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Dietary fat and breast cancer: comparison of results from food diaries and food frequency questionnaires in the UK Dietary Cohort Consortium[1-3]

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Short running head: Fat and breast cancer.

ABSTRACT

Background: Epidemiological studies of dietary fat and breast cancer risk are inconsistent and it has been suggested that a true relation may have been obscured by imprecise measurement of fat intake.

Objective: We examined the associations of fat with breast cancer risk using estimates of fat intake from food diaries and from food frequency questionnaires pooled from four prospective studies in the United Kingdom.

Design: A total of 657 cases of breast cancer in premenopausal and postmenopausal women were matched on study, age and recruitment date with 1911 controls. Nutrient intakes were estimated from both food diaries and food frequency questionnaires. Conditional logistic regression was used to estimate odds ratios for breast cancer associated with total, saturated, monounsaturated and polyunsaturated fat intakes, adjusting for relevant covariates.

Results: Neither the food diaries nor the food frequency questionnaires showed any positive association between fat intake and overall breast cancer risk. Odds ratios in the highest versus the lowest fifth of percent energy from total fat were 0.90 (95% CI: 0.66, 1.23) for food diaries and 0.80 (95% CI: 0.59, 1.09) for food frequency questionnaires.

Conclusion: In this study breast cancer risk was not associated with fat intake in middle-aged women in the United Kingdom, irrespective of whether diet was measured by food diaries or by food frequency questionnaires.

Keywords: breast cancer; food diary; food frequency questionnaire; fat; saturated fat.

Introduction

In 1966 Lea reported that breast cancer mortality in 23 countries was positively correlated with the supply of fat in those countries (1). Since then numerous studies have investigated the hypothesis that high intakes of fat may increase breast cancer risk, but most of the results from prospective studies have been null (2, 3). In 2003 Bingham et al. suggested that the food frequency questionnaires (FFQs) used to measure fat intake in most cohort studies were too imprecise to detect a relation between fat intake and breast cancer risk, and supported this proposal by reporting results from a small prospective study in which breast cancer risk was significantly positively associated with fat intake as measured by 7-day food diaries, but not with fat intake assessed by FFQs (4). A subsequent report from the control arm of the Women's Health Initiative trial also suggested that breast cancer risk in postmenopausal women was significantly positively associated with fat intake as measured by 4-day food diaries, but not with fat intake assessed by FFQs (5).

We report here a further analysis of breast cancer risk in relation to fat intake estimated both by food diaries and by FFQs in 4 prospective studies in the United Kingdom, the UK Dietary Cohort Consortium (6). The primary aim was to examine whether this extended study would confirm the results of Bingham et al (4). We also examined the association between fat and breast cancer in the subset of postmenopausal women not using hormone replacement therapy.

SUBJECTS AND METHODS

Subjects

We used data from four prospective cohort studies in the UK (Table 1): the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk (7), EPIC-Oxford (8), the UK Women's Cohort Study (UKWCS; 9), and Whitehall II (10); data from a fifth study in the UK Dietary Cohort Consortium were not included because FFQs were not available in that study (the Medical Research Council National Survey of Health and Development). Participants gave informed consent and each study was approved by the relevant ethics committee. Each cohort collected dietary information using food diaries and FFQs. Information on demographic and lifestyle factors was collected either in interviews or in questionnaires administered prior to or at the same time as completion of the food diary.

Follow-up and ascertainment of cases of breast cancer

Follow-up for diagnosis of breast cancer was through record linkage with the Office of National Statistics and local cancer registries. The 9th and 10th Revisions of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD) were used, and cancer of the breast was defined as codes 174 or C50, respectively. For each cohort in this study, closure dates of the study period were defined as the latest dates of complete follow-up for both cancer incidence and vital status and are given in Table 1.

Case patients were individuals who were free of cancer (except non-melanoma skin cancer) at the time of diary completion and who developed breast cancer at least 12 months later (6 months in EPIC-Oxford) and before the end of the study period. In total there were 637 cases, of which 110 were premenopausal, 113 peri-menopausal, 424 postmenopausal and 10 of unknown menopausal status at the time of diary completion.

Selection of matched controls

Each case was matched to control participants, selected at random from all cohort members free of cancer (except non-melanoma skin cancer) at the date of diary completion, and free of breast cancer at the end of follow-up, within the appropriate stratum of matching criteria. Matching criteria included: cohort, age at first day of diary completion, and calendar month of diary completion. There were some differences in the details of study design between cohorts, because this work had started before the establishment of the UK Dietary Cohort Consortium: age matching was ± 3 years except in EPIC-Oxford where it was ± 6 months; date of diary matching was ± 3 months except in EPIC-Oxford where it was ± 6 months; number of controls per case was up to 4 in EPIC-Norfolk and Whitehall II, up to 5 in UKWCS, and one in EPIC-Oxford; and in EPIC-Oxford women (cases and controls) who were using hormone replacement therapy at the time of diary completion were excluded.

