetables.

A recent analysis from the NIH-AARP study reported on the association of intake of red and processed meat in relation to the risk of 21 cancers. Positive associations were seen with several cancers, including those of the colorectum and lung, but not with breast cancer (25). The present paper extends the findings of Cross et al. with regard to breast cancer by presenting more detailed results relating to meat preparation and intake of meat mutagens for the subcohort with complete meat module data.

In a previous publication from the NIH-AARP study (26), saturated fat intake showed a significant positive association with postmenopausal breast cancer risk, hence, it's inclusion here as a covariate. However, in models omitting saturated fat intake, meat intake and use of high temperature preparation methods were not associated with breast cancer risk.

Previous epidemiologic studies that have examined the association of meat intake with breast cancer have yielded conflicting results. A meta-analysis of 31 studies with information on meat intake (27) obtained a summary relative risk for the highest compared to the lowest level of total meat intake of 1.17 (95% CI 1.06-1.29). However, a pooled analysis of 8 cohort studies (3 of which were included in the meta-analysis) found no association with intake of total meat, red meat, or white meat (28). In contrast to the meta-analysis, the pooled analysis included only cohort studies with at least 200 cases and which had used a validated food-frequency questionnaire and involved reanalysis of the raw data from each of the studies using a common approach. Our results are in agreement with those of the pooled analysis.

Of a smaller number of studies (both case-control and cohort) which examined meat preparation methods and/or degree of doneness of consumed meat and estimated intake of

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meat mutagens with breast cancer risk, several reported positive associations (6-10), whereas others found no association (11-13). Among those studies reporting positive associations, two found a strong association with HCA exposure or degree of doneness of meat (6, 7), whereas others observed a more modest association (9, 10). One study (10) observed a modest association for intake of grilled or barbecued and smoked meats over the life course in postmenopausal (but not premenopausal) women but no associations with FFQ-derived measures of PAHs or HCAs based on type of meat, cooking methods, and doneness. Several studies examined possible interactions between intake of meat or well-doneness and polymorphisms in genes involved in the metabolism of HCAs and PAHs (11-13, 29, 30-32). The results of these studies are inconsistent and several had very small numbers in the key subgroups to assess interactions (31, 32).

Strengths of the present study include the use of a detailed questionnaire to assess intake of different types of meat, meat preparation, and doneness preferences as well as a linked database to estimate exposure to meat mutagens. In addition, the present study had a wide range of variation in dietary intake. For example, among women in our study, median intake of red meat in the highest quintile was seven times that in the lowest quintile. Other strengths include the prospective nature of the study, completeness of follow-up, the large number of postmenopausal breast cancer cases, and the ability to adjust for a large number of potential confounding variables. The large sample size and the wide range of food consumption habits of the cohort enhanced the ability to detect an association and to examine possible interactions.

Limitations include the fact that we were not able to assess the association of meat-related variables with pre-menopausal breast cancer, due to the small number of such cancers in the cohort. Dietary intake based on FFQs is affected by measurement error (33, 34), which, if non-differential, could reduce an association. In this study, as in most previous studies, diet was assessed in midlife. Therefore, it is possible that meat intake and exposure to meat mutagens at a younger age, and particularly during adolescence when the breasts are developing, may affect the risk of breast cancer. We were also unable to examine the effect of genes involved in the metabolism of HCAs and PAHs, such as *N*-acetyltransferase 1 (*NAT1*) and *N*-acetyltransferase 2 (*NAT2*), cytochrome P450 1A2 (*CYP 1A2*), and glutathione transferases (*GSTs*).

In conclusion, results of this large prospective cohort of postmenopausal women do not support the hypothesis that a high intake of meat, red meat, processed meat, meat cooked at high temperatures, or meat mutagens is associated with increased risk of breast cancer.

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Table 1

Selected characteristics of women in the NIH-AARP Diet and Health Study, by red meat category (n=120,755).

