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Association Between Meat Consumption and Risk of Breast Cancer: findings from the Sister Study

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Abstract

Meat consumption has been postulated to increase the risk of breast cancer, but this association has not been consistently seen. We examined the association between consumption of different types of meat, meat mutagens, and incident invasive breast cancer. Information on consumption of different meat categories and meat cooking practice behaviors was obtained from 42,012 Sister Study participants who completed a Block 1998 food frequency questionnaire at enrollment (2003–2009) and satisfied eligibility criteria. Exposure to meat type and meat mutagens was calculated, and associations with invasive breast cancer risk were estimated using multivariable Cox proportional hazards regression. During follow-up (mean, 7.6 years), 1,536 invasive breast cancers were diagnosed at least 1 year after enrollment. Increasing consumption of red meat was associated with increased risk of invasive breast cancer ($HR_{\text{highest vs. lowest quartile}}$:1.23, 95% CI: 1.02–1.48, P_{trend} =0.01). Conversely, increasing consumption of poultry was associated with decreased invasive breast cancer risk ($HR_{\text{highest vs. lowest quartile}}$: 0.85; 95% CI: 0.72–1.00; P_{trend} = 0.03). In a substitution model with combined red meat and poultry consumption held constant, substituting poultry for red meat was associated with decreased invasive breast cancer risk ($HR_{\text{highest vs. lowest quartile}}$: 0.72, 95% CI: 0.58–0.89). No associations were observed for cooking practices, estimated heterocyclic amines, or heme iron from red meat consumption with breast cancer risk. Red meat consumption may increase the risk of invasive breast cancer, whereas poultry consumption may be associated with reduced risk. Substituting poultry for red meat could reduce breast cancer risk.

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DISCLOSURE
All authors declare no conflict of interest.

Keywords

red meat; poultry; breast cancer

INTRODUCTION

Breast cancer is the most common cancer in women in the U.S. and internationally [1]. Disparities in the rate of breast cancer across different countries are likely to arise from lifestyle and environmental factors, including diet [2]. In 2015, the International Agency for Research on Cancer (IARC) evaluated the carcinogenicity of red meat consumption and announced that it is “probably carcinogenic to humans” (Group 2A) [3]. Meat consumption has been indicated to increase the risk of breast cancer in ecological studies, but in several cohort studies, this association has not been consistent [2, 4–6].

Cooking methods and doneness of meat are likely to modify or mediate the magnitude of this association [7]. Certain cooking practices may be associated with higher risks of cancer, primarily through the exposure of mutagenic compounds such as polyaromatic hydrocarbons and heterocyclic amines related to meat preparation practices [8]. Few studies have examined general meat and poultry consumption, cooking methods, and doneness together in relation to breast cancer risk to examine potential effect modification or mediation of cooking methods or meat doneness on meat and poultry consumption [9].

Breast cancer has a heterogeneous etiology varied by hormone receptor status and menopausal status. Past studies are limited in the extent of information for tumor characteristics such as estrogen receptor status [8]. Furthermore, past studies were unable to account for changes in menopausal status after baseline [8]. To examine this relationship in a comprehensive manner, we investigated the relationship of general meat and poultry consumption as well as meat cooking methods, doneness, and meat mutagens to breast cancer incidence utilizing data from the Sister Study, a large, U.S.-based prospective cohort study.

MATERIALS AND METHODS

Study population

The Sister Study is a U.S. and Puerto Rico-based nationwide prospective cohort study that evaluates environmental and genetic risk factors for breast cancer. The enrollment period was between 2003–2009; eligible participants were 35 to 74-year old women who had no previous diagnosis of breast cancer and are sisters or half-sisters of women diagnosed with breast cancer. A total of 50,884 women completed the extensive baseline enrollment process, which consisted of comprehensive interview and self-completed questionnaires covering medical and family cancer history as well as lifestyle and demographic characteristics, including diet and a home exam during which height, weight, and weight and hip circumference were measured. Details of the study design, data collection, and outcome measurements are described elsewhere [10, 11]. The Sister Study was approved by National

Institute of Environmental Health Services/NIH and Copernicus Group Institutional Review Boards, and all participants provided written informed consent.

Exposure measurement

Dietary data were collected at baseline from a modified version of validated 110-item 1998 Block Food Frequency Questionnaire (FFQ) [12,13]. The FFQ asked participants to report their average frequency and serving size—small, medium, or large - of each food and beverage item listed, with a supplemental page visually representing the different serving sizes for reference. Based on the information obtained by FFQ, food groups were created using the Food Patterns Equivalents Database (FPED) 2011–2012, developed by the USDA [14]. Red meat consumption consists of the meat FPED component (beef, veal, pork, lamb, and game meat). White meat includes the poultry FPED component (chicken, turkey, Cornish hens, duck, goose, quail, and pheasant/game birds), the seafood high in *n*-3 fatty acids FPED component, and the seafood low in *n*-3 fatty acids FPED component[14]. Cured/processed meat consists of frankfurters, sausages, corned beef, cured ham and luncheon meat made from beef, pork, or poultry. All mentioned food categories have units of ounce-equivalents and were categorized into quartiles [14].

Cooking practices were determined from the participant’s responses to multiple-choice questions on the FFQ for individual meat items. For example, participants were asked “When you eat steak, how is it usually cooked” with options “Don’t eat steak”, “Pan Fried”, “Oven broiled”, and “Grilled or barbecued” for usual cooking method, and “When you eat steak how well done is it usually cooked” with options “Don’t eat steak”, “Rare”, “Medium rare”, “Medium”, “Medium well done”, “Well done”, “Very well done”, and “Charred” for usual doneness.

Meat mutagens were estimated using the Computerized Heterocyclic Amines Resource for Research in Epidemiology of Disease (CHARRED) version 1.7 (https://dceg.cancer.gov/tools/design/charred). Estimations of HCAs 2-amino-3,4,8-trimethyl-imidazo[4,5-*f*]quinoxaline (DiMeIQx), 2-amino-1-methyl-6-phenyl-imidazo[4,5-*b*]pyridine (PhIP), and 2-amino-3,8-dimethyl-imidazo[4,5-*f*]quinoxaline (MeIQx), in addition to polycyclic aromatic hydrocarbon (PAH) exposure marker benzo[*a*]pyrene (B[*a*]P) were calculated with CHARRED based on self-reported cooking methods from the FFQ for steak, hamburger, and pork chop [15]. Heme iron estimations based on steak, hamburger, and pork chop doneness and cooking methods were calculated from the NCI heme iron database [15].

Assessment of breast cancer

Breast cancer diagnoses were self-reported during annual follow-ups. Women who reported a breast cancer diagnosis were contacted for additional information about tumor characteristics and permission to retrieve medical records, which were obtained for 82% of cases. We did not systematically collect information on reasons why some women did not provide medical record authorization. Anecdotally, some women indicated that they did not see the need for medical records after providing the information themselves. Others had concerns about bothering their providers. Agreement between self-reported breast cancer diagnosis and medical records was high (positive predictive value over 99% for overall, invasive, and estrogen receptor-positive breast cancer; 83% for estrogen receptor-negative disease) and confirmation rates were not systemically different by demographic factors such as race/ethnicity or age.[11] Therefore, self-reported information was used when medical records were not obtained. Follow-up was through August 14, 2015 (data release 5.0.2).

