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COHORT STUDIES OF FAT INTAKE AND THE RISK OF BREAST CANCER — A POOLED ANALYSIS

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Abstract Background. Experiments in animals, international correlation comparisons, and case-control studies support an association between dietary fat intake and the incidence of breast cancer. Most cohort studies do not corroborate the association, but they have been criticized for involving small numbers of cases, homogeneous fat intake, and measurement errors in estimates of fat intake.

Methods. We identified seven prospective studies in four countries that met specific criteria and analyzed the primary data in a standardized manner. Pooled estimates of the relation of fat intake to the risk of breast cancer were calculated, and data from study-specific validation studies were used to adjust the results for measurement error.

Results. Information about 4980 cases from studies including 337,819 women was available. When women in the highest quintile of energy-adjusted total fat intake were compared with women in the lowest quintile, the

multivariate pooled relative risk of breast cancer was 1.05 (95 percent confidence interval, 0.94 to 1.16). Relative risks for saturated, monounsaturated, and polyunsaturated fat and for cholesterol, considered individually, were also close to unity. There was little overall association between the percentage of energy intake from fat and the risk of breast cancer, even among women whose energy intake from fat was less than 20 percent. Correcting for error in the measurement of nutrient intake did not materially alter these findings.

Conclusions. We found no evidence of a positive association between total dietary fat intake and the risk of breast cancer. There was no reduction in risk even among women whose energy intake from fat was less than 20 percent of total energy intake. In the context of the Western lifestyle, lowering the total intake of fat in midlife is unlikely to reduce the risk of breast cancer substantially. (N Engl J Med 1996;334:356-61.)

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THE age-adjusted incidence of breast cancer varies more than fivefold internationally,¹ and among descendants of migrants from low-incidence to high-incidence countries, the incidence rates of breast cancer are close to those of the new country.^{2,3} These observations indicate that lifestyle, environment, or both contribute to the development of breast cancer. Diet may be a major factor in the international variation in the incidence of breast cancer.⁴

In experiments in animals conducted more than 50 years ago, diets high in fat increased susceptibility to mammary tumors in rodents.⁵ In the 1970s, a strong positive correlation was reported between estimates of

national per capita fat consumption and national incidence and mortality rates for breast cancer.⁴ However, the quality of the data on national per capita fat consumption has been questioned,⁶ and at least part of the apparent correlation is due to a higher prevalence of breast cancer risk factors related to reproductive history in countries with higher levels of fat consumption.⁷⁻⁹

In the largest case-control study of this relation (2024 cases), no appreciable difference in fat intake was observed between the case and control patients.¹⁰ In a combined analysis of the original data from 12 other case-control studies with a total of 4312 cases, Howe et al.¹¹ observed a significant positive association between total- and saturated-fat intake and the risk of breast cancer. However, case-control studies can be susceptible to recall and selection biases that can lead to spurious associations.^{12,13} In a prospective (cohort) study, diet is assessed in a clearly defined sample of subjects before the onset of disease in those who become case patients.

The results of several large cohort studies of fat intake and breast cancer have been variable.¹⁴ Possible reasons for this variation include chance, errors in assessing diet, the use of various ranges of fat intake, and differences in the statistical analyses. Some of these factors can be mitigated in a conventional meta-analysis of the published data, but overcoming most of them requires a standardized analysis of the pri-

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mary data. We therefore pooled the primary data from seven major cohort studies of dietary fat and breast cancer.

METHODS

We searched for prospective studies that met the following criteria: (1) the study initially included at least 200 incident cases of breast cancer, (2) diet was studied at base line with a comprehensive questionnaire that studied food and energy intake during the previous year, and (3) data were available from a validation study of the diet-assessment instrument. We identified seven prospective studies that met these criteria (Table 1).¹⁴⁻²⁰ Follow-up was conducted through questionnaires and the inspection of medical records,²¹ through tumor-registry linkage,^{14,18-20} or both^{16,22} and was estimated to be more than 90 percent complete in all cohorts. Diet was assessed by food-frequency questionnaires in all studies, and the results were validated by comparing them with multiple 24-hour-recall interviews^{23,24} or with diet records²⁵⁻²⁸ (and Ljung H, Wolk A: unpublished data). The Nurses' Health Study was the only study to repeat the dietary assessment after base line; to take advantage of this and to make its duration of follow-up similar to those of the other cohorts, we divided the follow-up of this study into two periods — 1980 to the month of return of the 1986 questionnaire (Nurses' Health Study (a)) and 1986 to 1991 (Nurses' Health Study (b)).

