Association of Dietary Intake of Fat and Fatty Acids With Risk of Breast Cancer

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Context High intakes of fat and specific fatty acids, including total, animal, saturated, polyunsaturated, and *trans*-unsaturated fats, have been postulated to increase breast cancer risk.

Objective To determine whether intakes of fat and fatty acids are associated with breast cancer.

Design and Setting Cohort study (Nurses' Health Study) conducted in the United States beginning in 1976.

Participants A total of 88 795 women free of cancer in 1980 and followed up for 14 years.

Main Outcome Measure Relative risk (RR) of invasive breast cancer for an incremental increase of fat intake, ascertained by food frequency questionnaire in 1980, 1984, 1986, and 1990.

Results A total of 2956 women were diagnosed as having breast cancer. Compared with women obtaining 30.1% to 35% of energy from fat, women consuming 20% or less had a multivariate RR of breast cancer of 1.15 (95% confidence interval [CI], 0.73-1.80). In multivariate models, the RR (95% CI) for a 5%-of-energy increase was 0.97 (0.94-1.00) for total fat, 0.98 (0.96-1.01) for animal fat, 0.97 (0.93-1.02) for vegetable fat, 0.94 (0.88-1.01) for saturated fat, 0.91 (0.79-1.04) for polyunsaturated fat, and 0.94 (0.88-1.00) for monounsaturated fat. For a 1% increase in energy from *trans*-unsaturated fat, the values were 0.92 (0.86-0.98), and for a 0.1% increase in energy from omega-3 fat from fish, the values were 1.09 (1.03-1.16). In a model including fat, protein, and energy, the RR for a 5% increase in total fat, which can be interpreted as the risk of substituting this amount of fat for an equal amount of energy from carbohydrate, was 0.96 (95% CI, 0.93-0.99). In similar models, no significant association of risk was evident with any major types of fat.

Conclusion We found no evidence that lower intake of total fat or specific major types of fat was associated with a decreased risk of breast cancer.

JAMA. 1999;281:914-920 www.jama.com

High intake of total dietary fat has been postulated to increase breast cancer risk on the basis of animal studies,[1,2] international comparisons,[2-4] and a meta-analysis of case-control studies.[5] However, the meta-analysis has been criticized for ignoring heterogeneity among studies.[6] In addition, the dietary fat hypothesis has not been supported by cohort studies, which are less prone to bias than case-control studies.[7-9] In a pooled analysis of 7 international cohorts with nearly 5000 cases, the multivariate relative risk (RR) for the highest compared with the lowest quintile of total fat intake was 1.05 (95% confidence interval [CI], 0.94-1.16).[9] Some authors have suggested that fat intake be 20% or less of total energy intake for a protective effect to be evident and have maintained that such a protective effect has not been found in cohort studies because they were conducted in Western populations in whom the level of fat intake is rarely this low.[2]

Another possible explanation for the conflicting results of prospective and retrospective studies of diet and breast cancer is that the intake of specific fatty acids, rather than that of total fat, may influence breast cancer risk. In animal studies, certain fatty acids have modulated mammary tumor growth and metastasis; evidence is strongest for a promotional effect of polyunsaturated fat[1,10-15] and an inhibitory effect of omega-3 fat from marine sources.[11,16-20] These observations are supported by human ecological studies.[2,21-24]

Other epidemiologic studies have been limited in duration and have used information about dietary intake from only 1 point in time; thus, these investigations have not taken into account changes in diet over time. A few case-control studies have used adipose tissue levels of specific fatty acids as a marker of long-term intake. However, adipose tissue does not provide an assessment of total fat intake or intake of fatty acids that can

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be endogenously synthesized. Also, because results are expressed as the percentage of total fatty acids, an increase in 1 type of fat necessarily means a decrease in another, making interpretation difficult.

In this analysis we followed up 88 795 women for 14 years, extending our previous analysis[7] by 6 years and more than 1500 cases. This extended study is now large enough and long enough to assess the effect of very low fat intake (≤20% of energy) even though intake this low was still not common. We also examined type of fat consumed and the risk of breast cancer in detail, and we used dietary intake assessed at 4 different points to calculate a cumulative average intake that best represented long-term intake.

METHODS

The Nurses' Health Study Cohort

In 1976, the Nurses' Health Study (NHS) cohort was established when 121 700 female registered nurses from across the United States, aged 30 to 55 years, answered a mailed questionnaire on risk factors for cancer and cardiovascular disease. Every 2 years since, we have sent follow-up questionnaires to NHS participants. In 1980, a 61-item food-frequency questionnaire designed to assess dietary intake was added. In 1984, 1986, and 1990, an expanded food-frequency questionnaire was used. This analysis is based on the 88 795 women who answered the 1980 diet questionnaire, who did not have implausible scores for total energy intake (<2092 kJ [500 kcal] or >14 644 kJ [3500 kcal] per day, approximately 2% of returned diet questionnaires), and who did not have diagnosed cancer (other than nonmelanoma skin cancer, 3101 cases excluded) prior to 1980.

