The association of fat and other macronutrients with breast cancer: a case–control study from Greece

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Summary

The Greek diet is characterized by a high total fat but low saturated fat intake. In a hospital-based case–control study of female breast cancer conducted in Athens (1989–91), 820 patients with confirmed cancer of the breast were compared with 795 orthopaedic patient controls and 753 hospital visitor controls, matched to the cases by age and interviewer. Diet was ascertained through a semiquantitative food frequency questionnaire; macronutrient intakes were estimated from the nutrient content of a selected typical portion size for each specified food item, summed for all items. Logistic regression was used to analyse the data, controlling for demographic and reproductive risk factors for breast cancer as well as for total energy intake and mutual confounding among nutrients. There was no significant or suggestive association of total protein, total fat, categories of fat or total carbohydrates with breast cancer risk. Thus, the mutually adjusted relative risk per quintile and (in parenthesis) 95% confidence interval were: for protein, 1.06 (0.94–1.20); saturated fat, 0.99 (0.89–1.11); monounsaturated fat, 0.97 (0.88–1.07); polyunsaturated fat, 1.05 (0.97–1.13); and total carbohydrates, 1.03 (0.94–1.12). In alternative analytical approaches only total protein appeared to be positively associated to the occurrence of breast cancer with some consistency, but the results were far from statistically significant. These findings do not support a role for fat or other energy-generating nutrients in the aetiology of breast cancer.

The epidemiology of breast cancer has been studied more than that of any other disease, and several risk factors have been established (Kelsey, 1993). However, a substantial part of the variation in breast cancer occurrence between and within population groups cannot be explained in terms of the identified factors (Seidman et al., 1982; Hsieh et al., 1990). There seems to be little doubt that nutrition plays a central role in the aetiology of this disease, but investigators are divided as to the life stage during which nutritional factors exert their effect. Several scientists believe that qualitative aspects of diet during adult life may be critical determinants of breast cancer risk (Howe et al., 1990; Prentice & Sheppard, 1990), whereas others are of the opinion that the risk for breast cancer is affected by nutrition mainly before or during adolescence (Cole & MacMahon, 1969; Micocci, 1985; de Waard & Trichopoulos, 1988; Albanes & Wilick, 1988; Willett, 1989). The role of adult diet, and in particular fat intake, in the natural history of breast cancer has become the focus of intense debate (Sun, 1988; Michels & Willett, 1991). The collective evidence from case–control studies (La Vecchia et al., 1987; Toniolo et al., 1989; Ewertz & Gill, 1990; Howe et al., 1990; Boyd et al., 1993) suggests that fat intake in adult life may increase the risk for breast cancer, whereas with few exceptions (Knekt et al., 1990; Howe et al., 1991) cohort studies indicate no association between dietary fat in adult life and incidence of breast cancer (Hunter & Willett, 1993). Ecological data (Armstrong & Doll, 1975; Prentice et al., 1988; Prentice & Sheppard, 1990) also support a relationship between dietary fat and breast cancer, but are less powerful than data from retrospective and prospective studies in demonstrating causality. We have examined the association of dietary fat and other macronutrients with breast cancer in Athens through a large case–control study that utilized two independent control series. Average total fat intake is high in Greece, accounting for 42% of total calories, and the variability of fat intake is also considerable (Trichopoulou et al., 1993).

Subjects and methods

During a 3 year period from January 1989 to December 1991, all newly diagnosed women with breast cancer who were residents of the Greater Athens area (population about 3.5 million) were identified in four major hospitals, representing about 50% of breast cancer cases occurring in this area. The hospitals included in the study were: Athens Medical Center, Elena's Hospital for Women and Agios Savas Cancer Hospital in Athens and Metaxa Cancer Hospital in Piraeus. Eight hundred and seventy-three histologically confirmed cases were identified. It was not possible to interview 53 patients (6%), and 820 were eventually included in the study. Each case was interviewed in the hospital before the first discharge, by specially trained interviewers. The interview lasted 45–65 min and was based on a structured questionnaire.