Exclusion Criteria

In addition to the subjects excluded by the criteria originally applied to the individual studies, we excluded those for whom the estimate of total energy intake was more than 3 SD from the log_e-transformed mean intake of the base-line population of each study. We also excluded the small percentage of subjects who had received diagnoses of cancer (other than nonmelanoma skin cancer) at base line, since their recent diets may have been influenced by the cancers or their treatment. Because of these exclusions, and because of additional follow-up in the Iowa Women's Health Study and the Nurses' Health Study (b), for most studies the size of the base-line cohort and the number of cases are slightly different in our analysis (Table 1) from those in the original published analyses.

Selection of Cases and Sampling of Risk Sets

To reduce the computational burden, we analyzed five cohorts (the Adventist Health Study, the Iowa Women's Health Study, the New York State Cohort, the Nurses' Health Study (a), the Nurses' Health Study (b), and the Sweden Mammography Cohort) as nested case-control studies (shown to be efficient and unbiased alternatives to full cohort analysis),²⁹ matching 10 controls to each case patient. Case patients were assigned to the calendar year of their diagnoses, and their follow-up ceased in that year. For each case patient, from the risk set of women with the same year of birth, 10 controls were selected who were alive, were not known to have migrated from the study area, and had not received diagnoses of breast cancer before the year in which the case patient's cancer was diagnosed. Controls were selected without replacement within each year but were eligible to be chosen again or to be reclassified as case patients in subsequent years. A similar design was used for the Canadian Breast Screening Study,¹⁶ but the investigators of that study se-

lected two controls matched to each case patient on the basis of age (± 2 months) and then processed previously administered dietary questionnaires for these case patients and controls to minimize costs. In the Netherlands Cohort Study,¹⁹ the case-cohort design was used³⁰; case patients were identified within the cohort, and their dietary and other exposures were compared with those of a subcohort of 1812 women randomly sampled at base line.

Models and Analyses

The basic method used for these analyses was the proportional-hazards model.³¹ For the six studies for which nested case-control sampling was used, a conditional logistic-regression analysis was used to fit this model, with the use of SAS PROC PHREG.³² For the Netherlands Cohort Study, the variance was modified as required for the case-cohort design with the use of Epicure software.³³ To estimate the rate ratio, or relative risk, we exponentiated the appropriate conditional logistic-regression coefficient multiplied by a nutritionally meaningful increment for continuous variables, or we used indicator variables for categorical analyses. Two-sided 95 percent confidence intervals are given throughout.

Adjustment for Energy Intake

To provide information on the effect of dietary composition, such as would be obtained in an "isocaloric" metabolic study, we adjusted nutrient intakes for total energy intake in several ways, including the residuals approach³⁴ (in which the log_e-transformed nutrient is regressed against the log_e-transformed energy intake; the residual represents the nutrient intake independent of the energy intake), the standard multivariate method,¹⁴ and the energy-partition method.³⁵ Since each of these methods of energy adjustment can be transformed to yield an identical relative risk for the nutrient of interest,³⁶ we present the results obtained by the residuals method (standardized to a median energy intake of 1600 kcal) in units chosen to represent an achievable change in intake. We also modeled the effect of total fat as its "nutrient density" — that is, the ratio of energy from total fat in-

Table 1. Cohort Studies Included in the Pooled Prospective Analysis of Dietary Fat and the Risk of Breast Cancer.