Semiquantitative Food-Frequency Questionnaires

The food-frequency questionnaires have been described in detail, and their validity and reproducibility have been documented elsewhere.[25,26] A commonly used portion size was specified for each food (for example, 1 slice of bread or 1 egg). Participants were asked to average how frequently over the past year they had consumed that portion of food. The 9 prespecified responses ranged from "never" to "6 or more times per day." We also asked about the types of fat used for cooking and at the table.

We multiplied the frequency of consumption of each food by the nutrient content of the portion size, taking into account cooking fat, to obtain nutrient intakes. Nutrient values in foods were obtained from US Department of Agriculture sources.[27] We included all *trans* isomers of 18-carbon unsaturated fatty acids in the calculation of total *trans*; values for the *trans* content of food came primarily from analyses by Enig et al[28] and Slover et al.[29] Omega-3 fatty acid intake from fish represented the summation of eicosapentaenoic and docosahexaenoic acids. Correlations between intakes from the questionnaire used in 1986 and onward and intakes from repeated weighed diet records were 0.67 for total fat, 0.70 for saturated fat, 0.64 for polyunsaturated fat, and 0.69 for monounsaturated fat.[26]

Identification of Breast Cancer Cases

In each biennial questionnaire, participants were asked whether they had been diagnosed as having breast cancer in the previous 2 years. Deaths were identified by a report from a family member, the postal service, or the National Death Index; the ascertainment is 98% complete. Follow-up of the entire cohort through 1994 is 95% complete. Medical records were obtained for breast cancer cases identified by either self-report or vital records, and more than 99% of these records confirmed the self-report. Cases of carcinoma in situ were excluded.

Statistical Analysis

Each participant accumulated person-time beginning with the return of the 1980 questionnaire and ending with her cancer diagnosis, death, or June 1, 1994, whichever came first. In secondary analyses, we began follow-up at the time of return of the 1984 or 1988 questionnaire. Fat intake from each dietary questionnaire was classified as a percentage of total energy intake, and total energy intake was included in each regression model. We used pooled logistic regression using 2-year time intervals with RR as the measure of association.[30] To take into account dietary changes over time, we calculated the cumulative average intake of fat from all available dietary questionnaires up to the start of each 2-year interval. In this calculation, the 1980 diet was related to breast cancer incidence between 1980 and 1984; the average of the 1980 and 1984 diets was related to breast cancer incidence between 1984 and 1986; the average of the 1980, 1984, and 1986 diets was related to breast cancer incidence between 1986 and 1990; and the average of all 4 diets was related to breast cancer incidence between 1990 and 1994. In alternative analyses, only the 1980 baseline diet was related to breast cancer incidence. In "substitution" models, fat intake was simultaneously included as a nutrient density with total energy intake and protein intake as explanatory variables.[26] In these models, the coefficient for fat can be interpreted as substitution of a percentage of energy from fat for an equal percentage of energy from carbohydrates. Intake of dietary factors other than fat, such as total energy, carbohydrates, protein, alcohol, vitamin A, vitamin E, and total fiber, was calculated in the same manner as fat intake.

The following nondietary covariates were updated every 2 years: age, history of benign breast disease, menopausal status, age at menopause, use and duration of use of postmenopausal hormones, parity, age at first birth, and weight change since the age of 18 years. Age at menarche, height, and body mass index (weight in kilograms divided by the square of height in meters) at the age of 18 years were determined at baseline, and information on family history of breast cancer was sought in 1976, 1982, 1988, and 1992. Women of uncertain ovulatory status (mainly those who had undergone hysterectomy but had intact ovaries) were excluded from analyses including stratification by menopausal status. In tests for linear trend across categories of percentage of energy from fat, ordinal rank was assigned to each category.

Table 1. Multivariate Relative Risk of Breast Cancer Incidence Among 88 795 Women Between 1980 and 1994, According to Percentage of Energy Obtained From Fat in the Cumulatively Averaged Diet Reported for 1980, 1984, 1986, and 1990*

Energy From Fat, %	No. of Cases/ Person-Years	RR (95% CI)	No. of Premenopausal Cases/Person-Years	RR (95% CI)	No. of Postmenopausal Cases/Person-Years	RR (95% CI)
≤20	20/6539	1.15 (0.73-1.80)	4/1808	1.26 (0.46-3.42)	14/4136	1.09 (0.64-1.86)
20.1-25	81/29 836	0.96 (0.76-1.21)	11/7427	0.81 (0.44-1.49)	64/19 680	1.00 (0.77-1.30)
25.1-30	388/123 617	1.09 (0.97-1.23)	74/33 337	1.16 (0.89-1.53)	283/79 857	1.06 (0.92-1.22)
30.1-35	842/305 715	1.00 (Referent)	187/98 461	1.00 (Referent)	588/180 059	1.00 (Referent)
35.1-40	900/358 281	0.97 (0.88-1.07)	234/137 034	0.91 (0.75-1.11)	582/187 006	0.99 (0.88-1.11)
40.1-45	478/216 859	0.93 (0.83-1.05)	165/95 584	0.99 (0.80-1.23)	266/98 264	0.91 (0.78-1.06)
45.1-50	169/91 341	0.86 (0.73-1.03)	76/44 492	1.03 (0.78-1.37)	77/36 118	0.78 (0.61-1.00)
>50	78/39 839	0.96 (0.76-1.23)	33/19 470	1.03 (0.70-1.51)	39/15 209	1.01 (0.72-1.41)
Total	2956/1 172 028	. . .	784/437 613	. . .	1913/620 329	. . .
P value, trend		.03		.77		.06

*Values were adjusted for energy, age, energy-adjusted vitamin A, alcohol intake, time period, height, parity, age at first birth, weight change since age 18 years, body mass index at age 18 years, age at menopause, menopausal status and use of hormone replacement therapy, family history, benign breast disease, and age at menarche. Energy intake from alcohol was included in total energy. Women of uncertain menopausal status were included among all cases but not with premenopausal or postmenopausal cases. RR indicates relative risk; CI, confidence interval.

