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Olive oil, other dietary fats, and the risk of breast cancer (Italy)

Carlo La Vecchia, Eva Negri, Silvia Franceschi, Adriano Decarli, Attilio Giacosa, and Loren Lipworth

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Data from a multicenter case-control study on breast cancer conducted in Italy have been used to analyze the relationship of olive oil and other dietary fats to breast cancer risk. Cases were 2,564 women hospitalized with histologically confirmed, incident breast cancer. Controls were 2,588 women admitted to the same network of hospitals for acute, non-neoplastic, non-hormone related, non-digestive tract disorders. Cases and controls were interviewed between 1991 and 1994 using a validated food-frequency questionnaire. The data were modelled through multiple logistic regression controlling for demographic and reproductive breast-cancer risk factors, energy intake and, mutually, for types of dietary fat. For olive oil, compared with the lowest quintile, the odds ratios (OR) were 1.05, 0.99, 0.93, and 0.87 for increasing quintiles of intake; in a model postulating linear logit increase, the OR per unit (30g) was 0.89 (95 percent confidence interval [CI] = 0.81-0.99, $P = 0.03$). Among other oils or fats considered, the OR for the highest level of intake was 0.72 (CI = 0.6-0.9) for a group of specific seed oils (including safflower, maize, peanut, and soya) compared with nonusers. The ORs for the highest *cf* lowest level of intake were 0.80 for mixed or unspecified seed oils, 0.95 for butter, and 0.96 for margarine. The study, based on a large dataset from various Italian regions, shows an inverse relationship of breast cancer risk with intake of olive oil and other vegetable oils, but not with butter or margarine. *Cancer Causes and Control* 1995, 6, 545-550

Key words: Breast cancer, dietary fat, females, Italy, olive oil.

Introduction

Breast cancer rates have been relatively low in Mediterranean countries compared with most other Western countries,[1] although the components of the Mediterranean diet responsible for this favorable pattern have not been clearly identified.[2] Traditional Mediterranean diet is relatively rich in carbohydrates, fresh vegetables, and fruits, but total fat intake, in proportional terms, is not particularly low. What is typical of the Mediterranean diet, in terms of fat composition, is the low intake of animal fats and the predominance of olive oil among seasoning fats.[2,3]

Olive oil has antioxidant properties, is high in monounsaturated fats, and is relatively low in saturated fats as well as linoleic acid–which has been suggested to have a role in mammary tumor promotion in rats.[4] Further, rats fed with olive oil had reduced mammary tumor incidence compared with those fed with safflower oil.[5]

An earlier case-control study from northern Italy[6] found a nonsignificant inverse association between olive oil and breast cancer risk. At least two other studies, conducted in Spain[7] and Greece,[8] have suggested that

Authors are affiliated with Istituto di Statistica Medica e Biometria, Universita di Milano, Milano, Italy (Drs La Vecchia and Decarli); Istituto di Ricerche Farmacologiche "Mario Negri," Milano, Italy (Drs La Vecchia and Negri); Servizio di Epidemiologia, Centro di Riferimento Oncologico, Aviano (PN), Italy (Dr Franceschi); Istituto Nazionale Tumori, Milano, Italy (Dr Decarli); Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy (Dr Giacosa); and Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA (Ms Lipworth). Address correspondence to Ms Lipworth, Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA.

olive oil may be protective against breast carcinogenesis. In the Spanish study,[7] the estimated relative risk (RR) was 0.7 for women using more than one teaspoon of olive oil per day compared with nonconsumers. In the Greek study,[8] the RR was 0.75 for women using olive oil more than once per day compared with those using it once per day only. A smaller Spanish study[9] also found some indication of an inverse relationship between monounsaturated fatty acids (including olive oil as a major source) and breast cancer risk.

Using data from a multicenter Italian case-control study, we were able to provide a comprehensive quantification of intake of olive oil and other oils and fats. The results of these analyses are reported here.

