

# Types of dietary fat and breast cancer: a pooled analysis of cohort studies.

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## TYPES OF DIETARY FAT AND BREAST CANCER: A POOLED ANALYSIS OF COHORT STUDIES

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Recently, there has been interest in whether intakes of specific types of fat are associated with breast cancer risk independently of other types of fat, but results have been inconsistent. We identified 8 prospective studies that met predefined criteria and analyzed their primary data using a standardized approach. Holding total energy intake constant, we calculated relative risks for increments of 5% of energy for each type of fat compared with an equivalent amount of energy from carbohydrates or from other types of fat. We combined study-specific relative risks using a random effects model. In the pooled database, 7,329 incident invasive breast cancer cases occurred among 351,821 women. The pooled relative risks (95% confidence intervals [CI]) for an increment of 5% of energy were 1.09 (1.00–1.19) for saturated, 0.93 (0.84–1.03) for monounsaturated and 1.05 (0.96–1.16) for polyunsaturated fat compared with equivalent energy intake from carbohydrates. For a 5% of energy increment, the relative risks were 1.18 (95% CI 0.99–1.42) for substituting saturated for monounsaturated fat, 0.98 (95% CI 0.85–1.12) for substituting saturated for polyunsaturated fat and 0.87 (95% CI 0.73–1.02) for substituting monounsaturated for polyunsaturated fat. No associations were observed for animal or vegetable fat intakes. These associations were not modified by menopausal status. These data are suggestive of only a weak positive association with substitution of saturated fat for carbohydrate consumption; none of the other types of fat examined was significantly associated with breast cancer risk relative to an equivalent reduction in carbohydrate consumption.

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**Key words:** diet; fat; breast neoplasms; cohort studies; pooling

No association has been observed in summary analyses of cohort studies between intakes of total, saturated, monounsaturated, or polyunsaturated fat and breast cancer risk.<sup>1,2</sup> In contrast, summary analyses of case-control studies have suggested that intakes of total fat and in particular saturated fat and monounsaturated fat are positively associated with breast cancer risk.<sup>1,3</sup> Each of these summary analyses controlled for established breast cancer risk factors but only the combined analysis by Howe *et al.*<sup>3</sup> presented relative risks for specific types of fat that were adjusted for the intakes of other types of fat. Thus, we investigated the

independent association between intakes of specific types of fat and breast cancer risk in the Pooling Project of Prospective Studies of Diet and Cancer (hereafter referred to as the Pooling Project) using a standardized approach. In addition, we have updated the analyses in our initial report<sup>2</sup> by including additional cases from 4 cohorts and a new cohort, the New York University Women's Health Study.<sup>4</sup> Because we have the primary data from each of the cohort studies, we are able to apply standardized exposure categories and covariate definitions across studies, control for other dietary constituents and evaluate potential effect modification of dietary variables by nondietary risk factors.

### MATERIAL AND METHODS

The Pooling Project has been described previously.<sup>2,5</sup> Eight prospective studies<sup>4,6–12</sup> (Table I) were identified that met the following predefined criteria: i.- at least 200 incident breast cancer cases; ii.- assessment of usual intake of foods and nutrients; iii.- a validation study of the diet assessment method or a closely related instrument. The Nurses' Health Study was divided into 2 studies (1980–1986 and 1986–1996 follow-up periods) because it used repeated assessments of dietary intake. Following the underlying theory of survival data, blocks of person-time in different time periods are statistically independent, regardless of the extent that

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they are derived from the same people,<sup>13</sup> so pooling estimates from these 2 time periods is equivalent to using a single time period but takes advantage of the enhanced exposure assessment in 1986 compared with 1980. Follow-up of the Iowa Women's Health Study, Netherlands Cohort Study, Nurses' Health Study and Sweden Mammography Cohort has been extended from our previous Pooling Project publication.<sup>2</sup> In addition, the analyses presented in our study include data from the New York University Women's Health Study.<sup>4</sup>

Diet was measured at baseline in each study using a food frequency questionnaire. The number of food items on the questionnaires ranged from 45 in the Adventist Health Study to 150 in the Netherlands Cohort Study. Portion sizes were not given in 2 studies; participants specified portion sizes (as small, medium or large relative to a standard size) in 2 studies; and portion sizes were specified on the questionnaires in the remaining studies. The studies provided data on saturated, monounsaturated, polyunsaturated, animal, vegetable and total fat intakes; data were not obtained for omega-3 polyunsaturated fat or trans fat intakes. The polyunsaturated fat intake data corresponded to linoleic acid consumption for the Adventist Health Study and the New York University Women's Health Study and to total polyunsaturated fat consumption for the remaining studies.

