Dietary Fat and Postmenopausal Invasive Breast Cancer in the National Institutes of Health–AARP Diet and Health Study Cohort

Anne C. M. Thiébaut, Victor Kipnis, Shih-Chen Chang, Amy F. Subar, Frances E. Thompson, Philip S. Rosenberg, Albert R. Hollenbeck, Michael Leitzmann, Arthur Schatzkin

Background Although ecologic association and animal studies support a direct effect of dietary fat on the development of breast cancer, results of epidemiologic studies have been inconclusive.

Methods We prospectively analyzed the association between fat consumption and the incidence of postmenopausal invasive breast cancer in the National Institutes of Health–AARP Diet and Health Study, a US cohort comprising 188736 postmenopausal women who completed a 124-item food-frequency questionnaire in 1995–1996. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression models with adjustment for energy and potential confounding factors. All statistical tests were two-sided.

Results Over an average follow-up of 4.4 years, the cohort yielded 3501 cases of invasive breast cancer. The hazard ratio of breast cancer for the highest (median intake, 40.1% energy from total fat; 434 cases per 100000 person-years) versus the lowest (median intake, 20.3% energy from total fat; 392 cases per 100000 person-years) quintile of total fat intake was 1.11 (95% CI = 1.00 to 1.24; P_{trend} = .017). The corresponding hazard ratio for a twofold increase in percent energy from total fat on the continuous scale was 1.15 (95% CI = 1.05 to 1.26). Positive associations were also found for subtypes of fat (hazard ratio for a twofold increase in percent energy from saturated fat = 1.13; 95% CI = 1.05 to 1.22; from monounsaturated fat, HR = 1.12; 95% CI = 1.03 to 1.21; from polyunsaturated fat, HR = 1.10, 95% CI = 1.01 to 1.20). Correction for measurement error in nutrient intakes, on the basis of a calibration substudy that used two 24-hour dietary recalls, strengthened the associations, yielding an estimated hazard ratio for total fat of 1.32 (95% CI = 1.11 to 1.58). Secondary analyses showed that associations between total, saturated, and monounsaturated fat intakes were confined to women who were not using menopausal hormone therapy at baseline.

Conclusion In this large prospective cohort with a wide range of fat intake, dietary fat intake was directly associated with the risk of postmenopausal invasive breast cancer.

J Natl Cancer Inst 2007;99:451–62

Although the association between dietary fat and breast cancer has been examined for a long time, it remains one of the most controversial in nutritional epidemiology (1–3). In the early 1940s, animal studies suggested that high-fat diets could stimulate mammary carcinogenesis (4). This notion was subsequently reinforced by results of international correlation studies [e.g., (5)] and migrant studies [e.g., (6)]; the latter showed that migrant populations that replaced their indigenous low-fat diets with high-fat, Western diets experienced breast cancer incidence rates similar to those of the host populations. Beginning in the mid-1970s, case–control study reports tended to show positive associations between dietary fat intake and breast cancer (7). However, the possibility of differential recall of diet between case and control subjects cast doubt on these results (8). Although pooled analyses of subsequent cohort studies failed to show an association between fat intake and the risk of breast cancer (9,10), a more recent meta-analysis (11) of 14 cohort studies that adjusted for energy intake found that women who consumed the highest levels of total fat had a statistically significant 13% higher risk of breast cancer than those who consumed the lowest levels. Recently reported findings from the Women's Health Initiative (WHI) Randomized Controlled Dietary Modification

Affiliations of authors: Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics (ACMT, SCC, ML, AS), Biometry Research Group, Division of Cancer Prevention (VK), Applied Research Program, Division of Cancer Control and Population Sciences (AFS, FET), Biostatistics Branch, Division of Cancer Epidemiology and Genetics (PSR), National Cancer Institute, Bethesda, MD; AARP, Washington, DC (ARH).

Correspondence to: Anne C. M. Thiébaut, PhD, Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Blvd, Executive Plaza South Rm 3033, Bethesda, MD 20892 (e-mail: thiebauta@mail.nih.gov).

See "Notes" following "References."

DOI: 10.1093/jnci/djk094

CONTEXT AND CAVEATS

Prior knowledge

Ecologic association and animal studies have suggested that high-fat diets contribute to the development of breast cancer. However, epidemiologic studies of the association between dietary fat intake and the risk of breast cancer have been inconclusive.

Study design

Large prospective cohort study of the association between fat consumption (assessed with the use of a food frequency questionnaire) and the incidence of invasive breast cancer among postmenopausal women with a wide range of fat intake.

Contribution

A direct association between dietary fat intake—both total fat intake and intakes of the major fat subtypes—and the risk of invasive breast cancer was detected. The authors also found a statistically significant interaction between menopausal hormone use and dietary fat intake with respect to breast cancer risk.

Implications

The hypothesis that dietary fat increases the risk of invasive breast cancer remains viable and warrants continued investigation. Further studies are needed to examine whether use of menopausal hormone therapy mediates the association between dietary fat intake and the risk of breast cancer.

Limitations

Unmeasured confounders and measurement error could have influenced the observed associations.

Trial provided suggestive evidence that a low-fat diet can reduce the incidence of breast cancer incidence, although follow-up was shorter and the reduction in fat intake in the intervention group, smaller than originally planned (12).

At least two methodologic issues could contribute to the discrepant results among previous epidemiologic studies. First, dietary measurement error could have masked true associations (13). Second, many previous epidemiologic studies were conducted within homogenous populations that had relatively narrow ranges of fat intakes, which could make it difficult to detect an association between fat intake and breast cancer risk (14). Here we investigated the association between dietary fat intake and the risk of breast cancer in the National Institutes of Health (NIH)–AARP (formerly American Association of Retired Persons) Diet and Health Study, a large prospective cohort study of more than half a million US men and women among whom dietary fat intakes varied substantially (15).

Subjects and Methods

Study Population

Details of the NIH–AARP Diet and Health Study are given elsewhere (15). Briefly, the initial cohort consisted of 617 119 men and women who responded to a food-frequency questionnaire (FFQ) in 1995–1996. All respondents were members of AARP, were 50–71 years old at baseline (when they completed the questionnaire), and resided in one of six US states (California, Florida, Pennsylvania, New Jersey, North Carolina, or Louisiana) or two metropolitan areas (Atlanta, GA, or Detroit, MI). Cancer incidence in the cohort was ascertained by probabilistic linkage to cancer registries covering the eight states (16). Vital status was ascertained by annual linkage to the Social Security Administration Death Master File, by cancer registry linkage, and through responses to mailings. Address changes were ascertained through annual linkage to the National Change of Address database maintained by the US Postal Service (USPS), by receipt of USPS notification of undeliverable mail, via use of other address change update services, and by direct communication with participants. The NIH–AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the US National Cancer Institute (NCI). All participants agreed to give informed consent by virtue of completing the questionnaire.

From the initial respondents, we excluded 27 552 men and women who did not answer substantial portions of the questionnaire, 13 442 who indicated that they were not the intended respondent and did not complete the questionnaire, 8127 who had more than 10 recording errors (for example, more than one bubble filled in per question) or reported consuming fewer than 10 different foods, 824 who later requested to be removed from the study, six who did not provide information on sex, 179 who had completed duplicate questionnaires, 263 who died before study entry, 322 who moved out of the cancer registry ascertainment areas before study entry, and 15 760 who indicated that they were not the intended respondent but did complete the questionnaire. The remaining 550 644 participants included 325 176 men and 225 468 women; we further excluded 23 981 women who either reported a personal history of cancer in the baseline questionnaire or had a diagnosis of cancer before baseline (except for nonmelanoma skin cancer) identified by cancer registry match, and 529 women who, on the basis of death certificate reports, had died from a cancer at any site that did not appear in the registry-matching process. 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. On the basis of this definition, we restricted the study population to postmenopausal women by excluding 7291 premenopausal women and 2111 women with an uncertain menopausal status. Finally, of the remaining 191 556 postmenopausal women, we excluded those who had reported on the questionnaire extreme values (i.e., more than two interquartile ranges above the 75th percentile or below the 25th percentile on the logarithmic scale) for energy intake (n = 1543), total fat intake (n = 249), and percent energy from total fat (n = 1028), leaving 188 736 female study participants for the analysis.