STUDY NAME	STUDY LOCATION	YEARS OF FOLLOW-UP	COHORT SIZE AT BASE LINE*	AGE RANGE AT BASE LINE	NO. OF CASES OF BREAST CANCER (NO. OF CASES OF CARCINOMA IN SITU)*
				yr	
Adventist Health Study	California	1976-1982	15,172	28-90	153 (6)
Canadian Breast Screening Study	Canada	1982-1987	56,837	40-59	514 (85)
Iowa Women's Health Study	Iowa	1986-1991	34,406	55-69	723 (70)
Netherlands Cohort Study	Netherlands	1986-1989	62,412	55-69	434 (0)†
New York State Cohort	New York	1980-1987	18,475	50-93	376 (9)
Nurses' Health Study (a)	United States	1980-1986	89,046	34-59	1094 (71)
Nurses' Health Study (b)	United States	1986-1991	68,817	40-65	911 (105)
Sweden Mammography Cohort	Sweden	1987-1993	61,471	40-76	775 (103)
All studies			337,819‡		4980 (449)

*Excluded were subjects with previous cancer (other than nonmelanoma skin cancer), those for whom dietary data were incomplete, or those with outlying values for energy intake (in the Canadian Breast Screening Study these exclusions were made for case patients and controls in the nested case-control study, and in the Netherlands Cohort Study exclusions were made for case patients and subcohort members). In the Adventist Health Study, at least one nutrient intake variable was missing for a high proportion of subjects, and because of these exclusions, there were fewer than 200 case patients in the cohort we analyzed.

†Cases of carcinoma in situ were excluded in the Netherlands Cohort Study.

‡The 68,817 women in the Nurses' Health Study (b) were members of the Nurses' Health Study (a) cohort in whom breast cancer or other cancer had not developed by the month of return of the 1986 questionnaire.

take to total energy intake — since this is the formulation often used to make dietary recommendations.

Study-Specific and Pooled Results

We analyzed the relation between the intake of each nutrient and the risk of breast cancer by treating the energy-adjusted nutrient intake (according to the residuals method) as a continuous variable and categorizing the energy-adjusted nutrient intake in quintiles (Table 2).^{*} Since the nutrient intakes used in the Adventist Health Study represent a ranking index rather than an estimate of absolute intake, data from that study were included in the categorical analyses only. We used the “random effects” method developed by DerSimonian and Laird to combine \log_e relative risks from multiple studies.³⁷

Correction of Measurement Error

Error in the measurement of dietary variables can distort relative risks and confidence intervals; error in prospective studies is usually nondifferential and attenuates estimates of effect toward the null. The studies included here had validation studies available from which the measurement error associated with the main cohort questionnaire could be estimated; this information was used to estimate the true relative risk and confidence intervals after the effect of measurement error was accounted for.^{38,39} Although the measurements regarded as the gold standard or “truth” in these analyses were themselves measured with error, the procedures used to correct measurement error are valid, provided the error in the gold standard was unbiased and uncorrelated with the error in the data from the main cohort questionnaire.⁴⁰ To the extent that the gold standards used in each study-specific validation study are comparable, measurement-error correction will calibrate the studies.⁴¹ We adjusted simultaneously for error in the measurement of each nutrient and that of the total intake of energy.

RESULTS

Within-study differences in mean and median nutrient intake between case patients and controls were very small.* In no study was the difference in median intake between case patients and controls more than 1 g per day for energy-adjusted total, saturated, monounsaturated, or polyunsaturated fat. The median cholesterol intake was slightly higher among case patients in the Adventist Health Study, the Iowa Women's Health Study, the Nurses' Health Study (b), and the Sweden Mammography Cohort but lower among those in the Canadian Breast Screening Study and the New York State Cohort; again, these differences were small.

Overall Relative Risks

In Table 2 we show the pooled quintile-specific relative risks of breast cancer as compared with the lowest quintile. None of the results of the tests for trend among

Table 2. Pooled Relative Risks of Breast Cancer and 95 Percent Confidence Intervals for Quintiles of Energy-Adjusted Nutrient Intake in the Pooled Analysis of Cohort Studies.*