#### Statistical methods

For each data set, after applying the exclusion criteria used by that study, we excluded participants if they reported energy intakes greater or less than 3 standard deviations from the study-specific log<sub>e</sub>-transformed mean energy intake of the baseline population, had missing alcohol intake data or reported a history of cancer (except non-melanoma skin cancer) at baseline. As a result of these additional exclusions and expanded follow-up in some studies, the baseline cohort size and number of cases recorded in these analyses may differ from original study-specific publications.<sup>4,6-12</sup>

To reduce computational burden with little loss of statistical efficiency,<sup>14</sup> the Adventist Health Study, Iowa Women's Health Study, New York State Cohort, New York University Women's Health Study, Nurses' Health Study (a; 1980-1986 follow-up), Nurses' Health Study (b; 1986-1996 follow-up) and the Sweden Mammography Cohort were analyzed as nested case-control studies. For each participant diagnosed with invasive breast cancer, 10 controls were randomly selected from the subset of participants who had the same year of birth and who were alive, were not known to have migrated from the study area and had not been diagnosed with breast cancer before the year in which the case was diagnosed. A nested case-control design also was used in the Canadian National Breast Screening Study; the investigators of that study selected 2 controls for each case with invasive breast cancer. The Netherlands Cohort Study used a case-cohort design.<sup>15</sup>

For the nested case-control studies, incidence rate ratios were estimated by conditional logistic regression using SAS PROC PHREG;<sup>16</sup> for the Netherlands Cohort Study, Epicure software<sup>17</sup> was used. An indicator variable for missing responses within a study was created for measured covariates, when applicable. Two-sided 95% confidence intervals (CI) were calculated. The random effects model developed by DerSimonian and Laird<sup>18</sup> was used to combine log<sub>e</sub> relative risks from the multiple studies; individual study results were weighted by the inverse of their variance. We tested for heterogeneity among studies using the asymptotic DerSimonian and Laird Q statistic.<sup>18</sup>

We initially checked whether the associations for intakes of total fat and each type of fat were similar between the updated data set and the data set reported previously<sup>2</sup> using the original analytic approaches in which each type of fat was not adjusted for intakes of the other types of fat. We also analyzed associations for intakes of total fat and each type of fat as a percent of total calories. For each study, we corrected the relative risks for total, saturated, monounsaturated, and polyunsaturated fat for measurement error<sup>19</sup> using the regression coefficients between fat intakes estimated by the food frequency questionnaires and by the reference methods that were either multiple diet records<sup>20-23</sup> (H. Ljung, A. Wolk, D. Spiegelman, D. Hunter for the Study Group of the Multiple Risk Survey on Swedish Women for Eating Assessment; unpublished results) or 24-hr recalls.<sup>24-26</sup> We did not calculate measurement error-corrected relative risks for animal and vegetable fats because intakes of these fat subtypes were not calculated for the reference method in several studies.

We also conducted analyses using the multivariate nutrient density model in which, together with total caloric intake, saturated fat, monounsaturated fat, polyunsaturated fat, protein and alcohol intakes were specified in the same model as a percent of total calories.<sup>27</sup> We controlled for total energy intake because the range of energy intake necessary to maintain energy balance is relatively narrow for an individual.<sup>28</sup> In the multivariate nutrient density model, the coefficient for each type of fat can be interpreted as the effect of an increase in the percent of energy intake from the particular type of fat relative to an identical decrease in the percent of energy from carbohydrate. The effect of substituting one type of fat for another was calculated as the difference between the coefficients of the 2 types of fat. Similar analyses were conducted with intakes of animal fat, vegetable fat, protein, alcohol and calories in one model.

Analyses were conducted using the multivariate nutrient density model approach for each type of fat modeled as a continuous variable or as quartiles. Study-specific quartiles were assigned based on the distributions of the control populations for the nested case-control data sets and the subcohort in the Netherlands Cohort

TABLE 1—CHARACTERISTICS OF THE COHORT STUDIES INCLUDED IN THE POOLED ANALYSIS OF TYPE OF FAT INTAKE AND BREAST CANCER

Study	Years of follow-up	Baseline cohort	Age range <sup>1</sup> (years)	No. of cases <sup>2</sup>	Median intake (% kcal) <sup>3</sup>					
					SFAT	MFAT	PFAT	AFAT	VFAT	TFAT
Adventist Health Study	1976-82	15,172	28-90	160	11	13	9	12	21	37
Canadian National Breast Screening Study	1982-87	56,837	40-59	419	16	16	4	29	12	41
Iowa Women's Health Study	1986-95	34,406	55-69	1,130	12	13	6	19	14	34
Netherlands Cohort Study	1986-92	62,412	55-69	887	15	14	7	28	11	39
New York State Cohort	1980-87	18,475	50-93	367	10	13	5	20	10	33
New York University Women's Health Study	1985-94	14,006	34-65	385	16	14	6	21	18	40
Nurses' Health Study (a)	1980-86	89,046	34-59	1,020	16	16	5	29	10	40
Nurses' Health Study (b)	1986-96	68,817	40-65	1,638	11	12	6	18	14	33
Sweden Mammography Cohort	1987-97	61,467	40-76	1,323	13	11	4	N/A	N/A	30
Total		351,821		7,329						

<sup>1</sup>Age range of cases. <sup>2</sup>Cases consisted of women diagnosed with invasive breast cancer. <sup>3</sup>Data are provided for noncases only. SFAT, saturated fat; MFAT, monounsaturated fat; PFAT, polyunsaturated fat; AFAT, animal fat; VFAT, vegetable fat; TFAT, total fat.

Study. To calculate the  $p$ -value for the test of trend in the quartile analyses, participants were assigned the median value of their study-specific quartile of intake and this variable was entered as a continuous term in the conditional logistic regression model.