Dietary Data

The FFQ was a grid-based version of the NCI's Diet History Questionnaire (17,18). This questionnaire was designed to assess usual diet by inquiring about the frequency of consumption (in 10 categories that ranged from never to six or more times per day for beverages and from never to two or more times per day for foods) and portion size (presented as three ranges based on national dietary data for adults representing <25th, 25th–75th, and >75th percentiles of intake) of 124 food items over the past year. In addition, the

questionnaire included 21 questions about whether particular foods were consumed as versions that were sugar free, low fat, caffeine free, or whole grain, and details about the additions and types of fats, creamers, or sweeteners added to foods or used in food preparation. Portion size ranges and daily nutrient intakes were calculated using databases from the 1994–1996 US Department of Agriculture's Continuing Survey of Food Intake by Individuals (19). The FFQ was calibrated against two 24-hour dietary recalls (24HRs) that were administered to a stratified randomly chosen subset of the NIH–AARP participants (n = 2053) by telephone on an average of 25 days apart (15). Among women, the energy-adjusted Pearson correlation coefficients for the FFQ and the 24HR, adjusted for within-person random variation and total energy intake, were .69 for saturated fat, .62 for total and monounsaturated fat, and .56 for polyunsaturated fat (Thompson F: unpublished data).

Statistical Analysis

Person-years of follow-up were calculated from the date of response to the baseline questionnaire to the date of invasive breast cancer diagnosis or to censoring at the date of in situ breast cancer diagnosis, other cancer diagnosis (except for nonmelanoma skin cancer), death, emigration out of the study area, or December 31, 2000, whichever occurred first. Absolute rates for postmenopausal invasive breast cancer were standardized within 5-year age categories to the age distribution of person-years experienced by all study subjects. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression models with age as the primary time variable (20) and the Efron approximation method to handle ties (21). We verified that the proportional hazards assumption was not violated for our main exposure and other fixed covariates by including interaction terms with a function of age (either centered or log-transformed age), and we used the Wald chi-square procedure to test whether all coefficients equaled 0.

We used several energy adjustment methods to examine associations with fat intake independent of energy intake (22). Because alcohol intake is a well-established risk factor for breast cancer (23,24), we used nonalcohol sources of energy as a continuous variable to adjust for energy intake in all models and considered alcohol intake as a separate confounder in the multivariable models. We verified that results obtained after adjusting for total energy and alcohol intake were similar to those obtained after adjusting for nonalcohol energy and alcohol in multivariable models. Fat intake was included as the absolute amount per day (standard model), the residual of the regression of fat intake on nonalcohol energy intake (residual method), or the percentage of nonalcohol energy contributed by fat intake (density model) (22). In all models, the hazard ratio for fat represents the association of breast cancer risk with the substitution of fat for carbohydrate and protein, that is, when nonalcohol energy intake is held constant, an increase in fat intake is necessarily accompanied by a reduction in carbohydrate and protein intakes (25). In additional models, we further adjusted for protein intake to examine the effect of substituting total fat intake for carbohydrate intake alone. We also used the partition method to examine the association of breast cancer risk with adding fat intake to nonalcohol energy intake (25). The same energy adjustment models were fitted for subtypes of fat; the substitution effect of one subtype of fat for carbohydrates was investigated after adjusting fat subtypes mutually for each other and for protein and energy intakes.

In all models, the natural logarithm was used to transform intakes of total fat, fat subtypes, and energy. We performed all analyses using fat as either a continuous or categorical variable. We conducted continuous analyses after examination of the spline regression terms showed no departure of the logarithm of the hazard ratio from linearity (26). Hazard ratios on the continuous scale were calculated for a twofold increase in fat intake, for example, from 20% to 40% of energy from total fat in density models. In categorical analyses, quintiles of fat intake were based on the distribution observed in the study population at baseline. Tests for linear trend were performed by using the median intake level in each quintile.

Nondietary risk factors were identified by their independent associations with the risk of breast cancer. The following variables were examined as potential confounders of the fat intake and breast cancer association: race/ethnicity, education level, family history of breast cancer in the participant's mother or sister(s), a personal history of breast biopsy, adult height, body mass index (BMI) at baseline, age at menarche, age at first birth, parity, age at menopause, menopausal hormone use, smoking history, alcohol consumption levels, and type and frequency of physical activity at work or home. We selected a parsimonious model by including variables that were statistically significantly associated with the risk of breast cancer (at the conventional 5% level) and that changed the risk estimates for total fat intake by 10% or more (27). The final parsimonious model included alcohol consumption (in grams of ethanol per day, as a continuous variable), smoking history (ever versus never [reference category]), age at birth of first child and number of children combined (nulliparous, first birth before age 30 years with one or two children, first birth before age 30 years with three or more children [reference category], or first birth at age 30 years or older), age at menopause (<50, 50–54 [reference category], or ≥55 years), menopausal hormone therapy use (current user versus never used or former user), and BMI (<25 [reference category], 25 to <30, or ≥30 kg/m^2). We also considered variables that were available for a subset of the initial cohort (n = 119950, all of whom were included in this analysis) from a subsequent questionnaire that was mailed in late 1996 (15), namely, an alternative assessment of physical activity in terms of intensity and frequency, as well as lifetime (since age 18 years) and menopausal (since age 50 years) weight gain. We verified that all fat and breast cancer associations remained virtually unchanged despite the shorter follow-up and smaller sample size in this subcohort and after adjustment for additional variables.

We assigned missing values for the adjusting covariates to their respective reference category after checking that individuals with such missing values did not show a risk of breast cancer that was statistically significantly different from that of individuals in the reference category. Moreover, in sensitivity analyses, we verified that both the complete case analysis [which excluded subjects with missing values in any adjustment covariates (28)] and analyses that used the Horvitz–Thompson inverse probability weighting method (29) yielded results similar to those of the main analysis. However, only a small proportion of the study participants (5.4%) had missing values for at least one of the adjustment covariates included in the parsimonious models.

To correct for measurement error, we used data from the 873 participants who were included in the calibration substudy (15) and who met the inclusion criteria for this analysis. We used the two-step linear regression calibration procedure (30) to adjust the hazard ratios observed in the age- and energy-adjusted density models on the continuous scale. At the first step, we used the Seemingly Unrelated Measurement Error Model method (31) to estimate the slopes and their standard errors in the regressions of the 24HR-reported fat and energy intakes on age-adjusted fat and energy from the FFQ. The slope for fat resulting from the regression of 24HR-reported fat intake on FFQ-reported fat and energy intakes is the attenuation factor, whereas the slope for fat resulting from the regression of 24HR-reported energy intake on FFQ-reported fat and energy intakes gives an indication of the residual confounding by energy intake (32). At the second step, we corrected the hazard ratios using only the attenuation factors (33) because the residual confounding by energy intake was very small and not statistically significant for intakes of total fat and fat subtypes. The 95% confidence intervals for the corrected hazard ratios were calculated using the delta method (33) to take into account uncertainties in the estimated attenuation factors.

To identify potential effect modifiers, we evaluated fat–covariate interaction terms in relation to breast cancer risk in both categorical and continuous analyses. Tests for interaction were performed using the likelihood ratio test with fat intake considered as a continuous variable (one degree of freedom). The covariates examined included family history of breast cancer in mother or sister(s) (yes versus no), personal history of breast biopsy (ever versus never), BMI ($\geq$25 versus <25 kg/m^2), smoking history (ever versus never), alcohol consumption at baseline (drinker versus nondrinker), and menopausal hormone use (current user versus former user and nonuser). SAS statistical software (version 9.1; SAS Institute, Inc, Cary, NC) was used for all analyses. All statistical tests were two-sided; *P* values less than .05 were considered statistically significant.