For each case, two controls were to be selected: one from among hospital visitors (excluding first-degree relatives and women who have had breast cancer) in the same hospital; the other, an orthopaedic patient in the major accident hospital of Athens (for breast cancer cases who were residents of Athens and surroundings) or Piraeus (for cases who were residents of Piraeus and surroundings). Each control had to be ±5 years of age with respect to the index case, and all controls were residents of the same area. Eight hundred and thirty eligible hospital controls and 808 eligible visitor controls were identified. We were not able to interview 35 (4%) hospital controls and 55 (7%) visitor controls. Among the hospital controls, 342 (43%) had fractures, 223 (28%) had arthroplasty and the remaining 230 (29%) had other orthopaedic conditions. In none of these middle-aged or older women with fractures was alcohol intake reported as a contributing factor in the occurrence of the incident that had caused the fracture. All controls were interviewed in the hospital using the same questionnaire as for the cases. Every case–control triplet was interviewed by the same interviewer.

The questionnaire covered demographic, socioeconomic, reproductive and biomedical variables as well as including a semiquantitative food frequency section. Specifically, all subjects were asked to indicate the average frequency of consumption, over a period of 1 year before onset of the present

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disease (or before the interview for visitor controls), of 115 food items or beverage categories per month, per week or per day. For analysis, the frequency of consumption of different food items was quantified approximately in terms of the number of times per month the food was consumed, as done by Graham et al. (1978) and Katsouyanni et al. (1991a). Thus daily consumption was multiplied by 30 and weekly consumption by 4, while a value of 0 was assigned to food items rarely or never consumed.

Nutrient intakes for individuals were estimated by multiplying the nutrient contents of a selected typical portion, for each specified food item, by the frequency that the food item was eaten per month and adding these estimates for all food items. Food consumption data were based on a nutrient database developed in Greece by the Department of Nutrition and Public Health, Athens School of Public Health (Trichopoulou, 1992). The portion size estimation was based on the results from previous validation studies (Katsouyanni et al., 1991b; Giardelli et al., 1994), and the nutrient content was calculated on the basis of Greek recipes (Trichopoulou, 1992). The macronutrient intakes used were: protein (g), total fat (g), saturated, monounsaturated and polyunsaturated fat (g) and carbohydrates (g), as well as total energy (kcal). In order to investigate the relationship of the estimated nutrient intakes to breast cancer risk, a preliminary analysis was undertaken based on the comparison of the frequency distribution of cases and controls by marginal quintiles of individual nutritional factors. No differences have been found among methods for quantile classification of exposure levels in case-control studies; thus, use of the marginal frequencies was based on practical advantages (Hsieh et al., 1991). Since most nutrients are positively correlated with total energy (Willett & Stampfer, 1986), calorie adjustment was utilized. Nutrient intakes were alternately or simultaneously used as independent variables.

Controls were paired to cases in order to control for patient origin and interviewer identity. However, only 680 complete triplets were available, and for these conditional and unconditional logistic regression (controlling for the matching factors) generated identical results. Therefore all cases and controls were utilised, and the data were modelled through unconditional logistic regression using the SPSS (1980) statistical package. Comparison of breast cancer cases with either control series generated similar results, as will be seen in the Results section. Thus, for most analyses, the two control series were combined in order to increase the precision of the effect estimates. Furthermore, cross-tabulated analysis by hospital did not reveal any systematic or striking differences.

Since demographic and reproductive risk factors for breast cancer are well established, a core model was used that included: age (years), place of birth (urban, rural), Quetelet index (kg m⁻²), parity (parous, nulliparous), age at first pregnancy (years; among parous women), age at menarche (years) and menopausal status (post-menopausal, premenopausal). Exogenous oestrogens are rarely used in Greece, and there was no reason to control for use of oral contraceptives and menopausal oestrogens (among cases, 40 had ever used oral contraceptives and 57 menopausal oestrogens; among all controls, these were the corresponding numbers were 66 and 98).