We also estimated relative risks for combinations of specific types of fat. For these analyses, study-specific quartiles were assigned for each type of fat and 3 groups were formed based on the joint distribution of the 2 types of fat: i. the lowest quartile for fat subtype 1 and the highest quartile for fat subtype 2; ii. the highest quartile for fat subtype 1 and the lowest quartile for fat subtype 2; and iii. all remaining combinations. To increase the power for estimating the relative risks, the studies were combined into a single data set stratified by study; we reported previously that there was no statistically significant between-study heterogeneity in the dietary and non-dietary covariates.<sup>29</sup>

We evaluated whether several factors modified the association between breast cancer risk and each type of fat. For each factor of interest, a cross-product term of the ordinal score for the level of each factor and intake of a specific type of fat expressed as a continuous variable was included in the multivariate nutrient density model. Participants with missing values of the factor of interest were excluded from these analyses. The pooled  $p$ -value for effect modification was obtained using squared Wald statistics by pooling the study-specific interaction coefficients and dividing by the square of the standard error of the pooled interaction term. Because most studies collected information at baseline only, for analyses evaluating whether menopausal status modified the association between each type of fat and breast cancer risk, we assigned menopausal status at follow-up in each study using an algorithm based on an analysis of 42,531 Nurses' Health Study participants who were premenopausal in 1976 and remained premenopausal or had natural menopause by 1992.<sup>5</sup> Breast cancer cases and their age-matched controls who were premenopausal at baseline and whose age at follow-up was  $\leq 51$  years were considered to be premenopausal, between 51 and 55 years were considered as having an uncertain menopausal status and  $\geq 55$  years were considered to be postmenopausal.

## RESULTS

Fat intakes varied across studies. The median total fat intake ranged from 30% of total energy for the Sweden Mammography Cohort Study to 41% of total energy for the Canadian National Breast Screening Study. The range of median saturated fat and monounsaturated fat intakes was approximately 10% to 16% of total energy across studies; intakes of polyunsaturated fat were substantially lower (Table I). The lowest median animal fat consumption and highest median vegetable fat consumption were observed in the Adventist Health Study. Pearson correlations across studies between intakes of types of fat expressed as a percent of total energy ranged from 0.55 to 0.81 for saturated fat-monounsaturated fat intakes,  $-0.43$  to  $0.23$  for saturated fat-polyunsaturated fat intakes,  $0.01$  to  $0.84$  for monounsaturated fat-polyunsaturated fat intakes and  $-0.69$  to  $-0.29$  for animal fat-vegetable fat intakes.

### Individual models

As found in our initial report of a subset of the data presented here,<sup>2</sup> no association was observed for consumption of total fat and each type of fat in this updated data set using the original analytic approach that included invasive and *in situ* breast cancer cases and examined the calorie-adjusted consumption of each fat in grams per day in separate models (data not shown). When the analyses were restricted to invasive breast cancer cases only, intakes of each fat were expressed as a percent of energy and additional covariates were included, intakes of total fat and each type of fat again were not associated with breast cancer risk (Table II). In these analyses, there was marginally significant evidence of heterogeneity in the study-specific results for saturated fat; relative risks (RR) for an increment of 5% of energy from saturated fat ranged from 0.82

(95% CI 0.63–1.06) for the New York State Cohort to 1.20 (95% CI 1.04–1.37) for the Iowa Women's Health Study ( $p$ -value, test for heterogeneity = 0.04). The association was in the inverse direction for 4 studies but in the direction of increased risk for 5 studies. Only the result for the Iowa Women's Health Study was statistically significant.

Pooled relative risks corrected for measurement error<sup>19,30</sup> for an increment of 5% of energy were 1.03 (95% CI 0.97–1.08;  $p$ -value, test for heterogeneity = 0.45) for total fat; 1.06 (95% CI 0.92–1.24;  $p$ -value, test for heterogeneity = 0.26) for saturated fat; 1.01 (95% CI 0.86–1.19;  $p$ -value, test for heterogeneity = 0.36) for monounsaturated fat and 1.01 (95% CI 0.85–1.19;  $p$ -value, test for heterogeneity = 0.66) for polyunsaturated fat.

### Saturated, monounsaturated and polyunsaturated fat: multivariate nutrient density models

Using the multivariate nutrient density model approach, total calories and the percent of energy from saturated fat, monounsaturated fat, polyunsaturated fat, alcohol and protein intakes were included simultaneously in the analyses. In this model, the relative risk for each type of fat can be interpreted as the effect of substituting a specific type of fat with an equivalent reduction in the percent of energy from carbohydrates. We observed a marginally significant positive association of substituting saturated fat consumption for an equivalent amount of energy from carbohydrates (RR = 1.09 for an increment of 5% of energy; 95% CI 1.00–1.19) (Table III). The only statistically significant study-specific result was observed in the Netherlands Cohort Study. Monounsaturated and polyunsaturated fat intakes were not associated with breast cancer risk when substituted for carbohydrate consumption. Similar results were obtained if we did not adjust for body mass index. Substituting 5% of energy intake from saturated fat for monounsaturated fat was associated with a marginally significant 18% increase (RR = 1.18, 95% CI 0.99–1.42) in breast cancer risk. The reciprocal relative risk for substituting monounsaturated fat for saturated fat was 0.85 (95% CI 0.71–1.02). Substituting monounsaturated fat for polyunsaturated fat was suggestive of a decrease in breast cancer risk (RR = 0.87 for an increment of 5% of energy; 95% CI 0.73–1.02). There was no apparent effect of substituting saturated fat for polyunsaturated fat (RR = 0.98 for an increment of 5% of energy; 95% CI 0.85–1.12). Results were similar if energy-adjusted saturated fat, monounsaturated fat, polyunsaturated fat, protein and alcohol intakes were modeled instead of nutrient densities and expressed as an increment of 10 g/d (data not shown).