Statistical analysis

Participants were excluded from the study if they had missing FFQs (N=1,145), missing covariate data (N=3,481), a previous cancer diagnosis (N=2,757), extreme caloric consumption (<600 or >3,500 kcal/day, N=1,469), extreme body mass index (BMI) (<15 or >50 kg/m^2, N=284), or were pregnant at baseline (N=20), or less than one-year of follow-up (N=458), resulting in a total sample of 42,012 with 275,922 person-years of follow-up in the analysis after excluding first year of follow-up after enrollment to reduce bias from reverse-causality related to undetected tumors present at baseline (Supplemental Figure 1). Person-time was calculated from the age one year after enrollment until the age of breast cancer diagnosis or until death, last follow-up or when they dropped out of the study. Participants diagnosed with *in situ* breast cancer were censored at the time of diagnosis. If a participant was diagnosed with one type of breast cancer, they were censored for all other types of breast cancer at the time of diagnosis (i.e. if participant is diagnosed with ER+, she is censored for ER-).

Multivariable Cox proportional hazard models were implemented to estimate hazard ratios and 95% confidence intervals for total invasive breast cancer. Potential confounders were identified *a priori* based on literature review and presumed causal relationships among the covariates:[16] race/ ethnicity (non-Hispanic white, non-Hispanic black, other), household income (< $49,999, $50,000 to $99,999, ≥ $100,000), educational attainment (high school degree or less, some college, college degree or higher), baseline menopausal status (binary), BMI (continuous), interaction term between baseline menopausal status and BMI, waist-to-hip ratio (continuous), total energy intake (kcal/day), consumption of vegetables (quintiles), consumption of fruit (quintiles), percent calories from fat (quartiles), dairy consumption (quartiles), number of relatives diagnosed with breast cancer before the age of 50 (0, 1, ≥2), lifetime duration of breastfeeding (none and tertiles among women with any breastfeeding), hormone therapy (none, estrogen only, both estrogen and progesterone), parity (0, 1, 2, ≥3 births), birth control pill use (never, former, current), alcohol consumption (never drinker, former drinker, current drinker <1 drink/day, current drinker 1–1.9 drinks/day, current drinker ≥2 drinks/day), total MET-hours of leisure-time physical activity per week (quintiles), and smoking status (≥20 pack years, <20 and ≥10 pack years, < 10 and > 0 pack years, never smoker). The proportional hazards assumption was checked utilizing Martingale residuals and there was no significant departure from proportionality in hazards over time. For all analyses, age was used as the primary time scale.

Potential effect modification was analyzed with likelihood ratio tests for time varying menopausal status, physical activity, family history of breast cancer, and race/ethnicity. Time-varying menopausal status contributed to follow-up time at risk for either premenopausal or post-menopausal breast cancer and was considered for both incident cases and non-cases. A case-only analysis was applied to determine differences in the association between meat consumption and invasive breast cancer by ER status. A case-only analysis is often used to explore etiological heterogeneity with respect to the risk factor under study.[17–19] Tests for linear trend across quartiles of meat consumption were performed by modeling the median value of each quartile.

Addition models were implemented to investigate the effect of an independent increase in consumption of each type of meat with other meats held constant, and each type of meat was mutually adjusted for other meat categories [20]. To disentangle the breast cancer risk with the various nested sub-categories of meat, four addition models were utilized with sequentially more specific meat categories. The categories were the following: sum of all meat categories (poultry, seafood, red meat, and cured meat) (Model 1), white meat (combination of poultry and seafood) and sum of red and cured meat (Model 2), red meat, white meat, and cured meat (Model 3), and red meat, poultry, seafood, and cured meat (Model 4). Model 4, as it includes all individual meat categories, can be considered the most appropriate for inference. Substitution models were utilized to estimate hazard ratios for the substitution effects of one type of meat for the other type of meat while keeping consumption of two types of meat constant.[20–22] Here, consumption of two types of meat was held constant, such that an increase in one type of meat intake is offset by an equal decrease in the other type of meat. For example, in the substitution model including poultry and combined consumption of red meat and poultry, the regression coefficient for poultry consumption provides the estimate for the effect of substituting poultry for red meat.

In a sensitivity analysis, we repeated our main analyses after excluding BMI and waist-to-hip ratio in all models, since obesity might be both a confounder and mediator of associations between diet and breast cancer risk. In addition, we performed an additional adjustment for Healthy Eating Index (HEI)-2015 [23] to explore the effect of overall diet quality that may be related to a healthier lifestyle. Statistical significance was evaluated with two-sided tests, with the level of significance at 0.05. All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Descriptive characteristics of study participants by quartile of total meat consumption are shown in Table 1. In general, women who had higher consumption of meat were younger, had higher BMI, less physical activity, higher consumption of calories, vegetables, and dairy, higher percent calories from fat, shorter lifetime duration of breastfeeding, and were more likely to have smoked or consumed alcohol. Characteristics by quartile of red meat consumption and quartile of poultry consumption are shown in Supplemental Table 1. Study participants with higher red meat consumption had worse health behaviors overall and stronger family history of breast cancer compared to those with lower red meat consumption. In terms of poultry consumption, study participants with higher poultry consumption had more years of education and had stronger family history compared to those with lower poultry consumption.

A total of 1,536 cases of invasive breast cancer cases were diagnosed during follow-up from 1 year after enrollment (mean, 7.6 years including first year of follow-up). Associations between categories of meat consumption and risk of invasive breast cancer are displayed in Table 2 and Supplemental Table 3. Increased consumption of all meat was positively associated with risk of invasive breast cancer in age-adjusted model (Supplemental Table 2), but the significant association disappeared after multivariable-adjustment (Table 2). Covariates that accounted over a 10% change in the regression coefficient of the highest quartile of all meat intake from unadjusted and multivariable-adjusted models include: total calorie intake (kcal), vegetable consumption, percent of calories from fat, and BMI. In models including red and white meat (Model 2) and also cured meats (Model 3), higher consumption of red meat was associated with invasive breast cancer: Model 3 ($HR_{\text{highest to lowest quartile}}$ = 1.22, 95% CI: 1.01–1.46, P_{trend} = 0.02) and Model 4 ($HR_{\text{highest to lowest quartile}}$ =1.23, 95% CI: 1.02–1.48, P_{trend} = 0.04). White meat consumption was not associated with invasive breast cancer (Models 2 and 3), however when white meat from poultry and seafood were considered separately (Model 4), poultry consumption was found to be inversely associated with invasive breast cancer ($HR_{\text{highest to lowest quartile}}$ = 0.85, 95% CI: 0.73–1.00, P_{trend} = 0.02).