**Results**

Table I shows the distribution of cases and controls by age, place of birth, Quetelet index, parity, at first birth, age at menarche and menopausal status. The results are compatible with the established risk profile of breast cancer.

|        | Cases | Controls |
|--------|-------|----------|
| Age (years) | 56.4 (0.43) | 54.4 (0.32) |
| Place of birth |              |           |
| Urban | 620 (75.7) | 1106 (71.6) |
| Rural | 199 (24.3) | 439 (28.4) |
| Quetelet index (kg m⁻²) | 26.6 (1.02) | 25.9 (0.75) |
| Ever pregnant | Yes | 657 (80.2) | 1164 (75.2) |
| No | 162 (19.8) | 384 (24.8) |
| Age at first birth (years) | 26.4 (0.21) | 25.9 (0.16) |
| Age at menarche (years) | 12.9 (0.06) | 13.1 (0.04) |

Table I Distribution of 820 cases of breast cancer and 1,548 controls by age, place of birth, Quetelet index, parity, at first birth, age at menarche and menopausal status

| Variable | Groups or units | Relative risk | P-value (two tailed) |
|----------|----------------|---------------|---------------------|
| Age      | 1 year        | 1.03          | <10⁻³               |
| Birth place | Rural vs urban | 0.84          | 0.10                |
| Quetelet index | 1 kg m⁻² | 0.99          | 0.78                |
| Ever pregnant | Yes vs no | 0.79          | 0.38                |
| Age at first birth | 1 year | 1.02          | 0.07                |
| Age at menarche | 1 year | 0.94          | 0.03                |
| Menopausal status | Post vs pre | 0.56          | <10⁻¹               |

Table II Multiple logistic regression-derived, mutually adjusted relative risks for breast cancer, according to selected demographic and reproductive variables

over-report, which is accounted for in subsequent nutritional analyses by controlling for energy intake. There seems to be little evidence that any macronutrient is specifically and disproportionately associated with breast cancer risk. However, these data are inherently confounded and therefore not directly interpretable.

Table IV shows the nutrient-specific associations with breast cancer risk controlling for energy intake and the variables in the core model (Table II), but without mutual adjustment. The regression coefficients refer to a one quintile increase in the relevant nutrient. There is no evidence for a substantial or significant association of any macronutrient with breast cancer risk. The corresponding associations after controlling for mutual confounding among macronutrients as well as for the core variables are shown in Table V. Total fats are not included to avoid collinearity problems. Again, no energy-generating nutrient appears to be associated with breast cancer risk.

In Table VI adjustment for energy intake is done with the Willett–Stampfer (Willett & Stampfer, 1986) method, which uses nutrient residuals from the energy-predicted estimates for the corresponding nutrients. Furthermore, in Table VI, breast cancer cases are compared with each control series as well as with both control series combined. The purpose of this table is to explore whether alternative analytical approaches might generate different impressions. There is no such evidence. The results confirm that there are no significant or substantial associations between any of the macronutrient groups and breast cancer risk. Only protein appears to be positively associated with the risk for breast cancer in both Tables V and VI, but the results are not statistically significant. Modelling these data without mutual adjustment among macronutrients led to essentially the same conclusions. In addition, separate use of hospital controls with fractures and hospital controls with arthroplasty or other conditions did not generate inconsistent results.
Table III: Distribution of 820 cases and 1,548 controls by marginal quintiles of total energy and major macronutrient intake