No association was observed for saturated, monounsaturated and polyunsaturated fat intakes when they were included simultaneously in the analytic model as quartiles of consumption (Table IV).

### Saturated, monounsaturated and polyunsaturated fat: partition model

In analyses simultaneously adjusting for saturated fat, monounsaturated fat, polyunsaturated fat and nonfat calories (the partition model<sup>31</sup>), we also found no association for any of the specific types of fat (RR = 1.03, 95% CI 0.98–1.08 for saturated fat; RR = 0.97, 95% CI 0.92–1.02 for monounsaturated fat; RR = 1.02, 95% CI 0.98–1.07 for polyunsaturated fat for an increment of 45 calories per day).

### Saturated, monounsaturated and polyunsaturated fat: stratified analyses

To assess the joint effect of specific fat subtypes, we estimated the risk for combinations of specific fat subtypes using a single combined data set stratified by study. For analyses of saturated fat and monounsaturated fat intakes, participants in the lowest quartile of saturated fat intake and the highest quartile of monounsaturated fat intake were considered the reference group ( $n = 45$  cases). The comparable group of interest was participants in the highest quartile of saturated fat intake and lowest quartile of monounsaturated



TABLE II - MULTIVARIATE RELATIVE RISKS<sup>1</sup> (95% CI) OF BREAST CANCER FOR 5% OF ENERGY INCREASES FROM TOTAL FAT AND SPECIFIC FAT SUBTYPES, CONTINUOUS MODEL

Fat subtype	AHS <sup>2</sup>	CNBS	IWHS	NHS (a)	NHS (b)	NLCS	NYSC	NYU	SMC	Pooled	p-value, test for heterogeneity
Total	1.04 (0.79-1.36)	1.10 (0.98-1.24)	1.07 (1.00-1.13)	0.99 (0.95-1.04)	0.96 (0.91-1.00)	1.01 (0.92-1.09)	1.00 (0.93-1.08)	1.03 (0.94-1.13)	0.98 (0.92-1.04)	1.00 (0.98-1.03)	0.19
Saturated	1.15 (0.77-1.73)	1.14 (0.92-1.42)	1.20 (1.04-1.37)	0.95 (0.85-1.05)	0.95 (0.85-1.06)	1.13 (0.97-1.31)	0.82 (0.63-1.06)	1.09 (0.90-1.32)	0.96 (0.87-1.07)	1.03 (0.95-1.10)	0.04
Mono-unsaturated	1.09 (0.51-2.35)	1.20 (0.91-1.59)	1.15 (1.00-1.32)	0.99 (0.90-1.09)	0.89 (0.80-1.00)	0.94 (0.78-1.13)	1.02 (0.89-1.18)	1.12 (0.89-1.41)	0.93 (0.80-1.08)	1.00 (0.94-1.07)	0.16
Poly-unsaturated	1.14 (0.63-2.06)	1.40 (0.95-2.07)	1.05 (0.87-1.27)	1.04 (0.85-1.28)	0.90 (0.77-1.06)	0.94 (0.82-1.08)	1.13 (0.93-1.38)	1.08 (0.82-1.40)	1.02 (0.80-1.29)	1.01 (0.94-1.08)	0.48
Animal	1.10 (0.89-1.37)	1.03 (0.94-1.14)	1.07 (1.01-1.13)	0.98 (0.94-1.03)	1.00 (0.95-1.06)	1.01 (0.95-1.08)	0.90 (0.83-0.98)	0.99 (0.91-1.07)	N/A <sup>3</sup>	1.00 (0.97-1.04)	0.08
Vegetable	0.94 (0.77-1.14)	1.07 (0.94-1.22)	1.01 (0.94-1.08)	1.02 (0.96-1.08)	0.94 (0.89-1.00)	0.99 (0.93-1.05)	1.06 (1.00-1.13)	1.05 (0.96-1.14)	N/A <sup>3</sup>	1.01 (0.98-1.04)	0.15

<sup>1</sup>Relative risks were adjusted for age at menarche ( $\leq 11, 12, 13, 14, \geq 15$  years), parity (0, 1-2,  $\geq 3$ ), age at birth of first child ( $\leq 20, 21-25, 26-30, >30$  years), menopausal status at diagnosis (premenopausal, postmenopausal, uncertain), postmenopausal hormone use (ever, never), oral contraceptive use (ever, never), history of benign breast disease (no, yes), family history of breast cancer (no, yes), smoking status (ever, never), education ( $< \text{high-school graduate, high-school graduate, } > \text{high-school graduate}$ ), body mass index (weight in kilograms divided by the square of the height in meters; continuous), body mass index-menopausal status at diagnosis interaction term, height ( $< 1.60, 1.60-1.65, 1.65-1.70, 1.70-1.75, \geq 1.75$  m), alcohol intake (0,  $< 15, \geq 15$  g/d), fiber intake (quintiles) and energy intake (continuous). <sup>2</sup>AHS, Adventist Health Study; CNBS, Canadian National Breast Screening Study; IWHS, Iowa Women's Health Study; NHS (a), Nurses' Health Study (a); NHS (b), Nurses' Health Study (b); NLCS, Netherlands Cohort Study; NYSC, New York State Cohort; NYU, New York University Women's Health Study; SMC, Sweden Mammography Cohort. <sup>3</sup>Animal fat and vegetable fat intake data were not available for the Sweden Mammography Cohort.