Results

Table 1 presents the baseline characteristics of the study population across quintiles of total fat intake expressed as a percentage of energy. The median intakes of percentage energy obtained from total fat ranged from 20.3% in the lowest quintile to 40.1% in the

Table 1. Baseline characteristics by quintile of total fat intake as a percentage of energy among 188736 postmenopausal women in the National Institutes of Health–AARP Diet and Health Study

	Quintile of percent energy from total fat (median)				
Variable	**1 (20.3)**	**2 (26.0)**	**3 (30.0)**	**4 (34.2)**	**5 (40.1)**
No. of participants	37748	37747	37747	37747	37747
Mean age at study entry (y)	62.3	62.2	62.2	62.1	62.0
Education level (%)					
11 y or fewer	5.1	5.5	6.2	6.8	8.0
High school	21.9	24.7	25.9	27.8	28.8
Post–high school	34.5	34.7	35.5	35.7	36.9
College and postgraduate	35.2	32.0	29.3	26.4	22.8
Race (%)					
Non-Hispanic white	87.8	89.2	89.3	90.1	90.8
Non-Hispanic black	5.9	5.5	6.0	5.6	5.2
Hispanic	2.5	2.1	1.9	1.6	1.4
Other	2.2	1.7	1.4	1.3	1.1
Mean nonalcohol energy intake (kcal/day)	1467.3	1512.6	1568.5	1644.4	1702.8
Mean carbohydrate intake (g/day)	239.0	221.1	213.1	206.8	185.9
Mean protein intake (g/day)	55.5	59.1	61.1	63.4	64.7
Mean alcohol intake (g/day)	5.1	5.3	5.9	6.1	7.3
Breast cancer ever diagnosed in mother or sister(s) (%)	12.9	12.8	13.1	12.6	12.8
Ever had breast biopsy (%)	24.8	24.3	24.1	23.8	22.9
Ever smoked (%)	50.8	51.8	53.0	54.9	60.6
Mean body mass index at baseline (kg/m^2)	25.7	26.6	27.1	27.4	27.6
Mean height (m)	1.629	1.631	1.633	1.634	1.634
Age at menarche $\geq$13 y(%)	50.2	50.3	50.9	51.6	51.7
Age at birth of first child and parity (%)					
Nulliparous	16.1	14.8	15.0	14.3	14.3
First birth before age 30 y with 1–2 children	32.3	31.7	30.8	30.3	30.6
First birth before age 30 y with three or more children	44.8	46.8	47.9	49.3	49.3
First birth at age 30 y or older	6.3	6.1	5.7	5.4	5.0
Age at last menstruation (%)					
<50 y	56.4	57.5	59.0	60.3	62.1
50–54 y	34.1	33.1	32.1	31.1	29.7
$\geq$55 y	7.8	7.5	7.0	6.8	6.4
Ever used oral contraceptive (%)	37.2	38.4	38.7	39.2	39.1
Current use of menopausal hormone therapy at baseline (%)	45.4	46.3	45.6	44.2	41.6

Table 2. Energy- and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for invasive breast cancer risk in association with total fat intake among 188 736 postmenopausal women in the National Institutes of Health–AARP Diet and Health Study*

Energy adjustment model	Quintile of total fat intake					P_{trend}†	Total fat intake as a continuous variable‡
	1	2	3	4	5		
Standard§							
Median value (g/day)	24.2	36.1	47.4	61.6	90.5		
No. of cases/No. of person-years	686/165 686	688/165 912	711/165 814	718/165 531	698/165 403		
Energy-adjusted HR (95% CI)	1.00 (referent)	1.05 (0.94 to 1.18)	1.13 (1.00 to 1.27)	1.18 (1.02 to 1.35)	1.22 (1.03 to 1.45)	.013	1.15 (1.05 to 1.26)
Multivariable-adjusted HR (95% CI)	1.00 (referent)	1.04 (0.93 to 1.17)	1.11 (0.98 to 1.25)	1.16 (1.01 to 1.33)	1.22 (1.03 to 1.45)	.013	1.15 (1.05 to 1.26)
Residual‖							
Median value (g/day)	32.8	41.9	48.4	55.0	64.4		
No. of cases/No. of person-years	648/166 274	687/166 234	722/165 657	733/165 429	711/164 753		
Energy-adjusted HR (95% CI)	1.00 (referent)	1.06 (0.96 to 1.18)	1.12 (1.01 to 1.25)	1.14 (1.03 to 1.27)	1.12 (1.00 to 1.24)	.014	1.15 (1.05 to 1.26)
Multivariable-adjusted HR (95% CI)	1.00 (referent)	1.05 (0.95 to 1.17)	1.12 (1.00 to 1.24)	1.14 (1.02 to 1.26)	1.12 (1.00 to 1.24)	.014	1.15 (1.05 to 1.26)
Density¶							
Median value (% energy)	20.3	26.0	30.0	34.2	40.1		
No. of cases/No. of person-years	655/166 268	684/166 117	722/165 737	727/165 352	713/164 873		
Energy-adjusted HR (95% CI)	1.00 (referent)	1.05 (0.94 to 1.17)	1.11 (1.00 to 1.24)	1.13 (1.01 to 1.25)	1.11 (1.00 to 1.24)	.017	1.15 (1.05 to 1.26)
Multivariable-adjusted HR (95% CI)	1.00 (referent)	1.04 (0.94 to 1.16)	1.10 (0.99 to 1.23)	1.12 (1.01 to 1.25)	1.11 (1.00 to 1.24)	.017	1.15 (1.05 to 1.26)
Partition#							
Median value (g/day)	24.2	36.1	47.4	61.6	90.5		
No. of cases/No. of person-years	686/165 686	688/165 912	711/165 814	718/165 531	698/165 403		
Energy-adjusted HR (95% CI)	1.00 (referent)	1.04 (0.93 to 1.16)	1.10 (0.98 to 1.23)	1.14 (1.01 to 1.28)	1.16 (1.01 to 1.33)	.015	1.09 (1.03 to 1.16)
Multivariable-adjusted HR (95% CI)	1.00 (referent)	1.03 (0.92 to 1.14)	1.08 (0.97 to 1.21)	1.12 (1.00 to 1.27)	1.17 (1.02 to 1.34)	.012	1.10 (1.03 to 1.17)

* Energy-adjusted bivariate Cox regression models adjusted for nonalcohol energy (continuous), using age as the underlying time metric. Multivariable Cox regression models adjusted for alcohol and nonalcohol energy intakes (both continuous), smoking history (two categories, ever versus never), combined age at birth of first child and number of children (four categories, nulliparous, first birth before age 30 years with one or two children, first birth at age 30 years or older, versus first birth before age 30 years with three or more children), age at menopause (three categories, <50, ≥55, versus 50–54 years), menopausal hormone use (two categories, current versus never or former) and BMI (three categories, 25 to <30, ≥30, versus <25 kg/m^2).

† Two-sided Wald chi-square test for linear trend using median intake in each quintile.

‡ Hazard ratios presented for a twofold increase in total fat intake.

§ Standard models contain log-transformed total fat intake and log-transformed nonalcohol energy intake.

‖ Residual models contain the residual of the regression of log-transformed total fat intake on log-transformed nonalcohol energy intake (with predicted mean added) and log-transformed nonalcohol energy intake.

¶ Density models contain log-transformed percent of nonalcohol energy from total fat intake and log-transformed nonalcohol energy intake.

Partition models contain log-transformed total fat intake and log-transformed nonalcohol nonfat energy intake.

highest quintile. Compared with women in the lowest quintile of percent energy from total fat, those in the highest quintile were less likely to have a college or postgraduate education, consumed more alcohol, were more likely to be former or current smokers, had a higher BMI, had more children, had an earlier onset of menopause, and were less likely to use menopausal hormone therapy.

During up to 5.2 years of follow-up (mean [standard deviation] = 4.4 years [0.86]), 4255 women were diagnosed with breast cancer, 3501 of whom had invasive breast cancers. Women in the highest quintile of percent energy from total fat had an 11% higher incidence of invasive breast cancer than women in the lowest quintile (434 versus 392 cases per 100 000 person-years). Total fat intake was directly associated with the risk of postmenopausal invasive breast cancer (Table 2). When fat intake was considered as a categorical variable, the hazard ratios of invasive breast cancer for women in the highest versus the lowest quintile of fat intake were either statistically significant or borderline statistically significant depending on the method used to adjust for nonalcohol energy, but all tests for trend were statistically significant. When fat intake was considered as a continuous variable, the breast cancer hazard ratios for increasing fat intake were statistically significant for all energy adjustment models. For example, in examining the substitution of total fat for carbohydrates and protein in the density model, increasing fat from 20% to 40% of nonalcohol energy was associated with a hazard ratio of 1.15 (95% CI = 1.05 to 1.26). Adjusting for other confounding variables did

Table 3. Energy- and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for invasive breast cancer by subtypes of fat intake among 188 736 postmenopausal women in the National Institutes of Health–AARP Diet and Health Study*