|       | Quintilea | 1  | 2  | 3  | 4  | 5  | Total | α, linear trend | P-value |
|-------|-----------|----|----|----|----|----|-------|---------------|--------|
| Total energy (kcal) | Cases | 148 | 166 | 166 | 160 | 176 | 816 | 2.05 | 0.04 |
|       | Controls | 319 | 307 | 308 | 313 | 298 | 1,545 |        |        |
| Protein (g) | Cases | 145 | 160 | 184 | 142 | 188 | 819 | 2.66 | 0.01 |
|       | Controls | 329 | 312 | 290 | 331 | 285 | 1,547 |        |        |
| Total fat (g) | Cases | 157 | 164 | 175 | 153 | 170 | 819 | 1.13 | 0.26 |
|       | Controls | 315 | 310 | 300 | 319 | 303 | 1,547 |        |        |
| Saturated fat (g) | Cases | 154 | 157 | 176 | 155 | 177 | 819 | 1.85 | 0.06 |
|       | Controls | 319 | 316 | 298 | 318 | 296 | 1,547 |        |        |
| Monounsaturated fat (g) | Cases | 153 | 165 | 172 | 156 | 173 | 819 | 1.66 | 0.10 |
|       | Controls | 320 | 309 | 301 | 318 | 299 | 1,547 |        |        |
| Polyunsaturated fat (g) | Cases | 164 | 149 | 161 | 170 | 175 | 819 | 2.05 | 0.04 |
|       | Controls | 309 | 324 | 313 | 304 | 297 | 1,547 |        |        |
| Carbohydrates (g) | Cases | 143 | 160 | 181 | 173 | 162 | 819 | 2.02 | 0.04 |
|       | Controls | 330 | 313 | 293 | 300 | 311 | 1,547 |        |        |

*There are few missing values. The quintile ranges (per day) are as follows: total energy (kcal), ≤1,521.8, 1,521.9–1,752.8, 1,752.9–1,980.0, 1,980.1–2,266.0, ≥2,266.1; protein (g), ≤59.7, 59.8–67.2, 67.3–75.9, 76.0–89.4, ≥89.5; total fat (g), ≤79.9, 80.0–91.2, 91.3–101.9, 102.0–119.2, ≥119.3; saturated fat (g), ≤27.0, 27.1–32.4, 32.5–37.4, 37.5–44.7, ≥44.8; monounsaturated fat (g), ≤40.1, 40.2–44.7, 44.8–50.3, 50.4–59.0, ≥59.1; polyunsaturated fat (g), ≤8.7, 8.8–10.6, 10.7–12.6, 12.7–16.1, ≥16.2; carbohydrates (g), ≤137.2, 137.3–173.1, 173.2–203.3, 203.6–243.3, ≥243.1. α-values are age adjusted.

Table IV: Multiple logistic regression-derived coefficients for the major macronutrients

| Nutrient (g) | bα | s.e.α | P-value | Relative risk | 95% confidence interval |
|--------------|----|-------|---------|--------------|-------------------------|
| Protein      | 0.0703 | 0.0618 | 0.26 | 1.07 | 0.95–1.21 |
| Total fat    | -0.0585 | 0.0533 | 0.27 | 0.94 | 0.85–1.05 |
| Saturated fat| -0.0008 | 0.0469 | 0.99 | 1.00 | 0.91–1.10 |
| Monounsaturated fat | -0.0207 | 0.0467 | 0.66 | 0.98 | 0.89–1.07 |
| Polyunsaturated fat | 0.0404 | 0.0388 | 0.30 | 1.04 | 0.97–1.12 |
| Carbohydrates | 0.0508 | 0.0553 | 0.36 | 1.05 | 0.95–1.17 |

*Coefficients in this table are not mutually adjusted, but they are adjusted for age, place of birth, parity, age at first pregnancy, age at menarche, menopausal status, Quetelet index and total energy intake. αCoefficient (b) from logistic regression model, per quintile. bStandard error (s.e.) around the coefficient.