RESULTS

We identified 2956 incident cases of invasive breast cancer among 88 795 women during 1 172 028 person-years of follow-up between 1980 and 1994. Average intake of total fat as a percentage of energy intake was 39% in 1980, 36% in 1984, 33% in 1986, and 31% in 1990. Correlations between intakes of particular types of fat, averaged over the entire period studied, were 0.08 for saturated fat and polyunsaturated fat; 0.81 for saturated fat and monounsaturated fat; and 0.41 for polyunsaturated fat and monounsaturated fat.

TABLE 1 shows the multivariate RR and 95% confidence interval (CI) of breast cancer incidence according to the percentage of energy obtained from total fat, cumulatively averaged from 1980 through 1994. With 30.1% to 35% of energy from fat as the reference category, women consuming 20% or less of total energy as fat had a slightly increased risk of breast cancer (RR, 1.15; 95% CI, 0.73-1.80), and the overall linear trend for higher risk with lower fat intake was statistically significant ($P = .03$). Results were similar for both premenopausal and postmenopausal women.

In Tables 2 through 5, fat intakes are expressed as continuous variables. Intervals of intake for total fat and each type of fat were chosen to represent approximately the interquartile range of intake.

TABLE 2 shows the multivariate RR of breast cancer associated with intake of total energy and of various types of fat, cumulatively averaged for 1980 through 1994 and stratified by menopausal status at diagnosis. In the whole cohort and in both the premenopausal and postmenopausal groups there was no association of breast cancer incidence with intakes of energy, total fat, animal fat, vegetable fat, polyunsaturated fat, saturated fat, or cholesterol. Slight inverse associations were seen for monounsaturated fat among postmenopausal women only and for *trans*-unsaturated fat in the whole cohort and among postmenopausal women. A slight positive association was seen in the whole cohort and among postmenopausal women for omega-3 fats from fish.

Table 2. Multivariate Relative Risk of Breast Cancer in 88 795 Women Between 1980 and 1994, According to Cumulatively Averaged Intake of Energy, Total Fat, and Fat Subtypes in the 1980, 1984, 1986, and 1990 Diets*

Nutrient Increment per Day	Total Cases, RR (95% CI)	Premenopausal Cases, RR (95% CI)	Postmenopausal Cases, RR (95% CI)
Energy (100 kcal†)	0.99 (0.98-1.00)	0.99 (0.98-1.01)	0.99 (0.98-1.00)
Total fat (5% of energy)	0.97 (0.94-1.00)	0.99 (0.93-1.05)	0.96 (0.93-1.00)
Animal fat (5% of energy)	0.98 (0.96-1.01)	1.01 (0.96-1.06)	0.98 (0.94-1.02)
Vegetable fat (5% of energy)	0.97 (0.93-1.02)	0.99 (0.91-1.07)	0.96 (0.91-1.02)
Polyunsaturated fat (5% of energy)	0.91 (0.79-1.04)	0.99 (0.77-1.27)	0.88 (0.74-1.04)
Saturated fat (5% of energy)	0.94 (0.88-1.01)	0.98 (0.87-1.11)	0.93 (0.85-1.02)
Monounsaturated fat (5% of energy)	0.94 (0.88-1.00)	1.02 (0.91-1.15)	0.91 (0.84-0.99)
Trans-unsaturated fat (1% of energy)	0.92 (0.86-0.98)	1.00 (0.88-1.13)	0.91 (0.84-0.99)
Omega-3 fat from fish (0.1% of energy)	1.09 (1.03-1.16)	1.10 (0.96-1.26)	1.09 (1.02-1.17)
Cholesterol (100 mg/1000 kcal†)	1.00 (0.94-1.06)	1.09 (0.98-1.21)	0.96 (0.88-1.04)

*Values were adjusted for energy, age, energy-adjusted vitamin A intake, alcohol intake, time period, height, parity, age at first birth, weight change since age 18 years, body mass index at age 18 years, age at menopause, menopausal status and use of hormone replacement therapy, family history, benign breast disease, and age at menarche. Energy intake from alcohol was included in total energy. Women of uncertain menopausal status were included among all cases, but not with premenopausal or postmenopausal cases. RR indicates relative risk; CI, confidence interval.
†To convert kilocalories to kilojoules, multiply by 4.184.

The greater number of food items on the 1984 dietary questionnaire allowed more extensive calculation of intake of types of fat. **TABLE 3** provides data on the intake of an expanded list of types of fat averaged over the 1984, 1986, and 1990 diets, with follow-up from 1984 through 1994. Again, total fat intake was not associated with breast cancer incidence. Significant inverse associations with breast cancer incidence were seen for intakes of vegetable, polyunsaturated, monounsaturated, and *trans*-unsaturated fats as well as for oleic and linoleic acids, with RRs ranging from 0.82 (polyunsaturated fat) to 0.95 (linoleic acid).