fat intake ( $n = 50$  cases). All other combinations were grouped together. The relative risks were 1.06 (95% CI 0.68-1.65) for the highest quartile of saturated fat intake and lowest quartile of monounsaturated fat intake and 1.06 (95% CI 0.77-1.45) for all remaining combinations. The corresponding relative risks were 1.05 (95% CI 0.91-1.21) for the highest quartile of saturated fat intake and lowest quartile of polyunsaturated fat intake ( $n = 520$  cases) vs. the lowest quartile of saturated fat intake and highest quartile of polyunsaturated fat intake ( $n = 413$  cases) and 1.21 (95% CI 0.94-1.56) for the highest quartile of monounsaturated fat intake and lowest quartile of polyunsaturated fat intake ( $n = 175$  cases) vs. the lowest quartile of monounsaturated fat intake and highest quartile of polyunsaturated fat intake ( $n = 162$  cases).

#### Animal and vegetable fat: multivariate nutrient density models

Similar analyses were conducted that included calories and the percent of energy from animal fat, vegetable fat, alcohol and protein intakes. Breast cancer risk was not associated with either animal fat or vegetable fat consumption in the continuous (Table III) or quartile (Table IV) analyses.

#### Effect modification

Menopausal status at follow-up did not modify the association between each type of fat and breast cancer risk (Table V). Similar associations were observed for each type of fat for postmenopausal breast cancer diagnosed prior to age 62 compared with cancers diagnosed at 62 years and older (data not shown). In addition, for each type of fat, no significant interactions were observed for family history of breast cancer (categorized as yes, no), age at menarche ( $< 12, 12, 13, 14, \geq 15$  years), oral contraceptive use (never user, ever user), history of benign breast disease (yes, no), body mass index ( $< 21, 21-23, 23-25, 25-29, \geq 29$  kg/m<sup>2</sup>), height ( $< 1.60, 1.60-1.65, 1.65-1.70, 1.70-1.75, \geq 1.75$  m), smoking (never, ever) and education ( $< \text{high school, high school, } > \text{high school}$ ). Out of the 70 possible interaction analyses conducted, 6 interactions were statistically significant (Table VI), which could be the result of chance, as none of these was hypothesized *a priori*.

## DISCUSSION

Recently, there has been interest in evaluating whether intakes of specific types of fat are associated with the risk of breast cancer and other diseases independently of the intakes of other types of fat. Our analyses suggest that substituting saturated fat for carbohydrate intake may modestly increase breast cancer risk (RR = 1.09 for an increment of 5% of energy from saturated fat, 95% CI 1.00-1.19). When saturated fat was modeled as quartiles, rather than as a continuous variable, no association was apparent. However, residual confounding by the other types of fat and loss of power may be problematic in the quartile analyses. Increasing total fat, monounsaturated fat, polyunsaturated fat, animal fat or vegetable fat intakes relative to an equivalent reduction in the amount of energy from carbohydrates were not significantly associated with breast cancer risk.

The studies that have evaluated the association between intakes of specific types of fat and breast cancer risk after adjusting for the intakes of other types of fat have yielded inconsistent results.<sup>7,12,32-35</sup> In a 1989-1991 case-control study in Greece, no association was observed for saturated, monounsaturated and polyunsaturated fat intakes.<sup>34</sup> In contrast, a 1991-1994 Italian case-control study found a statistically significant positive association for saturated fat and a significantly inverse association for unsaturated fat consumption.<sup>33</sup> A case-control study conducted in Uruguay<sup>32</sup> observed a significant inverse association only for polyunsaturated fat consumption (OR = 0.38, 95% CI 0.20-0.74 for comparison of the highest vs. lowest quartile of intake); however, this result is difficult to interpret because it was adjusted for consumption of linoleic acid and linolenic acid (the main contributors to polyunsaturated fat consumption).<sup>36</sup>

**TABLE III – MUTUALLY ADJUSTED MULTIVARIATE RELATIVE RISKS<sup>1</sup> (95% CI) OF BREAST CANCER FOR 5% OF ENERGY INCREASES FROM SPECIFIC FAT SUBTYPES, CONTINUOUS MODEL**