Materials and methods

The data were derived from a case-control study of breast cancer[10] conducted between June 1991 and February 1994 in six Italian areas: Greater Milan, the province of Pordenone, the urban area of Genoa, and the province of Forlì in northern Italy; the province of Latina, in central Italy; and the urban area of Naples, in southern Italy. The same structured questionnaire and coding manual were used in all study centers, and all interviewers were centrally trained and tested for reliability and reproducibility. On average, less than four percent of cases and controls approached for interview refused to participate.

Cases were women with incident, histologically confirmed breast cancer, admitted to the major teaching and general hospitals in the areas under surveillance. A total of 2,569 cases aged 23 to 74 years (median age 55 years) were included in the present analysis.

Controls were women residing in the same geographic areas and admitted for acute conditions to the same network of hospitals where cases had been identified. Women were not included if they had been admitted for gynecologic, hormonal, neoplastic, or digestive diseases. A total of 2,588 controls, aged 20 to 74 years (median age 56 years), was interviewed. They were admitted to hospital for a wide spectrum of acute diseases or conditions, unrelated to known or likely risk factors for breast cancer. Of these, 22 percent had traumatic conditions (mostly fractures and sprains), 32 percent had non-traumatic orthopedic disorders (mostly low back pain and disc disorders), 16 percent were admitted for acute surgical conditions, 18 percent had eye diseases, and 12 percent had miscellaneous other illnesses, such as ear, nose and throat, and dental disorders.

The structured questionnaire included information on personal characteristics and habits, education and other socioeconomic factors, general lifestyle habits, such as smoking, alcohol and coffee consumption, a validated food-frequency consumption section,[11] a few indicators of physical activity, gynecologic and obstetric data, other elements of medical history, and history of lifetime use of oral contraceptives (OC), hormonal replacement therapies in menopause, and female hormone preparations for other indications.

The interviewer-administered food-frequency questionnaire (FFQ) was developed to assess the usual diet of subjects and, therefore, intake of total energy as well as macro- and micro-nutrients.[11] The FFQ included 78 foods, groups of foods or recipes subdivided into seven sections: (i) bread, cereals, and first courses; (ii) second courses (*i.e.*, meat and meat substitutes); (iii) side dishes (*i.e.*, vegetables); (iv) fruits; (v) sweets, desserts and soft drinks; (vi) milk, hot beverages and sweeteners; (vii) alcoholic beverages. Additional questions aimed at assessing fat intake pattern also were included in the FFQ. These addressed the type of fat used as a condiment for raw and cooked vegetables, to prepare meat dishes, to fry, and to prepare pasta or rice dishes (*i.e.*, specific seed oils—safflower, maize, peanut, and soya; mixed seed oils—including unspecified seed oils and cheaper brands with variable composition; butter and margarine); subjective judgment on quantity of fat used in seasoning (scarce, average, high); habits of eating or not eating the visible fat on meat, ham or chicken; and eating or leaving on the plate the seasoning or sauce. These questions, as well as portion size, were used to modulate estimates from the composition of recipes. Estimates of olive oil and other types of oil and fat intake were derived from frequency and self-assessed quantity of use of main seasoning fats, as well as from estimates of fats included in various foods and recipes.

Data analysis

Odds ratios (OR) of breast cancer, and the corresponding 95 percent confidence intervals (CI) for various measures of olive oil and other types of fat consumption were derived using unconditional multiple logistic regression, fitted by the method of maximum likelihood.[12] The regression equations included terms for: (i) study center, age, education, parity, age at first birth, menopausal status, alcohol, and total calorie intake, plus the various types of oils and fats considered; and (ii) all the above variables, plus age at menarche and at menopause, history of benign breast disease, family history of breast cancer, body mass index (BMI) (wt/ht^2), OC and hormone replacement treatment use. Since the results from the two models were not materially different, only those from the simplest are presented.