Measurement of food and nutrient intake

Food diaries (seven-day diaries in EPIC-Norfolk, EPIC-Oxford, Whitehall II, four-day diaries in the UKWCS) were completed at the time of recruitment (EPIC-Norfolk, Whitehall II), approximately 6 months after recruitment (EPIC-Oxford) or approximately 4 years after recruitment (UKWCS). Participants were asked to record all the foods and drinks they consumed, within times of day presented in the food diary (e.g. before breakfast; breakfast; mid-morning; etc.), and, except for the UKWCS, with photographs showing servings of representative food items to aid estimation of portion sizes. Information from the food diaries was coded to give nutrient intakes based on national food table data as described previously (6); for EPIC-Norfolk, EPIC-Oxford and Whitehall II the diaries were coded with the DINER programme (11) and for UKWCS diaries were coded with the DANTE programme (12).

The FFQs were completed at the time of recruitment and were derived from that used in the Nurses' Health Study (13) and further developed for use in the UK. The EPIC version had 130 items and was validated by comparison with weighed intakes and biomarkers (14). The UKWCS FFQ was extended to 217 items and its performance assessed in comparison with food diaries and plasma nutrient concentrations (9). The Whitehall II FFQ had 127 items and its performance was assessed in comparison with data from food diaries and serum and plasma nutrient concentrations (15).

Statistical methods

Conditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (95% CI) for breast cancer according to fifths of intake (based on intakes across all the studies) of each of total fat, saturated fat, monounsaturated fat, and polyunsaturated fat. Fat intakes were analysed using both the absolute intake and the relative intake expressed as a percentage of total energy intake. To test for trends in breast cancer risk over the distribution of intakes we calculated the ORs (95% CI) for an increase in fat intake of one standard deviation, the P value being obtained by comparing the ratio of the logarithm of the odds ratio and its standard error to the normal distribution.

Since the age matching between cases and controls was up to ± 3 years, analyses were adjusted for age as a continuous variable. The analyses were also adjusted for height (<158, 158-162, 163-167, ≥168 cm), weight (<60, 60-65, 66-71, ≥72 kg), menopausal status at recruitment (premenopausal, postmenopausal, other), parity (0, 1, 2, 3, ≥4), current use of hormone replacement therapy (no, yes), physical activity (low, low-medium, medium-high, high), alcohol intake (<1, 1-7, 8-19, ≥20 g/day) and total energy intake. For each of these variables a small number of values were unknown (height 15 missing, weight 29 missing, menopausal status 25 missing, parity 11 missing, current use of hormone replacement therapy 52 missing, physical activity 102 missing; in total 70 cases and 136 controls had missing values for some or all of these covariates); these observations were included in the analyses using a separate “missing” category for each of these variables. As well as calculating ORs for all of the women in the current analysis we also investigated breast cancer risks in the separate studies and in the following subsets: cases diagnosed at least 2 years after food diary commencement and their matched controls (to reduce the possible impact of reverse causality), and women who were postmenopausal and not using hormone replacement therapy at food diary completion.

Two-sided P values less than 0.05 were considered statistically significant. All statistical analyses were performed using Stata version 10 (16).

RESULTS

Six hundred and fifty-seven women diagnosed with breast cancer and 1911 matched controls without breast cancer were included in the analyses. The mean time from food diary completion to case diagnosis ranged from 2.4 years in the UKWCS study to 7.8 years in Whitehall II, with an average of 5.2 years (**Table 1**).

Characteristics of the cases and controls are presented in **Table 2**. Mean age at diary completion in cases was 56.4 years, compared to 57.2 years in controls. 65.5% of cases were postmenopausal at recruitment, compared with 71.7% of controls. Mean height was 1.63 m in cases, compared to 1.62 m in controls. The other non-dietary characteristics did not differ significantly between cases and controls. For the dietary characteristics, food diary estimates of energy, alcohol, monounsaturated fat and polyunsaturated fat were higher in cases than in controls, whereas for estimates from the FFQs the only significant difference was that alcohol intake was significantly higher in cases than in controls. Apart from alcohol, mean nutrient intakes in cases and controls, estimated from both the food diary and the FFQ, did not differ by more than 5%.

The correlations between fat intakes as percent of energy estimated from the food diaries and the FFQs were 0.51 for total fat, 0.61 for saturated fat, 0.40 for monounsaturated fat and 0.37 for polyunsaturated fat. Mean intakes of total fat as a percent of energy as estimated from the food diaries were 32.9% in EPIC-Norfolk, 33.3% in EPIC-Oxford, 32.5% in UKWCS and 33.6% in Whitehall II. The corresponding estimates for the FFQs were 32.0% in EPIC-Norfolk, 31.0% in EPIC-Oxford, 31.6% in UKWCS and 31.9% in Whitehall II.

