

A Prospective Study of Association of Monounsaturated Fat and Other Types of Fat With Risk of Breast Cancer

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Background: Animal studies suggest that monounsaturated and polyunsaturated fat may have opposite effects on the risk of breast cancer.

Methods: We performed a population-based prospective cohort study, including 61 471 women aged 40 to 76 years from 2 counties in central Sweden who did not have any previous diagnosis of cancer; 674 cases of invasive breast cancer occurred during an average follow-up of 4.2 years. All subjects answered a validated 67-item food frequency questionnaire at baseline. Cox proportional hazards models were used to obtain adjusted rate ratio (RR) estimates with 95% confidence intervals (CIs).

Results: After mutual adjustment of different types of fat, an inverse association with monounsaturated fat and a positive association with polyunsaturated fat were found. The RR for each 10-g increment in daily intake of monoun-

saturated fat was 0.45 (95% CI, 0.22-0.95), whereas the RR for a 5-g increment of polyunsaturated fat was 1.69 (95% CI, 1.02-2.78); the increments correspond to approximately 2 SDs of intake in the population. Comparing the highest quartile of intake with the lowest, we found an RR of 0.8 (95% CI, 0.5-1.2) for monounsaturated fat and 1.2 (95% CI, 0.9-1.6) for polyunsaturated fat. Saturated fat was not associated with the risk of breast cancer.

Conclusions: Our results indicate that various types of fat may have specific opposite effects on the risk of breast cancer that closely resemble the corresponding effects in experimental animals. Research investigations and health policy considerations should take into account the emerging evidence that monounsaturated fat might be protective for risk of breast cancer.

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STUDIES IN animals suggest that monounsaturated fatty acids may reduce mammary tumor incidence^{1,2} while diets rich in polyunsaturated linoleic acid (18:2, n=6) may increase the incidence and likelihood of metastasis of mammary tumors.³⁻⁵ A majority of analytical epidemiological studies⁶⁻¹³ and meta-analyses^{14,15} have shown that intake of total fat in adult life has little if any effect on risk of breast cancer. However, mutual adjustment between types of fat has not been regularly attempted in the evaluation of the effects, if any, of specific types of fat. This is an important issue, since types of fat tend to be positively and strongly correlated.

Recently, 4 case-control studies from Spain,^{16,17} Greece,¹⁸ and Italy¹⁹ indicated that consumption of olive oil, the main source of monounsaturated fat in the Mediterranean diet, was associated with a decreased risk of breast cancer. The authors of these studies speculated that the effect might be specific for olive oil. We have evaluated the effects on risk of breast cancer of specific

types of dietary fats in Sweden, a country with very low consumption of olive oil.

RESULTS

The mean (SD) age of women at entry to the cohort was 53.7 (9.7) years. During an average of 4.2 years of follow-up the cohort included 258 828 person-years of observation. Among women in this cohort, the expected relations with established risk factors for breast cancer were demonstrated: a decreasing risk with increasing parity, and an increasing risk with higher age at first child's birth, family history of cancer, and higher body mass index (**Table 1**). In these data, total energy intake was positively associated with the risk of breast cancer; an increment of 420 kJ (100 kcal) corresponded to a rate ratio of 1.03 (95% CI, 1.01-1.05) in a model adjusted

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SUBJECTS AND METHODS

THE SWEDISH MAMMOGRAPHY SCREENING COHORT

From 1987 to 1990 a population-based mammography screening program was introduced in 2 counties in central Sweden. In Västmanland County all women born between 1917 and 1948 received a mailed invitation to be screened by mammography between March 1987 and March 1989 (n=41 786) together with a 6-page questionnaire; 31 735 women (76%) returned the completed questionnaires. In Uppsala County all women born between 1914 and 1948 were invited to the screening and received the same questionnaire between January 1988 and December 1990 (n=48 517); 34 916 women (72%) returned the completed questionnaires. Hence, questionnaires completed before undergoing mammography were obtained from 66 651 women (73.8%) in the source population. These questionnaires included items about parity, age at first child's birth, history of breast cancer in family (mother or/and sister), weight (kilograms), height (centimeters), education, and diet.