Intake quintiles for various fats were computed on:

(i) absolute levels (g), and (ii) the residuals of the regression of the nutrient on energy following the method suggested by Willett and Stampfer.[13] Both analyses yielded similar results, but only the results from the latter approach were chosen for presentation on the basis of presumed validity and in order to facilitate comparability with other studies. Tests for trend were based on the likelihood ratio test between the models with and without a variable whose value was the number of the quintile to which the subject belonged.[12] Various types of fats also were introduced in the model as continuous variables. In these models, the unit measure was set as the difference between the upper cutpoint of the fourth quintile (except for margarine and specific seed oils) and that of the first one. Wald's test was used to assess the significance of the coefficients for the continuous variables.[12]

Results

Table 1 gives the distribution of breast cancer cases and the comparison group according to age and other major identified covariates. Compared with control women, cases were more educated and less frequently nulliparous and in pre-menopause, and they reported earlier first birth, somewhat higher alcohol intake, and higher total energy intake.

Table 2 gives the distribution of cases and controls according to approximate quantiles of intakes of olive oil, other vegetable oils, butter, and margarine.

The corresponding ORs are presented in Table 3. For olive oil, compared with the lowest quintile, the ORs were 1.05, 0.99, 0.93, and 0.87 for increasing levels of intake, and the OR per unit was 0.89 (CI = 0.81-0.99, $P = 0.03$). For the group of specific seed oils (safflower, maize, peanut, and soya), the OR for the highest quantile of intake was 0.72 (CI = 0.6-0.9). The ORs for the highest level of intake were 0.80 (CI = 0.7-1.0) for mixed or unspecified seed oils, 0.95 (CI = 0.8-1.1) for butter, and 0.96 (CI = 0.7-1.3) for margarine. The ORs per continuous unit were 0.88 ($P < 0.001$) for specific seed oils, 0.98 for mixed seed oils ($P = 0.06$), 1.00 for butter ($P = 0.96$), and 0.96 for margarine ($P = 0.48$).

No consistent interaction pattern emerged when consumption of oils and fats was considered in separate strata of menopausal status (Table 4). For instance, the association was significant for specific seed oils in pre-menopause only and for mixed seed oils in post-menopause, and no material difference was observed for olive oil, butter, and margarine between pre- and postmenopausal women. Only for mixed seed oils was a significant heterogeneity observed in strata of menopausal status ($\chi^2_1 = 5.39$, $P < 0.05$).

Discussion

This study, based on a large dataset from various Italian regions, shows no positive association between several types of oils and fats and breast cancer risk. In fact, inverse relationships with breast cancer were observed with intake of olive oil and various types of seed oils, although not with butter or margarine. Thus, this study confirms that oils and fats do not increase breast cancer risk, while olive oil and selected seed oils may provide some protection.

Estimated intakes of various sources of dietary fats in this study were based on a validated food frequency

Table 1. Distribution of 2,569 cases of breast cancer and 2,588 controls[a] according to age and selected covariates, Italy, 1991-94

	Cases		Controls	
	No.	(%)	No.	(%)
Age				
<35	87	(3.4)	140	(5.4)
35-44	383	(14.9)	332	(12.8)
45-54	772	(30.1)	692	(26.7)
55-64	799	(31.1)	784	(31.1)
65-74	528	(20.6)	804	(24.0)
Education				
<7 years	1,259	(49.0)	1,569	(60.0)
7-11 years	714	(27.8)	642	(24.8)
≥12 years	582	(22.7)	354	(13.7)
Unknown	14	(0.5)	23	(0.9)
Menopausal status				
Premenopausal	986	(38.4)	842	(32.5)
Postmenopausal	1,578	(61.4)	1,745	(67.4)
Parity				
Nulliparous	402	(15.7)	380	(14.7)
1-2	1,551	(60.4)	1,043	(54.2)
≥3	613	(23.9)	803	(31.0)
Age at first birth[b]				
<25 years	902	(35.1)	1,179	(5.6)
≥25 years	1,265	(49.2)	1,029	(39.8)
Alcohol intake (g/day)				
<1.6	979	(39.1)	1,107	(42.8)
1.6-11.9	515	(20.1)	491	(19.0)
12-25.9	465	(18.1)	439	(17.0)
≥26	610	(23.7)	551	(21.3)
Total energy intake (kcal/day)				
<1,510	444	(17.3)	587	(22.7)
1,510-1,795	522	(20.3)	509	(19.7)
1,795-2,053	534	(20.8)	498	(19.2)
2,053-2,409	547	(21.3)	489	(18.7)
≥2420	572	(20.3)	509	(19.7)

[a] For some variables, the sum of strata does not add up to the total because of missing values.
[b] Parous women only.