Table 3 presents the associations between fat intake and overall breast cancer risk. Median total fat intakes in the lowest and highest fifths of intake were 41.0 and 94.7 g/day respectively based on estimates from the food diaries, and 40.0 and 108.5 g/day respectively based on estimates from the FFQs. As a percentage of energy, median total fat intakes in the lowest and highest fifths of intake were 25.7 and 40.3% respectively based on estimates from the food diaries, and 24.2 and 39.3% respectively based on estimates from the FFQs. There was no evidence that total fat intake was positively associated with breast cancer risk; ORs in the top fifth of fat intake were 0.87 (95% CI: 0.54, 1.41) and 0.80 (95% CI: 0.50, 1.30) for the food diary and FFQ, respectively, and the corresponding values for percent energy from fat were 0.90 (95% CI: 0.66, 1.23) and 0.80 (95% CI 0.59, 1.09), respectively.

Median saturated fat intakes in the lowest and highest fifths of intake were 14.1 and 37.2 g/day respectively based on estimates from the food diaries, and 13.7 and 43.0 g/day respectively based on estimates from the FFQs. As a percentage of energy, median saturated fat intakes in the lowest and highest fifths of intake were 8.5 and 16.5% respectively based on estimates from the food diaries, and 7.9 and 16.4% respectively based on estimates from the FFQs. There was no evidence that saturated fat intake was positively associated with breast cancer risk; ORs in the top fifth of saturated fat intake were 0.86 (95% CI: 0.57, 1.30) and 0.67 (95% CI: 0.44, 1.02) for the food diary and FFQ, respectively, and the corresponding values for percent energy from saturated fat were 0.81 (95% CI: 0.60, 1.10) and 0.81 (95% CI: 0.60, 1.09), respectively. There was also no evidence that intakes of monounsaturated fat or polyunsaturated fat were associated with breast cancer risk (**Table 3**).

Table 4 shows the ORs for breast cancer associated with an increase of one standard deviation in the intake of fats estimated from the food diary and the FFQs overall and in the four contributing studies, together with the tests for heterogeneity between studies. For all women combined, breast cancer risk was not significantly associated with a standard deviation increase in any of the fat components, either estimated from the food diaries or from the FFQs. For the food diary estimates there was significant heterogeneity between studies for saturated fat as g and as percent energy, and for polyunsaturated fat as percent energy. This heterogeneity was due to the results from the UKWCS, for which there were significant reductions in risk associated with an increase in intake of saturated fat and a significant increase in risk associated with an increase in intake of polyunsaturated fat. For the FFQ estimates, there was significant heterogeneity between studies for polyunsaturated fat as percent energy, which was due to the results from EPIC-Norfolk where there was a significant reduction in risk in association with an increase in the intake of polyunsaturated fat as percent energy. The analyses of food diary estimates of fat intake and breast cancer risk were repeated without the UKWCS. The ORs (95% CIs) for a one standard deviation increase in percent energy from fat were 0.97 (0.87, 1.07) for total fat, 1.00 (0.91, 1.11) for saturated fat, 0.98 (0.89, 1.09) for monounsaturated fat and 0.93 (0.84, 1.03) for polyunsaturated fat.

ORs for breast cancer associated with an increase of one standard deviation in the intake of fats estimated from the food diary and the FFQs for two subsets of women are shown in **Table 5**. There were no significant associations of fat with breast cancer risk in the subset of 548 cases (and 1620 matched controls) diagnosed at least 2 years after completing their food diary. In the subset of women who were postmenopausal and not using hormone replacement therapy at the time of completing the food diary (286 cases and 699 matched controls), fat intake was inversely associated with risk, and this inverse association was statistically significant for several fat intake variables estimated from the food diaries.

DISCUSSION

In this analysis overall breast cancer risk was not associated with the intake of dietary total or saturated fat as estimated from food diaries or from FFQs. Thus we did not confirm the previous findings of Bingham et al (4) and Freedman et al (5), who reported that breast cancer risk was significantly associated with some measures of fat intakes from food diaries but not from FFQs. Although both Bingham et al (4) and Freedman et al (5) reported significant associations with diary estimates of fat, their results differed: in Bingham et al (4) the association was not significant for total fat but was significant for saturated fat, whereas in Freedman et al (5) the association was significant for total fat but not for saturated fat. Furthermore, although these authors highlighted the differences in their results between the food diaries and the FFQs, their results for total fat from FFQs were in the same direction as their results from diaries. We cannot identify any reason why our results are somewhat different from those of Bingham et al (5); it should be noted that the results of Bingham et al

(4) were based on 168 breast cancer cases out of the 657 cases included in the current analysis, and that as the current results are based on nearly four times as many cases they should be more reliable.