For the present analyses, we excluded women who were outside the age range of 40 through 76 years (n=165), those with missing (n=707) and incorrect identification numbers (n=413), as well as those lacking date on the questionnaire (n=608), missing day for moving out of the study area (n=79), or day of death (n=16). After further exclusion of 793 women with extreme energy intake estimates, probably reflecting careless completion of the dietary questionnaire (below or above mean±3 SDs for log-transformed joules; cutoff points of 1751 and 15 662 kJ), the cohort was restricted to 63 870 women. By linkage to the Swedish Cancer Registry, we identified and excluded all women with a previous diagnosis of cancer other than

nonmelanoma skin cancer (n=2399). Thus, the study cohort included 61 471 women at the start of follow-up.

DIETARY ASSESSMENT

The self-administered food frequency questionnaire included 67 commonly eaten foods. We asked how often, on average, during the past 6 months the participants had consumed these foods. There were also open-ended questions about the number of slices of crisp bread, whole grain bread, white bread, or other bread consumed per day, and about the number of glasses of milk consumed per day. For the other foods we used 8 predefined frequency categories ranging from "never to seldom" to "4 or more times per day." The questionnaire also included questions about the type of fat commonly used at the table (5 types) and the type of fat used for food preparation (5 types); we also inquired about the usual fat layer on sandwiches (thick, thin, very thin, or no fat). For nutrient calculations we used age-specific portion sizes (≤ 52 , 53-65, or ≥ 66 years) based on mean values from 5922 days of weighed food records among 213 women. Nutrient composition values from the Swedish National Food Administration database²⁰ were used for calculation.

The validity of nutrient estimates based on the self-reported food frequencies was evaluated in a subsample of 129 women from the cohort. During four 7-day periods, 3 to 4 months apart, each participant weighed and recorded all foods consumed. After completion of diet recording, a subcutaneous adipose tissue sample was taken from the participants by needle aspiration. The validity of energy-adjusted fat estimates from the food frequency questionnaire (assessed by Pearson correlation coefficients between the food frequency questionnaire and weighed food records-derived estimates) was as follows: total fat, $r=0.5$; saturated fat, $r=0.4$; monounsaturated fat, $r=0.5$; and polyunsaturated fat, $r=0.4$. The validity of polyunsaturated fat

Table 1. Age-Adjusted, Cox Regression-Derived, Mutually Adjusted Relative Risks for Breast Cancer, According to Selected Demographic and Reproductive Variables

Variable	Groups or Units	Relative Risks* (95% Confidence Interval)	P
Parity	1-4 vs 0	0.84 (0.66-1.06)	.12
	≥ 5 vs 0	0.36 (0.20-0.64)	<.001
Age at first child's birth, y	≥ 35 vs others	1.80 (1.24-2.62)	.001
Family history†	Yes vs no	1.39 (1.08-1.79)	.01
BMI‡ (continuous)	1 kg/m ²	1.024 (1.004-1.043)	.02
Education	High school vs elementary school	0.92 (0.70-1.21)	.55

*Also adjusted for nutritional variables as in Table 3 (continuous form).

†Breast cancer in mother or/and sister.

‡BMI indicates body mass index, which is a measure of weight in kilograms divided by the square of the height in meters.

for nonnutritional variables as well as types of fat, cholesterol, alcohol, and fiber, including energy in continuous form.

Table 2 shows hazard rate ratios and corresponding CIs by quartiles of intake for total fat and specific types of fat. These estimates are derived from Cox models that

adjust for nonnutritional variables and total energy intake as well as for alcohol, fiber, and cholesterol. The latter 3 variables were introduced because of reports in the literature that alcohol,²³ fiber,²⁴ and cholesterol¹³ might be associated with risk of breast cancer, even though in our data they were not significant. In Table 2 rate ratios for specific types of fat were not mutually adjusted but instead they were derived from independent models. Neither total fat nor any of the types of fat was significantly associated with risk of breast cancer.

Table 3 presents rate ratios for specific types of fat simultaneously included in the same Cox model and, therefore, these rate ratios are mutually adjusted. Results are presented for categorical (quartiles) and continuous variables (increment specified). Saturated fat intake was not significantly associated with breast cancer. However, an increased consumption of monounsaturated fat was associated with significantly decreased risk, whereas consumption of polyunsaturated fat was associated with significantly increased risk. Different increments were used for saturated, monounsaturated, and polyunsaturated fat to correspond to the respective ranges of variation (approximately 2 SDs) in the studied population, but this choice of units does not influence the significance testing. Exclusion of extreme values

estimated from the food questionnaire (as a percentage of total fatty acids) in comparison with adipose tissue composition was $r=0.5$. Comparing with the food records, the food frequency questionnaire-based intakes were underestimated on average by 12% for saturated fat and monounsaturated fat and by 18% for polyunsaturated fat.

