Intakes of dietary iron and heme-iron and risk of postmenopausal breast cancer in the National Institutes of Health–AARP Diet and Health Study[1–3]

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ABSTRACT

Background: Intakes of dietary iron and, in particular, heme iron may increase breast cancer risk because of the prooxidant properties of iron. However, few studies have examined the association of iron and heme-iron intakes with breast cancer risk.

Objective: We assessed the association of intakes of dietary iron and heme iron with risk of postmenopausal breast cancer.

Design: We used data from the National Institutes of Health–AARP Diet and Health Study to assess intakes of total dietary iron, iron from meat, iron from red meat, and heme iron in relation to breast cancer risk in 116,674 postmenopausal women who completed a detailed questionnaire regarding meat preparation methods and degrees of doneness. During 6.5 y of follow-up, 3396 cases of invasive breast cancer were identified. Cox proportional hazards models were used to compute hazard ratios (HRs) and 95% CIs.

Results: After adjustment for covariates, HRs for the highest compared with the lowest quintiles of intakes of total iron, iron from meat, iron from red meat, and heme iron were all close to unity, and there were no increasing trends with increasing intakes. The multivariable-adjusted HR for the highest compared with the lowest quintile of heme-iron intake was 1.01 (95% CI: 0.89, 1.14; *P* for trend = 0.97). In addition, no associations were seen when iron variables were stratified by possible effect modifiers or hormone receptor status.

Conclusion: The results of this large cohort study do not support an association between iron or heme-iron intakes and postmenopausal breast cancer. *Am J Clin Nutr* 2010;92:1478–83.

INTRODUCTION

Breast cancer is the leading cause of cancer in women worldwide (1), and rates of breast cancer are highest in countries with a high standard of living and a high consumption of meat (2). However, the first generation of dietary studies of breast cancer turned up few dietary risk factors for which the evidence is clear and consistent (3, 4). In large prospective studies, intakes of saturated fat and red meat have not consistently been associated with increased risk of breast cancer (4–6).

One aspect of diet that might influence breast cancer risk and has received relatively little attention is intake of iron. Because of a high meat intake, fortification of foods with iron, and the wide use of iron-containing dietary supplements, some postmenopausal women appear to have high circulating iron concentrations (7, 8). Because of its prooxidant properties, iron may contribute to oxidative stress and lead to DNA damage and lipid peroxidation and, thereby, increase risk of breast cancer (9–11). Oxidative damage due to iron may add to damage from alcohol and steroid hormones (12, 13). In addition, heme iron, the most bioavailable form of iron and the major form of iron present in red meat, is the major contributor to stored iron (14).

Few studies have examined dietary iron and, in particular, heme iron in relation to breast cancer risk (15–19). Furthermore, previous studies have used a relatively crude estimate of heme-iron intake, which failed to take into account meat-cooking methods and degrees of doneness, which may affect the iron and heme-iron contents of meat consumed. For these reasons, we assessed the association of iron and heme-iron intakes with postmenopausal breast cancer risk in the National Institutes of Health–AARP (NIH-AARP) Diet and Health Study, which is a prospective cohort study that has a wide range of dietary intakes that enhanced the ability to detect an effect of dietary exposures.

SUBJECTS 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 previously described (20). AARP members aged between 50 and 71 y who resided in 6 US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and 2 metropolitan areas (Atlanta, GA, and Detroit, MI) were mailed self-administered questionnaires that covered demographic characteristics, food intakes, and other

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health-related behaviors. The questionnaires were satisfactorily completed by 567,169 subjects, of whom 227,021 were women (20). 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.

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 sizes of 124 food items (20). A diet-calibration substudy within the NIH-AARP study cohort showed good correlations between red-meat intake from the FFQ and two 24-h dietary recalls (0.62 and 0.70 for men and women, respectively) (20).

Within 6 mo after the initial questionnaire, baseline respondents were sent a second FFQ that included a meat-cooking module (21). The questionnaire was completed by 334,908 men and women (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; and 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, and very well done or gray brown dry; for chicken: just until done or still juicy, well done or somewhat dry, and very well done or very dry) (21).