Fat subtype	Quintile of intake					P_{trend}†	Fat intake as a continuous variable‡
	1	2	3	4	5		
Saturated fat							
Median value (% energy)	5.8	7.6	9.1	10.7	13.2		
No. of cases/No. of person-years	658/166480	703/165981	694/165676	697/165428	749/164782		
Energy-adjusted HR (95% CI)	1.00 (referent)	1.08 (0.97 to 1.20)	1.07 (0.96 to 1.19)	1.08 (0.97 to 1.21)	1.18 (1.06 to 1.31)	.006	1.12 (1.05 to 1.21)
Multivariable-adjusted HR (95% CI)	1.00 (referent)	1.07 (0.96 to 1.19)	1.06 (0.96 to 1.18)	1.08 (0.97 to 1.21)	1.18 (1.06 to 1.31)	.004	1.13 (1.05 to 1.22)
Monounsaturated fat							
Median value (% energy)	7.2	9.5	11.2	12.8	15.2		
No. of cases/No. of person-years	661/166080	679/166259	746/165580	693/165572	722/164857		
Energy-adjusted HR (95% CI)	1.00 (referent)	1.03 (0.93 to 1.15)	1.14 (1.03 to 1.27)	1.06 (0.96 to 1.18)	1.12 (1.00 to 1.24)	.032	1.11 (1.03 to 1.21)
Multivariable-adjusted HR (95% CI)	1.00 (referent)	1.02 (0.92 to 1.14)	1.13 (1.02 to 1.26)	1.06 (0.95 to 1.18)	1.12 (1.00 to 1.24)	.028	1.12 (1.03 to 1.21)
Polyunsaturated fat							
Median value (% energy)	4.5	5.9	6.9	8.1	10.3		
No. of cases/No. of person-years	647/165902	715/165967	678/165691	730/165662	731/165126		
Energy-adjusted HR (95% CI)	1.00 (referent)	1.11 (1.00 to 1.23)	1.05 (0.94 to 1.17)	1.13 (1.02 to 1.26)	1.13 (1.02 to 1.26)	.022	1.10 (1.02 to 1.18)
Multivariable-adjusted HR (95% CI)	1.00 (referent)	1.10 (0.99 to 1.22)	1.04 (0.94 to 1.16)	1.12 (1.00 to 1.24)	1.12 (1.01 to 1.25)	.040	1.10 (1.01 to 1.20)

* The results are shown for the density model after fat and energy intakes were log-transformed. Energy-adjusted bivariate Cox regression models adjusted for nonalcohol energy (continuous), using age as the underlying time metric. Multivariable Cox regression models adjusted for alcohol and nonalcohol energy intakes (both continuous), smoking history (two categories, ever versus never), combined age at birth of first child and number of children (four categories, nulliparous, first birth before age 30 years with one or two children, first birth at age 30 years or older, versus first birth before age 30 years with three or more children), age at menopause (three categories, <50, ≥55, versus 50–54 years), menopausal hormone use (two categories, current versus never or former) and BMI (three categories, 25 to <30, ≥30, versus <25 kg/m^2).

† Two-sided Wald chi-square test for linear trend using median intake in each quintile.

‡ Hazard ratios presented for a twofold increase in percent energy from fat.

not appreciably alter the fat–breast cancer hazard ratio in all the energy adjustment models (Table 2). For example, in the density model, the hazard ratio remained unchanged at 1.11 (95% CI = 1.00 to 1.24; P_{trend} = .017) for the highest compared with the lowest quintile of total fat intake and at 1.15 (95% CI = 1.05 to 1.26) for a twofold increase in percent energy from total fat as a continuous variable. When we further adjusted for protein intake to estimate the effect of substituting total fat for carbohydrates only, the hazard ratio for total fat remained unchanged at 1.15 (95% CI = 1.05 to 1.26) on the continuous scale, whereas the association between protein intake and the risk of invasive breast cancer was null (data not shown). Moreover, when we excluded from the analysis the first year of follow-up for all subjects to rule out an effect of early disease on diet (a procedure that eliminated 694 cases), the association between total fat intake and the risk of invasive breast cancer remained statistically significant on the continuous scale.

In this population, the major fat subtype was monounsaturated fat (ranging from 7.2% [10th percentile] to 15.2% energy [90th percentile]; Table 3), followed by saturated fat (5.8% to 13.2% energy), and polyunsaturated fat (4.5% to 10.3% energy). The main food sources for saturated fat were butter and margarine (15.7%), milk (9.6%), beef (8.5%), poultry (5.3%), and cheese (5.1%). Major foods contributing to monounsaturated fat intake were butter and margarine (15.5%), vegetable oil and salad dressing (9.1%), cakes (7.9%), beef (8.2%), and poultry (6.0%). Vegetable oil was the main food source of polyunsaturated fat (20.4%), followed by butter and margarine (13.3%), and mayonnaise (10.5%). Saturated and monounsaturated fat intakes were highly correlated with each other (Pearson correlation coefficient between percent energy from each subtype, 0.81) and with total fat (0.87 and 0.97, respectively). Correlations with polyunsaturated fat intake were slightly less (0.78 with total fat, 0.42 with saturated fat, and 0.74 with monounsaturated fat).

In general, the association between total fat intake and the risk of invasive breast cancer held for all subtypes of fat (Table 3). In the energy-adjusted models, the hazard ratios of invasive breast cancer for a twofold increase in percent energy on a continuous scale were 1.12 (95% CI = 1.05 to 1.21) for saturated fat, 1.11 (95% CI = 1.03 to 1.21) for monounsaturated fat, and 1.10 (95% CI = 1.02 to 1.18) for polyunsaturated fat. The corresponding hazard ratios for animal fat and vegetable fat were 1.07 (95% CI = 1.01 to 1.12) and 1.06 (95% CI = 1.01 to 1.12), respectively (data not shown). The risk estimates remained virtually unchanged after adjustment for other covariates: the hazard ratios of invasive breast cancer for a twofold increase in percent energy on a continuous scale became 1.13 (95% CI = 1.05 to 1.22) for saturated fat,

1.12 (95% CI = 1.03 to 1.21) for monounsaturated fat, and 1.10 (95% CI = 1.01 to 1.20) for polyunsaturated fat (Table 3). When we included all the fat subtypes (saturated, monounsaturated, polyunsaturated) with protein in the models to estimate the effect of substituting the intake of a given fat subtype for carbohydrate intake, only the association between saturated fat intake and the risk of invasive breast cancer remained statistically significant. When all three subtypes were considered as continuous variables, the hazard ratios for a twofold intake increase were 1.17 (95% CI = 1.02 to 1.34) for saturated fat, 0.91 (95% CI = 0.74 to 1.11) for monounsaturated fat, and 1.09 (95% CI = 0.97 to 1.23) for polyunsaturated fat (data not shown).

To correct for measurement error, we estimated the attenuation factor for total fat in the density model to be 0.501 (standard error [SE] = 0.029) from the calibration subsample. In the density model, the uncalibrated regression coefficient (which equals the natural logarithm of the hazard ratio) for a twofold increase in total fat intake with respect to breast cancer was 0.1408 with a standard error of 0.0448 ($e^{0.1408} = 1.15$, the hazard ratio reported in Table 2 for the energy-adjusted density model on the continuous scale, and exp{0.1408 ± 1.96 × 0.0448} = 1.05 to 1.26, its corresponding 95% CI). After correction for measurement error in fat and energy intakes, the calibrated regression coefficient thus became 0.1408/0.501 = 0.2810 (SE = 0.0908). Consequently, the corrected hazard ratio of invasive breast cancer for a twofold increase of percent energy from total fat on the continuous scale was $e^{0.2810} = 1.32$ (95% CI = 1.11 to 1.58). The corrected hazard ratios of invasive breast cancer for a twofold increase of percent energy from specific subtypes of fat were 1.20 (95% CI = 1.07 to 1.34) for saturated fat, 1.21 (95% CI = 1.05 to 1.40) for monounsaturated fat, and 1.34 (95% CI = 1.06 to 1.69) for polyunsaturated fat. Figure 1 presents the continuous original (uncalibrated) and corrected (calibrated) risk estimates for invasive breast cancer as a function of percent energy from total fat intake.

Analyses of associations between fat intake and the risk of invasive breast cancer stratified by family history of breast cancer, history of breast biopsy, BMI, smoking history, and alcohol consumption did not suggest any effect modification by these factors (data not shown). However, we did find a statistically significant interaction between fat intake and current use of menopausal hormone therapy with respect to the risk of invasive breast cancer (Table 4). Among women who were not using menopausal hormone therapy at baseline, the multivariable hazard ratio for the highest versus the lowest quintile of percent energy from total fat was 1.25 (95% CI = 1.07 to 1.46; P_{trend}<.001; 386 versus 306 cases per 100 000 person-years). Among women in the lowest quintile of percent energy from total fat, those who were using menopausal hormone therapy at baseline had a higher risk of invasive breast cancer compared with those who were not (HR = 1.72; 95% CI = 1.47 to 2.01; 501 versus 306 cases per 100 000 person-years); however, the risk was not further increased as total fat intake increased. Among the users of menopausal hormone therapy, the hazard ratio of invasive breast cancer for those in the highest compared with the lowest quintile of percent energy from total fat was 1.04 (95% CI = 0.89 to 1.21; 514 versus 501 cases per 100 000 person-years) (data not shown). Statistically significant interactions were also found for saturated and monounsaturated fat but not for polyunsaturated fat (Table 4) and were consistent across other energy adjustment methods (data not shown).