Characteristics	Quintiles of red meat, g/1000 kcals				
	≤13.0	>13.0 and ≤ 21.9	>21.9 and ≤ 31.1	>31.1 and ≤ 43.7	>43.7
Means					
Red meat, g/1000 kcal*	7.4	17.5	26.4	36.8	59.1
Age (years)	62.6	62.7	62.5	62.2	61.8
Body mass index (kg/m^2)	25.3	26.2	26.7	27.3	28.1
Height (inches)	64.2	64.3	64.3	64.3	64.2
Alcohol intake (g/day)†	5.7	6.8	6.4	6.1	5.5
Energy intake (kcal/day)†	1538	1545	1568	1618	1680
Saturated fat intake (g/1000 kcals)†	8.0	9.5	10.4	11.2	12.3
Proportions					
Education, college graduate or post-graduate (%)	39.5	33.1	30.1	27.7	24.4
Race, African-American (%)	7.2	5.3	4.7	3.9	3.6
Age at menarche ≥13 y (%)	9.0	9.0	9.1	9.1	9.1
Parity, nulliparous (%)	17.2	15.2	14.5	14.7	14.2
Age at first live birth, 30+ yrs (%)	6.7	5.9	5.8	5.7	5.3
Age at menopause ≥50 y (%)	43.7	41.8	40.7	39.4	37.7
Breast cancer diagnosed in mother or sisters (%)	12.7	12.7	12.6	12.6	12.0
Ever had breast biopsy (%)	24.5	24.7	24.2	24.1	23.6
Smoking status:					
Never %	47.9	46.9	46.1	45.1	42.7
Former %	44.1	41.5.	40.2	38.7	37.3
Current %	8.1	11.6	13.7	16.2	20.0
Heavy physical activity, ≥5 times per week (%)	24.7	18.5	15.8	13.6	12.1
Ever used oral contraceptives (%)	37.5	38.0	38.8	39.6	40.2
Current use of menopausal therapy at baseline (%)	45.5	46.2	45.2	45.0	42.5

*Nutrient density energy adjusted.

†Energy adjusted in general linear models.

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Table 2

Hazard Ratios (HR) and 95% confidence intervals (95% CI) for meat intake and postmenopausal breast cancer (n = 3,818 cases) in the NIH-AARP Diet and Health Study.[1]

Type of Meat	Quintiles of daily meat intake, g/1000 kcal					p for trend[2]
	Q1	Q2	Q3	Q4	Q5	
Total Meat	≤38.2	>38.2 and ≤53.7	>53.7 and ≤68.9	>68.9 and ≤89.1	>89.1	
Cases/person-years	728/ 172,445	800/ 172,025	791/ 172,163	765/ 169,741	734/ 163,452	
Age-adjusted HR (95% CI)[3]	1.00 (ref.)	1.10 (1.00-1.22)	1.10 (0.99-1.21)	1.08 (0.98-1.20)	1.09 (0.98-1.21)	0.21
Multivariable-adjusted HR[4] (95% CI)	1.00 (ref.)	1.07 (0.96-1.18)	1.04 (0.94-1.15)	1.02 (0.92-1.13)	1.03 (0.93-1.15)	0.91
Red Meat	≤13.0	>13.0 and ≤21.9	>21.9 and ≤31.1	>31.1 and ≤43.7	>43.7	
Cases/person-years	718/ 175,830	791/ 172,628	818/ 170,852	768/ 167,837	723/ 162,679	
Age-adjusted HR (95% CI)	1.00 (ref)	1.12 (1.02-1.24)	1.18 (1.06-1.30)	1.13 (1.02-1.26)	1.11 (1.00-1.23)	0.07
Multivariable adjusted HR (95% CI)	1.00 (ref)	1.09 (0.98-1.21)	1.13 (1.02-1.26)	1.07 (0.97-1.20)	1.05 (0.93-1.18)	0.66
White Meat	≤14.9	>14.9 and ≤24.1	>24.1 and ≤35.0	>35.0 and ≤52.2	>52.2	
Cases/person-years	771/ 168,214	757/ 169,927	769/ 171,786	787/ 171,507	734/ 168,394	
Age-adjusted HR (95% CI)	1.00 (ref)	0.96 (0.87-1.06)	0.96 (0.87-1.07)	0.99 (0.90-1.10)	0.96 (0.87-1.06)	0.68
Multivariable adjusted HR (95% CI)	1.00 (ref)	0.94 (0.85-1.04)	0.94 (0.85-1.04)	0.96 (0.87-1.06)	0.93 (0.84-1.04)	0.36
Processed Meat	≤2.2	>2.2 and ≤4.4	>4.4 and ≤7.3	>7.3 and ≤12.5	>12.5	
Cases/person-years	752/ 173,867	790/ 173,015	722/ 170,070	817/ 167,420	737/ 165,454	
Age-adjusted HR (95% CI)	1.00 (ref)	1.06 (0.95-1.17)	0.98 (0.88-1.09)	1.13 (1.02-1.25)	1.03 (0.92-1.14)	0.32
Multivariable adjusted HR (95% CI)	1.00 (ref)	1.02 (0.92-1.13)	0.95 (0.86-1.06)	1.09 (0.98-1.21)	1.00 (0.90-1.12)	0.55
Meat cooked at high temperatures	≤3.5	>3.5 and ≤7.0	>7.0 and ≤11.2	>11.2 and ≤18.0	>18.0	
Cases/person-years	738/ 174,952	765/ 172,608	805/ 171,225	773/ 167,160	737/ 163,882	
Age-adjusted HR (95% CI)	1.00 (ref)	1.05 (0.95-1.16)	1.12(1.01-1.24)	1.11 (1.00-1.24)	1.10 (0.98-1.22)	0.07
Multivariable adjusted HR (95% CI)	1.00 (ref)	1. 00 (0.90-1.12)	1.02 (0.91-1.14)	1.02 (0.91-1.15)	0.98 (0.86-1.11)	0.80