The main strength of the current study is that it is a moderately large study with data on fat intake from both food diaries and FFQs, designed to examine the possibility that food diaries are better able to detect the putative association between fat and breast cancer. Weaknesses are that the sample size is not large enough to exclude small associations of dietary fat with breast cancer risk, and that although the research in the four cohorts was standardized in the analysis phase there were some differences between the contributing cohorts in study design (format of food diaries and FFQs, eligibility, and control selection). Examination of results from the individual studies showed no evidence of heterogeneity for total fat intake, but there was some heterogeneity for subtypes of fat. The largest departures from the overall estimates were for the food diary estimates in the UKWCS, in which risk was inversely associated with saturated fat but positively associated with polyunsaturated fat. We were not able to identify any reason for this heterogeneity, which could be due to chance, a real difference between the cohorts, or perhaps related to the different method of coding the food diaries in the UKWCS. Exclusion of the data from this cohort had no material impact on the overall results.

Validation studies using biomarkers have shown that the food diary used in these British cohorts is more accurate than the FFQ for estimating absolute intakes of some nutrients, particularly nitrogen and potassium, and it has been argued that is a better method overall (14, 17). For total fat, however, there is no direct biomarker and it cannot be assumed that the diary is better than the FFQ. In comparisons with 16 days of weighed food intakes, the correlations of total fat intake (as percent energy) with estimates from the 7-day food diary and the FFQ were 0.77 and 0.64, respectively (14). Some information on the validity of estimates of intake of saturated fat can be gained by examining its association with plasma low density lipoprotein (LDL) cholesterol; in EPIC-Norfolk, percent energy from saturated fat was positively associated with plasma LDL cholesterol for both the food diary (P trend <0.001) and the FFQ (P trend =0.011) (17). For polyunsaturated fat, a validation study in women in the Whitehall II study (15) showed almost identical correlations between serum cholesteryl ester polyunsaturated fatty acids and dietary polyunsaturated fatty acids as a percentage of total dietary fatty acids as measured by the food diary (0.49) or the FFQ (0.50). Thus the available evidence from validation studies suggests that both of the methods used in these British cohorts provide reasonably valid estimates of the intake of fat, but does not show that either method is better than the other.

We conducted two subset analyses. In the first, we examined the associations of fat with breast cancer risk in cases (and their matched controls) who had completed their food diary at least two years before diagnosis, to exclude any effects of prediagnostic events on diet; this analysis provided similar results to the overall analysis. We also examined the subset of women who were postmenopausal and not using hormone replacement therapy at the time that they completed their food diary. This subset was of interest because in the National Institutes of Health-AARP study the positive associations of total, saturated and monounsaturated fat with breast cancer risk were confined to women in this subset (18), and because the adverse effect of obesity (which might be associated with fat intake) on breast cancer risk is also largely seen in this subset (19). However, in our analysis the point estimates of the association of fat with breast cancer risk in this subset were all less than one and nearly all were lower than the corresponding point estimates for all women, and for several fat intake variables estimated from the food diary the association was significantly inverse. Thus in our analysis there was no evidence that fat intake is positively associated with breast cancer risk in the subset of postmenopausal women not taking hormone replacement therapy.

The results of other prospective studies of dietary fat intake in adult women and breast cancer risk are summarized in **Table 6**. In a pooled analysis of eight studies which all used FFQs, there was no association of total or saturated fat intake with breast cancer risk (2). In a subsequent meta-analysis of 14 prospective studies published up to 2003, including four studies which used food record or interview-based methods of assessing diets and also seven of the eight studies in the pooled analysis (2), the relative risks were 1.11 (95% CI: 0.99, 1.25) and 1.15 (95% CI: 1.02, 1.30) for the highest versus the lowest level of total fat and saturated fat, respectively (20). In subsequent studies using FFQs, there was no association of total or saturated fat intake with breast cancer risk in a Swedish cohort (21), whereas in the National Institutes of Health-AARP study (18) both total and saturated fat were weakly but significantly positively associated with risk (relative risks for high intake of 1.11 (95% CI: 1.00, 1.26) and 1.18 (95% CI: 1.06, 1.31), respectively). In the largest single study, using data from women in ten European countries (22) based mostly on FFQs (with some data from diet history methods and food records) total fat was not associated with risk whereas there was a small but significant positive association of risk with intake of saturated fat (relative risk for high intake 1.10 (95% CI: 1.01, 1.19)); it should be noted that there is some overlap between this study and the current study, since the FFQ data from EPIC-Norfolk and EPIC-Oxford are included in both analyses. In an analysis of data from both food records and FFQs for women in the control arm of the Women's Health Initiative (5) there was a large and significant association of total fat intake estimated from food records with risk (relative risk 2.09 (95% CI: 1.21, 3.61)), but no other significant associations. In two randomized controlled trials, a reduction in total fat intake did not significantly affect breast cancer risk (23, 24). Overall, the prospective studies on fat intake in adult women and breast cancer risk suggest either no association or at the most a small positive association. The earlier report of Bingham et al (4) and the study of Freedman et al (5) suggested that data from food diaries/records might give larger associations than those observed using FFQs, but the current study does not support this and suggests that any inconsistencies in the literature on the association between dietary fat and breast cancer risk are not likely to be explained simply by differences between the dietary assessment methods.