Dietary iron included iron from all sources, such as cereals, vegetables, and meat, and values were calculated by using databases from the US Department of Agriculture's Continuing Survey of Food Intake by Individuals (1994–1996) (22). Previous studies have estimated heme-iron intakes by using standard proportions of total iron from meat (23, 24); however, heme iron in meat can be converted to nonheme iron depending on the cooking method (25–30). With the use of a new heme-iron database that is based on measured values from meats cooked by different methods and to varying doneness levels (21), in conjunction with the detailed meat-cooking questionnaire, we quantitatively assessed heme-iron intakes.

We restricted attention to women who had completed the second questionnaire that contained the meat module (n = 138,057) and excluded subjects who had questionnaires completed by proxy respondents or who had prevalent cancers (n = 13,222). Women who reported that they still menstruated and were not taking hormones were classified as premenopausal. Women who reported that their periods had stopped because of natural menopause, surgery, radiation, or chemotherapy, women who had had both ovaries or their uterus removed, and women >57 y of age were classified as postmenopausal. On the basis of this definition, the study population was further restricted to 116,674 postmenopausal women by excluding women who were premenopausal or with uncertain menstrual status (n = 8161).

Cohort follow-up and case ascertainment

Cancer cases were identified by linkage to 11 state cancer registries, which includes the 8 original states plus 3 additional states where participants commonly move to (Texas, Arizona, and Nevada), and to the US National Death Index for the inclusive years 1995 and 2003. These databases were estimated to identify 90% of all cancer cases in our cohort (31). The hormone receptor status of breast cancer was available from 7 state cancer registries (Arizona, California, Georgia, Louisiana, New Jersey, Nevada, and North Carolina). The vital status of cohort participants was also ascertained by linkage to the Social Security Administration Death Master File.

For this analysis, we included registry-confirmed incident primary invasive breast cancer (*International Classification of Diseases for Oncology, 3rd edition*; codes 8500, 8520, 8522, 8523, and 8524) that occurred in postmenopausal women in the cohort. A total of 3396 cases were identified in 116,674 women with complete information on the baseline questionnaire and complete meat-cooking module data. The mean interval between completion of the second questionnaire and the diagnosis of breast cancer was 3.4 y (range: 0.003–7.1 y).

Statistical analyses

Person-years of follow-up for this analysis were calculated from the date of scanning of the second questionnaire to the date of invasive breast cancer diagnosis or censoring at the date of other cancer diagnoses (except for nonmelanoma skin cancer), death, emigration out of the study area, or 31 December 2003, whichever occurred first.

Generalized linear models were used to estimate the means of the baseline variables within each quintile of intake of heme iron 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 (HRs) and 95% CIs. Analyses that used age as the underlying time metric gave similar results, and we present the results for person-years. Iron-intake variables included the following: total dietary iron, iron from meat, iron from red meat, iron from white meat, heme iron, heme iron from red meat, and heme iron from white meat. Iron intake and other dietary variables were energy adjusted by using the density method (32) with energy included in the model because most dietary variables were correlated with total energy intake. Quintiles and deciles of the iron-intake variables were created on the basis of the distribution in all women in our cohort. Models that used unadjusted iron intake but with calories as a covariate were also fitted; these models gave similar results to those obtained by using the multivariable nutrient-density method (results were also presented on a continuous scale as shown in **Table 2** footnote 5). To test for trends in risk with increasing levels of exposure, we assigned the corresponding median value to each quantile and fitted the medians as a continuous variable in the risk models.

Our multivariable models were constructed by individually adding potential confounding variables to 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 (in kcal/d) did not meet these criteria, it was included on a priori grounds. The following variables were included in the fully adjusted model: age (continuous), body mass index (BMI, in kg/m^2: <25, 25–29, 30–34, or ≥35), age at first menstrual period (<11, 11–12, 13–14, or ≥15 y), age at first live birth (<20, 20–24, 25–29, 30–34, or ≥35 y), age at menopause (<40, 40–44, 45–49, 50–54, or ≥55 y),

TABLE 1
Selected characteristics of women in the National Institutes of Health–AARP Diet and Health Study by quintile of heme-iron intake (n = 116,674)