Fat subtype	AHS <sup>2</sup>	CNBSS	IWHS	NHS (a)	NHS (b)	NLCS	NYSC	NYU	SMC	Pooled	<i>p</i> -value, test for heterogeneity
Saturated (also adjusted for mono-unsaturated and polyunsaturated fat)	1.66 (0.77–3.55)	1.24 (0.87–1.75)	1.19 (0.97–1.46)	0.88 (0.73–1.06)	1.04 (0.88–1.22)	1.25 (1.02–1.53)	0.84 (0.40–1.77)	1.04 (0.82–1.32)	1.13 (0.94–1.35)	1.09 (1.00–1.19)	0.25
Monounsaturated (also adjusted for saturated and polyunsaturated fat)	0.52 (0.15–1.77)	0.88 (0.55–1.41)	1.02 (0.80–1.30)	1.09 (0.91–1.31)	0.87 (0.71–1.06)	0.82 (0.65–1.02)	0.89 (0.44–1.81)	1.05 (0.75–1.45)	0.69 (0.47–1.01)	0.93 (0.84–1.03)	0.34
Polyunsaturated (also adjusted for saturated and monounsaturated fat)	1.67 (0.74–3.74)	1.50 (0.92–2.45)	1.02 (0.79–1.30)	0.97 (0.75–1.26)	1.04 (0.85–1.27)	1.02 (0.87–1.19)	1.39 (0.58–3.35)	1.02 (0.75–1.40)	1.58 (0.94–2.65)	1.05 (0.96–1.16)	0.58
Animal (also adjusted for vegetable fat)	1.10 (0.84–1.45)	1.10 (0.97–1.25)	1.10 (1.02–1.18)	0.99 (0.94–1.04)	0.96 (0.90–1.02)	1.02 (0.93–1.11)	0.88 (0.77–1.00)	1.01 (0.91–1.12)	N/A <sup>3</sup>	1.01 (0.96–1.06)	0.05
Vegetable (also adjusted for animal fat)	0.95 (0.77–1.18)	1.11 (0.94–1.31)	1.05 (0.97–1.14)	1.00 (0.93–1.08)	0.97 (0.91–1.03)	1.00 (0.91–1.11)	1.03 (0.95–1.11)	1.04 (0.93–1.16)	N/A <sup>3</sup>	1.01 (0.98–1.04)	0.71

<sup>1</sup>Relative risks also were adjusted for percent of energy from protein (continuous), percent of energy from alcohol (continuous), age at menarche ( $\leq 11$ , 12, 13, 14,  $\geq 15$  years), parity (0, 1–2,  $\geq 3$ ), age at birth of first child ( $\leq 20$ , 21–25, 26–30,  $> 30$  years), menopausal status at diagnosis (premenopausal, postmenopausal, uncertain), postmenopausal hormone use (ever, never), oral contraceptive use (ever, never), history of benign breast disease (no, yes), family history of breast cancer (no, yes), smoking status (ever, never), education ( $<$ high-school graduate, high-school graduate,  $>$ high-school graduate), body mass index (weight in kilograms divided by the square of the height in meters; continuous); body mass index-menopausal status at diagnosis interaction term, height ( $< 1.60$ ,  $1.60 - < 1.65$ ,  $1.65 - < 1.70$ ,  $1.70 - < 1.75$ ,  $\geq 1.75$  m), fiber intake (quintiles) and energy intake (continuous).<sup>2</sup>AHS, Adventist Health Study; CNBSS, Canadian National Breast Screening Study; IWHS, Iowa Women's Health Study; NHS (a), Nurses' Health Study (a); NHS (b), Nurses' Health Study (b); NLCS, Netherlands Cohort Study; NYSC, New York State Cohort; NYU, New York University Women's Health Study; SMC, Sweden Mammography Cohort.<sup>3</sup>Animal fat and vegetable fat intake data were not available for the Sweden Mammography Cohort.

**TABLE IV** – POOLED MUTUALLY ADJUSTED MULTIVARIATE<sup>1</sup> RELATIVE RISKS (95% CI) OF BREAST CANCER FOR QUARTILES OF INTAKES OF SPECIFIC FAT SUBTYPES

Fat subtype	Pooled RR (95% CI)				<i>p</i> -value, test for trend
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Mutually adjusted saturated, monounsaturated and polyunsaturated fat					
Saturated fat	1.00 (ref)	0.99 (0.91–1.08)	0.95 (0.87–1.04)	1.01 (0.89–1.16)	0.85
Monounsaturated fat	1.00 (ref)	1.03 (0.95–1.12)	1.04 (0.94–1.14)	0.97 (0.86–1.09)	0.78
Polyunsaturated fat	1.00 (ref)	1.04 (0.96–1.13)	1.05 (0.95–1.17)	1.04 (0.95–1.14)	0.53
Mutually adjusted animal and vegetable fat					
Animal fat	1.00 (ref)	0.98 (0.88–1.10)	0.93 (0.82–1.04)	0.96 (0.84–1.09)	0.34
Vegetable fat	1.00 (ref)	1.02 (0.93–1.12)	1.04 (0.95–1.13)	0.99 (0.90–1.08)	0.93

<sup>1</sup>Relative risks were adjusted for the covariates listed in Table III.

**TABLE V** – POOLED MULTIVARIATE RELATIVE RISKS (95% CI) OF BREAST CANCER FOR 5% OF ENERGY INCREASES FROM SPECIFIC FAT SUBTYPES BY MENOPAUSAL STATUS DURING FOLLOW-UP, CONTINUOUS MODEL

Fat subtype	Pooled RR <sup>1</sup> (95% CI)		<i>p</i> -value test for interaction
	Premenopausal	Postmenopausal	
Saturated fat <sup>2</sup>	1.10 (0.91–1.35)	1.07 (0.93–1.24)	0.61
Monounsaturated fat	0.87 (0.63–1.19)	0.81 (0.65–1.03)	0.46
Polyunsaturated fat	1.12 (0.88–1.41)	1.28 (0.96–1.69)	0.72
Animal fat <sup>3</sup>	1.01 (0.91–1.12)	0.99 (0.95–1.03)	0.93
Vegetable fat	1.03 (0.93–1.13)	0.99 (0.94–1.04)	0.54

<sup>1</sup>Relative risks were adjusted for the covariates listed in Table III. For both premenopausal and postmenopausal breast cancer, menopausal status and the body mass index menopausal status interaction terms are not included in the model. For premenopausal breast cancer, postmenopausal hormone use also is not included. The Iowa Women's Health Study, Netherlands Cohort Study and New York State Cohort enrolled postmenopausal women only and were not included in the interaction analyses.<sup>–2</sup>Estimates for saturated fat, monounsaturated fat and polyunsaturated fat intakes are mutually adjusted.<sup>–3</sup>Estimates for animal fat and vegetable fat intakes are mutually adjusted.