In conclusion, this study shows no evidence that breast cancer risk is associated with fat intake in middle-aged women in the UK, irrespective of whether the diet was measured by food diaries or by FFQs.

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TABLE 1

Characteristics of the 4 cohorts participating in analyses of dietary fat and breast cancer risk in the UK Dietary Cohort Consortium[1]

Cohort	Participants	Years of food diary completion	Years of food frequency questionnaire completion	Last follow up date	Mean (SD) time to diagnosis of cases (years)	Cases	Controls	Mean (SD) age at first day of food diary completion (years)
EPIC-Norfolk	General population in Norfolk	1993-1998	1993-1998	December 31, 2006	6.0 (3.0)	353	1252	59.3 (8.6)
EPIC-Oxford	General population and vegetarians in the UK	1993-1999	1993-1999	December 31, 2004	3.5 (1.9)	194	194	53.3 (10.8)
UKWCS	Middle aged women in the UK	1999-2002	1995-1998	March 31, 2006	2.4 (1.3)	42	202	56.6 (9.1)
Whitehall II	Civil servants in the UK	1991-1993	1991-1993	September 30, 2005	7.8 (3.2)	68	263	50.5 (6.0)

[1] EPIC, European Prospective Investigation into Cancer and Nutrition; UKWCS, United Kingdom Women's Cohort Study.

TABLE 2

Characteristics of cases and controls[1]

Characteristic	Controls	Cases	P for difference[2]
N	1911	657	
Age at first day of diary completion, y	57.2 (9.2)	56.4 (9.7)	0.046
Age at menarche, y*	12.9 (1.7)	12.8 (1.5)	0.251
Parity, n (%)*			
0	366 (19.2)	148 (22.6)	
1	249 (13.1)	84 (12.8)	
2	752 (39.5)	266 (40.6)	
3	361 (19.0)	112 (17.1)	
4+	174 (9.1)	45 (6.9)	0.148
Menopausal status, n (%)*			
Pre-menopausal	344 (18.1)	110 (17.0)	
Peri-menopausal	192 (10.1)	113 (17.5)	
Postmenopausal	1360 (71.7)	424 (65.5)	<0.001
Height, m*	1.62 (0.06)	1.63 (0.07)	<0.001
Weight, kg*	67.3 (12.2)	67.9 (11.6)	0.274
Body mass index, kg/m^2*	25.8 (4.5)	25.7 (4.5)	0.688
Physical activity, n (%)*			
Inactive	495 (26.7)	176 (28.7)	
Moderately inactive	629 (33.9)	211 (34.4)	
Moderately active	416 (22.5)	139 (22.7)	
Active	313 (16.9)	87 (14.2)	0.426
Hormone replacement therapy use, n (%)*			
Never	1291 (69.0)	457 (71.0)	
Previous	232 (12.4)	69 (10.7)	
Current	349 (18.6)	118 (18.3)	0.489
Nutrient intake estimated from the food			

diaries			
Energy intake, MJ/d	7.36 (1.68)	7.58 (1.65)	0.004
Alcohol consumption, g/d	8.9 (13.0)	10.4 (13.7)	0.008
Total fat consumption, g/d	66.4 (21.2)	68.3 (20.8)	0.051
Total fat consumption (% energy)	33.0 (5.7)	33.0 (5.7)	0.984
Saturated fat consumption, g/d	25.1 (9.6)	25.5 (9.4)	0.334
Saturated fat consumption (% energy)	12.4 (3.1)	12.3 (3.2)	0.450
Monounsaturated fat consumption, g/d	22.7 (7.4)	23.6 (7.5)	0.014
Monounsaturated fat consumption (% energy)	11.3 (2.2)	11.4 (2.2)	0.404
Polyunsaturated fat consumption, g/d	12.6 (4.8)	13.2 (5.1)	0.007
Polyunsaturated fat consumption (% energy)	6.3 (1.8)	6.4 (1.8)	0.272
Nutrient intake estimated from the FFQs			
Energy intake, MJ/d	8.23 (2.42)	8.38 (2.69)	0.175
Alcohol consumption, g/d*	6.0 (8.8)	7.4 (10.2)	0.001
Total fat consumption, g/d	71.7 (27.7)	72.6 (30.5)	0.493
Total fat consumption (% energy)	31.9 (5.9)	31.6 (6.1)	0.293
Saturated fat consumption, g/d	27.0 (12.3)	27.1 (13.2)	0.867
Saturated fat consumption (% energy)	12.0 (3.3)	11.7 (3.5)	0.131
Monounsaturated fat consumption, g/d	23.6 (9.7)	24.0 (10.4)	0.358
Monounsaturated fat consumption (% energy)	10.5 (2.3)	10.4 (2.4)	0.852
Polyunsaturated fat consumption, g/d	14.1 (6.4)	14.3 (6.9)	0.331
Polyunsaturated fat consumption (% energy)	6.3 (2.1)	6.3 (2.1)	0.946

[1] Values are means (SD) except where indicated. [2] Based on independent samples t-tests for continuous variables and chi-square tests of association for categorical variables. * Unknown for some participants.