[1] 3,818 postmenopausal breast cancer cases among 120,755 female cohort subjects.

[2] P for trend calculated using median values for each quintile.

[3] Cox proportional hazards models used to calculate hazard ratios. All meats are adjusted for energy by the density method (g/1000 kcal), with energy additionally in the model and relevant meat groups adjusted simultaneously for each other (i.e. white and red; processed and non-processed; high-temperature and low-temperature cooked).

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[4]Models additionally adjusted for age at entry (continuous), body mass index (kg/m^2: <18.5, 18.5-<25, 25-<30, 30-<35, 35+), age at first menstrual period (<11, 11-12, 13-14, 15+), age at first live birth (never, <20, 20-24, 25-29, 30-34, 35+), family history of breast cancer (yes, no), hormone replacement therapy (never, <5 years, 5-9 years, 10+ years), education (less than high school graduate, high school graduate, some college, college graduate or post college, missing), race (non-Hispanic white, non-Hispanic black, other or unknown), total energy intake (continuous), gm saturated fat (continuous), alcohol intake (none, 0 to <5, 5 to <15, 15 to <30, 30+ g/d), physical activity (never/rarely, 1-3 times/mo, 1+ times/wk), smoking (never, quit >yrs ago, quit 1-4 yrs ago, quit <1 yr or current smoker, missing), age at menopause (<40, 40-44, 45-49, 50-54, 55+), number of breast biopsies (none, 1, 3, 3+, missing), height (<62, 62-<63, 63-<64, 64-<66, ≥67).

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Table 3

Hazard Ratios (HR) and 95% confidence intervals (95% CI) for meat cooking methods, doneness levels, and postmenopausal breast cancer (n = 3,818 cases) in the NIH-AARP Diet and Health Study.[1]

	Level of meat intake, g/1000 kcal				
Variable	**1**	**2**	**3**	**4**	**P trend**
	Meat cooking method Grilled or barbecued meat				
	≤0.05	>0.05 and ≤5.3	>5.3 and ≤14.3	>14.3	
Cases/person-years	763/ 170,555	987/ 226,243	1021/ 226, 679	1047/ 226,349	
Age-adjusted HR (95% CI)	1.00 (referent)	0.98 (0.89-1.08)	1.02 (0.93-1.12)	1.07 (0.97-1.17)	0.08
Multivariable HR (95% CI)	1.00 (referent)	0.96 (0.87-1.05)	0.98 (0.89-1.08)	0.99 (0.90-1.10)	0.91
	Pan-fried meat				
	0	>0 and ≤0.4	>0.4 -≤2.8	>2.8	
Cases/person-years	1517/ 340,815	774/ 170,582	788/ 169,687	739/ 168,738	
Age-adjusted HR (95% CI)	1.00 (referent)	1.05 (0.97-1.14)	1.08 (1.00-1.17)	1.01 (0.93-1.10)	0.33
Multivariable HR (95% CI)	1.00 (referent)	1.01 (0.93-1.10)	1.03 (0.94-1.12)	0.96 (0.88-1.05)	0.65
	Oven-broiled meat				
	0	>0 and ≤3.8	>3.8 -≤10.9	>10.9	
Cases/person-years	2413/ 539,286	484/ 103,713	462/ 103,492	459/ 103,332	
Age-adjusted HR (95% CI)	1.00 (referent)	1.05 (0.95-1.15)	1.00 (0.91-1.11)	1.00 (0.91-1.11)	0.85
Multivariable HR (95% CI)	1.00 (referent)	1.05 (0.95-1.15)	0.99 (0.89-1.09)	0.98 (0.89-1.08)	0.87
	Sauteed, baked, or microwaved meat				
	0	>0 and ≤2.3	>2.3-≤8.1	>8.1	
Cases/person-years	1198/ 285,684	870/ 187,983	867/ 188,003	883/ 188,152	
Age-adjusted HR (95% CI)	1.00 (referent)	1.10 (1.01-1.19)	1.09 (1.00-1.18)	1.11 (1.02-1.21)	0.03
Multivariable HR (95% CI)	1.00 (referent)	1.06 (0.97-1.15)	1.04 (0.95-1.14)	1.06 (0.97-1.16)	0.20
	Meat doneness level Rare / medium done cooked meat				
	0	>0 and ≤5.9	>5.9-≤16.4	>16.4	
Cases/person-years	999/ 240,970	904/ 203,412	980/ 203,216	935/ 202,223	
Age-adjusted HR (95% CI)	1.00 (referent)	1.07 (0.99-1.16)	1.17 (1.08-1.27)	1.14 (1.05-1.23)	0.0009
Multivariable HR (95% CI)	1.00 (referent)	1.01 (0.92-1.11)	1.06 (0.97-1.16)	1.00 (0.91-1.10)	0.71
	Well / very well-done cooked meat				