In the validation subsample, mean intake of energy from total fat was 30% and the means of the bottom and the top quartiles were 23% and 37%, respectively; similar values were observed for the whole cohort. A mean (\pm SD) energy intake in the validation subsample was 7106 ± 1466 kJ and a mean (\pm SD) body mass index (a measure of weight in kilograms divided by the square of the height in meters) was 24.77 ± 3.72 kg/m²; in the whole cohort the mean (\pm SD) corresponding values were 5585 ± 1579 kJ and 24.74 ± 3.93 kg/m².

IDENTIFICATION OF CASES OF BREAST CANCER AND FOLLOW-UP OF THE COHORT

Between March 1987 and March 1993 a total of 674 incident, histologically confirmed, invasive cases of breast cancer occurred among women in the cohort. These cases were identified through computerized registers of diagnoses of breast cancer in the 2 counties. The registers received pathological reports within 1 to 2 weeks after a histological investigation. Dates of deaths in the cohort were ascertained through the Swedish Death Register and information about the date of moving out from the study area was obtained by matching of the cohort with the Swedish Population Register.

The study was approved by the ethical committee at Uppsala University Hospital in Uppsala, Sweden.

STATISTICAL ANALYSIS

Cox proportional hazards models were used to estimate hazard rate ratios with 95% confidence intervals (CIs), relat-

ing different explanatory variables to the occurrence of invasive breast cancer. Follow-up was ceased at date of death, date of migration out of the area, or at the end of the follow-up period.

Energy adjustment of nutrients was performed by using the residuals methodological procedure recommended by Willett and Stampfer.²¹ In the first step of the method, each nutrient is regressed on total energy (both variables in continuous form), then residuals from this procedure are used together with total energy intake in the models. We used dietary variables in both categorized and continuous form. As a basis for the trend tests, scores were constructed from the categorized variables as successive integers. These scores were used in further analyses and the results are presented as tests for trend. Use of categorized variables implies no specific assumption about the functional form (eg, linear) of the effect of the variable, and the pattern of the estimated parameters makes it possible to judge what might be a reasonable representation of the effects. However, there is a drawback that we assume that the effect of a variable is constant within a certain interval, then abruptly changes, and again stays constant. Moreover, given a certain effect of the variable in continuous form, use of the variable in categorized form is an inefficient way of using the available data. Therefore, we have also used variables in their natural continuous form, which was possible because overall the results from our categorized analyses were not incompatible with the assumption that the effects are linear (on the logarithmic risks). To further clarify the results we also performed stratified analyses of one type of fat by strata of another type of fat. A model containing separate terms for energy from the nutrients of special interest (saturated fat-energy, monounsaturated fat-energy, and polyunsaturated fat-energy) and for energy from other sources (protein-energy and carbohydrate-energy) was also fitted, the so-called partition model.²²

Table 2. Cox Regression-Derived Risk Estimates for Invasive Breast Cancer by Quartile of Energy-Adjusted Intake of Different Types of Fats*

Fats	Quartiles of Fat Intake†				P for Trend
	Q ₁ (Referent)	Q ₂	Q ₃	Q ₄	
Total g/d	<40.3	40.3-45.2	45.3-50.2	>50.2	
Rate ratios (95% CI)‡	1.0	1.24 (0.99-1.56)	1.15 (0.90-1.47)	1.00 (0.76-1.32)	.82
Saturated, g/d	<16.3	16.3-18.8	18.9-21.7	>21.7	
Rate ratios (95% CI)‡	1.0	1.20 (0.96-1.50)	1.05 (0.82-1.35)	1.09 (0.83-1.42)	.83
Monounsaturated, g/d	<14.4	14.4-16.4	16.5-18.4	>18.4	
Rate ratios (95% CI)‡	1.0	1.30 (1.04-1.62)	1.10 (0.86-1.40)	0.95 (0.72-1.24)	.38
Polyunsaturated, g/d	<5.3	5.3-6.2	6.3-7.7	>7.7	
Rate ratio (95% CI)‡	1.0	1.10 (0.88-1.38)	1.12 (0.90-1.39)	1.01 (0.80-1.26)	.92

* Types of fat in separate models, not mutually adjusted. CI indicates confidence interval.

† The quartile limits refer to values energy adjusted to a total energy intake of 5586 kJ/d (mean in the study population).