	Quintiles of heme-iron intake (μg/1000 kcal): median				
Characteristic	38.9	83.4	124.6	177.5	281.3
Age (y)	62.7± 5.2[1]	62.7 ± 5.2	62.5 ± 5.1	62.2 ± 5.2	61.7 ± 5.2
BMI (kg/m^2)	25.2 ± 5.5	26.2 ± 5.6	26.7 ± 5.6	27.2 ± 5.9	27.9 ± 6.3
Alcohol intake (g/d)[2]	6.3 ± 23.2	6.5 ± 20.2	6.1 ± 17.5	6.0 ± 14.8	5.8 ± 13.3
Energy intake (kcal/d)	1577 ± 783	1567 ± 732	1581 ± 713	1598 ± 762	1598 ± 788
Red meat (g/1000 kcal)[3]	11.1 ± 8.6	20.2 ± 9.9	27.1 ± 11.2	34.8 ± 12.9	51.7 ± 20.0
Total fat intake (g/1000 kcal)[2]	27.9 ± 8.6	31.4 ± 8.0	33.4 ± 7.8	35.1 ± 7.6	37.6 ± 7.7
Total fiber (g/1000 kcal)[2]	14.0 ± 5.0	12.1 ± 3.9	11.4 ± 3.6	10.8 ± 3.3	10.0 ± 3.2
Education (% college graduate or postgraduate)	38.8	33.3	31.4	29.8	28.2
Race (% African American)	6.0	5.4	4.9	4.4	3.8
Age at menarche ≥15 y (%)	9.6	8.9	9.0	8.9	8.8
Parity (% nulliparous)	16.7	15.0	14.3	14.7	15.4
Age at first live birth ≥30 y (%)	6.7	6.0	5.7	5.7	5.6
Age at menopause ≥50 y (%)	44.2	41.8	40.8	39.7	38.4
Breast cancer diagnosed in mother or sisters (%)	12.5	12.6	12.8	12.8	12.0
Ever had breast biopsy (%)	24.2	24.5	24.8	24.6	23.8
Smoking status (%)					
Never	49.3	46.8	46.0	45.1	42.7
Former	39.7	39.1	38.3	37.7	37.3
Current	11.0	14.1	15.7	17.2	20.0
Physical activity ≥3 times/wk (%)	54.1	45.1	42.7	40.0	36.7
Ever used oral contraceptives (%)	37.0	37.4	38.3	38.9	41.0
Current use of menopausal hormone therapy at baseline (%)	44.6	45.6	45.7	45.2	44.3

[1] Mean ± SD (all such values).
[2] Energy adjusted in general linear models.
[3] Nutrient-density energy adjusted.

number of breast biopsies (none, 1, 2, or ≥3), family history of breast cancer (no or yes), menopausal hormone therapy (never, former, current user, or missing), education (high school graduate or less, post high school, some college, college graduate or postgraduate, missing), race (non-Hispanic white, non-Hispanic black, or other), total energy intake (kcal/d, continuous), total fat intake (g fat/1000 kcal, continuous), total fiber intake (g fiber/1000 kcal, continuous), alcohol intake (g alcohol/d, continuous); physical activity (never or rarely, 1–3 times/m or 1–2 times/wk, ≥3 times/wk, or missing), and smoking (never smoker, quit >5 y ago, quit 1–4 y ago, quit <1 y ago or current smoker, or missing).

Additional analyses were carried out with stratification by hormone receptor status, which was available for 61% of breast cancer cases. Of cases with known hormone receptor status, 84% of subjects were estrogen receptor positive (ER+), 16% of subjects were ER negative (ER−), 71% of subjects were progesterone receptor positive (PR+), and 29% of subjects were PR negative (PR−). Numbers of cases were adequate to examine the association in ER+ and PR+ (n = 1037), ER+ and PR− (n = 220), and ER− and PR− (n = 219) cases.

We further examined the association of heme-iron intake with breast cancer within strata of potential effect modifiers, including BMI (<25, 25–29, 30–34, or ≥35), parity, menopausal hormone therapy (never, current, or former), alcohol consumption (0, 0–0.8, 0.9–4.6, or ≥4.7 g alcohol/d), total fat intake (g fat/1000 kcal, quintiles), fiber intake (g/1000 kcal, quintiles), vitamin and mineral supplement use (use of multivitamins and use of supplemental iron), and physical activity (never or rarely, 1–3 times/m or 1–2 times/wk, or ≥3 times/wk). All statistical significance tests were 2-sided. All analyses were performed with SAS software (version 9; SAS Institute, Cary, NC).