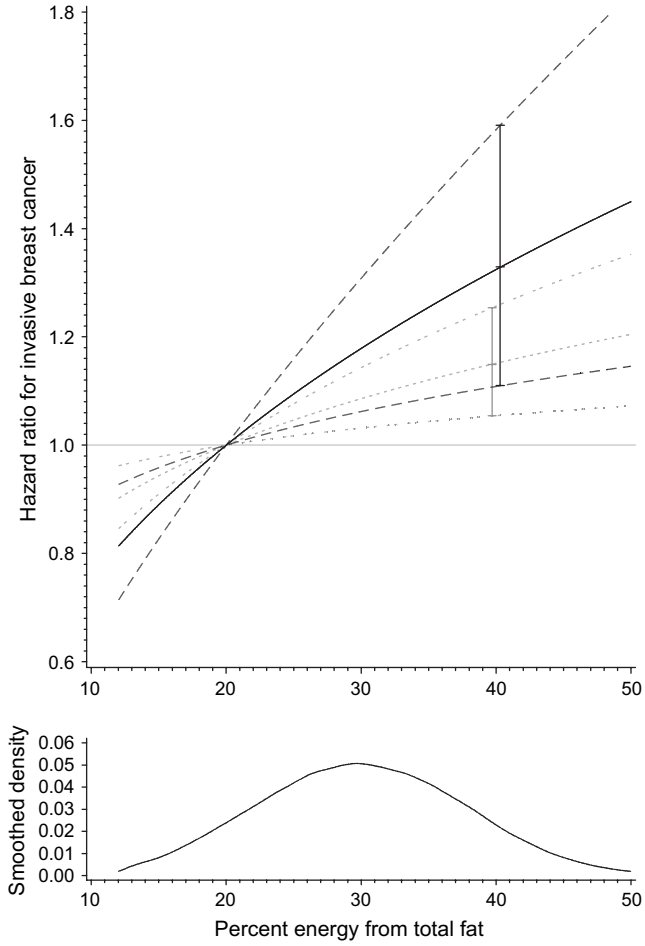

Fig. 1. Hazard ratios and 95% confidence intervals for invasive breast cancer in association with total fat intake, before and after correction for measurement error. **Upper panel**: **gray dotted line** = uncalibrated hazard ratio, before correction for measurement error (plotted function y = exp{[ln(x) – ln(20)] × 0.1408/ln(2)}); **gray broken dotted lines** = uncalibrated 95% confidence interval (plotted function y = exp{[ln(x) – ln(20)] × 0.1408/ln(2) ± 1.96 [ln(x) – ln(20)] × 0.0448/ln(2)}); **black solid line** = calibrated hazard ratio, after correction for measurement error (plotted function y = exp{[ln(x) – ln(20)] × 0.2810/ln(2)}); **black dashed lines** = calibrated 95% confidence interval (plotted function y = exp{[ln(x) – ln(20)] × 0.2810/ln(2) ± 1.96 [ln(x) – ln(20)] × 0.0908/ln(2)}). **Vertical lines** show 95% confidence intervals before (**gray**) and after (**black**) correction for measurement error around a twofold increase in percent energy from total fat, with 20% energy (the median of the lowest quintile) chosen as the reference point. The **bottom panel** represents the smoothed distribution of percent energy from total fat in the study population using univariate Gaussian kernel density estimation in SAS statistical software.

Discussion

In this large cohort of postmenopausal US women, we detected a direct association between dietary fat intake and the risk of invasive breast cancer. The positive association was observed for all subtypes of fat, and it persisted regardless of the energy adjustment method used and after correction for measurement error.

Our results from various energy adjustment methods that addressed the "isocaloric" substitution of fat for other energy

Table 4. Energy- and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for breast cancer by fat intake and current use of menopausal hormonal therapy (MHT) among 188 736 postmenopausal women in the National Institutes of Health–AARP Diet and Health Study*

Fat subtype	Quintile of intake					P_{trend}†	Fat intake as a continuous variable‡	$P_{interaction}$§
	1	2	3	4	5			
Total fat								
Median value (% energy)	20.3	26.0	30.0	34.2	40.1			
Non-MHT users								
No. of cases/No. of person-years	287/90 742	308/89 203	337/90 217	369/92 116	375/95 957			
Energy-adjusted HR (95% CI)	1.00 (referent)	1.10 (0.93 to 1.29)	1.19 (1.02 to 1.39)	1.28 (1.10 to 1.49)	1.26 (1.08 to 1.47)	.0005	1.32 (1.17 to 1.50)	
Multivariable-adjusted HR (95% CI)	1.00 (referent)	1.10 (0.93 to 1.29)	1.18 (1.01 to 1.39)	1.28 (1.10 to 1.49)	1.25 (1.07 to 1.46)	.0007	1.32 (1.16 to 1.50)	
Current MHT users								
No. of cases/No. of person-years	368/75 526	376/76 914	385/75 520	358/73 236	338/68 917			
Energy-adjusted HR (95% CI)	1.63 (1.40 to 1.91)	1.64 (1.41 to 1.92)	1.72 (1.47 to 2.00)	1.65 (1.41 to 1.93)	1.66 (1.42 to 1.95)	.78	1.03 (0.91 to 1.16)	.005
Multivariable-adjusted HR (95% CI)	1.72 (1.47 to 2.01)	1.71 (1.47 to 2.00)	1.79 (1.53 to 2.09)	1.72 (1.47 to 2.01)	1.72 (1.47 to 2.02)	.95	1.01 (0.90 to 1.15)	.003
Saturated fat								
Median value (% energy)	5.8	7.6	9.1	10.7	13.2			
Non-MHT users								
No. of cases/No. of person-years	282/89 432	303/88 164	327/89 582	364/93 118	400/97 939			
Energy-adjusted HR (95% CI)	1.00 (referent)	1.10 (0.93 to 1.29)	1.17 (1.00 to 1.37)	1.26 (1.08 to 1.47)	1.33 (1.14 to 1.55)	<.0001	1.26 (1.14 to 1.40)	
Multivariable-adjusted HR (95% CI)	1.00 (referent)	1.10 (0.93 to 1.29)	1.16 (0.99 to 1.37)	1.25 (1.07 to 1.47)	1.32 (1.13 to 1.53)	.0001	1.25 (1.13 to 1.39)	
Current MHT users								
No. of cases/No. of person-years	376/77 048	400/77 818	367/76 093	333/72 311	349/66 843			
Energy-adjusted HR (95% CI)	1.64 (1.40 to 1.91)	1.74 (1.49 to 2.02)	1.64 (1.40 to 1.91)	1.57 (1.34 to 1.84)	1.80 (1.53 to 2.10)	.58	1.04 (0.94 to 1.15)	.007
Multivariable-adjusted HR (95% CI)	1.72 (1.48 to 2.01)	1.81 (1.55 to 2.11)	1.70 (1.45 to 1.99)	1.63 (1.39 to 1.91)	1.85 (1.58 to 2.17)	.80	1.02 (0.92 to 1.13)	.005
Monounsaturated fat								
Median value (% energy)	7.2	9.5	11.2	12.8	15.2			
Non-MHT users								
No. of cases/No. of person-years	289/90 713	298/89 159	352/90 028	346/92 490	391/95 845			
Energy-adjusted HR (95% CI)	1.00 (referent)	1.05 (0.90 to 1.24)	1.24 (1.06 to 1.44)	1.19 (1.02 to 1.39)	1.30 (1.12 to 1.52)	.0002	1.29 (1.15 to 1.45)	
Multivariable-adjusted HR (95% CI)	1.00 (referent)	1.05 (0.90 to 1.24)	1.23 (1.06 to 1.44)	1.19 (1.02 to 1.39)	1.30 (1.11 to 1.51)	.0003	1.29 (1.15 to 1.45)	
Current MHT users								
No. of cases/No. of person-years	372/75 367	381/77 100	394/75 552	347/73 082	331/69 012			
Energy-adjusted HR (95% CI)	1.64 (1.41 to 1.92)	1.65 (1.42 to 1.92)	1.74 (1.50 to 2.03)	1.59 (1.36 to 1.86)	1.61 (1.38 to 1.89)	.77	0.98 (0.88 to 1.10)	.0007
Multivariable-adjusted HR (95% CI)	1.73 (1.48 to 2.02)	1.72 (1.47 to 2.00)	1.82 (1.57 to 2.12)	1.66 (1.42 to 1.94)	1.68 (1.43 to 1.97)	.64	0.97 (0.87 to 1.09)	.0005
Polyunsaturated fat								
Median value (% energy)	4.5	5.9	6.9	8.1	10.3			
Non-MHT users								
No. of cases/No. of person-years	321/94 034	332/91 234	336/90 830	323/90 817	364/91 318			
Energy-adjusted HR (95% CI)	1.00 (referent)	1.07 (0.91 to 1.24)	1.09 (0.93 to 1.27)	1.04 (0.89 to 1.22)	1.17 (1.01 to 1.36)	.074	1.12 (1.01 to 1.24)	
Multivariable-adjusted HR (95% CI)	1.00 (referent)	1.07 (0.92 to 1.25)	1.09 (0.93 to 1.27)	1.04 (0.89 to 1.21)	1.17 (1.00 to 1.36)	.082	1.12 (1.01 to 1.24)	
Current MHT users								
No. of cases/No. of person-years	326/71 867	383/74 732	342/74 860	407/74 845	367/73 808			
Energy-adjusted HR (95% CI)	1.41 (1.21 to 1.65)	1.59 (1.37 to 1.85)	1.42 (1.22 to 1.65)	1.68 (1.45 to 1.95)	1.53 (1.32 to 1.78)	.21	1.06 (0.96 to 1.17)	.42
Multivariable-adjusted HR (95% CI)	1.48 (1.27 to 1.73)	1.66 (1.43 to 1.93)	1.48 (1.27 to 1.73)	1.76 (1.52 to 2.03)	1.60 (1.37 to 1.86)	.24	1.05 (0.95 to 1.17)	.42