**TABLE VI** – POOLED MULTIVARIATE RELATIVE RISKS (95% CI) OF BREAST CANCER FOR 5% OF ENERGY INCREASES FROM SPECIFIC FAT SUBTYPES FOR STATISTICALLY SIGNIFICANT INTERACTIONS

Fat subtype	Effect modifier	Pooled RR <sup>1</sup> (95% CI) by categories of the effect modifier					<i>p</i> -value, test for interaction
Saturated <sup>2,4</sup>	Parity	0	1–2	≥3			
		1.00 (0.87–1.15)	1.05 (0.94–1.17)	1.16 (1.01–1.33)			0.04
Polyunsaturated <sup>2</sup>	Fiber (quintiles)	1	2	3	4	5	
		0.85 (0.69–1.04)	1.17 (0.92–1.49)	1.22 (1.03–1.45)	1.12 (0.94–1.33)	1.12 (0.95–1.33)	0.02
Polyunsaturated <sup>2,4,5,6</sup>	Hormone-replacement therapy use	Never	Past	Current			
		1.01 (0.89–1.15)	1.03 (0.80–1.34)	1.60 (1.25–2.06)			0.01
Animal <sup>3,6</sup>	Age at first birth (years)	≤20	>20–25	>25–30	>30		
		1.06 (0.98–1.15)	1.05 (0.97–1.14)	1.03 (0.95–1.12)	0.93 (0.86–1.00)		0.05
Vegetable <sup>3,4,6,7</sup>	Alcohol intake g/d	0	>0–<15	≥15			
		0.96 (0.92–1.01)	1.04 (0.97–1.11)	1.02 (0.95–1.10)			0.05
Vegetable <sup>3,4,5,6</sup>	Hormone-replacement therapy use	Never	Past	Current			
		0.99 (0.94–1.04)	0.99 (0.91–1.09)	1.15 (1.06–1.26)			0.002

<sup>1</sup>Relative risks were adjusted for the covariates listed in Table III.<sup>–2</sup>Estimates for saturated fat, monounsaturated fat and polyunsaturated fat intakes are mutually adjusted.<sup>–3</sup>Estimates for animal fat and vegetable fat intakes are mutually adjusted.<sup>–4</sup>The New York University Women's Health Study was not included in this analysis.<sup>–5</sup>The New York State Cohort was not included in this analysis.<sup>–6</sup>The Sweden Mammography Cohort was not included in this analysis.<sup>–7</sup>The Adventist Health Study was not included in this analysis.

Results also have differed among the 3 cohort studies that have reported mutually adjusted relative risks previously;<sup>7,12,35</sup> 2 of these studies are included in the present analysis. Monounsaturated fat, but not saturated fat or polyunsaturated fat, was significantly associated with breast cancer risk in the Breast Cancer Detection Demonstration Project Followup Cohort Study<sup>35</sup> (RR = 1.82, 95% CI 0.89–3.71; *p*-value, test for trend = 0.03). In the Sweden Mammography Cohort, breast cancer risk was not associated with saturated fat, was significantly inversely associated with monounsaturated fat and was significantly positively associated with polyunsaturated fat.<sup>12</sup> Weaker results were observed in our analyses of this study, which included an additional 3 years of follow-up, utilized a nested case-control design and controlled for different covariates. In the Nurses' Health Study,<sup>7</sup> there was no association

for saturated fat, monounsaturated fat or polyunsaturated fat consumption. In our analyses using a multivariate nutrient density model, the only statistically significant association observed for these 3 types of fat in the 6 additional studies comprising the Pooling Project was the positive association for saturated fat intake observed in the Netherlands Cohort Study.

A potential factor contributing to the discrepancies observed across the studies that have reported mutually adjusted risk estimates may be that there were differences in the macronutrients controlled for in the analyses, leading to differences in the interpretations of the risk estimates for each type of fat. However, even studies using the same analytic approach have yielded conflicting results. In the Nurses' Health Study, intakes of the individual types

of fat, protein, alcohol and energy were modeled together so that the coefficient of each type of fat is interpreted as the effect of substituting that particular fat for carbohydrate consumption.<sup>7</sup> Three studies<sup>12,32,35</sup> controlled for intakes of the individual types of fat, alcohol and energy; thus, the coefficient for a particular type of fat is interpreted as the effect of substituting that particular fat for the combined intakes of carbohydrates and protein. In contrast, in the Italian<sup>33</sup> and Greek<sup>34</sup> case-control studies, the coefficient for each type of fat is interpreted as the effect of increasing consumption of that fat, rather than substituting the fat for another macronutrient, because total energy intake was not controlled for in the analysis. Differences in dietary patterns among populations and, consequently, the correlations between the types of fat, also may lead to differential effects on the association observed between each type of fat and breast cancer risk if intakes of the other types of fat are not controlled for in the same manner.