TABLE 4 shows the results of analysis with "substitution" models: each model included total energy, percentage of energy from protein, and percentage of energy from total fat or from types of fat. In this analysis, the coefficient for fat can be interpreted as substitution of a percentage of energy from fat for an equal percentage of energy from carbohydrate. For models in which types of fat are assessed, all major components of fat that contribute to total fat intake are included. For example, animal and vegetable fats are included in the same model, as are saturated, polyunsaturated, monounsaturated, and *trans*-unsaturated fats. Substitution of fat for carbohydrate energy was not associated with higher risk of breast cancer; the RRs for all fats except monounsaturated were slightly inverse, although not statistically significant. The slight inverse association previously observed with monounsaturated fat intake was reversed but remained statistically insignificant after intakes of other fats and protein were taken into account. Analysis of these substitution models stratified by menopausal status showed similar results for premenopausal and postmenopausal breast cancer.

TABLE 5 shows the results of alternative assessments of the relationship between total fat intake and breast cancer incidence. In models A, B, and C, the 1980 baseline diet was used, and start of follow-up was delayed 0, 4, and 8 years, respectively. No substantial variation in risk was observed. In model D we adjusted for cumulatively averaged intakes of folate, fiber, and vitamin E from foods; again, no substantial difference in results was seen. In 1994 we asked participants retrospectively about the use of screening mammography. In model E we limited the analysis to those women who had had a screening mammogram before 1994. No relation was observed between fat intake and risk of breast cancer. To address the possibility that underreporting of total energy intake had biased the associations, we used models F and G, calculating the ratio of reported energy intake to expected basal metabolic rate (based on age and weight) for each woman during each dietary period.[31] In the analysis for each dietary period, we excluded women who fell into the bottom 20%—and then the bottom 40%—of the distribution of these ratios. Even after these exclusions, the RR did not change appreciably. To address the possibility that obesity is an intermediary step between fat intake and breast cancer, we did not adjust in model H for BMI at the age of 18 years or weight change since the age of 18 years. The results remained similar.

We also examined the relation between total fat intake and breast cancer incidence between 1980 and 1994 within strata of established breast cancer risk factors. Again, there was no association of fat intake with breast cancer among women with or without a family history of breast cancer (in a mother or sister) or among women with or without a personal history of benign breast disease, or within categories of BMI. In postmenopausal women, there was no association of fat intake with breast cancer within categories of current, past, or no use of postmenopausal hormones.

We also examined associations of fat-containing foods averaged from 1980 through 1994, with breast cancer incidence. The only significant positive association was with fish intake (RR for 1 84- to 140-g [3- to 5-oz] serving of fish per day, 1.25; 95% CI, 1.05-1.50).

COMMENT

In this large prospective study, we found no evidence that higher total fat intake was associated with an increased risk of breast cancer, even though the relationship was assessed many different ways. Contrary to the prevailing hypothesis, the overall trend was inverse and statistically significant.

Table 3. Multivariate Relative Risk of Breast Cancer Between 1984 and 1994 Among 77 519 Women (2097 Cases) According to Cumulatively Averaged Intake of Total Fat and Fat Subtypes Reported for the 1984, 1986, and 1990 Diets*

Nutrient Increment per Day	RR (95% CI)
Total fat (5% of energy)	0.96 (0.92-1.00)
Animal fat (5% of energy)	1.01 (0.97-1.06)
Vegetable fat (5% of energy)	0.92 (0.87-0.97)
Polyunsaturated fat (5% of energy)	0.82 (0.71-0.96)
Saturated fat (5% of energy)	0.96 (0.87-1.06)
Monounsaturated fat (5% of energy)	0.88 (0.80-0.98)
trans-Unsaturated fat (1% of energy)	0.87 (0.79-0.95)
Omega-3 fat from fish (0.1% of energy)	1.08 (1.03-1.13)
Cholesterol (100 mg/1000 kcal†)	1.09 (1.00-1.18)
Oleic acid (5% of energy)	0.86 (0.77-0.96)
Palmitic acid (5% of energy)	0.91 (0.75-1.10)
Myristic acid (1% of energy)	1.04 (0.91-1.19)
Stearic acid (1% of energy)	0.96 (0.89-1.03)
Linoleic acid (1% of energy)	0.95 (0.92-0.98)
Linolenic acid (1% of energy)	0.75 (0.54-1.03)
Arachidonic acid (0.03% of energy)	1.05 (1.00-1.10)
Eicosapentaenoic acid (0.03% of energy)	1.06 (1.02-1.10)
Docosahexaenoic acid (0.03% of energy)	1.04 (1.01-1.06)

*Values were adjusted for energy, age, energy-adjusted vitamin A intake, alcohol intake, time period, height, parity, age at first birth, weight change since age 18 years, body mass index at age 18 years, age at menopause, menopausal status and use of hormone replacement therapy, family history, benign breast disease, and age at menarche. Energy intake from alcohol was included in total energy. RR indicates relative risk; CI, confidence interval.
†To convert kilocalories to kilojoules, multiply by 4.184.