RESULTS

Mean BMI, energy intake, and saturated fat intake increased with increasing heme-iron intake, as did the proportion of subjects who used oral contraceptives (Table 1). In contrast, the proportions of women who had higher education, were African American, nulliparous, had a first birth at ≥30 y of age, were never smokers, engaged in physical activity ≥5 times/wk, were ≥50 of age at the onset of menopause, and consumed fruit and vegetables decreased with increasing heme-iron intake.

Age-adjusted and multivariable-adjusted HRs for total dietary iron, iron from meat, iron from red meat, and heme iron were close to 1.00 (Table 2). Several HRs were slightly elevated, and some of these reached statistical significance; however, there was no evidence of a linear trend with increasing intake. The multivariable-adjusted HR for the highest compared with the lowest quintiles of heme-iron intake was 1.01 (95% CI: 0.89, 1.14; P for trend = 0.97). Furthermore, the examination of risk by deciles of these variables showed no significant alterations in risk (data not shown). In a sensitivity analysis that excluded cases diagnosed during the first 3 y of follow-up, the results were unchanged.

When iron-intake variables were stratified by amount of alcohol intake, menopausal hormone therapy, BMI, level of physical activity, total fat intake, fiber intake, and multivitamin use and supplemental iron use, none of the iron-intake variables were associated with altered risk. In addition, there was no association of iron-intake variables with breast cancer risk when the tumor

TABLE 2
Dietary iron and heme-iron intakes and postmenopausal breast cancer (n = 3396 cases) in the National Institutes of Health–AARP Diet and Health Study[1]

	Quintiles of dietary iron variables (units/1000 kcal)					
Variable	1	2	3	4	5	P for trend[2]
Total dietary iron (mg)[3]						
Median	6.1	7.3	8.2	9.3	11.3	—
Range	<6.8	≥6.8 to <7.7	≥7.7 to <8.7	≥8.7 to <10.1	≥10.1	—
No. of cases/person-years	682/151,389	678/151,830	673/151,993	662/152,664	701/152,442	—
Age-adjusted HR (95% CI)[4]	1.00 (ref)	0.99 (0.89, 1.10)	0.97 (0.88, 1.08)	0.95 (0.85, 1.06)	1.00 (0.90, 1.12)	0.81
Multivariable-adjusted HR (95% CI)[5]	1.00 (ref)	0.98 (0.88, 1.10)	0.98 (0.87, 1.09)	0.96 (0.85, 1.08)	1.02 (0.90, 1.15)	0.94
Iron from meat (mg)[6]						
Median	0.4	0.7	1.0	1.2	1.7	—
Range	<0.6	≥0.6 to 0.9	≥0.9 to <1.1	≥1.1 to <1.4	≥1.4	—
No. of cases/person-years	624/152,300	749/152,407	678/152,313	658/151,813	687/151,484	—
Age-adjusted HR (95% CI)[4]	1.00 (ref)	1.20 (1.08, 1.34)	1.09 (0.98, 1.22)	1.07 (0.96, 1.19)	1.13 (1.02, 1.26)	0.32
Multivariable-adjusted HR (95% CI)[5]	1.00 (ref)	1.16 (1.04, 1.29)	1.03 (0.92, 1.15)	1.00 (0.89, 1.12)	1.05 (0.93, 1.17)	0.55
Iron from red meat (mg)[7]						
Median	0.1	0.3	0.5	0.7	1.1	—
Range	<0.2	≥0.2 to <0.4	≥0.4 to <0.6	≥0.6 to <0.9	≥0.9	—
No. of cases/person-years	627/152,647	697/152,608	721/152,159	679/151,718	672/151,186	—
Age-adjusted HR (95% CI)[4]	1.00 (ref)	1.11 (1.00, 1.24)	1.16 (1.04, 1.29)	1.10 (0.98, 1.22)	1.10 (0.99, 1.23)	0.15
Multivariable-adjusted HR (95% CI)[5]	1.00 (ref)	1.08 (0.97, 1.21)	1.11 (0.99, 1.24)	1.04 (0.92, 1.17)	1.03 (0.92, 1.17)	0.94
Heme iron (μg)[8]						
Median	38.9	83.4	124.6	177.5	281.3	—
Range	<62.9	≥62.9 to <103.5	≥103.5 to <148.7	≥148.7 to <216.7	≥216.7	—
No. of cases/person-years	622/152,647	701/152,608	725/152,159	704/151,718	644/151,186	—
Age-adjusted HR (95% CI)[4]	1.00 (ref)	1.13 (1.01, 1.26)	1.17 (1.05, 1.31)	1.15 (1.03, 1.28)	1.07 (0.95, 1.19)	0.24
Multivariable-adjusted HR (95% CI)[5]	1.00 (ref)	1.10 (0.98, 1.22)	1.12 (1.00, 1.25)	1.09 (0.97, 1.22)	1.01 (0.89, 1.14)	0.97

[1] HR, hazard ratio; ref, reference. There were 3396 postmenopausal breast cancer cases in 116,674 female cohort subjects. Cox proportional hazards models were used to calculate HRs.