Table V: Multiple logistic regression-derived, mutually adjusted coefficients for the major macronutrients

| Variable | bα | s.e.α | P-value | Relative risk | 95% confidence interval |
|----------|----|-------|---------|--------------|-------------------------|
| Protein  | 0.0589 | 0.0625 | 0.35 | 1.06 | 0.94–1.20 |
| Saturated fat | -0.0097 | 0.0569 | 0.86 | 0.99 | 0.89–1.11 |
| Monounsaturated fat | -0.0297 | 0.0479 | 0.53 | 0.97 | 0.88–1.07 |
| Polyunsaturated fat | 0.0486 | 0.0390 | 0.21 | 1.05 | 0.97–1.13 |
| Carbohydrates | 0.0286 | 0.0437 | 0.51 | 1.03 | 0.94–1.12 |

*Controlling also for age, place of birth, parity, age at first pregnancy, age at menarche, menopausal status, Quetelet index and total energy intake. αCoefficient (b) from logistic regression model, per quintile. bStandard error (s.e.) around the coefficient.

Table VI: Multiple logistic regression-derived, mutually adjusted coefficients for the major macronutrients, controlling for the core variables and for energy intake with the Willett–Stampfer approach (Willett & Stampfer, 1986) and considering each control series separately as well as together

| Variable | bα | s.e.α | P-value | b | s.e. | P-value | Combined control seriesα | b | s.e. | P-value |
|----------|----|-------|---------|---|-----|---------|--------------------------|---|-----|--------|
| Saturated fat | 0.0068 | 0.0457 | 0.88 | 0.0456 | 0.0637 | 0.47 | -0.0311 | 0.0227 | 0.56 |
| Monounsaturated fat | 0.0339 | 0.0538 | 0.53 | -0.0025 | 0.0564 | 0.96 | -0.0111 | 0.0475 | 0.82 |
| Polyunsaturated fat | 0.0508 | 0.0419 | 0.23 | -0.0125 | 0.0433 | 0.77 | -0.0010 | 0.0366 | 0.98 |
| Carbohydrates | 0.1029 | 0.0704 | 0.14 | -0.0749 | 0.0841 | 0.37 | -0.0627 | 0.0697 | 0.37 |
| Protein | 0.0758 | 0.0417 | 0.07 | 0.0166 | 0.0425 | 0.70 | 0.0534 | 0.0363 | 0.14 |

*Calculation of residuals from a combined database and a different constellation of confounding factors when the control series are combined explain why the ‘combined’ regression coefficients deviate from the means of the control series-specific regression coefficients. αCoefficient (b) from logistic regression model, per quintile. bStandard error (s.e.) around the coefficient. αTo avoid collinearity, protein estimates were derived from a model in which protein was substituted for carbohydrates.
Discussion

This study is large, which reduces the role of chance variation to acceptable levels. Adjustment for known demographic and reproductive risk factors for breast cancer controlled for this source of confounding, whereas mutual confounding among macronutrients was accounted for to the extent permitted by the limited variability of dietary assessment in any investigation in nutritional epidemiology (Tzonou et al., 1986). As in any case–control study, the dominant concerns are selection and information bias. Low rates of non-response among all three series and similarity of findings when cases were compared with either of the two control series suggest that overt selection bias was not operating in the investigation.

Some breast cancer patients are likely to report more completely or over-report their dietary intakes in comparison with women in the control series. This was evident in the present study (Table III) as well as in many earlier case–control investigations (Toniolo et al., 1989; review by Hunter & Willett, 1993). However, over-reporting, or more complete reporting, by cases is likely to cover foods in general rather than specific food items with particularly high or low contents of specific nutrients. Few persons, and certainly very few Greek women, have specific ideas let alone beliefs, about the nutritional aetiology of breast cancer and sufficient knowledge about the nutritional content of the various food items. When over-reporting is general (Table III), adjustment for energy intake (Willett & Stampfer, 1986; Willett, 1990) eliminates the consequences of over-reporting in information bias (Trichopoulos et al., 1991). Indeed, in a comparison of prospective and retrospective assessment of diet in the aetiology of breast cancer (Giovannucci et al., 1993), retrospective (case–control) data on fat consumption with over-reporting by cases generated a null result after adjustment for energy intake (P ~ 0.78). This appears to be biologically more plausible than the finding of the prospective component of the investigation, suggesting an almost significant inverse association between fat intake and breast cancer (Table 4 of Giovannucci et al., 1993). Furthermore, in the Giovannucci et al. (1993) study, retrospective data were available for only 77% of the study subjects included in the prospective component. Information bias does not appear to be an intractable problem in adequately planned and carefully analysed case–control studies of diet and cancer.