Associations between red meat and poultry and total invasive breast cancer risk and by estrogen receptor status as well as time-varying menopausal status with substitution and addition models are displayed on Table 3 and Supplemental Table 3. From the substitution models, substituting red meat for poultry increased total breast cancer risk when total consumption of red meat and poultry is held constant ($HR_{\text{highest to lowest quartile}}$ =1.29, 95% CI: 1.03–1.61, P_{trend} = 0.01). Substituting poultry for red meat was found to have an inverse association with breast cancer when holding total red meat and poultry consumption fixed ($HR_{\text{highest to lowest quartile}}$ = 0.72, 95% CI: 0.58–0.89, P_{trend} = 0.002). Overall, associations with meat and poultry consumption did not differ significantly by estrogen receptor status. For postmenopausal invasive breast cancer, red meat consumption was positively associated ($HR_{\text{highest to lowest quartile}}$ = 1.28, 95% CI: 1.04–1.56, P_{trend} = 0.006), whereas poultry consumption was inversely associated. ($HR_{\text{highest to lowest quartile}}$ = 0.80, 95% CI: 0.66–0.96, P_{trend} = 0.005). Premenopausal breast cancer was not significantly associated with meat consumption patterns. Patterns were also similar in substitution models for postmenopausal breast cancer.

Stratified analyses (by ethnicity, family history, and physical activity) for the association between meat and invasive breast cancer are shown in Supplemental Table 4. The positive association between meat and breast cancer was more pronounced among women with more relatives that were diagnosed with breast cancer before the age of 50 ($HR_{\text{highest to lowest quartile}}$= 1.40, 95% CI: 1.20–1.78), whereas the inverse association between poultry consumption and invasive breast cancer risk was more pronounced in women who did not have a relative that was diagnosed with breast cancer before the age of 50 ($HR_{\text{highest to lowest quartile}}$ = 0.80, 95% CI: 0.61–1.03), although significant interactions were not observed. We also found a significant interaction of physical activity on the association between red meat consumption and invasive breast cancer risk ($P_{interaction}$= 0.004), indicating that among women with high physical activity, increasing red meat consumption contributed to a greater risk of invasive breast cancer (P_{trend} = 0.001) compared to women with lower physical activity (P_{trend} = 0.9).

The association of cooking method, doneness, estimated heterocyclic amines, and estimated heme iron from red meat consumption with total invasive breast cancer is shown in Table 4. Grilled red meat (combined consumption of steak, pork chop, and hamburger in grams per day) and at least well/very well done red meat were not associated with invasive breast cancer risk. Consumption of both grilled and at least well/very well done red meat was not associated with invasive breast cancer risk. Levels of DiMeIQx, MeIQx, PhIP, and B[*a*]P were not associated with invasive breast cancer risk. There was no significant pattern of association between increasing quartiles of heme iron and invasive breast cancer risk. No differences were observed by ER status or by menopausal status (data not shown). When we analyzed the data after excluding BMI and waist-to-hip ratio in all models, findings were not materially changed (data not shown). Sensitivity analyses with an additional adjustment for the HEI-2015 did not materially change the overall results (Supplemental Table 5).

DISCUSSION

In this large prospective cohort study, we found that red meat consumption increased the risk of invasive breast cancer, whereas poultry consumption was associated with reduced risk, particularly for postmenopausal invasive breast cancer. These associations were more pronounced in substitution models, indicating that substituting poultry for red meat decreases breast cancer risk when the total consumption of red meat and poultry is fixed and substituting red meat for poultry increases breast cancer risk when total consumption of red meat and poultry is fixed.

There are inconsistent findings across previous epidemiological studies of the association between red meat consumption and breast cancer. Anderson et al. reported no association between red meat consumption and breast cancer risk in a meta-analysis of 11 prospective cohorts, whereas Farvid et al. reported borderline significant positive associations between red meat consumption and breast cancer risk in a meta-analysis of 13 cohort, 3 nested case–control and 2 clinical trial studies [5, 24]. An association between red meat and breast cancer may be due to dietary heme iron, fat, and *N*-glycolylneuraminic acid as these compounds found in red meat are indicated to possibly increase tumor formation [25]. However, we did not find significant association between quartiles of heme iron and breast cancer risk in the present study (Table 4). Another plausible explanation for this association may be the carcinogenic byproducts resulting from the high-heat cooking practices of meat such as polycyclic aromatic hydrocarbons and heterocyclic amines [8, 25, 26]. As we found that cooking practices were not associated with breast cancer in our analyses, there is a need for further studies on the possible explanations of the association.

We observed a significant inverse association between poultry consumption and risk of breast cancer in the present study. Many studies found non-significant associations between poultry and breast cancer risk [9, 27–29] and non-significant inverse associations [8, 30, 31] whereas a few studies found significant inverse associations of poultry and white meat consumption with breast cancer [32–35]. One study found a significant inverse association with poultry and white meat consumption only among Hispanic women [33], another found a significant inverse association with white meat among Uruguayan women [34, 35]. A study of Californian women found that white meat and chicken consumption were significantly protective of breast cancer risk [32]. The inconsistencies between past findings for poultry and breast cancer risk may relate to whether diets captured poultry with or without skin to examine this association [34]. Basing poultry consumption on the lean portion only (i.e. without skin and extra fat) may contribute to the inverse association with breast cancer found in our study [14]. This association may also be due, in part, to residual confounding, as those who reported higher consumptions of poultry had generally healthier dietary patterns compared to those with lower consumptions of poultry. Individuals who consume higher amounts of poultry may also have healthier lifestyle patterns compared to those who consume lower amounts of poultry, although we accounted for such differences in our models. The fact that the inverse association with poultry was more pronounced in the substitution analysis suggests that association between poultry and breast cancer risk may arise from differences between red meat and poultry, such as saturated fat content or heme iron [21]. Past literature suggests that poultry consumption, in comparison to red meat consumption, may promote lower levels of mutagenic activity, oxidative stress, and DNA damage [21, 36]. Further research should examine possible mechanisms for a protective effect of poultry consumption on risk of breast cancer.

As breast cancer risk differs by menopausal status, the association between red meat consumption and breast cancer risk could differ between premenopausal and postmenopausal women [37]. Some studies have found that associations were similar for premenopausal and postmenopausal women [7, 9, 33, 38], whereas others found differences in the association by menopausal status [24, 28, 34, 39, 40] in which postmenopausal women generally had larger effect sizes for all meat types compared to premenopausal women. In this study, we found greater associations of red meat consumption and poultry consumption among postmenopausal women compared to premenopausal women. However, we did not find significant interaction with menopausal status, perhaps because of substantially lower power for premenopausal analyses.

To our knowledge, four cohort studies [27, 29, 37, 41, 42] and one pooled case-control analysis [33] examined meat consumption and breast cancer risk by estrogen receptor status with most finding no significant differences by estrogen receptor status [5]. Our findings are consistent with past literature as we found that there was no significant heterogeneity in meat-associated breast cancer risk by estrogen receptor status.

Although we did not find a significant association between red meat cooking practices and breast cancer risk, there is some evidence in the literature indicating a positive association between certain meat cooking practices, notably those that utilize high temperatures/ smoking, and cancer risk, but the associations between breast cancer and meat cooking practices are not conclusive [8, 26, 43, 44]. A study found that there was an association between consumption of well-done red meat and breast cancer risk, but it is unclear what components of well-done red meat are associated with this increase in breast cancer risk [26, 32]. In our study there were no overall associations between degree of meat doneness or cooking methods and breast cancer risk.