Table 4. Multivariate Relative Risk of Breast Cancer Among 88 795 Women (2956 Cases), According to Cumulatively Averaged Intake of Fat Subtypes or Total Fat Reported in the 1980, 1984, 1986, and 1990 Diets*

Fat	RR (95% CI)
Total fat (5% of energy)	0.96 (0.93-0.99)
Animal fat (5% of energy, adjusted for vegetable fat intake)	0.96 (0.93-1.00)
Vegetable fat (5% of energy, adjusted for animal fat intake)	0.95 (0.91-1.00)
Polyunsaturated fat (5% of energy, adjusted for saturated, monounsaturated, and *trans*-unsaturated fat)	0.97 (0.81-1.16)
Saturated fat (5% of energy, adjusted for polyunsaturated, monounsaturated, and *trans*-unsaturated fat)	0.93 (0.82-1.05)
Monounsaturated fat (5% of energy, adjusted for saturated, polyunsaturated, and *trans*-unsaturated fat)	1.03 (0.89-1.18)
trans-Unsaturated fat (1% of energy, adjusted for saturated, polyunsaturated, and monounsaturated fat)	0.93 (0.85-1.02)

*Animal fat and vegetable fat were mutually adjusted for each other. Saturated, polyunsaturated, monounsaturated, and *trans*-unsaturated fats were mutually adjusted for each other. Values were adjusted for energy, age, energy-adjusted vitamin A intake, protein intake, alcohol intake, time period, height, parity, age at first birth, weight change since age 18 years, body mass index at age 18 years, age at menopause, menopausal status and use of hormone replacement therapy, family history, benign breast disease, and age at menarche. Energy intake from alcohol was included in total energy. RR indicates relative risk; CI, confidence interval.

Long-term averaged diet might not be the best way to express the relationship between diet and breast cancer; a considerable latency period could exist between fat intake and its effect on disease. However, beginning follow-up as late as 8 years after the initial dietary assessment did not change the results. In some studies, breast cancer risk has been inversely associated with increased intake of folate, fiber, and vitamin E from foods[5,32]; correlations of these nutrients with fat intake could potentially confound the association between fat intake and breast cancer. However, adjustment for the intake of these additional nutrients did not change the results.

Consuming a low-fat diet may be correlated with a whole set of health-conscious behaviors, such as participation in mammographic screening, which may detect cancers earlier and thus artificially increase the incidence of breast cancer among women with low-fat diets. However, limiting the analysis to women who had undergone screening mammography did not change the results.

Underreporting of energy and macronutrient intake, particularly by those persons who are overweight, has been postulated to bias estimations of the effect of fat on the development of long-term disease.[33-35] We excluded women with the greatest likelihood of underreporting intake—first the lowest 20% and then the lowest 40% of the distribution—when comparing reported energy intake with expected energy intake based on age and weight. The results were unchanged. Obesity has been postulated as an intermediary between fat intake and breast cancer. Postmenopausal breast cancer risk has been positively associated with BMI among women who never used hormone replacement in this cohort, and risk has been positively associated with weight gain since the age of 18 years as well.[36] However, leaving out of the model BMI at the age of 18 years and weight change since the age of 18 years did not change the association of breast cancer risk with fat intake. None of the various modeling techniques used in Table 5 made any difference in the association of fat intake with breast cancer risk. In each case the RR was very close to 1.00, and the 95% CIs all included 1.00. In those models for total fat, the data are incompatible with more than a 4% increase in risk per 5% increase in fat intake.

Animal studies have generally supported a promoting effect of polyunsaturated fats (particularly linoleic acid) as well as an inhibitory effect of omega-3 fatty acids on breast cancer development and metastases. The results of observational studies have been mixed. A case-control study with 128 participants found significantly lower levels of omega-3 fatty acids in adipose tissue among cases.[37] The European Community Multicenter Study on Antioxidants, Myocardial Infarction, and Breast Cancer (EURAMIC) case-control study with 642 participants found the ratio of omega-3 to omega-6 to be inversely associated with breast cancer.[38] However, 2 other case-control studies, with 309 and 999 participants each, found no association of omega-3 fatty acids with breast cancer.[39,40] These last 2 case-control studies, like the large pooled prospective study,[9] found no association for linoleic acid[39] or polyunsaturated fats.[40] A third case-control study with 140 cases found that polyunsaturated fats and linoleic acid both had breast cancer risk.[41] However, a large prospective study from Sweden with 674 breast cancer cases recently reported a positive, if only marginally, significant association of polyunsaturated fat with breast cancer risk (RR, 1.89; 95% CI, 1.02-2.78 for an intake increment of 8 g/d as assessed by food-frequency questionnaire); this is the only previous study to mutually adjust for other types of fat.[42]

In addition to these fatty acids, animal fats (the major source of saturated

Table 5. Multivariate Relative Risk of Breast Cancer, According to Total Fat Intake: Comparison of Various Methods of Assessing Fat Intake and Covariate Adjustment*