* The results are shown for the density model after fat and energy intakes were log transformed. Energy-adjusted bivariate Cox regression models adjusted for nonalcohol energy (continuous), using age as the underlying time metric. Multivariable Cox regression models adjusted for alcohol and nonalcohol energy intakes (both continuous), smoking history (two categories, ever versus never), combined age at birth of first child and number of children (four categories, nulliparous, first birth before age 30 years with one or two children, first birth at age 30 years or older, versus first birth before age 30 years with three or more children), age at menopause (three categories, <50, ≥55, versus 50–54 years), and BMI (three categories, 25 to <30 kg/m^2, ≥30 kg/m^2, versus <25 kg/m^2).

† Two-sided Wald chi-square test for linear trend using median intake in each quintile.

‡ Hazard ratios presented for a twofold increase in percent energy from fat.

§ Likelihood ratio test on the continuous scale with one degree of freedom.

sources as well as the addition of fat suggest that intake of fat, independent of its energy content, is a risk factor for postmenopausal invasive breast cancer (25). Such a conclusion is consistent with results of Tannenbaum's (4) landmark experiments in mice, which showed that high-fat diets increased the incidence of breast carcinoma compared with low-fat isocaloric diets, results that were subsequently confirmed by other animal studies (34). However, the relevance of animal models to human carcinogenesis remains debatable, and our findings contradict those of many epidemiologic cohort studies that failed to detect an association between dietary fat intake and the risk of breast cancer (9,10). One possible explanation for this lack of association in some prospective studies is that they had limited statistical power because of narrow ranges of fat intakes in the study cohort. It has been hypothesized (35) that a threshold effect may exist for dietary fat, such that it would be difficult to detect an association between fat intake and breast cancer risk in Western populations in which relatively few people consume diets containing 20% or less of energy from fat. In Asian populations with low fat intakes (i.e., those consuming diets that contain 15%–20% of energy from fat), statistically significant (36–39) and borderline statistically significant (40) associations between fat intake and the risk of breast cancer have been shown in some case–control studies but not in any cohort study (41,42). However, the latter studies had small numbers of breast cancer case subjects and thus limited statistical power to detect an association. By contrast, a pooled analysis of seven cohort studies from North America and northern Europe that included nearly 5000 case subjects showed no evidence of an association between intakes of total fat or fat subtypes and the risk of breast cancer (9). The results were essentially unchanged after these cohorts were updated and another US cohort was added (yielding 7329 breast cancer case subjects) (10). In these pooled analyses, however, only a small proportion of subjects (fewer than 2% of those diagnosed with breast cancer) reported consuming a diet that contained less than 20% of energy from total fat (9).

Compared with previous cohort studies, the NIH–AARP Diet and Health Study was larger and, presumably, had a wider range of fat intake, with 10% of the cohort participants and 289 breast cancer case subjects reporting that they consumed diets that contained less than 20% of energy from fat. It could be argued that the apparently wider range of intake in the NIH–AARP cohort is due to FFQ-based measurement error. We note, however, that, although measurement error in general artificially increases the range of reported, as opposed to true, intake (43), the FFQ measurement error in the NIH–AARP cohort is comparable to that for the FFQs in other cohorts (18). Therefore, it is unlikely that the relatively wider range of fat intake in the NIH–AARP cohort is due to measurement error; it more likely reflects the diversity of the study population (15) and the increasing consumption of low-fat foods in recent decades (44,45).

It is informative to consider our findings in light of the recently reported results from the WHI (12). Although the WHI findings were suggestive of a direct association between the risk of invasive breast cancer and a high-fat diet, the trial had limited statistical power to show a statistically significant reduction in invasive breast cancer incidence between the intervention and control groups because only 14.4% of the women in the intervention group reached the dietary target of 20% of energy from fat (12). It is interesting that, in the WHI, women who reported the highest levels of fat intake at baseline (i.e., those who consumed diets containing >36.8% of energy from fat), and therefore may have achieved the greatest reduction in fat intake, had a statistically significant decreased risk of breast cancer (12). This result further suggests that a sufficient variability in fat intake is important for detecting associations between fat intake and the risk of breast cancer.

Our findings are consistent with those of three recent cohort studies (46–48) that assessed fat intake by using dietary assessment methods that are potentially superior to the traditional FFQ alone. A cohort study of postmenopausal Swedish women found a direct association between the risk of breast cancer and intakes of total, monounsaturated, and polyunsaturated fat, which were assessed by using both a 7-day menu book and an FFQ (46). In the Norfolk cohort of the European Prospective Investigation into Cancer and Nutrition, statistically significant positive associations were found between the risk of breast cancer and both total and saturated fat intakes, which were assessed by 7-day food diaries, but these associations were not statistically significant when intakes were assessed by FFQ (47). More recently, in the control group of the WHI Randomized Controlled Dietary Modification Trial, statistically significant positive associations with the risk of breast cancer were observed for intakes of total, monounsaturated, and polyunsaturated fat, which were measured by 4-day food records, whereas the comparable associations based on intakes measured by an FFQ were null (48).

Previous studies have suggested that, of the various subtypes of fat, intakes of saturated fat may be the most strongly related to breast cancer risk (11,47,49). The most recent meta-analysis of the published literature on dietary fat and breast cancer risk (11) found a statistically significantly increased risk of breast cancer among women consuming the highest compared with the lowest amounts of saturated fat in the combined cohort studies (HR = 1.15; 95% CI = 1.02 to 1.30), whereas the risk increases were not statistically significant for monounsaturated fat (HR = 1.10; 95% CI = 0.83 to 1.44) or polyunsaturated fat (HR = 1.11; 95% CI = 1.00 to 1.22). In the NIH–AARP cohort, we found that intakes of total fat as well as intakes of all subtypes of fat were positively associated with the risk of breast cancer. When the subtypes of fat were mutually adjusted, only the association between saturated fat intake and breast cancer risk remained statistically significant. However, it is difficult to interpret this finding because of the high correlation between saturated and monounsaturated fat intakes, which shared several common food sources in this population (i.e., butter and margarine, beef, and poultry), and potentially because of the high correlation between their measurement errors. When we adjusted for the foods or food groups that contributed to dietary intakes of saturated and monounsaturated fat (i.e., total, red, white, and processed meat, as well as total dairy products, milk, yogurt, and cheese), the statistically significant associations between dietary fat and breast cancer risk remained. Therefore, the association we found in the NIH–AARP cohort was not clearly driven by a specific fat subtype or food group.