NUTRIENT	QUINTILE 1†	QUINTILE 2	QUINTILE 3	QUINTILE 4	QUINTILE 5	P VALUE FOR TREND
Total fat	1.00	1.01 (0.89–1.14)	1.12 (1.01–1.25)	1.07 (0.96–1.19)	1.05 (0.94–1.16)	0.21
Saturated fat	1.00	1.03 (0.93–1.14)	1.04 (0.94–1.14)	1.00 (0.90–1.11)	1.07 (0.95–1.20)	0.41
Monounsaturated fat	1.00	1.07 (0.97–1.18)	1.11 (1.01–1.23)	1.10 (0.99–1.22)	1.01 (0.88–1.16)	0.73
Polyunsaturated fat	1.00	1.07 (0.97–1.18)	1.03 (0.94–1.14)	1.06 (0.96–1.16)	1.07 (0.97–1.17)	0.32
Animal fat	1.00	0.96 (0.85–1.09)	0.96 (0.81–1.13)	0.92 (0.78–1.09)	0.99 (0.87–1.13)	0.70
Vegetable fat	1.00	1.01 (0.87–1.17)	1.01 (0.90–1.14)	1.01 (0.91–1.13)	1.00 (0.88–1.13)	1.00
Cholesterol	1.00	1.04 (0.94–1.15)	1.02 (0.89–1.16)	1.05 (0.93–1.18)	1.08 (0.97–1.21)	0.19
Energy	1.00	1.01 (0.91–1.12)	1.13 (1.02–1.25)	1.04 (0.92–1.17)	1.11 (0.99–1.25)	0.15

*Relative risks are adjusted for the following variables: age at menarche (≤ 11 , 12, 13, 14, or ≥ 15 years), menopausal status (premenopausal, postmenopausal), parity (0, 1 to 2, ≥ 3), age at birth of first child (≤ 20 , 21 to 25, 26 to 30, ≥ 31 years), body-mass index (the weight in kilograms divided by the square of the height in meters) (≤ 21 , >21 to ≤ 23 , >23 to ≤ 25 , >25 to ≤ 29 , >29), height (<1.60 , 1.60 to <1.64 , 1.64 to <1.68 , ≥ 1.68 m), education ($<$ high-school graduation, high-school graduation, $>$ high-school graduation), history of benign breast disease (no, yes), maternal history of breast cancer (no, yes), history of breast cancer in a sister (no, yes), oral contraceptive use ever (no, yes), fiber intake (quintiles), alcohol intake (0, >0 to <1.5 , 1.5 to <5 , 5 to <15 , 15 to <30 , ≥ 30 g per day), and energy intake (on a continuous scale).

†Quintile 1 values are the reference values.

quintiles approached statistical significance, and proportional-hazards assumptions were satisfied. For comparisons of values in the highest and the lowest quintiles, the results of the test for heterogeneity among studies did not indicate a significant difference for any nutrient, suggesting that the pooled relative risks are an appropriate summary of the data. For energy intake, the only study with a significant positive association was the Sweden Mammography Cohort; however, the pooled relative risk was not statistically significant (relative risk, 1.11; 95 percent confidence interval, 0.99 to 1.25). For energy-adjusted total fat, women in the highest quintile in the Iowa Women's Health Study were at significantly higher risk than those in the lowest quintile (relative risk, 1.34; 95 percent confidence interval, 1.02 to 1.76). Similar significant positive associations for saturated and monounsaturated fat in the Iowa Women's Health Study were not reflected in the other studies or in the pooled relative risks. The quintile-specific pooled estimates for other nutrients did not suggest departures from linearity in the overall absence of association (Table 2).

In Table 3, we present relative risks derived by treating each nutrient as a continuous variable (the Adventist Health Study is excluded from these analyses, as previously stated). None of the tests for heterogeneity indicated statistical significance. Significant positive associations were observed for energy-adjusted total and saturated fat in the Iowa Women's Health Study, whereas the pooled relative risks were close to unity. The only pooled relative risk that was marginally significant was for cholesterol (relative risk for each 100-mg increase in cholesterol intake, 1.04; 95 percent confidence interval, 1.00 to 1.07).