Our pooled results differ from those of a recent meta-analysis of 88 sets of experiments in rats that investigated whether saturated fat, monounsaturated fat, n-3 polyunsaturated fat and n-6 polyunsaturated fat intakes had differential effects on mammary tumor incidence.<sup>37</sup> The model used in the meta-analysis of animal studies included terms for saturated fat, monounsaturated fat, n-3 polyunsaturated fat and n-6 polyunsaturated fat intakes and a variable describing the percent of energy restriction. Only the association for n-6 polyunsaturated fat was statistically significant (RR = 1.05 for an increment of 1% of energy, 95% CI 1.03–1.06). The effect for saturated fat (RR = 1.01, 95% CI 0.99–1.03) was significantly different compared with the effect for n-6 polyunsaturated fat ( $p = 0.001$ ), whereas the effects for monounsaturated fat (RR = 1.03, 95% CI 0.99–1.07) and n-6 polyunsaturated fat were not significantly different from each other ( $p = 0.375$ ). Generalizability of animal studies to humans is uncertain given the large doses of carcinogens used in the animal studies and the very high intakes of polyunsaturated fat compared with those in human populations. However, a methodological strength of animal experiments compared with epidemiologic studies is that diet can be more strictly controlled.

Ecologic studies of breast cancer incidence rates<sup>38,39</sup> have reported mutually adjusted risk estimates that are more dramatic for saturated fat than those reported in the meta-analysis of animal studies.<sup>37</sup> The main advantage of ecologic studies is the large variability in exposure information across countries; however, control of potential confounding factors is limited and latency effects may be problematic. In an ecologic study of 20 countries that used 1973–1977 breast cancer incidence data and 1975–1977 United Nations Food and Agriculture Organization Food Balance Sheets, significant positive associations with age-standardized breast cancer incidence rates were observed for both saturated fat (partial correlation coefficient = 0.58) and polyunsaturated fat intakes (partial correlation coefficient = 0.51).<sup>38</sup> Monounsaturated fat consumption was not associated with breast cancer incidence (partial correlation coefficient = -0.01). In an ecologic study of 21 countries that used more recent incidence data (1978–1982) and the same intake data, breast cancer risk was estimated to be significantly lower by 43% ( $p = 0.0004$ ) and 55% ( $p = 0.03$ ) for an approximate 50% reduction in the U.S. levels of saturated fat and polyunsaturated fat intakes, respectively.<sup>39</sup>

One of the advantages of the Pooling Project is the large sample size and, therefore, the enhanced statistical power to examine potential interactions with dietary factors. Previous studies have suggested that associations between total or saturated fat and breast cancer risk are modified by non-dietary breast cancer risk factors such as menopausal status<sup>40</sup> and history of benign breast

disease.<sup>35</sup> In our analyses, few significant interactions with non-dietary breast cancer risk factors, including menopausal status and benign breast disease, were observed for the specific fat subtypes and breast cancer risk. Only 6 of the 70 interactions tested were statistically significant; most of the significant associations are probably due to chance since none was hypothesized *a priori*.

In summary, the relationship between breast cancer risk and intakes of specific types of fat independent of intakes of other types of fat has been inconsistent across cohort, case-control, ecologic and animal studies. A problem common to cohort, case-control and ecologic studies is the strong correlation between the specific types of fat, which reduces the statistical power to disentangle the effect of each type of fat. This problem was demonstrated in our stratified analyses in which less than 2% of the cases were in the opposite extreme quartiles of saturated fat and monounsaturated fat intakes. In addition, as a result of including more than one type of fat in a model simultaneously, the coefficient for each type of fat was less precise compared with coefficients from models that included only one type of fat and other non-dietary breast cancer risk factors,<sup>27</sup> however, these analyses allow for estimation of the independent effect of each type of fat.

Another limitation is that fat consumption is measured with error in ecologic, case-control and cohort studies. In ecologic studies, food disappearance data typically are used to estimate consumption; these data tend to overestimate intake because they do not account for food preparation methods and waste. Case-control and cohort studies frequently measure dietary intake using food frequency questionnaires that have been shown to underestimate fat consumption. Techniques to correct for measurement error in estimates of dietary intake from food frequency questionnaires have been developed.<sup>19,30</sup> In our analyses in which each type of fat was analyzed separately, correcting for measurement error did not substantially change the results, although the confidence intervals became wider. In the multivariate nutrient density model analyses, we did not correct for measurement error because currently available measurement error-correction techniques require larger validation study subsamples than we had available when several strongly correlated variables are included in a model simultaneously. This collinearity among the types of fat could be reduced by examination of cohorts with high intakes of oils rich in monounsaturated fats, such as olive or canola oil.<sup>41</sup>

Our pooled analyses are suggestive of only a weak positive association for substituting saturated fat consumption for carbohydrate consumption; none of the other types of fat examined was associated with breast cancer risk relative to an equivalent reduction in carbohydrate consumption. However, substituting monounsaturated fat consumption for either saturated fat or polyunsaturated fat intakes was associated with a nonsignificantly lower breast cancer risk. These results, although nonsignificant, are compatible with the significant reductions in breast cancer risk that have been observed for higher intakes of olive oil, a rich source of monounsaturated fat, in studies conducted in Greece,<sup>42</sup> Italy<sup>43</sup> and Spain.<sup>44</sup>

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