[2] Calculated by using median values for each quintile.

[3] Energy adjusted by the covariate method on a continuous scale per 10-mg/d increment (HR: 0.99; 95% CI: 0.88, 1.10).

[4] Adjusted for energy by the density method (g/1000 kcal).

[5] Additionally adjusted for age at entry (continuous), BMI (in kg/m^2; <18.5, 18.5 to <25, 25 to <30, 30 to <35, or ≥35), age at first menstrual period (<11, 11–12, 13–14, or ≥15 y), age at first live birth (never or <20, 20–24, 25–29, 30–34, or ≥35 y), family history of breast cancer (yes or no), menopausal hormone therapy (never, former, current, or missing), education (less than high school graduate, high school graduate, some college, college graduate or postcollege, or missing), race (non-Hispanic white, non-Hispanic black, other, or unknown), total energy intake (kcal/d, continuous), total fat (g fat/1000 kcal, continuous), total fiber intake (g fiber/1000 kcal, continuous), alcohol intake (g alchohol/d, continuous), physical activity (never or rarely, 1–2 times/mo, ≥3 times/wk, or missing), smoking (never, quit ≥5 y ago, quit 1–4 y ago, quit <1 y ago or current smoker, or missing), age at menopause (<40, 40–44, 45–49, 50–54, or ≥55 y), and number of breast biopsies (none, 1, 2, ≥3, or missing).

[6,7] Energy adjusted by the covariate method on a continuous scale per 1-mg/d increment: [6]HR, 1.00 (95% CI: 0.96, 1.03); [7]HR, 1.00 (95% CI: 0.96, 1.05).

[8] Energy adjusted by the covariate method on a continuous scale per 100-μg/d increment (HR: 1.00; 95% CI: 0.98, 1.02).

was stratified by hormone receptor status (ER+ and PR+, ER+ and PR−, or ER− and PR−).

DISCUSSION

This large prospective cohort of AARP members provided no support for the hypothesis that intakes of total iron, meat iron, red meat iron, or heme iron are associated with increased risk of postmenopausal breast cancer. Furthermore, our results do not indicate that intakes of any of these sources of iron affected breast cancer risk in subgroups, such as women who were obese, consumed alcohol, used menopausal hormone therapy, had low physical activity, had high intakes of total fat, or had low fiber intakes. In addition, no associations were seen with hormone receptor–specific breast cancer.

Because of the toxicity of iron, effective mechanisms have evolved to regulate the production of reactive oxygen species by free iron. However, iron homeostasis can be disturbed by a number of factors that ultimately leads to the formation of the hydroxyl radical, which is a potent oxidizing species that can promote lipid peroxidation, mutagenesis, DNA-strand breaks, oncogene activation, and tumor suppressor gene inhibition (10, 33). Some evidence has suggested that free iron may interact with estradiol, ethanol, and ionizing radiation and, thereby, induce breast carcinogenesis (34–36). In addition, the contribution of free iron to oxidative stress may be modified by the availability of dietary antioxidants (37, 38) or other dietary factors, such as saturated fat (17). Finally, an individual's genetic make-up and, specifically, variants of genes involved in the metabolism and detoxification of reactive oxygen species, including free iron, are likely to modify the role of iron in breast carcinogenesis (39).

Few studies have examined iron intake or intake of heme iron in relation to breast cancer risk (15–19). Two case-control studies, one from Italy (18) and another from Germany (15), showed no association of dietary iron intake with breast cancer

risk. In contrast, in a large population-based, case-control study conducted in Shanghai, China, with 3452 breast cancer cases and an equal number of control subjects, Kallianpur et al (17) reported that animal-derived (largely heme) iron intake was positively associated with breast cancer risk [odds ratio (OR): 1.49; 95% CI: 1.25, 1.78; P for trend < 0.01). The observed effect was similar in pre- and postmenopausal women. In addition, a significant interaction between iron and fat from animal sources was observed.