Method	Follow-up, y	No. of Women	No. of Cases	RR (95% CI)†
A. 1980 Diet; follow-up 1980-1994; baseline diet	14	88 795	2956	0.99 (0.97-1.01)
B. 1980 Diet; follow-up 1984-1994; baseline diet, delayed 4 y	10	87 145	2308	0.99 (0.96-1.02)
C. 1980 Diet; follow-up 1988-1994; baseline diet, delayed 8 y	6	84 805	1457	1.00 (0.96-1.03)
D. 1980, 1984, 1986, and 1990 Cumulatively averaged diet; follow-up 1980-1994; additionally adjusted for dietary intake of folate, fiber, and vitamin E from foods	14	88 795	2956	0.97 (0.94-1.00)
E. 1980, 1984, 1986, and 1990 Cumulatively averaged diet; follow-up 1980-1994; including only women who had had a mammogram before 1994	14	75 287	2364	0.98 (0.94-1.01)
F. 1980, 1984, 1986, and 1990 Cumulatively averaged diet; follow-up 1980-1994; excluding women in the lowest 20% of the distribution for reported energy intake divided by expected energy intake	14	88 795	2342	1.00 (0.96-1.03)
G. 1980, 1984, 1986, and 1990 Cumulatively averaged diet; follow-up 1980-1994; excluding women in the lowest 40% of the distribution for reported energy intake divided by expected energy intake	14	88 795	1413	0.99 (0.94-1.04)
H. 1980, 1984, 1986, and 1990 Cumulatively averaged diet; follow-up 1980-1994; without adjusting for body mass index at age 18 y or weight change since age 18 y	14	88 795	2956	0.97 (0.94-1.00)

*Values were adjusted for energy, age, energy-adjusted vitamin A intake, protein intake, alcohol intake, time period, height, parity, age at first birth, weight change since age 18 years, body mass index at age 18 years, age at menopause, menopausal status and use of hormone replacement therapy, family history, benign breast disease, and age at menarche. Energy intake from alcohol was included in total energy. RR indicates relative risk; CI, confidence interval.
†Relative risks shown are for an increase of 5% of energy from fat.

fat) and *trans*-unsaturated fats have been hypothesized to increase the risk of breast cancer, and olive oil (predominantly composed of monounsaturated fat) to decrease the risk of breast cancer. The hypothesis that saturated fat, particularly animal fat, is associated with breast cancer has come primarily from ecological studies[3,4,24] but in general has not been supported by either case-control studies[39-41] or prospective studies.[9,42] The EURAMIC case-control study found a positive association for *trans*-unsaturated fat in adipose tissue, with an odds ratio of 1.40 (95% CI, 1.02-1.93) for the difference between the 25th and 75th percentiles[38]; however, no association was found in a similar study by London et al.[40] Three case-control studies have supported an inverse association of olive oil intake with breast cancer risk,[43-45] and 1 found an inverse association of monounsaturated fat and breast cancer risk.[41] The Swedish cohort study documented an inverse association with monounsaturated fat (RR, 0.45; 95% CI, 0.22-0.95 for an increment of 10 g/d mutually adjusted for other types of fat),[39] whereas the pooled cohort analysis (not adjusted for other types of fat) found no association.[9]

In contrast to the predominant hypotheses, we saw no increased risk of breast cancer with increased intake of animal fat, polyunsaturated fat, saturated fat, or *trans*-unsaturated fat in models in which fat intake replaced carbohydrate intake. Likewise, we found no evidence of decreased risk of breast cancer with increased intake of vegetable fat or monounsaturated fat in similar models. Also contrary to the predominant hypothesis, we found an increased risk of breast cancer associated with omega-3 fat from fish.

This study had several strengths: It was prospective, few subjects have been lost to follow-up, and it was not prone to the biases of case-control studies.[46] It included more cases, longer follow-up, and more person-time than any previously published individual prospective study on diet and breast cancer. The assessment of diet at multiple times during the follow-up period allowed more accurate quantification of long-term diet.

Our previous inability to find an association between fat intake and breast cancer in this cohort has been attributed by some to measurement error.[33] However, measurement error is highly unlikely to account for our findings. Even in the previous analysis with half the present number of cases and a single baseline measure of dietary fat, the 95% CI excluded the magnitude of risk predicted by the international correlations even after taking measurement error into account.[7] In addition, the multiple assessments of diet over time in this analysis decreased misclassification,[26] and the same dietary measurements and methods in this cohort strongly predict coronary heart disease, even with fewer than one-third the number of cases.[47] These findings strongly suggest that international correlations between fat consumption and breast cancer are severely confounded by other factors, including delayed onset of menses,[48] weight gain after the age of 18 years,[36] and hormone replacement therapy.[36]

Our capacity to examine risks of breast cancer at the extremes of fat intake is limited by the small proportion of women and greater probability of misclassification of dietary intake in these categories. However, the fact that the risk of breast cancer tended to be highest among those with the lowest fat intake makes an important reduction of risk in this group unlikely.

In conclusion, we found no evidence that lower intake of total fat or particular types of fat over 14 years of follow-up was associated with a decreased risk of breast cancer. These findings suggest that reductions in total fat intake during midlife are unlikely to prevent breast cancer and should receive less emphasis. Rather, women's decision about fat intake should be guided primarily by risk of heart disease, which is strongly influenced by the type but not total amount of fat.[49]

Funding/Support: The work reported in this article was supported by the National Institutes of Health grant CA40356. In addition, Dr Holmes was supported by the 50th Anniversary Program for Scholars in Medicine at Harvard Medical School, and Drs Hunter, Colditz, and Willett were supported by the Harvard Center for Cancer Prevention.