‡ Adjusted for age (continuous), parity (0, 1-4, 5-6), age at first child's birth (<35 y, ≥ 35 y), family history of breast cancer (no or yes), body mass index (a measure of weight in kilograms divided by the square of the height in meters) (continuous), education (university, high school, or other), cholesterol (milligrams per day) (continuous), fiber (grams per day) (continuous), alcohol (grams of ethanol per day) (continuous), and total energy intake (kilojoules per day) (continuous).

(outliers) from the analysis of mutually adjusted types of fat in continuous form did not change the results substantially. Results based on quartiles of intake were in the same direction but not statistically significant.

The Pearson correlation coefficient between energy-adjusted monounsaturated fat and polyunsaturated fat was $r=0.69$ and between monounsaturated and saturated fat, $r=0.61$, while no correlation was evident be-

Table 3. Cox Regression–Derived, Mutually Adjusted Risk Estimates for Invasive Breast Cancer by Quartiles and by Specified Increments of Energy-Adjusted Intake of Different Types of Fat*

Fats	Quartiles of Fat Intake				Trend Over Categories <i>P</i>	Intake in Continuous Form	
	Q ₁ (Referent)	Q ₂	Q ₃	Q ₄		Unit of Increment†	<i>P</i>
Saturated							
Rate ratios (95% CI)‡	1.0	1.19 (0.94-1.50)	1.08 (0.83-1.41)	1.20 (0.89-1.63)	.31	Per 10 g/d, 1.26 (0.92-1.74)	.15
Monounsaturated							
Rate ratios (95% CI)‡	1.0	1.18 (0.92-1.53)	0.96 (0.70-1.33)	0.80 (0.52-1.21)	.10	Per 10 g/d, 0.45 (0.22-0.95)	.04
Polyunsaturated							
Rate ratios (95% CI)‡	1.0	1.10 (0.86-1.40)	1.16 (0.89-1.51)	1.18 (0.85-1.64)	.20	Per 5 g/d, 1.69 (1.02-2.78)	.04

*CI indicates confidence interval. See footnote to Table 2 for explanation of quartiles of fat intake.

†Unit of increase corresponds to approximately 2 SDs of daily intake in the studied population.

‡Adjusted for age (continuous), parity (0, 1-4, 5-6), age at first child's birth (<35 y, ≥35 y), family history of breast cancer (no or yes), body mass index (a measure of weight in kilograms divided by the square of the height in meters) (continuous), education (university, high school, or other), cholesterol milligrams per deciliter (continuous), fiber (grams per day) (continuous), alcohol (grams of ethanol per day) (continuous), and total energy intake (kilojoules per day) (continuous).

Table 4. Cox Regression–Derived Risk Estimates* for Invasive Breast Cancer by Quartiles and by 10-g Increments of Energy-Adjusted Monounsaturated Fat Intake Stratified by Quartiles of Polyunsaturated Fat

Quartiles of Polyunsaturated Fat	Quartiles of Monounsaturated Fat				Trend Over Categories <i>P</i>	Intake in Continuous Form	
	Q ₁ (Referent)	Q ₂	Q ₃	Q ₄		Per 10 g of Monounsaturated Fat	<i>P</i> for Trend
Q ₁	1.0	1.34	1.15	1.40	.28	2.46	.10
Q ₂	1.0	1.12	0.83	0.86	.39	0.60	.50
Q ₃	1.0	1.07	0.98	0.66	.30	0.27	.06
Q ₄	1.0	0.57	0.38	0.31	.02	0.46	.10

*Adjusted for age (continuous), parity (0, 1-4, 5-6), age at first child's birth (<35 y, ≥35 y), family history of breast cancer (no or yes), body mass index (a measure of weight in kilograms divided by the square of the height in meters) (continuous), education (university, high school, or other), cholesterol (milligrams per day) (continuous), fiber (grams per day) (continuous), alcohol (grams of ethanol per day) (continuous), saturated fat (grams per day) (continuous), and total energy intake (kilojoules per day) (continuous). See footnote to Table 2 for an explanation of the quartiles of fat intake.

tween polyunsaturated and saturated fat ($r=0.01$). Because of the high correlation between monounsaturated and polyunsaturated fat, there were relatively few women simultaneously in the highest intake category of one but the lowest intake category of the other; thus, we had limited power to directly compare women in these extremes. However, **Table 4** shows in more detail the effect of monounsaturated fat within strata formed from the quartiles of polyunsaturated fat. In the 3 highest quartiles of polyunsaturated fat, we can clearly see the lower risk associated with higher intake of monounsaturated fat, both with the variables in categorized and continuous form. Although the estimates as expected are insignificant in most cases, the pattern shown confirms the earlier multivariate results from Table 3.