We also found that an association between red meat and breast cancer was more apparent among women with a strong family history of breast cancer whereas the converse was true for poultry. Our cohort includes women who all have a family history of breast cancer. Women with a sister with breast cancer may have a higher prevalence of gene variants related to breast cancer risk, including those related to metabolic factors associated with meat and poultry consumption. Thus, to the extent that there are gene and diet interactions, associations between specific types of meat and breast cancer may be easier to detect in this sister-based cohort [45]. Having two or more relatives with breast cancer may indicate a higher genetic risk for breast cancer as compared to women with only a single affected relative. Nonetheless, the exclusion of women with no family history of breast cancer from our cohort makes it more difficult to find interactions between family history and diet patterns in relation to breast cancer risk.

Strengths of the present study include large sample size, comprehensive baseline risk factor assessment, and ability to account for time-varying menopausal status and to explore impact of family history and other behavioral and lifestyle factors. The Sister Study also is prospective in design with high retention rates among participants [10]. Potential limitations include the use of a single food-frequency questionnaire administered at baseline. This will result in some errors in quantifying meat consumption as well as other dietary confounders. Another concern would be non-differential misclassification of exposure due to the self-report nature of the FFQ, which may have led to the null results observed. Furthermore, the questionnaire for cooking practices may also be unable to accurately capture complete meat mutagen information in this population of women, possibly resulting in the lack of association found between meat mutagens and breast cancer risk.

In summary, the findings from this prospective cohort of women with a first-degree history of breast cancer support the hypothesis that red meat may increase the risk of breast cancer. It may be beneficial to replace red meat with poultry to reduce the overall risk of breast cancer. Further investigation is needed to understand the possible reasons behind the protective association of poultry on breast cancer risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of abbreviations:

BMI	Body mass index
CIs	Confidence intervals
ER	Estrogen receptor

FFQ	Food frequency questionnaire
FPED	Food Patterns Equivalents Database
HRs	Hazard ratios
SD	Standard deviation

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136: E359–E86. [PubMed: 25220842]
2. Lacey JV, Devesa SS, Brinton LA. Recent trends in breast cancer incidence and mortality. Environ Mol Mutagen 2002;39: 82–8. [PubMed: 11921173]
3. Johnson IT. The cancer risk related to meat and meat products. Br Med Bull 2017;121: 73–81. [PubMed: 27989995]
4. Anderson JJ, Darwis NDM, Mackay DF, Celis-Morales CA, Lyall DM, Sattar N, Gill JMR, Pell JP. Red and processed meat consumption and breast cancer: UK Biobank cohort study and meta-analysis. Eur J Cancer 2018;90: 73–82. [PubMed: 29274927]
5. Farvid MS, Stern MC, Norat T, Sasazuki S, Vineis P, Weijenberg MP, Wolk A, Wu K, Stewart BW, Cho E. Consumption of red and processed meat and breast cancer incidence: A systematic review and meta-analysis of prospective studies. Int J Cancer 2018;143: 2787–99. [PubMed: 30183083]
6. Wu J, Zeng R, Huang J, Li X, Zhang J, Ho JC-M, Zheng Y. Dietary Protein Sources and Incidence of Breast Cancer: A Dose-Response Meta-Analysis of Prospective Studies. Nutrients 2016;8: 730.
7. Di Maso M, Talamini R, Bosetti C, Montella M, Zucchetto A, Libra M, Negri E, Levi F, La Vecchia C, Franceschi S, Serraino D, Polesel J. Red meat and cancer risk in a network of case–control studies focusing on cooking practices. Ann Oncol 2013;24: 3107–12. [PubMed: 24121119]
8. Dai Q, Shu X-o, Jin F, Gao Y-T, Ruan Z-X, Zheng W. Consumption of Animal Foods, Cooking Methods, and Risk of Breast Cancer. Cancer Epidemiol Biomarkers Prev 2002;11: 801–8. [PubMed: 12223422]
9. Missmer SA, Smith-Warner SA, Spiegelman D, Yaun S-S, Adami H-O, Beeson WL, van den Brandt PA, Fraser GE, Freudenheim JL, Goldbohm RA, Graham S, Kushi LH, et al. Meat and dairy food consumption and breast cancer: a pooled analysis of cohort studies. Int J Epidemiol 2002;31: 78–85. [PubMed: 11914299]
10. Sandler DP, Hodgson ME, Deming-Halverson SL, Juras PS, D'Aloisio AA, Suarez LM, Kleeberger CA, Shore DL, DeRoo LA, Taylor JA, Weinberg CR, Sister Study Research T. The Sister Study Cohort: Baseline Methods and Participant Characteristics. Environ Health Perspect 2017;125: 127003. [PubMed: 29373861]
11. D'Aloisio AA, Nichols HB, Hodgson ME, Deming-Halverson SL, Sandler DP. Validity of self-reported breast cancer characteristics in a nationwide cohort of women with a family history of breast cancer. BMC Cancer 2017;17: 692. [PubMed: 29058598]
12. Block GHA, Dresser CM, Carroll MD, Gannon J, Gardner L. A data-based approach to diet questionnaire design and testing. Am J Epidemiol 1986: 453–69. [PubMed: 3740045]
13. Park YM, Steck SE, Fung TT, Merchant AT, Elizabeth Hodgson M, Keller JA, Sandler DP. Higher diet-dependent acid load is associated with risk of breast cancer: Findings from the sister study. Int J Cancer 2019;144: 1834–43. [PubMed: 30247761]
14. Bowman S, Clemens J, Friday J, Theorig R, Moshfegh A. Food Patterns Equivalents Database 2011–12: Methodology and User Guide In: Agriculture USDo, ed. Beltsville, Maryland: Food Surveys Research Group, Beltsville Human Nutrition Research Center, Agricultural Research Service, 2014.
15. Sinha R, Cross A, Curtin J, Zimmerman T, McNutt S, Risch A, Holden J. Development of a food frequency questionnaire module and databases for compounds in cooked and processed meats. Mol Nutr Food Res 2005;49: 648–55. [PubMed: 15986387]

16. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology 1999;10: 37–48. [PubMed: 9888278]
17. Begg CB, Zhang ZF. Statistical analysis of molecular epidemiology studies employing case-series. Cancer Epidemiol Biomarkers Prev 1994;3: 173–5. [PubMed: 8049640]
18. Martinez ME, Cruz GI, Brewster AM, Bondy ML, Thompson PA. What can we learn about disease etiology from case-case analyses? Lessons from breast cancer. Cancer Epidemiol Biomarkers Prev 2010;19: 2710–4. [PubMed: 20870734]
19. Moorman PG, Iversen ES, Marcom PK, Marks JR, Wang F, Lee E, Ursin G, Rebbeck TR, Domchek SM, Arun B, Susswein L, Isaacs C, et al. Evaluation of established breast cancer risk factors as modifiers of BRCA1 or BRCA2: a multi-center case-only analysis. Breast Cancer Res Treat 2010;124: 441–51. [PubMed: 20309627]
20. Kipnis V, Freedman LS, Brown CC, Hartman A, Schatzkin A, Wacholder S. Interpretation of energy adjustment models for nutritional epidemiology. Am J Epidemiol 1993;137: 1376–80. [PubMed: 8333419]
21. Daniel CR, Cross AJ, Graubard BI, Hollenbeck AR, Park Y, Sinha R. Prospective investigation of poultry and fish intake in relation to cancer risk. Cancer Prev Res (Phila) 2011;4: 1903–11. [PubMed: 21803982]
22. Kulldorff M, Sinha R, Chow WH, Rothman N. Comparing odds ratios for nested subsets of dietary components. Int J Epidemiol 2000;29: 1060–4. [PubMed: 11101548]
23. Krebs-Smith SM, Pannucci TE, Subar AF, Kirkpatrick SI, Lerman JL, Tooze JA, Wilson MM, Reedy J. Update of the Healthy Eating Index: HEI-2015. J Acad Nutr Diet 2018;118: 1591–602. [PubMed: 30146071]
24. Anderson JJ, Darwis NDM, Mackay DF, Celis-Morales CA, Lyall DM, Sattar N, Gill JMR, Pell JP. Red and processed meat consumption and breast cancer: UK Biobank cohort study and meta-analysis. Eur J Cancer 2018;90: 73–82. [PubMed: 29274927]
25. Wu J, Zeng R, Huang J, Li X, Zhang J, Ho JC, Zheng Y. Dietary Protein Sources and Incidence of Breast Cancer: A Dose-Response Meta-Analysis of Prospective Studies. Nutrients 2016;8.
26. Zheng W, Gustafson DR, Moore D, Hong C-P, Anderson KE, Kushi LH, Sellers TA, Folsom AR, Sinha R, Cerhan JR. Well-Done Meat Intake and the Risk of Breast Cancer. J Natl Cancer Inst 1998;90: 1724–9. [PubMed: 9827527]
27. Inoue-Choi M, Sinha R, Gierach GL, Ward MH. Red and processed meat, nitrite, and heme iron intakes and postmenopausal breast cancer risk in the NIH-AARP Diet and Health Study. Int J Cancer 2016;138: 1609–18. [PubMed: 26505173]
28. Taylor EF, Burley VJ, Greenwood DC, Cade JE. Meat consumption and risk of breast cancer in the UK Women's Cohort Study. Br J Cancer 2007;96: 1139–46. [PubMed: 17406351]
29. Genkinger JM, Makambi KH, Palmer JR, Rosenberg L, Adams-Campbell LL. Consumption of dairy and meat in relation to breast cancer risk in the Black Women's Health Study. Cancer Causes & Control 2013;24: 675–84. [PubMed: 23329367]
30. Zhang C-X, Ho SC, Chen Y-M, Lin F-Y, Fu J-H, Cheng S-Z. Meat and egg consumption and risk of breast cancer among Chinese women. Cancer Causes & Control 2009;20: 1845–53. [PubMed: 19533390]
31. Ambrosone CB, Freudenheim JL, Sinha R, Graham S, Marshall JR, Vena JE, Laughlin R, Nemoto T, Shields PG. Breast cancer risk, meat consumption and N-acetyltransferase (NAT2) genetic polymorphisms. Int J Cancer 1998;75: 825–30. [PubMed: 9506525]
32. Delfino R, Sinha R, Smith C, West J, White E, Lin H, Liao S-Y, S.Y. Gim J, L Ma H, Butler J, Anton-Culver H. Breast cancer, heterocyclic aromatic amines from meat and N-acetyltransferase 2 genotype. Carcinogenesis 2000;21: 607–15. [PubMed: 10753193]
33. Kim AE, Lundgreen A, Wolff RK, Fejerman L, John EM, Torres-Mejía G, Ingles SA, Boone SD, Connor AE, Hines LM, Baumgartner KB, Giuliano A, et al. Red meat, poultry, and fish intake and breast cancer risk among Hispanic and Non-Hispanic white women: The Breast Cancer Health Disparities Study. Cancer Causes & Control 2016;27: 527–43. [PubMed: 26898200]
34. Ronco AL, De Stéfani E. Nutrition and Breast Cancer in Premenopausal and Postmenopausal Women in Uruguay. In: Hollins Martin CJ, Watson RR, Preedy VR. Nutrition and Diet in Menopause Totowa, NJ: Humana Press, 2013: 281–92.

35. Ronco AL, De Stéfani E, Fabra A. White meat intake and the risk of breast cancer: a case-control study in Montevideo, Uruguay. Nutr Res 2003;23: 151–62.

36. Tappel A Heme of consumed red meat can act as a catalyst of oxidative damage and could initiate colon, breast and prostate cancers, heart disease and other diseases. Med Hypotheses 2007;68: 562–4. [PubMed: 17045417]

37. Cho E, Chen WY, Hunter DJ, et al. Red meat intake and risk of breast cancer among premenopausal women. Arch Intern Med 2006;166: 2253–9. [PubMed: 17101944]

38. Diallo A, Deschasaux M, Latino-Martel P, Hercberg S, Galan P, Fassier P, Alles B, Gueraud F, Pierre FH, Touvier M. Red and processed meat intake and cancer risk: Results from the prospective NutriNet-Sante cohort study. Int J Cancer 2018;142: 230–7. [PubMed: 28913916]

39. Mourouti N, Kontogianni MD, Papavagelis C, Plytzanopoulou P, Vassilakou T, Psaltopoulou T, Malamos N, Linos A, Panagiotakos DB. Meat consumption and breast cancer: a case-control study in women. Meat Sci 2015;100: 195–201. [PubMed: 25460125]

40. Holmes MD, Colditz GA, Hunter DJ, Hankinson SE, Rosner B, Speizer FE, Willett WC. Meat, fish and egg intake and risk of breast cancer. Int J Cancer 2003;104: 221–7. [PubMed: 12569578]

41. Alexander DD, Morimoto LM, Mink PJ, Cushing CA. A review and meta-analysis of red and processed meat consumption and breast cancer. Nutr Res Rev 2010;23: 349–65. [PubMed: 21110906]

42. Larsson SC, Bergkvist L, Wolk A. Long-term meat intake and risk of breast cancer by oestrogen and progesterone receptor status in a cohort of Swedish women. Eur J Cancer 2009;45: 3042–6. [PubMed: 19464165]

43. Di Maso M, Talamini R, Bosetti C, Montella M, Zucchetto A, Libra M, Negri E, Levi F, La Vecchia C, Franceschi S, Serraino D, Polesel J. Red meat and cancer risk in a network of case–control studies focusing on cooking practices. Ann Oncol 2013;24: 3107–12. [PubMed: 24121119]

44. Gertig DM, Hankinson SE, Hough H, Spiegelman D, Colditz GA, Willett WC, Kelsey KT, Hunter DJ. N-acetyl transferase 2 genotypes, meat intake and breast cancer risk. Int J Cancer 1999;80: 13–7. [PubMed: 9935222]

45. Weinberg CR. Toward a Clearer Definition of Confounding. Am J Epidemiol 1993;137: 1–8. [PubMed: 8434568]

Novelty and Impact:

Meat consumption and certain meat cooking practices may increase the risk of breast cancer, and few epidemiologic studies have examined different categories of meat in conjunction to meat cooking practices and meat mutagens. This study examines these associations to overall invasive breast cancer risk and also by time-varying menopausal status and estrogen receptor status. Red meat consumption may increase the risk of breast cancer, whereas poultry consumption may be protective against breast cancer risk.

Table 1.