Comparisons of the extreme deciles of the energy-

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adjusted estimates of intake of each nutrient yielded similar results. The multivariate-adjusted pooled relative risks comparing the top with the bottom decile were the following: for energy, 0.96 (95 percent confidence interval, 0.79 to 1.16); for total fat, 1.01 (0.82 to 1.25); for saturated fat, 1.11 (0.95 to 1.29); for monounsaturated fat, 0.96 (0.79 to 1.17); for polyunsaturated fat, 1.06 (0.92 to 1.21); for animal fat, 1.06 (0.90 to 1.25); for vegetable fat, 1.14 (0.93 to 1.38); and for cholesterol, 1.15 (1.00 to 1.32).

To examine further the risk of breast cancer at the lowest fat intakes, we calculated the percentage of energy from fat and compared 5 percent increments of this scale, using the level representing 30 to less than 35 percent of energy from fat as the reference category (Fig. 1). Above the reference category we saw little evidence of an increase in risk, and below it little evidence of a decrease in risk. In the lowest category (<20 percent of calories from fat), the pooled relative risk was 1.06 (95 percent confidence interval, 0.83 to 1.37). For women reporting less than 15 percent energy from fat, relative risks were above 1.5 in all four of the studies that contributed data (the New York State Cohort, the Nurses' Health Study (a), the Nurses' Health Study (b), and the Sweden Mammography Cohort); the pooled relative risk was 2.12 (95 percent confidence interval, 1.34 to 3.36), on the basis of 26 case patients and 134 controls with levels of energy from fat below 15 percent.

Separate results for postmenopausal women (3465 case patients), in whom an association between breast cancer and dietary fat intake has been hypothesized to be strongest, were similar to those for the entire population; the pooled estimate of the energy-adjusted relative risk for a change of 25 g in total fat intake was 1.01 (95 percent confidence interval, 0.91 to 1.12). The results for premenopausal women were similar, as were the results when case patients receiving diagnoses in

the first year of follow-up were excluded. Excluding 480 case patients with carcinoma in situ or an unknown degree of invasion had little influence on the results.

Influence of Measurement Error

Correlation coefficients between total fat intake estimated on the basis of the food-frequency questionnaires and that estimated by the reference methods (diet records or multiple 24-hour-recall interviews) were 0.34 in the Adventist Health Study, 0.45 in the Canadian Breast Screening Study, 0.54 in the Iowa Women's Health Study, 0.48 in the Netherlands Cohort Study, 0.40 in the New York State Cohort, 0.52 in the Nurses' Health Study (a), 0.51 in the Nurses' Health Study (b), and 0.49 in the Sweden Mammography Cohort.

Pooled relative risks corrected for measurement error were 1.07 for total fat (per 25 g; 95 percent confidence interval, 0.86 to 1.34), 1.08 for saturated fat (per 10 g; 0.93 to 1.26), 1.01 for monounsaturated fat (per 10 g; 0.80 to 1.28), 1.05 for polyunsaturated fat (per 10 g; 0.83 to 1.34), and 1.07 for cholesterol (per 100 mg; 1.01 to 1.14).

DISCUSSION

Epidemiologic evidence of an association between dietary fat and breast cancer has been contradictory. Ecologic studies,^{4,42,43} a pooled analysis of some case-control studies,¹¹ and a meta-analysis of case-control studies⁴⁴ have suggested a positive association, whereas the results of cohort studies have tended to be null or only weakly positive. The deficiencies of dietary analyses in ecologic and case-control studies have been reviewed,⁸ and the prospective data have been criticized as misleading because of the lack of statistical power of individual studies, the limited range of fat intake in the populations studied, and the misclassification of fat intake, which tends to attenuate associations.^{45,46} To ad-

Table 3. Relative Risks and 95 Percent Confidence Intervals for Continuous Estimates of Energy-Adjusted Nutrient Intake in the Pooled Analysis of Cohort Studies.*