TABLE 3
Quintiles of fat intake and odds ratios for breast cancer[1]

	Quintile of fat intake 1 (referent)	2	3	4	5	P value for trend
Nutrient intake estimated from the food diaries						
Total fat (g/d)						
Median	41.0	54.7	65.8	76.6	94.7	
Cases/Controls	116/397	124/391	141/371	131/383	145/369	
Odds ratio (95% CI)	1.00	1.02 (0.74, 1.41)	1.10 (0.79, 1.54)	0.94 (0.64, 1.39)	0.87 (0.54, 1.41)	0.392
Total fat (% energy)						
Median	25.7	30.3	33.2	35.8	40.3	
Cases/Controls	132/382	132/382	139/374	123/391	131/382	
Odds ratio (95% CI)	1.00	1.00 (0.75, 1.35)	1.01 (0.75, 1.36)	0.88 (0.65, 1.20)	0.90 (0.66, 1.23)	0.504
SFA (g/d)						
Median	14.1	19.8	24.3	29.0	37.2	
Cases/Controls	122/391	128/387	135/378	133/381	139/374	
Odds ratio (95% CI)	1.00	0.97 (0.72, 1.33)	1.02 (0.73, 1.40)	0.92 (0.64, 1.32)	0.86 (0.57, 1.30)	0.224
SFA (% energy)						
Median	8.5	10.8	12.3	13.7	16.5	
Cases/Controls	139/375	139/375	119/394	137/377	123/390	
Odds ratio (95% CI)	1.00	0.99 (0.73, 1.32)	0.80 (0.59, 1.08)	1.01 (0.75, 1.35)	0.81 (0.60, 1.10)	0.343
MUFA (g/d)						
Median	13.8	18.6	22.5	26.3	32.7	
Cases/Controls	116/398	120/394	146/366	122/393	153/360	
Odds ratio (95% CI)	1.00	0.99 (0.71, 1.37)	1.23 (0.88, 1.73)	0.91 (0.62, 1.34)	1.03 (0.65, 1.62)	0.697
MUFA (% energy)						
Median	8.6	10.3	11.4	12.4	14.1	
Cases/Controls	124/390	139/375	134/379	120/394	140/373	
Odds ratio (95% CI)	1.00	1.13 (0.83, 1.53)	1.05 (0.77, 1.43)	0.87 (0.63, 1.19)	1.06 (0.78, 1.44)	0.813
PUFA (g/d)						
Median	7.3	9.9	12.0	14.5	19.1	
Cases/Controls	126/388	116/398	129/384	141/372	145/369	
Odds ratio (95% CI)	1.00	0.83 (0.61, 1.14)	0.88 (0.63, 1.21)	0.90 (0.64, 1.27)	0.77 (0.53, 1.13)	0.667
PUFA (% energy)						
Median	4.3	5.3	6.1	7.0	8.6	
Cases/Controls	129/385	122/392	135/378	126/388	145/368	
Odds ratio (95% CI)	1.00	0.87 (0.64, 1.19)	1.01 (0.75, 1.36)	0.84 (0.62, 1.14)	0.97 (0.71, 1.31)	0.565
Nutrient intake estimated from the FFQs						
Total fat (g/d)						
Median	40.0	54.9	67.7	82.7	108.5	
Cases/Controls	138/375	123/392	123/390	134/380	139/374	