Baseline characteristics of participants by quartile of total meat[a] consumption

Characteristic	Total meat consumption Quartile 1 0–48.6g N =10,497	Quartile 2 >48.6–75.0g N=10,507	Quartile 3 >75.0–110.8g N=10,504	Quartile 4 >110.8g N=10,504
Total person-years minus first year follow-up	68,316	69,133	69,149	69,322
Mean (SD)				
Age at baseline, y	56.0 (9.1)	55.5 (9.0)	55.0 (8.8)	54.7 (8.6)
Body mass index, kg/m^2	26.5 (5.5)	27.1 (5.6)	27.8 (5.8)	28.9 (6.3)
Waist-to-hip ratio	0.80 (0.08)	0.80 (0.08)	0.81 (0.08)	0.82 (0.08)
Total energy intake, kcal/d	1,251 (427)	1,469 (430)	1,681 (453)	2,072 (537)
Total MET-h/wk of leisure-time physical activity	15.6 (18.9)	14.5 (16.9)	14.0 (17.1)	13.7 (17.1)
Vegetable consumption, cup eq.	1.6 (1.2)	1.9 (1.2)	2.2 (1.2)	2.6 (1.4)
Fruit consumption, cup eq.	1.4 (1.0)	1.4 (1.0)	1.4 (1.0)	1.4 (1.0)
Dairy consumption, cup eq.	1.3 (1.0)	1.4 (1.0)	1.5 (1.0)	1.6 (1.0)
Percent calories from fat, %	35.0 (7.7)	36.6 (7.0)	37.6 (6.6)	39.0 (6.4)
Lifetime duration of breastfeeding, wk [b]	68.6 (76.2)	66.2 (74.1)	65.6 (71.3)	64.1 (70.9)
Proportions (%)				
Race/ethnicity				
Non-Hispanic White	78.8	85.0	87.1	88.5
Non-Hispanic Black	8.5	7.4	7.8	8.0
Other	8.8	6.7	6.4	7.0
Household income				
< $49,999	28.9	24.4	22.5	22.7
$50,000-$99,999	40.3	40.9	41.4	41.5
≥ $100,000	30.8	34.7	36.1	35.8
Educational attainment				
High school degree or less	17.8	15.7	13.5	12.6
Some college	32.5	33.5	33.2	33.8
College degree or higher	51.2	51.4	52.8	52.1
No. of relatives diagnosed with breast cancer before the age of 50				
0	43.7	42.9	42.4	40.6
1	51.0	51.8	52.2	53.9
≥2	5.3	5.2	5.4	5.5
Smoking status				
≥20 pack-y	11.1	11.6	11.6	13.8
<20 and ≥10 pack-y	8.4	8.9	9.4	9.6
<10 and > 0 pack-y	21.8	21.9	21.8	22.3

	Total meat consumption			
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**
	0–48.6g	**>48.6–75.0g**	**>75.0–110.8g**	**>110.8g**
Characteristic	**N =10,497**	**N=10,507**	**N=10,504**	**N=10,504**
Never	58.7	57.7	57.1	54.4
Use of hormone therapy				
None	56.8	57.2	58.7	59.4
Estrogen only	20.2	18.9	19.2	18.5
Both estrogen and progesterone	23.0	23.9	22.1	22.1
Parity				
0	19.4	17.7	16.9	19.0
1	14.3	14.1	14.4	15.0
2	35.1	37.0	39.0	37.2
≥3	31.2	31.2	29.8	28.9
Use of birth control pill				
Never	17.8	15.4	14.3	13.6
Former	78.9	80.8	82.2	83.0
Current	3.4	3.7	3.6	3.4
Alcohol consumption				
Current alcohol consumption				
≥2 drinks/d	4.0	4.6	5.1	5.7
1–1.9 drinks/d	7.2	8.9	9.0	10.3
<1 drink/d	66.3	68.9	69.2	67.5
Former	17.3	14.2	13.5	13.7
Never	5.1	3.4	3.3	2.8
Menopause	66.8	64.8	63.0	62.2

Presented as mean (SD) and proportion (%).

Abbreviations: MET, metabolic equivalent; kcal, kilocalories; cup eq., cup equivalent.

[a]Total meat: combination of all meat consumption including poultry, red meat, organ meat, cured meat, and seafood.

[b]Among women who ever breastfed (n =24,222).

Table 2.

Adjusted hazard ratios and 95% confidence intervals for the associations between meat consumption and risk of invasive breast cancer in “Addition” models (N=42,012)

	Total Invasive BC				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
Model 1					
All Meat, No. of cases	352	379	412	393	
Person-years	68,316	69,133	69,149	69,323	
Median, g (range)	34.6 (0–48.6)	61.6 (>48.6–75.0)	90.6 (>75.0–110.8)	143.6 (>110.8–650.1)	
HR (95% CI)	1.00 (ref)	1.04 (0.90–1.21)	1.12 (0.96–1.30)	1.01 (0.85–1.20)	0.7
Model 2					
Red and Cured Meat[a], No. of cases	349	380	392	415	
Person-years	68,371	69,114	69,062	69,374	
Median, g (range)	13.4 (0–20.4)	27.4 (>20.4–35.0)	43.8 (>35.0–56.5)	77.2 (>56.5–529.8)	
HR (95% CI)	1.00 (ref)	1.06 (0.91–1.23)	1.09 (0.93–1.28)	1.11 (0.93–1.32)	0.2
White Meat[b], No. of cases	374	392	363	407	
Person-years	68,388	68,922	69,450	69,160	
Median, g (range)	13.4 (0–20.0)	26.6 (>20.0–34.1)	43.1 (>34.1–55.6)	76.5 (>55.6–400.0)	
HR (95% CI)	1.00 (ref)	1.02 (0.88–1.18)	0.91 (0.78–1.07)	1.00 (0.85–1.18)	0.7
Model 3					
Red Meat[c], No. of cases	340	366	398	432	
Person-years	68,262	69,173	68,956	69,530	
Median, g (range)	7.4 (0–11.6)	16.2 (>11.6–21.1)	27.5 (>21.1–36.3)	52.7 (>36.3–415.5)	
HR (95% CI)	1.00 (ref)	1.03 (0.88–1.20)	1.11 (0.94–1.31)	**1.22 (1.01–1.46)**	0.02
Cured Meat[d], No. of cases	343	427	393	373	
Person-years	68,894	69,013	68,747	69,267	
Median, g (range)	4.4 (0–6.5)	8.8 (>6.5–11.3)	14.5 (>11.3–19.4)	28.2 (>19.4–165.6)	
HR (95% CI)	1.00 (ref)	1.18 (1.01–1.46)	1.04 (0.88–1.24)	0.94 (0.78–1.13)	0.8
White Meat[b], No. of cases	374	392	363	407	

	Total Invasive BC				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
HR (95% CI)	1.00 (ref)	1.01 (0.87–1.17)	0.91 (0.78–1.07)	1.01 (0.85–1.19)	0.2
Model 4					
Red Meat[c], No. of cases	340	366	398	432	
HR (95% CI)	1.00 (ref)	1.03 (0.88–1.20)	1.11 (0.94–1.32)	**1.23 (1.02–1.48)**	0.04
Cured Meat[d], No. of cases	343	427	393	373	
HR (95% CI)	1.00 (ref)	**1.19 (1.02–1.39)**	1.06 (0.89–1.25)	0.97 (0.80–1.17)	0.3
Poultry, No. of cases	392	407	371	366	
Person-years	68,477	68,639	69,650	69,155	
Median, g (range)	6.4 (0–10.2)	14.4 (>10.2–19.6)	25.7 (>19.6–34.0)	50.8 (>34.0–300)	
HR (95% CI)	1.00 (ref)	0.98 (0.85–1.14)	0.87 (0.75–1.02)	0.85 (0.72–1.00)	0.02
Seafood, No. of cases	359	363	416	398	
Person-years	68,631	68,688	69,340	69,262	
Median, g (range)	3.3 (0–5.8)	8.2 (>5.8–11.2)	15.0 (>11.2–20.8)	31.4 (>20.8–296.8)	
HR (95% CI)	1.00 (ref)	0.96 (0.83–1.12)	1.08 (0.93–1.25)	1.02 (0.87–1.20)	0.5

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval.