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	Level of meat intake, g/1000 kcal				
Variable	**1**	**2**	**3**	**4**	**P trend**
	0	>0 and ≤4.9	>4.9-≤14.4	>14.4	
Cases/person-years	300/ 65,378	1186/ 261,152	1180/ 261,762	1152/ 261,530	
Age-adjusted HR (95% CI)	1.00 (referent)	1.06 (0.98-1.16)	1.05 (0.96-1.15)	1.04 (0.95-1.13)	0.61
Multivariable HR (95% CI)	1.00 (referent)	0.98 (0.89-1.07)	0.97 (0.89-1.07)	0.98 (0.89-1.07)	0.64

[2]P for trend calculated using median values for each quantile.

[3]Cox proportional hazards models used to calculate hazard ratios. All meats are adjusted for energy by the density method (g/1000 kcal), with energy additionally in the model).

[4]Models additionally adjusted for age at entry (continuous), body mass index (kg/m^2: <18.5, 18.5-<25, 25-<30, 30-<35, 35+), age at first menstrual period (<11, 11-12, 13-14, 15+), age at first live birth (never, <20, 20-24, 25-29, 30-34, 35+), family history of breast cancer (yes, no), hormone replacement therapy (never, <5 years, 5-9 years, 10+ years), education (less than high school graduate, high school graduate, some college, college graduate or post college, missing), race (non-Hispanic white, non-Hispanic black, other or unknown), total energy intake (continuous), gm saturated fat (continuous), alcohol intake (none, 0 to <5, 5 to <15, 15 to <30, 30+ g/d), physical activity (never/rarely, 1-3 times/mo, 1+ times/wk), smoking (never, quit >yrs ago, quit 1-4 yrs ago, quit <1 yr or current smoker, missing), age at menopause (<40, 40-44, 45-49, 50-54, 55+), number of breast biopsies (none, 1, 3, 3+, missing), height (<62, 62-<63, 63-<64, 64-<66, ≥67).

[1]3,818 postmenopausal breast cancer cases among 120,755 female cohort subjects.

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Table 4

Hazard Ratios (HR) and 95% confidence intervals (95% CI) for intake of meat mutagens, mutagenic activity index, and postmenopausal breast cancer (n = 3,818 cases) in the NIH-AARP Diet and Health Study.[1]