Odds ratio (95% CI)	1.00	0.83 (0.61, 1.13)	0.81 (0.58, 1.13)	0.78 (0.54, 1.12)	0.80 (0.50,1.30)	0.525
Total fat (% energy)						
Median	24.2	28.7	32.0	34.9	39.3	
Cases/Controls	151/363	137/377	108/405	132/382	129/384	
Odds ratio (95% CI)	1.00	0.94 (0.70, 1.26)	0.68 (0.50, 0.92)	0.85 (0.63, 1.14)	0.80 (0.59, 1.09)	0.366
SFA (g/d)						
Median	13.7	19.7	24.8	31.2	43.0	
Cases/Controls	148/366	125/388	117/396	135/380	132/381	
Odds ratio (95% CI)	1.00	0.79 (0.58, 1.06)	0.72 (0.52, 0.98)	0.78 (0.55, 1.11)	0.67 (0.44, 1.02)	0.606
SFA (% energy)						
Median	7.9	10.1	11.7	13.3	16.4	
Cases/Controls	155/359	127/387	129/384	118/396	128/385	
Odds ratio (95% CI)	1.00	0.76 (0.57, 1.03)	0.84 (0.63, 1.13)	0.76 (0.56, 1.03)	0.81 (0.60, 1.09)	0.434
MUFA (g/d)						
Median	12.7	17.8	22.2	27.4	36.0	
Cases/Controls	131/383	132/382	121/392	133/381	140/373	
Odds ratio (95% CI)	1.00	1.04 (0.76, 1.41)	0.84 (0.60, 1.16)	0.85 (0.59, 1.22)	0.91 (0.58, 1.43)	0.725
MUFA (% energy)						
Median	7.5	9.2	10.5	11.6	13.4	
Cases/Controls	139/375	137/377	114/399	134/380	133/380	
Odds ratio (95% CI)	1.00	1.05 (0.79, 1.40)	0.79 (0.58, 1.07)	0.97 (0.72, 1.30)	0.91 (0.67, 1.24)	0.705
PUFA (g/d)						
Median	7.2	10.2	12.7	16.1	22.8	
Cases/Controls	124/390	138/375	134/380	123/391	138/375	
Odds ratio (95% CI)	1.00	1.11 (0.83, 1.49)	1.01 (0.74, 1.37)	0.80 (0.57, 1.12)	0.91 (0.63, 1.31)	0.603
PUFA (% energy)						
Median	4.0	5.0	5.9	7.0	9.1	
Cases/Controls	137/377	130/384	126/387	125/389	139/374	
Odds ratio (95% CI)	1.00	0.93 (0.69, 1.24)	0.86 (0.64, 1.16)	0.83 (0.62, 1.11)	0.94 (0.71, 1.26)	0.546

[1] Conditional logistic regression adjusted for age, alcohol consumption, parity, menopausal status, current hormone replacement therapy use, physical activity, height, weight and energy intake. Analyses are based on 657 cases and 1911 matched controls. P values relate to tests for trend obtained using the continuous intake variable.

TABLE 4

Odds ratios (95% CI) for breast cancer associated with a one standard deviation increase in fat intake, estimated from the food diaries and the FFQs, overall and subdivided by cohort[1]

Nutrient intake (one standard deviation)	All women[2]	EPIC-Norfolk[3]	EPIC-Oxford[4]	UKWCS[5]	Whitehall II[6]	P for heterogeneity between cohorts
Estimated from the food diaries						
Total fat (21.1 g/d)	0.92 (0.77, 1.11)	0.83 (0.65, 1.05)	1.00 (0.67, 1.50)	1.01 (0.50, 2.05)	1.31 (0.73, 2.36)	0.622
Total fat (5.7 % energy)	0.97 (0.88, 1.07)	0.92 (0.81, 1.05)	0.99 (0.79, 1.24)	0.97 (0.67, 1.42)	1.29 (0.91, 1.83)	0.201
SFA (9.6 g/d)	0.92 (0.80, 1.06)	0.96 (0.78, 1.17)	0.84 (0.62, 1.13)	0.41 (0.22, 0.77)*	1.37 (0.89, 2.10)	0.015
SFA (3.2 % energy)	0.95 (0.87, 1.05)	0.98 (0.86, 1.12)	0.89 (0.72, 1.10)	0.53 (0.34, 0.83)*	1.31 (0.96, 1.78)	0.002
MUFA (7.5 g/d)	0.97 (0.82, 1.14)	0.84 (0.67, 1.05)	1.03 (0.72, 1.46)	0.98 (0.56, 1.74)	1.59 (0.93, 2.71)	0.476
MUFA (2.2 % energy)	0.99 (0.89, 1.09)	0.92 (0.81, 1.05)	1.00 (0.80, 1.25)	0.97 (0.69, 1.37)	1.48 (1.04, 2.09)*	0.081
PUFA (4.9 g/d)	0.97 (0.86, 1.10)	0.84 (0.70, 1.01)	1.27 (0.97, 1.66)	1.97 (1.18, 3.28)*	0.66 (0.42, 1.03)	0.101
PUFA (1.8 % energy)	0.97 (0.88, 1.07)	0.88 (0.77, 1.01)	1.19 (0.96, 1.46)	1.60 (1.10, 2.33)*	0.77 (0.54, 1.10)	0.009
Estimated from the FFQs						
Total fat (28.5 g/d)	0.94 (0.76, 1.15)	0.85 (0.65, 1.12)	1.00 (0.62, 1.61)	0.85 (0.38, 1.92)	1.28 (0.70, 2.35)	0.529
Total fat (6.0 % energy)	0.96 (0.87, 1.05)	0.93 (0.82, 1.06)	0.93 (0.75, 1.15)	0.86 (0.53, 1.39)	1.16 (0.85, 1.57)	0.423
SFA (12.5 g/d)	0.96 (0.82, 1.12)	1.02 (0.82, 1.25)	0.76 (0.53, 1.10)	0.77 (0.41, 1.43)	1.16 (0.78, 1.75)	0.742
SFA (3.4 % energy)	0.96 (0.87, 1.06)	1.01 (0.88, 1.15)	0.80 (0.63, 1.00)*	0.71 (0.43, 1.18)	1.14 (0.86, 1.51)	0.116
MUFA (9.9 g/d)	0.97 (0.81, 1.16)	0.87 (0.68, 1.12)	1.23 (0.82, 1.84)	0.96 (0.49, 1.87)	1.20 (0.65, 2.20)	0.450
MUFA (2.3 % energy)	0.98 (0.89, 1.08)	0.94 (0.82, 1.08)	1.02 (0.83, 1.25)	1.00 (0.64, 1.56)	1.18 (0.84, 1.64)	0.428
PUFA (6.5 g/d)	0.97 (0.85, 1.10)	0.83 (0.69, 0.99)*	1.30 (0.95, 1.78)	1.16 (0.70, 1.90)	1.06 (0.71, 1.59)	0.056
PUFA (2.1 % energy)	0.97 (0.88, 1.07)	0.86 (0.76, 0.98)*	1.19 (0.95, 1.49)	1.17 (0.77, 1.78)	1.09 (0.82, 1.46)	0.033