All models are addition models investigating the effect of an independent increase in consumption of each type of meat with other meats held constant. Four addition models are analyzed with the various sub-categories of meat.

All models are adjusted for age (as the primary time scale), race/ ethnicity (non-Hispanic White, non-Hispanic Black, or other), household income (< $49,999, $50,000-$99,999, or ≥$100,000), educational attainment (high school degree or less, some college, or college degree or higher), baseline menopausal status (binary), body mass index (BMI; continuous), interaction term between baseline menopausal status and BMI, waist-to-hip ratio (continuous), total energy intake (kcal/day), consumption of vegetables (quintiles), consumption of fruit (quintiles), percent calories from fat (quartiles), dairy consumption (quartiles), number of relatives diagnosed with breast cancer before the age of 50 (0, 1, or ≥2), lifetime duration of breastfeeding (none and tertiles among women with any breastfeeding, wk), use of hormone therapy (none, estrogen only, or both estrogen and progesterone), parity (0, 1, 2, or ≥3 births), use of birth control pill (never, former, or current), alcohol consumption (never, former, current <1 drink/day, current 1–1.9 drinks/day, or current ≥ 2 drinks/day), total MET-hours per week of leisure-time physical activity (quintiles), and smoking status (≥20 pack years, <20 and ≥10 pack years, < 10 and > 0 pack years, or never); and additional adjustment for consumption of other meat categories (quartiles) including organ meat (organ meat from beef, veal, pork, lamb, game, and poultry) in models 2 through 4.

[a]Includes total of red meat (beef, veal, pork, lamb, and game meat) and cured meat (frankfurters, sausage, corned beef, cured ham, and luncheon meat made from beef, pork, poultry).

[b]Includes total of seafood (seafood high in *n*-3 fatty acids and seafood low in *n*-3 fatty acids) and poultry (chicken, turkey, Cornish hens, duck, goose, quail, and pheasant/game birds).

[c]Includes total of red meat (beef, veal, pork, lamb, and game meat) not including cured meat.

[d]Includes frankfurters, sausage, corned beef, cured ham, and luncheon meat made from beef, pork, poultry.

Table 3.

Adjusted hazard ratios and 95% confidence intervals for the associations between red meat and poultry and total invasive breast cancer risk by estrogen receptor and time-varying menopausal status[a] using "Addition" and "Substitution" models

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
Total Invasive Breast Cancer					
Red Meat					
No. of cases	340	366	398	432	
Addition model[b]	1.00 (ref)	1.03 (0.88–1.20)	1.11 (0.94–1.32)	**1.23 (1.02–1.48)**	0.01
Substitution model[c]	1.00 (ref)	1.02 (0.87–1.21)	1.13 (0.93–1.37)	**1.29 (1.03–1.61)**	0.01
Poultry					
No. of cases	392	407	371	366	
Addition model[b]	1.00 (ref)	0.98 (0.85–1.14)	0.87 (0.75–1.02)	0.85 (0.72–1.00)	0.03
Substitution model[c]	1.00 (ref)	0.93 (0.79–1.09)	**0.78 (0.65–0.94)**	**0.72 (0.58–0.89)**	0.002
ER+ Invasive Breast Cancer					
Red Meat					
No. of cases	258	269	304	329	
Addition model[b]	1.00 (ref)	1.01 (0.84–1.21)	1.15 (0.94–1.39)	**1.27 (1.03–1.57)**	0.01
Substitution model[c]	1.00 (ref)	1.00 (0.83–1.20)	1.13 (0.91–1.41)	**1.29 (1.00–1.67)**	0.03
Poultry					
No. of cases	291	308	285	276	
Addition model[b]	1.00 (ref)	1.02 (0.86–1.21)	0.93 (0.77–1.11)	0.90 (0.75–1.10)	0.2
Substitution model[c]	1.00 (ref)	0.96 (0.80–1.15)	0.81 (0.66–1.00)	**0.74 (0.58–0.95)**	0.01
ER- Invasive Breast Cancer					
Red Meat					
No. of cases	38	48	51	56	
Addition model[b]	1.00 (ref)	1.13 (0.72–1.78)	1.17 (0.72–1.89)	1.24 (0.73–2.09)	0.5
Substitution model[c]	1.00 (ref)	1.12 (0.70–1.80)	1.33 (0.77–2.30)	1.67 (0.87–3.22)	0.1

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
Poultry					
No. of cases	51	49	43	50	
Addition model[b]	1.00 (ref)	0.76 (0.51–1.15)	**0.61 (0.39–0.95)**	0.66 (0.41–1.04)	0.1
Substitution model[c]	1.00 (ref)	0.71 (0.45–1.10)	**0.59 (0.35–0.99)**	0.66 (0.36–1.22)	0.4
Premenopausal Invasive Breast Cancer					
Red Meat					
No. of cases	64	71	93	73	
Addition model[b]	1.00 (ref)	1.05 (0.73–1.51)	1.32 (0.90–1.93)	1.06 (0.69–1.62)	1.0
Substitution model[c]	1.00 (ref)	0.98 (0.67–1.43)	1.15 (0.75–1.76)	0.92 (0.56–1.52)	0.6
Poultry					
No. of cases	66	68	76	91	
Addition model[b]	1.00 (ref)	0.85 (0.59–1.21)	0.88 (0.61–1.27)	1.06 (0.73–1.55)	0.4
Substitution model[c]	1.00 (ref)	0.75 (0.51–1.12)	0.73 (0.47–1.13)	0.93 (0.56–1.53)	0.6
Postmenopausal Invasive Breast Cancer					
Red Meat					
No. of cases	276	295	303	358	
Addition model[b]	1.00 (ref)	1.02 (0.86–1.22)	1.07 (0.88–1.29)	**1.28 (1.04–1.56)**	0.006
Substitution model[c]	1.00 (ref)	1.03 (0.86–1.24)	1.12 (0.90–1.39)	**1.41 (1.10–1.81)**	0.002
Poultry					
No. of cases	326	338	294	274	
Addition model[b]	1.00 (ref)	1.02 (0.87–1.19)	0.87 (0.73–1.04)	**0.80 (0.66–0.96)**	0.005
Substitution model[c]	1.00 (ref)	0.97 (0.81–1.15)	**0.79 (0.64–0.96)**	**0.66 (0.52–0.84)**	0.0002

Abbreviations: ER, estrogen receptor.