If the association is causal, dietary fat could influence the initiation and growth of breast tumors through several mechanisms,

including the stimulation of endogenous steroid hormone production (50), the modulation of immune function (51), and the regulation of gene expression (52). The steroid hormone pathway is a particularly plausible explanation because most of the established epidemiologic risk factors for breast cancer are related to alterations in endogenous hormone metabolism (53), and high levels of serum sex hormones have been demonstrated as risk factors for breast cancer (54,55). There are some indications in the literature that a reduction in fat intake is associated with a decrease in the concentrations of bioavailable serum sex hormones (50,56), although it is difficult to separate the effects of fat reduction from those resulting from simultaneous dietary modification and weight loss (12,57). The statistically significant interaction we found between menopausal hormone use and fat intake supports the notion that hormones mediate an association between dietary fat and the risk of breast cancer. In postmenopausal women who were not using hormone therapy, high fat intake could have increased levels of bioavailable estrogens, thus increasing the risk of breast cancer. In postmenopausal women who were using hormone therapy, the increase in sex hormones resulting from high fat intake would have been small relative to the already high levels of serum hormones derived from exogenous therapy. Among women in the lowest quintile of fat intake, the multivariable hazard ratio for invasive breast cancer for menopausal hormone users compared with nonusers was 1.72 (95% CI = 1.47 to 2.02). This finding suggests that exogenous hormone use, even among women who have a low fat intake, may be associated with a greater risk of breast cancer than high dietary fat intake (HR = 1.25, 95% CI = 1.07 to 1.46 for high-fat consumers who did not use menopausal hormone therapy). We verified that neither BMI nor age was an explanation for the observed interaction. To our knowledge, this is the first report of an interaction between dietary fat intake and menopausal hormone therapy with respect to breast cancer risk. Further studies of this interaction are warranted, especially studies that can distinguish among different hormone therapy regimens. It is unclear whether the failure to take into account this interaction with menopausal hormone therapy may explain the null results reported in some earlier cohort studies (9,10).

Two study limitations need to be considered. First, although we cannot rule out the possibility of spurious associations due to the presence of unmeasured confounders, the estimates yielded by parsimonious multivariable models were quite close to those from energy-adjusted models. When we added other potential breast cancer risk factors to the parsimonious models, the observed associations between fat intake and the risk of breast cancer were essentially unchanged.

Second, measurement error in FFQ-reported dietary intake, which remains one of the major problems in nutritional epidemiology, could have affected our results. When we adjusted for measurement error in fat and energy intakes, we found statistically significant hazard ratios of invasive breast cancer for intakes of total fat and subtypes of fat that were as high as 1.34. Indeed, the size of the NIH–AARP calibration substudy, which was larger than that in most previously published cohort studies, allowed us to estimate measurement error correction factors with substantial precision. Consequently, in our study, although the 95% confidence intervals for the corrected hazard ratios were somewhat larger than those for the uncorrected hazard ratios because of the uncertainty in the estimated correction factors, they still reflect a statistically significant direct association between dietary fat intake and breast cancer risk.

Moreover, we acknowledge that the use of 24HRs to correct for measurement error may not accurately adjust for the error in the FFQ because the self-reported recalls may involve systematic errors that are correlated with errors in the FFQ (58). However, evidence from the Observing Protein and Energy Nutrition (OPEN) study, in which protein and energy intakes that were assessed using 24HRs and a FFQ were compared with those obtained from urinary nitrogen and doubly labeled water, respectively, as dietary biomarkers, suggests that measurement error correction that is based on the 24HRs would be in the right direction but may still underestimate the true hazard ratio (43). To get an idea of the magnitude of a more fully corrected hazard ratio for total fat, we used estimates of the attenuation factors for female participants in the OPEN study. For both protein and nonprotein intakes expressed as percent of energy intake, the attenuation factors were estimated to be 0.35 when the 24HRs were used as the reference instrument and 0.47 when biomarker measurements were used as the reference (43). Assuming that total fat as a macronutrient would behave similarly to protein and nonprotein and that the OPEN study population was similar to the NIH–AARP cohort, we calculated that the attenuation factor of 0.501 that we estimated using 24HRs may be closer to $0.501 \times [1 - (0.47 - 0.35)/0.47] = 0.373$ [a smaller value means greater attenuation (32)]. In that case, the hazard ratio of 1.15 that we estimated for a twofold increase in percent energy from total fat in our study would be comparable to a hazard ratio of 1.46.

In conclusion, we detected an association between dietary fat—both total fat and the major subtypes of fat—and the risk of breast cancer in a large cohort of postmenopausal US women with a wide range of fat intake. Further work is needed to fully understand the measurement error structure in the assessment of dietary intakes of fat, other macronutrients, and total energy to provide a better picture of the true magnitude of the association. Meanwhile, results from this large prospective cohort with a wide intake range should contribute to the ongoing debate about the association between dietary fat and the risk of breast cancer.

References

(1) Willett W. Dietary fat and breast cancer. In: Willett W, editor. Nutritional epidemiology. 2nd ed. New York (NY): Oxford University Press; 1998. p. 377–413.

(2) Greenwald P. Role of dietary fat in the causation of breast cancer: point. Cancer Epidemiol Biomarkers Prev 1999;8:3–7.

(3) Hunter DJ. Role of dietary fat in the causation of breast cancer: counterpoint. Cancer Epidemiol Biomarkers Prev 1999;8:9–13.

(4) Tannenbaum A. The genesis and growth of tumors. III. Effects of a high-fat diet. Cancer Res 1942;2:468–75.

(5) Armstrong B, Doll R. Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. Int J Cancer 1975;15:617–31.

(6) Buell P. Changing incidence of breast cancer in Japanese-American women. J Natl Cancer Inst 1973;51:1479–83.

(7) Howe GR, Hirohata T, Hislop TG, Iscovich JM, Yuan JM, Katsouyanni K, et al. Dietary factors and risk of breast cancer: combined analysis of 12 case-control studies. J Natl Cancer Inst 1990;82:561–9.

(8) Michels KB. The role of nutrition in cancer development and prevention. Int J Cancer 2005;114:163–5.