Table 2. Distribution of 2,569 cases of breast cancer and 2,588 controls according to quintiles of intake of selected oils and fats, Italy, 1991-94

Oil or fat	Quintile of intake					
	1 (low)	2	3	4	5 (high)	χ^2_1 (trend)[a]
Olive oil						
Upper limits (g/day)	10.7	19.1	28.1	40.7	—	
Cases	469	525	529	524	522	2.97
Controls	567	507	503	507	509	
Specific seed oils[b]						
Upper limits (g/day)	0	3.8	9.5	—	—	
Cases	1,304	443	442	380	—	8.80[c]
Controls	1,281	414	415	478	—	
Mixed seed oils						
Upper limits (g/day)	0.2	0.4	0.8	3.0	—	
Cases	491	504	560	527	487	5.29[c]
Controls	492	485	547	520	544	
Butter						
Upper limits (g/day)	0.4	0.9	1.7	4.9	—	
Cases	491	504	560	527	487	0.08
Controls	492	485	547	520	544	
Margarine						
Upper limits (g/day)	0	4.2	—	—	—	
Cases	2,355	104	120	—	—	0.23
Controls	2,355	119	114	—	—	

[a] Derived from unconditional multiple logistic regression equations including terms for study center, age, education, parity, age at first birth, menopausal status, alcohol, total energy intake, and the various types of oils and fats.
[b] Safflower, maize, peanut, or soya.
[c] $P < 0.05$.

Table 3. Odds ratios[a] of breast cancer (and 95% confidence intervals) according to quintiles of intake of selected oils and fats, Italy, 1991-94

Oil or fat	Quintiles of intake					OR[c]
	1 (low)[b]	2	3	4	5 (high)	
Olive oil	1	1.05	0.99	0.93	0.87	0.89
(unit = 30 g)	—	(0.9-1.3)	(0.8-1.2)	(0.7-1.2)	(0.7-1.1)	(0.81-0.99)
Specific seed oils[d]	1	1.01	0.94	0.72	—	0.88
(unit = 9.5 g)	—	(0.8-1.2)	(0.8-1.1)	(0.6-0.9)	—	(0.83-0.94)
Mixed seed oils	1	0.96	0.94	0.88	0.80	0.98
(unit = 2.8 g)	—	(0.8-1.1)	(0.8-1.1)	(0.7-1.1)	(0.7-1.0)	(0.96-1.00)
Butter	1	0.85	1.00	0.97	0.95	1.00
(unit = 4.5g)	—	(0.8-1.0)	(0.8-1.2)	(0.8-1.2)	(0.8-1.1)	(0.95-1.06)
Margarine	1	0.90	0.96	—	—	0.96
(unit = 4.2 g)	—	(0.7-1.2)	(0.2-1.3)	—	—	(0.85-1.08)

[a] Estimates from unconditional multiple logistic regression equations including terms for study center, age, education, parity, age at first birth, menopausal status, alcohol, total energy intake, and the various types of oils and fats.
[b] Reference category.
[c] OR = odds ratio, continuous per unit.
[d] Safflower, maize, peanut, or soya.