NUTRIENT (DAILY INCREMENT)	CBSS	IWHS	NLCS	NYSC	NHSa	NHSb	SMC	POOLED RELATIVE RISK	P VALUE FOR HETEROGENEITY
Total fat (per 25 g)	1.21 (0.89-1.65)	1.28 (1.03-1.59)	0.90 (0.67-1.22)	1.04 (0.88-1.22)	0.97 (0.86-1.10)	0.93 (0.77-1.12)	0.98 (0.78-1.22)	1.02 (0.94-1.11)	0.24
Saturated fat (per 10 g)	1.07 (0.85-1.35)	1.26 (1.04-1.53)	1.08 (0.87-1.35)	0.90 (0.69-1.19)	0.95 (0.85-1.07)	0.99 (0.84-1.17)	1.02 (0.87-1.19)	1.03 (0.95-1.11)	0.27
Monounsaturated fat (per 10 g)	1.14 (0.85-1.53)	1.21 (0.99-1.48)	0.77 (0.60-1.01)	1.03 (0.92-1.16)	0.98 (0.89-1.09)	0.89 (0.75-1.06)	0.91 (0.73-1.14)	0.99 (0.90-1.08)	0.10
Polyunsaturated fat (per 10 g)	1.38 (0.95-2.01)	1.10 (0.84-1.45)	0.94 (0.77-1.14)	1.09 (0.93-1.26)	1.01 (0.81-1.27)	0.93 (0.73-1.18)	0.98 (0.69-1.38)	1.03 (0.95-1.12)	0.57
Animal fat (per 10 g)	1.01 (0.91-1.12)	1.06 (0.98-1.16)	1.00 (0.92-1.09)	0.91 (0.83-1.00)	0.99 (0.94-1.03)	1.03 (0.95-1.12)	NA	1.00 (0.96-1.03)	0.27
Vegetable fat (per 10 g)	1.08 (0.95-1.23)	1.05 (0.95-1.15)	0.98 (0.89-1.07)	1.04 (0.99-1.09)	1.01 (0.94-1.08)	0.93 (0.85-1.01)	NA	1.01 (0.97-1.05)	0.22
Cholesterol (per 100 mg)	0.97 (0.84-1.11)	1.08 (0.99-1.17)	1.03 (0.84-1.26)	1.02 (0.95-1.10)	1.00 (0.95-1.06)	1.12 (1.03-1.23)	1.06 (0.93-1.21)	1.04 (1.00-1.07)	0.35
Energy (per 100 kcal)	1.00 (0.98-1.03)	1.00 (0.98-1.02)	1.01 (0.97-1.05)	0.98 (0.93-1.03)	1.00 (0.98-1.01)	1.00 (0.99-1.02)	1.05 (1.02-1.07)	1.01 (0.99-1.02)	0.08

*Relative risks are adjusted for the variables given in the first footnote to Table 2. CBSS denotes Canadian Breast Screening Study, IWHS Iowa Women's Health Study, NLCS Netherlands Cohort Study, NYSC New York State Cohort, NHSa Nurses' Health Study from 1980 to 1986, NHSb Nurses' Health Study from 1986 to 1991, SMC Sweden Mammography Cohort, and NA not available.

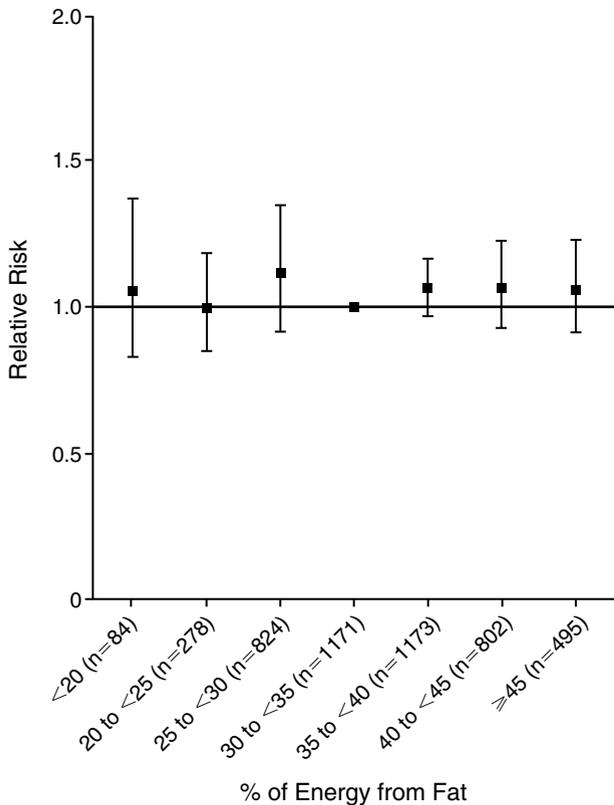


Figure 1. Pooled Relative Risks and 95 Percent Confidence Intervals for Various Levels of Energy from Fat.