Two cohort studies have investigated the association between heme-iron intake and breast cancer risk. Analyses of a large Canadian, prospective cohort study (16) with 2545 breast cancer cases ascertained in 49,654 women aged 40–59 at enrollment and followed for an average of 16 y showed no association between intakes of total dietary iron, meat iron, red meat iron, or heme iron and breast cancer risk. In addition, no associations were seen within strata of alcohol consumption or hormone therapy use. Ferrucci et al (19) analyzed data on 1205 breast cancer cases identified in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial during 8 y of follow-up. Dietary iron showed a modest association with breast cancer risk (HR: 1.25; 95% CI: 1.02, 1.52), whereas iron from meat and heme iron showed no association. Our results are consistent with those of previous null studies.

A nested case-control study of postmenopausal women from the American Cancer Society Prevention II Nutrition Cohort (39) examined associations of polymorphisms in genes involved in iron-related oxidative stress pathways (ie, *Nrf2*, *NQ01*, *NOS3*, *and HO-1*) and breast cancer risk. Women who carried $\geq$3 at-risk alleles had an OR of 1.56 (95% CI: 0.97, 2.51). In addition, there was a significant interaction between genetic profiles, iron intakes, and breast cancer risk. In women in the highest tertile of iron intake and in users of supplemental iron, the carriage of $\geq$3 high-risk alleles resulted in a $>$2-fold increased risk compared with women with no high-risk alleles [OR: 2.27; 95% CI: 0.97, 5.29 (P for trend = 0.02); and OR: 2.39; 95% CI: 1.09, 5.26 (P for trend = 0.02) respectively]. However, the authors did not address whether there was an association between iron intakes and breast cancer risk independent of genetic profiles.

The current study has a number of strengths, including the use of a detailed questionnaire to assess intakes of different types of meat, meat preparation, and doneness preferences as well as a linked database to estimate exposure to iron from meat and heme iron. In addition, the study population had a wide range of dietary intakes. For example, in women in our study, a median intake of red meat in the highest quintile was 7 times that in the lowest quintile. The range of intakes of heme iron was of a similar magnitude. Therefore, our null results are not likely due to a narrow range of intakes. Other strengths included the prospective nature of the study, 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 effect modification by breast cancer risk factors and factors that affected oxidative stress.

To assess the generalizability of our results to the entire NIH-AARP cohort, we compared women who responded to the meat-module questionnaire (n = 138,057) with women who did not respond to the meat-module questionnaire (n = 67,975) and with women who moved out of the study area (n = 16,229). Responders were similar to the 2 other groups on variables included in Table 1. Because information on covariates was obtained in the original interview, but the date of completion of the meat-module questionnaire was used as the baseline for our analysis (on average, 6 mo later), there was a possibility that changes in some covariates (eg, smoking status and hormone use) resulted in misclassification. However, because of the short interval between the return of the 2 questionnaires, such misclassification was likely to be minimal.

Other limitations of our study included that we did not have quantitative information on supplemental intakes of iron (ie, dosage, frequency, and duration). Thus, we were unable to estimate the association between breast cancer and supplemental iron intake or total iron (from diet and supplements). In addition, we were unable to assess the association of iron-related variables with premenopausal breast cancer because of the small number of such cancers in the cohort. Furthermore, no information was available on variants of genes involved in iron metabolism and detoxification. Finally, dietary intakes on the basis of FFQs is affected by measurement error (40, 41), which, if nondifferential, might attenuate true associations. In this study, as in most previous studies, diet was assessed in midlife. Therefore, it was possible that intakes of iron or heme iron at a younger age, and particularly during adolescence when the breasts are developing, may affect the risk of breast cancer.

In conclusion, results of this large prospective cohort of postmenopausal women do not support the hypothesis that a relatively a high intake of dietary iron or heme iron is associated with increased risk of breast cancer.

The authors' responsibilities were as follows—GCK: conceived the study, performed data analyses and interpretation, and drafted the manuscript; AJC, RS, and TER: conceived the study; AJC and RS: developed the heme-iron database and made substantial contributions to the manuscript; YP, AS, ARH: made substantial contributions to the manuscript; and TER: discussed the study design and analyses and made substantial contributions to the manuscript. None of the authors had a conflict of interest.

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