Results obtained from the partition model—in which energy intake in continuous form from saturated, monounsaturated, and polyunsaturated fats were included simultaneously with energy intake from protein and carbohydrates—were similar (data not shown) to results from the residual method presented in Table 3. The main sources of different types of fat in the cohort were as follows: saturated fat: dairy, 52% (including butter), meat, 22% (including chicken), and margarine, 7%; monounsaturated fat: dairy, 26%, meat, 29%, and margarine, 20%; and polyunsaturated fat: dairy, 11%, meat, 17%, margarine, 33%, and bread and cereals, 23%.

COMMENT

In this large prospective cohort study we found no positive association between intake of total fat and risk of invasive breast cancer after adjustment for total energy intake. We found, however, that 2 individual constituents of total fat, monounsaturated fat and polyunsaturated fat, had independent opposite effects: monounsaturated fat was significantly inversely and polyunsaturated fat was significantly positively associated with risk of invasive breast cancer.

In 4 recent case-control studies from Spain,^{16,17} Greece,¹⁸ and Italy,¹⁹ a protective effect of olive oil, the main source of monounsaturated fat in the Mediterranean countries, on incidence of breast cancer was reported and the authors have speculated that olive oil, rather than monounsaturated fat in general, is responsible. Our findings for monounsaturated fat are in agreement with those evident in the prospective Nurses Health Study,⁹ and in conjunction with the animal data, suggesting that monounsaturated fat, irrespective of its origin, is inversely associated with risk of breast cancer.

Two of the case-control studies^{18,19} and the Nurses Health Study,⁹ as well as ours, have 1 property in common—they all addressed possible mutual confounding among the various types of dietary fat. This mutual confounding is generated by the positive association between monoun-

saturated fat and polyunsaturated fat that have apparently opposing effects on risk of breast cancer. The effect of mutual confounding on risk estimates for these 2 specific types of fat was particularly strong in our data because of the relatively high positive correlation between these 2 fats ($r=0.69$). Does it mean that multicollinearity invalidates our results? The basic consequence of multicollinearity is to make the estimates less precise, but provided that all variables are retained in the model the estimates are not biased. In a situation with severe multicollinearity, we typically obtain large SEs (broad range confidence intervals), so that we fail to detect real effects of variables. However, in our study we obtained significant results for monounsaturated fat and polyunsaturated fat.

Our results on the role of monounsaturated, polyunsaturated, and saturated fats in humans are in remarkable agreement with animal data. The effects of type of fat on the promotion of chemically induced mammary cancer have been studied in many experimental animal models.^{1-5,25-33} Collectively, these studies suggest that monounsaturated fat may have a protective effect on development of breast cancer in animals, in contrast with the effect of other types of fat. Whereas saturated fats have generally been unrelated to tumorigenesis, increasing amounts of essential fatty acids, primarily linoleic acid (the major polyunsaturated fat in the Western diet), increase the incidence and likelihood of metastasis of chemically induced and transplanted mammary tumors.³⁻⁵ Essential fatty acids influence immune responses, cell proliferation, tissue invasiveness, and metastatic spread³⁰ as well as fluidity of cellular membranes, which could affect cell surface receptors³¹ or cell-to-cell interactions.³² Polyunsaturated fatty acids in cell membranes may also alter the risk of breast cancer by increasing the formation of free radicals that can damage DNA and promote tumor development.³³

A positive association of total energy intake with risk of breast cancer apparent in our cohort has not been observed in other prospective cohort studies.⁶⁻¹² Therefore, our finding could be attributable to chance but, nevertheless, emphasizes the importance of controlling for energy intake in analyses of diet in relation to cancer.

The inverse association of monounsaturated fat and the positive association of polyunsaturated fat with the risk of breast cancer, if confirmed by additional studies, could have profound public health implications. Long-term compliance with reduction in total fat may be difficult for the general population because a substantial decrease in total fat intake requires major changes in dietary practices. In contrast, changes in the type of dietary fats may be more realistic because dietary advice for food preparation may focus on substitution of margarine and different vegetable oils (with the monosaturated-polyunsaturated fat ratio most often being 1:2) by olive oil (with the monosaturated-polyunsaturated fat ratio 5:1). Nevertheless, the results of our study should be confirmed in additional prospective cohort studies before those major dietary changes are recommended because the high correlation between nutrients reduces the precision of effect estimates.

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