The hypothesis linking dietary fat to breast cancer risk is biologically credible. Animal data are widely considered as compatible with a promoting or growth-enhancing effect of fat on breast cancer in other species (Tannenbaum, 1942; National Academy of Sciences, 1982; Birt, 1986; National Research Council, 1989; Freedman et al., 1990; World Health Organization, 1990). Ecological correlations and time trends are frequently viewed as supportive of a positive association between fat intake and breast cancer risk (Prentice et al., 1988; Prentice & Sheppard, 1990). Dietary fat also has been shown in small human studies to be correlated with oestrogenic levels (Goldin et al., 1986; Rose et al., 1987; Boyar et al., 1988; Adlercreutz, 1990; Bennett & Ingram, 1990; Prentice et al., 1990), and several well-conducted case–control studies have suggested that there may indeed be a weak positive association between fat intake and breast cancer (La Vecchia et al., 1987; Toniolo et al., 1989; Howe et al., 1990). However, the animal studies often have been confounded by total energy intake; the ecological studies are susceptible to extensive confounding; the metabolic studies have for the most part lacked appropriate control groups; and selection bias could not be excluded in some case–control studies (Willett & Stampfer, 1990). By contrast, the results of the largest cohort study undertaken until now, the Nurses’ Health Study (Willett et al., 1992), do not support the existence of a positive association, and the collective evidence from other smaller cohort studies on fat intake and breast cancer risk is compatible with the absence of an association or a minimal increase of risk (Hunter & Willett, 1993).

Some scientists have argued that the lack of an association in the Nurses’ Health Study may be due to the limited range of variation in that population (Prentice et al., 1988; Toniolo et al., 1989; Prentice et al., 1990). This is an unlikely explanation, since the post estimates of regression coefficients do not depend on the range of variation and the power implications, under realistic conditions, are generally small. In any case, the range of variation of fat intake in the present study was wide. With total fat expressed as a percentage of calories, these Greek women had a mean contribution of fat energy from fat of 60% in the highest quintile and of 36% in the lowest quintile. The corresponding figures in an Italian study that reported a significant association of fat intake with breast cancer risk were 46% and 26% (Toniolo et al., 1989).

The present study was large and, in all evidence, adequately controlled with two independent control series. Variation of fat intake was substantial in the study base, the dietary questionnaire was designed to ensure that the analysis adequately accounted for confounding by energy intake, for mutual confounding among nutrients and for bias due to case-over-reporting. The results do not support hypotheses invoking fat, saturated fat, other fats or other macronutrients in the adult diet as important risk factors for breast cancer. It should be added that in earlier case–control studies conducted in Greece, total fat and animal fat-containing foods (meat and meat products) have been found to significantly increase the risk of coronary heart disease (Tzonou et al., 1993) and cancer of the large bowel (Manousos et al., 1983; Trichopoulou et al., 1992), whereas in an earlier, independent, smaller case–control study of diet and breast cancer no association with fat was noted (Katsouyanni et al., 1986; Katsouyanni et al., 1988). The relatively low mortality from breast cancer in Greece (about 65% of the corresponding mortality in the USA) is in itself an argument against an important role of dietary fat in the genesis of breast cancer, since fat intake, mostly in the form of olive oil, is very high in Greece (about 42% of total energy intake) (Trichopoulou et al., 1993).

There was no evidence in the present study for a substantial, significant or differential effect of any fat category, total carbohydrates or total protein. Nevertheless, protein was the only macronutrient for which the evidence was not altogether reassuring (Tables IV and V). Protein intake has not been generally considered an important risk factor in breast carcinogenesis. Given the constraints of the study design, it was not possible to examine directly the hypotheses that intake of energy or particular macronutrients (including fats or proteins) in early life stages may be important determinants of breast cancer risk.

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