REFERENCES

1. Aylsworth CF, Jone C, Trosko JE, Meltes J, Welsch CW. Promotion of 7,12-dimethylbenz[a]anthracene-induced mammary tumorigenesis by high dietary fat in the rat: possible role of intercellular communication. *J Natl Cancer Inst.* 1984;72:637-645.

2. Prentice RL, Kakar F, Hursting S, Sheppard L, Klein R, Kushi LH. Aspects of rationale for the Women's Health Trial. *J Natl Cancer Inst.* 1988;80:802-814.

3. Wynder EL, Fujita Y, Harris RE, Hirayama T, Hiyama T. Comparative epidemiology of cancer between the United States and Japan: a second look. *Cancer.* 1991;67:746-763.

4. Carroll KK, Khor HT. Dietary fat in relation to tumorigenesis. *Prog Biochem Pharmacol.* 1975;10:308-313.

5. Howe GR, Hirohata T, Hislop TG, et al. Dietary factors and risk of breast cancer: combined analysis of 12 case-control studies. *J Natl Cancer Inst.* 1990;82:561-569.

6. Colditz GA, Burdick E, Mosteller F. Heterogeneity in meta-analysis of data from epidemiologic studies: a commentary. *Am J Epidemiol.* 1995;142:371-382.

7. Willett WC, Hunter DJ, Stampfer MJ, et al. Dietary fat and fiber in relation to risk of breast cancer: an 8-year follow-up. *JAMA.* 1992;268:2037-2044.

8. Hunter DJ, Willett WC. Diet, body size and breast cancer. *Epidemiol Rev.* 1993;15:110-132.

9. Hunter DJ, Spiegelman D, Adami H-O, et al. Cohort studies of fat intake and the risk of breast cancer: a pooled analysis. *N Engl J Med.* 1996;334:356-361.

10. Cave WT, Jurkowski JJ. Dietary lipid effects on the growth, membrane composition, and prolactin-binding capacity of rat mammary tumors. *J Natl Cancer Inst.* 1984;73:185-191.

11. Jurkowski JJ, Cave WT. Dietary effects of menhaden oil on the growth and membrane lipid composition of rat mammary tumors. *J Natl Cancer Inst.* 1985;74:1145-1150.

12. Cohen LA, Thompson DO, Choi K, Karmali RA, Rose DP. Dietary fat and mammary cancer, II: modulation of serum and tumor lipid composition and tumor prostaglandins by different dietary fats: association with tumor incidence patterns. *J Natl Cancer Inst.* 1986;77:43-51.

13. Katz EB, Boylan ES. Stimulatory effect of high polyunsaturated fat diet on lung metastasis from the 13762 mammary adenocarcinoma in female retired breeder rats. *J Natl Cancer Inst.* 1987;79:351-358.

14. Hubbard NE, Erickson KL. Enhancement of metastasis from a transplantable mouse mammary tumor by dietary linoleic acid. *Cancer Res.* 1987;47:671-675.

15. Connolly JM, Liu XH, Rose DP. Dietary linoleic acid-stimulated human breast cancer cell growth and metastasis in nude mice and their suppression by indomethacin, a cyclooxygenase inhibitor. *Nutr Cancer.* 1996;25:231-240.

16. Karmali RA, Marsh J, Fuchs C. Effect of omega-3 fatty acids on growth of a rat mammary tumor. *J Natl Cancer Inst.* 1984;73:457-461.

17. Rose DP, Connolly J. Effects of dietary omega-3 fatty acids on human breast cancer growth and metastases in nude mice. *J Natl Cancer Inst.* 1993;85:1743-1747.

18. Gonzalez MJ, Schemmel RA, Dugan L, Gray JI, Welsch CW. Dietary fish oil inhibits human breast carcinoma growth: a function of increased lipid peroxidation. *Lipids.* 1993;28:827-832.

19. Kinoshita K, Noguchi M, Earashi, M, Tanaka M, Sasaki T. Inhibitory effects of purified eicosapentaenoic acid and docosahexaenoic acid on growth and metastasis of murine transplantable mammary tumor. *In Vivo.* 1994;8:371-374.

20. Rose DP, Connolly JM, Rayburn J, Coleman M. Influence of diets containing eicosapentaenoic or docosahexaenoic acid on growth and metastasis of breast