Relative risks are adjusted for the variables listed in the first footnote to Table 2. A level of 30 to less than 35 percent of total energy from fat was designated as the reference category. N denotes the number of cases in each category.

dress these problems, we pooled the available prospective data to increase the statistical power, examined effects between the extremes of intake in the various studies, and incorporated information on the validity of each diet-assessment method to account for measurement error. These prospective data are not susceptible to the recall and selection biases that may arise in conventional case-control studies.²⁹

We observed no positive association between total dietary fat intake and the incidence of breast cancer among seven independent populations from four countries. These seven studies involved almost 5000 incident cases among more than 335,000 women with prospectively collected dietary information and follow-up periods of up to seven years. Before and after adjustment for known risk factors for breast cancer, these data suggested that the risk among women with high fat intake is the same as the risk among those with low fat intake. This conclusion holds whether we consider total, saturated, monounsaturated, or polyunsaturated fat or animal or vegetable fat. The method of adjustment for energy intake had relatively little effect on these results. Analyses that were limited to postmenopausal women and that excluded women whose disease was diagnosed in the first year of follow-up yielded

equivalent results. We included cases of carcinoma in situ, since there is little evidence that nutritional risk factors for these early lesions are different from those for invasive disease; excluding the 9 percent of case patients who had carcinoma in situ did not materially alter the results. The results of other prospective studies with too few cases to meet the criteria for this pooled analysis⁴⁷⁻⁵⁰ are compatible with these results.

To assess the risk of breast cancer associated with fat intakes that are very low by Western standards, we used the large sample made available by pooling multiple studies and saw no evidence of lower risk with a fat intake of less than 20 percent of calories from fat. In most individual studies, even the lowest deciles of fat intake correspond to about 25 to 30 percent of calories from fat, a level still above the targeted group average of 20 percent of energy from fat for the intervention group in the Women's Health Initiative clinical trial,⁵¹ and substantially above the 15 percent of energy from fat consumed by some women in Asian countries with low breast cancer rates. A recent case-control study conducted in two populations in China, with 834 case patients and controls whose diets supplied an interquartile range of 15 to 35 percent of energy from fat, did not show a significant relation between dietary-fat intake and the risk of breast cancer.⁵² These data provide no support for the hypothesis that a very low fat intake protects against breast cancer.

Nondifferential error in measuring fat intake in epidemiologic studies could obscure an association with breast cancer risk.^{42,46} However, we corrected relative-risk estimates for measurement error using data from study-specific validation studies; the uncorrected relative risks were still close to unity for total fat and subtypes of fat. More important, even when the 95 percent confidence intervals were expanded to account for measurement error, they remained narrow and excluded substantial positive associations.

It has been suggested that it is the type of fat, rather than the total amount of fat, that is relevant; specifically, monounsaturated fats may be inversely associated with the risk of breast cancer after other types of fat are accounted for.⁵³ Distinguishing the associations of various types of fat with the risk of breast cancer is difficult because of multicollinearity among the types of fat; we are currently investigating this issue and other aspects of diet that may influence the risk of breast cancer.

In the analyses treating nutrients as continuous variables, we did observe a small increase in the pooled estimate among women consuming more dietary cholesterol; the only study in which this was independently significant was the Nurses' Health Study (b). Several large prospective studies^{54,55} have observed no relation between serum cholesterol and the incidence of breast cancer, suggesting that the weak positive association that we observed may be due to chance.

The possibility that aspects of diet during childhood or adolescence, including energy intake and total fat intake, may be associated with the risk of breast cancer decades later cannot be ruled out on the basis of the re-

sults of prospective studies of adult women. Nonetheless, it appears unlikely that a reduction in total fat consumption by middle-aged and older women will substantially reduce their risk of breast cancer.

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