(9) Hunter DJ, Spiegelman D, Adami HO, Beeson L, van den Brandt PA, Folsom AR, et al. Cohort studies of fat intake and the risk of breast cancer: a pooled analysis. N Engl J Med 1996;334:356–61.
(10) Smith-Warner SA, Spiegelman D, Adami HO, Beeson WL, van den Brandt PA, Folsom AR, et al. Types of dietary fat and breast cancer: a pooled analysis of cohort studies. Int J Cancer 2001;92:767–74.
(11) Boyd NF, Stone J, Vogt KN, Connelly BS, Martin LJ, Minkin S. Dietary fat and breast cancer risk revisited: a meta-analysis of the published literature. Br J Cancer 2003;89:1672–85.
(12) Prentice RL, Caan B, Chlebowski RT, Patterson R, Kuller LH, Ockene JK, et al. Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA 2006;295:629–42.
(13) Schatzkin A, Kipnis V. Could exposure assessment problems give us wrong answers to nutrition and cancer questions? J Natl Cancer Inst 2004;96:1564–5.
(14) Riboli E, Kaaks R. Invited commentary: the challenge of multi-center cohort studies in the search for diet and cancer links. Am J Epidemiol 2000;151:371–4.
(15) Schatzkin A, Subar AF, Thompson FE, Harlan LC, Tangrea J, Hollenbeck AR, et al. Design and serendipity in establishing a large cohort with wide dietary intake distributions: the National Institutes of Health-American Association of Retired Persons Diet and Health Study. Am J Epidemiol 2001;154;1119–25.
(16) Michaud DS, Midthune D, Hermansen S, Leitzmann M, Harlan LC, Kipnis V, et al. Comparison of cancer registry case ascertainment with SEER estimates and self-reporting in a subset of the NIH-AARP Diet and Health Study. J Regist Manag 2005;32:70–5.
(17) Subar AF, Ziegler RG, Thompson FE, Johnson CC, Weissfeld JL, Reding D, et al. Is shorter always better? Relative importance of questionnaire length and cognitive ease on response rates and data quality for two dietary questionnaires. Am J Epidemiol 2001;153:404–9.
(18) Subar AF, Thompson FE, Kipnis V, Midthune D, Hurwitz P, McNutt S, et al. Comparative validation of the Block, Willett, and National Cancer Institute food frequency questionnaires: the Eating at America's Table Study. Am J Epidemiol 2001;154:1089–99.
(19) Subar AF, Midthune D, Kulldorff M, Brown CC, Thompson FE, Kipnis V, et al. Evaluation of alternative approaches to assign nutrient values to food groups in food frequency questionnaires. Am J Epidemiol 2000;152:279–86.
(20) Thiébaut ACM, Bénichou J. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. Stat Med 2004;23: 3803–20.
(21) Hertz-Picciotto I, Rockhill B. Validity and efficiency of approximation methods for tied survival times in Cox regression. Biometrics 1997;53:1151–6.
(22) Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol 1986;124:17–27.
(23) Smith-Warner SA, Spiegelman D, Yaun SS, van den Brandt PA, Folsom AR, Goldbohm RA, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. JAMA 1998;279:535–40.
(24) Collaborative Group on Hormonal Factors in Breast Cancer. Alcohol, tobacco and breast cancer: collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. Br J Cancer 2002;87:1234–45.
(25) 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.
(26) Greenland S. Dose-response and trend analysis in epidemiology: alternatives to categorical analysis. Epidemiology 1995;6:356–65.
(27) Rothman KJ, Greenland S, editors. Modern epidemiology. 2nd ed. Philadelphia (PA): Lippincott Williams & Wilkins; 1998.
(28) Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic regression analyses. Am J Epidemiol 1995; 142:1255–64.
(29) Horvitz DG, Thompson DJ. A generalization of sampling without replacement from a finite universe. J Am Stat Assoc 1952;47:663–85.
(30) Rosner B, Spiegelman D, Willett WC. Correction of logistic regression relative risk estimates and confidence intervals for measurement error: the case of multiple covariates measured with error. Am J Epidemiol 1990; 132:734–45.
(31) Carroll RJ, Midthune D, Freedman LS, Kipnis V. Seemingly unrelated measurement error models, with application to nutritional epidemiology. Biometrics 2006;62:75–84.
(32) Kipnis V, Freedman LS, Brown CC, Hartman AM, Schatzkin A, Wacholder S. Effect of measurement error on energy-adjustment models in nutritional epidemiology. Am J Epidemiol 1997;146:842–55.
(33) Rosner B, Willett WC, Spiegelman D. Correction of logistic regression relative risk estimates and confidence intervals for systematic within-person measurement error. Stat Med 1989;8:1051–69.
(34) Freedman LS, Clifford C, Messina M. Analysis of dietary fat, calories, body weight, and the development of mammary tumors in rats and mice: a review. Cancer Res 1990;50:5710–9.
(35) Wynder EL, Cohen LA, Muscat JE, Winters B, Dwyer JT, Blackburn G. Breast cancer: weighing the evidence for a promoting role of dietary fat. J Natl Cancer Inst 1997;89:766–75.
(36) Yu SZ, Lu RF, Xu DD, Howe GR. A case-control study of dietary and nondietary risk factors for breast cancer in Shanghai. Cancer Res 1990; 50:5017–21.
(37) Qi XY, Zhang AY, Wu GL, Pang WZ. The association between breast cancer and diet and other factors. Asia Pac J Public Health 1994; 7:98–104.
(38) Wakai K, Dillon DS, Ohno Y, Prihartono J, Budiningsih S, Ramli M, et al. Fat intake and breast cancer risk in an area where fat intake is low: a case-control study in Indonesia. Int J Epidemiol 2000; 29:20–8.
(39) Bala DV, Patel DD, Duffy SW, Cherman S, Patel PS, Trivedi J, et al. Role of dietary intake and biomarkers in risk of breast cancer: a case control study. Asian Pac J Cancer Prev 2001;2:123–30.
(40) Do MH, Lee SS, Jung PJ, Lee MH. Intake of dietary fat and vitamin in relation to breast cancer risk in Korean women: a case-control study. J Korean Med Sci 2003;18:534–40.
(41) Gago-Dominguez M, Yuan JM, Sun CL, Lee HP, Yu MC. Opposing effects of dietary n-3 and n-6 fatty acids on mammary carcinogenesis: The Singapore Chinese Health Study. Br J Cancer 2003;89:1686–92.
(42) Wakai K, Tamakoshi K, Date C, Fukui M, Suzuki S, Lin Y, et al. Dietary intakes of fat and fatty acids and risk of breast cancer: a prospective study in Japan. Cancer Sci 2005;96:590–9.
(43) Kipnis V, Subar AF, Midthune D, Freedman LS, Ballard-Barbash R, Troiano RP, et al. Structure of dietary measurement error: results of the OPEN biomarker study. Am J Epidemiol 2003;158:14–21.
(44) Kennedy ET, Bowman SA, Powell R. Dietary-fat intake in the US population. J Am Coll Nutr 1999;18:207–12.
(45) Chanmugam P, Guthrie JF, Cecilio S, Morton JF, Basiotis PP, Anand R. Did fat intake in the United States really decline between 1989–1991 and 1994–1996? J Am Diet Assoc 2003;103:867–72.
(46) Wirfält E, Mattisson I, Gullberg B, Johansson U, Olsson H, Berglund G. Postmenopausal breast cancer is associated with high intakes of ω6 fatty acids (Sweden). Cancer Causes Control 2002;13:883–93.
(47) Bingham SA, Luben R, Welch A, Wareham N, Khaw KT, Day N. Are imprecise methods obscuring a relation between fat and breast cancer? Lancet 2003;362:212–4.
(48) Freedman LS, Potischman N, Kipnis V, Midthune D, Schatzkin A, Thompson FE, et al. A comparison of two dietary instruments for evaluating the fat-breast cancer relationship. Int J Epidemiol 2006;35:1011–21.
(49) Cho E, Spiegelman D, Hunter DJ, Chen WY, Stampfer MJ, Colditz GA, et al. Premenopausal fat intake and risk of breast cancer. J Natl Cancer Inst 2003;95:1079–85.
(50) Wu AH, Pike MC, Stram DO. Meta-analysis: dietary fat intake, serum estrogen levels, and the risk of breast cancer. J Natl Cancer Inst 1999; 91:529–34.
(51) Hwang D. Fatty acids and immune responses—a new perspective in searching for clues to mechanism. Annu Rev Nutr 2000;20:431–56.
(52) Jump DB, Clarke SD. Regulation of gene expression by dietary fat. Annu Rev Nutr 1999;19:63–90.
(53) Key TJ, Verkasalo PK, Banks E. Epidemiology of breast cancer. Lancet Oncol 2001;2:133–40.

(54) Endogenous Hormones and Breast Cancer Collaborative Group. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. J Natl Cancer Inst 2002;94:606–16.
(55) Kaaks R, Rinaldi S, Key TJ, Berrino F, Peeters PHM, Biessy C, et al. Postmenopausal serum androgens, oestrogens and breast cancer risk: the European Prospective Investigation into Cancer and Nutrition. Endocr Relat Cancer 2005;12:1071–82.
(56) Prentice R, Thompson D, Clifford C, Gorbach S, Goldin B, Byar D. Dietary fat reduction and plasma estradiol concentration in healthy postmenopausal women. The Women's Health Trial Study Group. J Natl Cancer Inst 1990;82:129–34.
(57) Berrino F, Bellati C, Secreto G, Camerini E, Pala V, Panico S, et al. Reducing bioavailable sex hormones through a comprehensive change in diet: the diet and androgens (DIANA) randomized trial. Cancer Epidemiol Biomarkers Prev 2001;10:25–33.
(58) Kipnis V, Midthune D, Freedman LS, Bingham S, Schatzkin A, Subar A, et al. Empirical evidence of correlated biases in dietary assessment instruments and its implications. Am J Epidemiol 2001;153: 394–403.

Notes

The authors are grateful to Douglas Midthune for his contribution to the data analysis. The investigators are indebted to all participants for prviding the data and for their commitment to the NIH–AARP Diet and Health Study.

Cancer incidence data from the Atlanta metropolitan area were collected by the Georgia Center for Cancer Statistics, Department of Epidemiology, Rollins School of Public Health, Emory University, GA. Cancer incidence data from California were collected by the California Department of Health Services, Cancer Surveillance Section, CA. Cancer incidence data from the Detroit metropolitan area were collected by the Michigan Cancer Surveillance Program, Community Health Administration, MI. The Florida cancer incidence data used in this report were collected by the Florida Cancer Data System under contract to the Department of Health (DOH), FL. The views expressed herein are solely those of the authors and do not necessarily reflect those of the contractor or DOH. Cancer incidence data from Louisiana were collected by the Louisiana Tumor Registry, Louisiana State University Medical Center in New Orleans, LA. Cancer incidence data from New Jersey were collected by the New Jersey State Cancer Registry, Cancer Epidemiology Services, New Jersey State Department of Health and Senior Services, NJ. Cancer incidence data from North Carolina were collected by the North Carolina Central Cancer Registry, NC. Cancer incidence data from Pennsylvania were supplied by the Division of Health Statistics and Research, Pennsylvania Department of Health, Harrisburg, PA. The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations or conclusions. The authors take sole responsibility for the study design, data collection and analysis, interpretation of the data, and the preparation of the manuscript.

Manuscript received September 6, 2006; revised January 11, 2007; accepted January 25, 2007.