cancer cells in nude mice. *J Natl Cancer Inst.* 1995;87:587-592.
21. Lund E, Bonaa KH. Reduced breast cancer mortality among fishermen's wives. *Cancer Causes Control.* 1993;4:283-287.
22. Noguchi M, Rose DP, Earashi M, Miyazaki I. The role of fatty acids and eicosanoid synthesis inhibitors in breast carcinoma. *Oncology.* 1995;52:265-271.
23. Godley PA. Essential fatty acid consumption and risk of breast cancer. *Breast Cancer Res Treat.* 1995;35:91-95.
24. Caygill CPJ, Charlett A, Hill MJ. Fat, fish, fish oil and cancer. *Br J Cancer.* 1996;74:159-164.
25. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol.* 1985;122:51-65.
26. Willett WC. *Nutritional Epidemiology.* 2nd ed. New York, NY: Oxford University Press; 1998.
27. US Department of Agriculture. *Composition of Foods: Raw, Processed, and Prepared, 1963-1992.* Washington, DC: US Dept of Agriculture; 1993. Agricultural Handbook Series No. 8.
28. Enig MG, Pallansch LA, Sampugna J, Keeney M. Fatty acid composition of the fat in selected food items with emphasis on *trans* components. *J Am Oil Chem Soc.* 1983;60:1788-1795.
29. Slover HT, Thompson RH Jr, Davis CS, Merola GV. Lipids in margarines and margarine-like foods. *J Am Oil Chem Soc.* 1985;62:775-786.
30. D'Agostino RB, Lee M-L, Belanger AJ, Cupples LA, Anderson K, Kannel WB. Relation of pooled logistic regression to time dependent Cox regression analysis: the Framingham Heart Study. *Stat Med.* 1990;9:1501-1515.
31. Black AE. Physical activity levels from a meta-analysis of doubly labeled water studies for validating energy intake as measured by dietary assessment. *Nutr Rev.* 1996;54:170-174.
32. Freudenheim JL, Marshall JR, Vena JE, et al. Premenopausal breast cancer risk and the intake of vegetables, fruits, and related nutrients. *J Natl Cancer Inst.* 1996;88:340-348.
33. Prentice RL. Measurement error and results from analytic epidemiology: dietary fat and breast cancer. *J Natl Cancer Inst.* 1996;88:1738-1747.
34. Price GM, Paul AA, Cole TJ, Wadsworth ME. Characteristics of the low-energy reporters in a longitudinal national dietary survey. *Br J Nutr.* 1997;77:833-851.
35. Johnson RK, Black AE, Cole TJ. Dietary fat intake and the risk of coronary heart disease in women. *N Engl J Med.* 1998;338:918-919.
36. Huang Z, Hankinson SE, Colditz GA, et al. Dual effects of weight and weight gain on breast cancer risk. *JAMA.* 1997;278:1407-1411.
37. Zhu ZR, Agren S, Mannisto P, et al. Fatty acid composition of breast adipose tissue in breast cancer patients and in patients with benign breast disease. *Nutr Cancer.* 1995;24:151-160.
38. Simonsen N, van't Veer P, Strain JJ, et al. Adipose tissue omega-3 and omega-6 fatty acid content and breast cancer in the EURAMIC study. *Am J Epidemiol.* 1998;147:342-352.
39. Petrek JA, Hudgins LC, Levine B, Ho M, Hirsch J. Breast cancer risk and fatty acids in the breast and abdominal tissues. *J Natl Cancer Inst.* 1994;86:53-56.
40. London SJ, Sacks FM, Stampfer MJ, et al. Fatty acid composition of subcutaneous adipose tissue and risk of proliferative benign breast disease and breast cancer. *J Natl Cancer Inst.* 1993;85:785-793.
41. Witte JS, Ursin G, Siemiatycki J, Thompson WD, Paganini-Hill A, Haile RW. Diet and premenopausal bilateral breast cancer: a case-control study. *Breast Cancer Res Treat.* 1997;42:243-251.
42. Wolk A, Bergstrom R, Hunter DJ, et al. A prospective study of association of monounsaturated fat and other types of fat with risk of breast cancer. *Arch Intern Med.* 1998;158:41-45.
43. La Vecchia C, Negri E, Franceschi S, Decarli A, Giacosa A, Lipworth L. Olive oil, other dietary fats, and the risk of breast cancer (Italy). *Cancer Causes Control.* 1995;6:545-550.
44. Martin-Moreno JM, Willett WC, Gorgojo L, et al. Dietary fat, olive oil intake and breast cancer risk. *Int J Cancer.* 1994;58:774-780.
45. Trichopoulou A, Katsouyanni K, Stuver S, et al. Consumption of olive oil and specific food groups in relation to breast cancer risk in Greece. *J Natl Cancer Inst.* 1995;87:110-116.
46. Giovannucci E, Stampfer MJ, Colditz GA, et al. A comparison of prospective and retrospective assessments of diet in the study of breast cancer. *Am J Epidemiol.* 1993;137:502-511.
47. Hu FB, Stampfer MJ, Manson JE, et al. Dietary fat intake and the risk of coronary heart disease in women. *N Engl J Med.* 1997;337:1491-1499.
48. Marshall JR, Qu Y, Chen J, Parpia B, Campbell TC. Additional ecologic evidence: lipids and breast cancer mortality among women aged 55 and over in China. *Eur J Cancer.* 1992;28A:1720-1727.
49. National Research Council. *Diet and Health: Implications for Reducing Chronic Disease Risk: Report of the Committee on Diet and Health, Food and Nutrition Board.* Washington, DC: National Academy Press; 1989.

> Our senses perceive no extreme. Too much sound deafens us; too much light dazzles us; too great distance or proximity hinders our view. Too great length and too great brevity of discourse tend to obscurity; too much truth is paralysing.
>
> —Blaise Pascal (1623-1662)