[a]Time-varying menopausal status contributed to follow-up time at risk for either premenopausal or post-menopausal breast cancer and was considered for both incident cases and non-cases.

[b]Addition model: adjusted for age (as the primary time scale), race/ ethnicity (non-Hispanic White, non-Hispanic Black, or other), household income (< $49,999, $50,000-$99,999, or ≥$100,000), educational attainment (high school degree or less, some college, college degree or higher), baseline menopausal status (binary), body mass index (BMI; continuous), interaction term between baseline menopausal status and BMI, waist-to-hip ratio (continuous), total energy intake (kcal/day), consumption of vegetables (quintiles), consumption of fruit (quintiles), percent calories from fat (quartiles), dairy

consumption (quartiles), number of relatives diagnosed with breast cancer before the age of 50 (0, 1, or ≥2), lifetime duration of breastfeeding (none and tertiles among women with any breastfeeding, wk), hormone therapy (none, estrogen only, or both estrogen and progesterone), parity (0, 1, 2, or ≥3 births), birth control pill use (never, former, or current), alcohol consumption (never, drinker, current <1 drink/day, current 1–1.9 drinks/day, or current s≥ 2 drinks/day), total MET-hours of leisure-time physical activity per week (quintiles), and smoking status (≥20 pack years, <20 and ≥10 pack years, < 10 and > 0 pack years or never smoker); and additional adjustment for consumption of other meat categories (quartiles).

[c] Substitution model: adjusted for the same covariates as addition model, except that poultry consumption is replaced by combined consumption of red meat and poultry (quartiles) in a substitution model of red meat, whereas red meat consumption is replaced by combined consumption of red meat and poultry (quartiles) in a substitution model of poultry.

Table 4.

Adjusted hazard ratios and 95% confidence intervals for the associations of breast cancer risk by quartiles of gram per 1,000 kcal of red meat consumed in categories of cooking methods and doneness, as well as by quartiles of meat mutagens

Characteristic	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
Cooking practices and doneness					
Grilled red meat[b]					
Median (range) (g per 1,000 kcal)	0 (0.0)	1.0 (>0.0–1.8)	3.5 (>1.8–5.9)	11.7 (>5.9–160)	
No. of cases (person-years)	483 (83,014)	297 (53,297)	395 (69,148)	356 (69,643)	
HR (95% CI)	1.0 (ref)	0.99 (0.85–1.14)	1.02 (0.89–1.17)	0.89 (0.77–1.03)	0.08
Medium well done, well done, very well done, and/or charred red meat					
Median (range) (g per 1,000 kcal)	0 (0.0)	1.0 (>0.0–1.8)	3.4 (>1.8–5.7)	10.9 (>5.7–135.9)	
No. of cases (person-years)	490 (86,316)	292 (51,677)	384 (68,643)	365 (68,465)	
HR (95% CI)	1.0 (ref)	1.02 (0.88–1.18)	1.02 (0.89–1.16)	0.97 (0.84–1.12)	0.57
Grilled and medium well done, well done, very well done, and/or charred red meat					
Median (range) (g per 1,000 kcal)	0 (0.0)		1.4 (>0–3.1)	6.6 (>3.1–135.9)	
No. of cases (person-years)	831 (143,595)		331 (9,522)	369 (10,469)	
HR (95% CI)	1.0 (ref)		0.96 (0.84–1.09)	0.98 (0.87–1.11)	0.82
Meat mutagens					
DiMeIQx, 2-Amino-3,4,8-trimethylimidazo[4,5-f] quinoxaline					
Median (range), ng per day	0.0 (0)	0.3 (>0–0.5)	0.8 (>0.5–1.6)	2.9 (>1.6–97.6)	
No. of cases (person-years)	533 (97.099)	216 (40,913)	393 (65,245)	394 (72,664)	
HR (95% CI)	1.00 (ref)	1.00 (0.85–1.17)	1.13 (0.99–1.29)	1.01 (0.88–1.15)	0.94
MeIQx, 2-Amino-3,8-dimethylimidazo[4,5-f] quinoxaline					
Median (range), ng per day	0.3 (0–2.4)	5.2 (>2.4–9.7)	15.5 (>9.7–23.9)	41.8 (>23.9–754.8)	
No. of cases (person-years)	356 (69,099)	373 (69,305)	431 (68,718)	376 (68.799)	
HR (95% CI)	1.00 (ref)	1.05 (0.91–1.22)	1.24 (1.07–1.43)	1.07 (0.92–1.25)	0.51
PhIP, 2-Amino-1-methyl-6-phenylimidazo (4,5-b) pyridine					
Median (range), ng per day	0.0 (0–6.4)	12.3 (>6.4–18.3)	30.8 (>18.3–47.7)	88.6 (>47.7–3,417.23)	

Characteristic	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P for trend
No. of cases (person-years)	363 (69,507)	385 (67,983)	424 (73,343)	364 (65,089)	
HR (95% CI)	1.00 (ref)	1.10 (0.95–1.27)	1.13 (0.98–1.30)	1.08 (0.93–1.26)	0.61
B[*a*]P, benzo[a]pyrene					
Median (range), ng per day	0.0 (0–0.1)	0.6 (>0.1–3.6)	11.7 (>3.6–27.4)	51.0 (>27.4–553.4)	
No. of cases (person-years)	403 (68,845)	396 (68,350)	347 (68,917)	390 (69,809)	
HR (95% CI)	1.00 (ref)	0.99 (0.86–1.14)	0.92 (0.79–1.06)	1.00 (0.87–1.16)	0.80
Heme iron					
Median (range), µg	0 (0–28.5)	62.6 (28.5–97.4)	136.4 (97.4–193.7)	297.2 (193.8–1,774.8)	
No. of cases (person-years)	354 (68,390)	385 (69,624)	383 (67,871)	414 (70,037)	
HR (95% CI)	1.00 (ref)	1.09 (0.93–1.26)	1.09 (0.94–1.26)	1.11 (0.96–1.29)	0.24

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; ng, nanogram; g, gram.

[a] All models are adjusted for age (as the primary time scale), race/ ethnicity (non-Hispanic White, non-Hispanic Black, or other), household income (< $49,999, $50,000-$99,999, or ≥$100,000), educational attainment (high school degree or less, some college, or college degree or higher), baseline menopausal status (binary), body mass index (BMI; continuous), interaction term between baseline menopausal status and BMI, waist-to-hip ratio (continuous), total energy intake (kcal/day), consumption of vegetables (quintiles), consumption of fruit (quintiles), percent calories from fat (quartiles), dairy consumption (quartiles), number of relatives diagnosed with breast cancer before the age of 50 (0, 1, or ≥2), lifetime duration of breastfeeding (none and tertiles among women with any breastfeeding, wk), hormone therapy (none, estrogen only, or both estrogen and progesterone), parity (0, 1, 2, or ≥3 births), birth control pill use (never, former, or current), alcohol consumption (never, former, current <1 drink/day, current 1–1.9 drinks/day, or current ≥2 drinks/day), total MET-hours of leisure-time physical activity per week (quintiles), and smoking status (≥20 pack years, <20 and ≥10 pack years, < 10 and > 0 pack years, or never smoker).

[b] Includes steak, pork chop, and hamburger.