Table 4. Odds ratios[a] of breast cancer according to quintiles of intake of selected oils and fats in strata of menopausal status, Italy, 1991-94

Oil or fat	Quintiles of intake					OR[c]	(CI)[d]
	1 (low)[b]	2	3	4	5 (high)		
Olive oil							
Pre-menopause	1	1.1	1.2	1.0	0.9	0.91	(0.77-1.07)
Post-menopause	1	1.0	0.9	0.9	0.8	0.90	(0.78-1.02)
Specific seed oils							
Pre-menopause	1	1.0	0.8	0.6	—	0.89	(0.81-0.97)
Post-menopause	1	1.1	1.1	0.8	—	0.88	(0.81-0.95)
Mixed seed oils							
Pre-menopause	1	1.2	1.2	1.2	1.0	1.01	(0.98-1.05)
Post-menopause	1	0.9	0.8	0.8	0.7	0.97	(0.95-1.00)
Butter							
Pre-menopause	1	0.8	1.0	1.0	1.0	1.03	(0.94-1.12)
Post-menopause	1	0.8	1.1	1.0	1.0	0.98	(0.91-1.06)
Margarine							
Pre-menopause	1	0.9	1.0	—	—	1.01	(0.80-1.29)
Post-menopause	1	0.9	1.0	—	—	0.94	(0.82-1.08)

[a] Estimates from unconditional multiple logistic regressions equations including terms for study center, age, education, parity, age at first birth, menopausal status, alcohol and total energy intake.
[b] Reference category.
[c] OR = odds ratio, continuous per unit.
[d] CI = 95% confidence interval.
[e] Safflower, maize, peanut, or soya.

questionnaire (average correlation coefficients for various types of fats and fatty acids 0.64 for reproducibility, 0.45 for validity),[11] and included measures of fats both in foods and seasoning and in various recipes. Thus, at variance with previous work,[6-9,14] the computation of fat intake was not based only on self-reported use of different types of fat for seasoning but on an estimate of the content of fat for seasoning in a number of different dishes, modulated by frequency of consumption of each dish and individual fat intake pattern, as reported in an *ad hoc* section of the food frequency questionnaire. Although this approach is not immune from arbitrariness (*e.g.*, with regard to recipe composition), it should allow a more accurate assessment of fat-intake pattern than simple questions such as number of tablespoons of olive oil per day.

The RR estimates presented were adjusted for education (as an indicator of social class), major reproductive factors, alcohol and calorie intake. None of the estimates was modified materially when further adjustment was made for BMI, hormone replacement, and a large number of other known or likely risk factors for breast cancer.

This study shares the strengths and some of the limitations of other hospital-based case-control studies.[12,15] Although case identification was not strictly population-based, cases were identified in the major public hospitals in the areas under surveillance, reducing the scope for selection bias. With reference to the comparison group, only acute conditions, unrelated to known or likely risk factors for breast cancer, were included. Further, separate comparison of cases with major diagnostic categories of controls produced mutually consistent results. Selective differential recall of fat intake by cases and controls, and particularly fat type-specific recall, is highly unlikely in the present dataset, since issues concerning diet and cancer are not entertained widely in Italy. Finally, the hospital-based design is likely to have improved the comparability of diet recall by cases and controls, and the participation was practically complete for both cases and controls.

The results of this study are consistent with the large body of evidence indicating that dietary fats do not increase the risk for breast cancer.[16,17] With reference to types of oils and fats, these results are generally consistent with the findings that emerged from Spanish[7,9] and Greek[8] data, suggesting that olive oil may be protective against breast carcinogenesis, as well as those from a previous study in northern Italy[6] showing a moderate inverse association between olive oil intake and breast cancer risk. This apparent effect of

olive oil was consistent in strata of age and menopausal status. The quantitative differences in point estimates across various studies may be due to chance or to different measures of olive oil intake in various Mediterranean populations.

It appears, therefore, that olive oil and other vegetable oils may have a more favorable effect than butter or margarine—and hence saturated fatty acids—on breast carcinogenesis. In terms of potential biologic mechanisms, whether this is attributable to the fatty acid composition of olive oil (mainly oleic acid, a monounsaturated fatty acid) and seed oils (essentially a mixture of mono- and polyunsaturated fatty acids), with a consequent reduced intake of saturated fatty acids, to their content of specific micronutrients (*e.g.*, vitamin E, with its antioxidant properties),[18] or to a combination of both mechanisms is not clear.

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