	Quintiles of daily meat mutagen intake					p for trend[2]
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	
Overall mutagenic activity, revertant colonies/1000 kcal						
	≤254	>254 and ≤640	>640 and ≤1232	>1232 and ≤2414	>2414	
Cases/person-years	754/ 170,077	791/ 169,541	797/ 169,583	772/ 169,995	704/ 170,666	
Age-adjusted HR (95% CI)[3]	1.00 (ref.)	1.04 (0.95-1.15)	1.07 (0.97-1.19)	1.03 (0.94-1.14)	0.95 (0.86-1.05)	0.34
Multivariable-adjusted HR[4] (95% CI)	1.00 (ref.)	1.02 (0.92-1.13)	1.04 (0.94-1.16)	1.02 (0.92-1.13)	0.94 (0.84-1.04)	0.27
2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline (DiMeIQx), ng/1000 kcal						
	0	>0 and ≤0.05	>0.05 and ≤0.30	>0.30 and ≤0.83	>0.83	
Cases/person-years	1442/ 316,166	98/ 23,862	784/ 169,459	783/ 170,089	711/ 170,245	
Age-adjusted HR (95% CI)	1.00 (ref)	0.94 (0.77-1.16)	1.00 (0.92-1.09)	1.01 (0.93-1.11)	0.92 (0.84-1.01)	0.25
Multivariable adjusted HR (95% CI)	1.00 (ref)	0.97 (0.79-1.20)	1.02 (0.93-1.11)	1.04 (0.95-1.13)	0.95 (0.86-1.04)	0.60
2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MelQx), ng/1000 kcal						
	≤1.1	>1.1 and ≤3.0	>3.0 and ≤6.2	>6.2 and ≤12.7	>12.7	
Cases/person-years	742/ 170,214	789/ 170,117	761/ 169,778	776/ 169,594	750/ 170,119	
Age-adjusted HR (95% CI)	1.00 (ref)	1.07 (0.96-1.18)	1.04 (0.94-1.15)	1.09 (0.99-1.21)	1.00 (0.91-1.11)	0.79
Multivariable adjusted HR (95% CI)	1.00 (ref)	1.04 (0.94-1.15)	1.03 (0.93-1.14)	1.07 (0.96-1.18)	1.00 (0.89-1.11)	0.87
2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP), ng/1000 kcal						
	≤3.6	>3.6 and ≤11.4	>11.4 and ≤26.0	>26.0 and ≤60.9	>60.9	
Cases/person-years	761/ 181,617	731/ 157,877	851/ 169,686	740/ 169,678	735/ 170,964	
Age-adjusted HR (95% CI)	1.00 (ref)	1.10 (1.00-1.22)	1.15 (1.04-1.27)	1.07 (0.98-1.19)	1.01 (0.91-1.12)	0.95
Multivariable adjusted HR (95% CI)	1.00 (ref)	1.06 (0.96-1.18)	1.11 (1.00-1.23)	1.04 (0.93-1.15)	0.98 (0.88-1.09)	0.57
Benzo(a)pyrene [B(a)P], ng/1000 kcal						
	≤0.4	>0.4 and ≤2.1	>2.1 and ≤6.8	>6.8 and ≤18.6	>18.6	
Cases/person-years	766/ 169,516	764/ 169,283	751/ 170,240	758/ 170,234	795/ 170,548	
Age-adjusted HR (95% CI)	1.00 (ref)	1.00 (0.90-1.10)	0.98 (0.89-1.09)	1.00 (0.90-1.10)	1.06 (0.96-1.18)	0.27
Multivariable adjusted HR (95% CI)	1.00 (ref)	0. 96 (0.88-1.05)	0.99 (0.91-1.08)	0.98 (0.90-1.08)	0.96 (0.88-1.06)	0.68

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[1] 3,818 postmenopausal breast cancer cases among 120,755 female cohort subjects.

[2] P for trend calculated using median values for each quintile.

[3] Cox proportional hazards models used to calculate hazard ratios.

[4] Models additionally adjusted for age at entry (continuous), body mass index (kg/m^2: <18.5, 18.5-<25, 25-<30, 30-<35, 35+), age at first menstrual period (<11, 11-12, 13-14, 15+), age at first live birth (never, <20, 20-24, 25-29, 30-34, 35+), family history of breast cancer (yes, no), hormone replacement therapy (never, <5 years, 5-9 years, 10+ years), education (less than high school graduate, high school graduate, some college, college graduate or post college, missing), race (non-Hispanic white, non-Hispanic black, other or unknown), total energy intake (continuous), gm saturated fat (continuous), alcohol intake (none, 0 to <5, 5 to <15, 15 to <30, 30+ g/d), physical activity (never/rarely, 1-3 times/mo, 1+ times/wk), smoking (never, quit >yrs ago, quit 1-4 yrs ago, quit <1 yr or current smoker, missing), age at menopause (<40, 40-44, 45-49, 50-54, 55+), number of breast biopsies (none, 1, 3, 3+, missing), height (<62, 62-<63, 63-<64, 64-<66, ≥67).

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