[1] Conditional logistic regression adjusted for age, alcohol consumption, parity, menopausal status and current hormone replacement therapy use where applicable, physical activity, height, weight and energy intake.
[2] Analyses are based on 657 cases and 1911 matched controls.
[3] Analyses are based on 353 cases and 1252 matched controls.
[4] Analyses are based on 194 cases and 194 matched controls.
[5] Analyses are based on 42 cases and 202 matched controls.
[6] Analyses are based on 68 cases and 263 matched controls.
* P<0.05 (P values relate to tests for trend obtained using the continuous intake variable).

TABLE 5

Odds ratios (95% CI) for breast cancer associated with a one standard deviation increase in fat intake, estimated from the food diaries and the FFQs, in subsets of follow up and menopausal status[1]

Nutrient intake (one standard deviation)	Cases diagnosed at least 2 years after diary commencement[2]	Women who were postmenopausal and **not** using hormone replacement therapy at diary commencement[3]
Estimated from the food diaries		
Total fat (21.1 g/d)	0.93 (0.76, 1.14)	0.70 (0.52, 0.95)*
Total fat (5.7 % energy)	0.98 (0.87, 1.09)	0.81 (0.69, 0.95)*
SFA (9.6 g/d)	1.00 (0.85, 1.17)	0.81 (0.64, 1.02)
SFA (3.2 % energy)	1.01 (0.91, 1.13)	0.85 (0.73, 1.00)*
MUFA (7.5 g/d)	0.93 (0.77, 1.12)	0.76 (0.58, 1.01)
MUFA (2.2 % energy)	0.97 (0.87, 1.09)	0.83 (0.71, 0.98)*
PUFA (4.9 g/d)	0.88 (0.76, 1.02)	0.87 (0.71, 1.07)
PUFA (1.8 % energy)	0.91 (0.81, 1.02)	0.89 (0.76, 1.04)
Estimated from the FFQs		
Total fat (28.5 g/d)	0.94 (0.75, 1.17)	0.78 (0.56, 1.08)
Total fat (6.0 % energy)	0.95 (0.85, 1.06)	0.89 (0.76, 1.03)
SFA (12.5 g/d)	0.99 (0.84, 1.17)	0.84 (0.66, 1.07)
SFA (3.4 % energy)	0.98 (0.88, 1.10)	0.90 (0.78, 1.05)
MUFA (9.9 g/d)	0.96 (0.79, 1.17)	0.82 (0.62, 1.09)
MUFA (2.3 % energy)	0.97 (0.87, 1.08)	0.89 (0.76, 1.05)
PUFA (6.5 g/d)	0.93 (0.81, 1.07)	0.98 (0.81, 1.19)
PUFA (2.1 % energy)	0.93 (0.84, 1.03)	0.96 (0.83, 1.11)

[1] Conditional logistic regression adjusted for age, alcohol consumption, parity, menopausal status and current hormone replacement therapy use where applicable, physical activity, height, weight and energy intake.
[2] Analyses are based on 548 cases and 1620 matched controls.
[3] Analyses are based on 286 cases and 699 matched controls.
* $P<0.05$ (P values relate to tests for trend obtained using the continuous intake variable).

TABLE 6

Prospective studies of total fat, saturated fat and breast cancer risk

Reference		Study	n cases	Dietary assessment	Exposure category and model	Relative risk (95% CI), total fat	Relative risk (95% CI), saturated fat
Pooled analysis							
	Smith-Warner et al 2001 (2)	Pooled analysis of 8 prospective studies, 7 of which are included in Boyd et al 2003	7329	Food frequency questionnaires	5% increase in energy from fat, adjusted for total energy	1.00 (0.98, 1.03)	1.03 (0.95, 1.10)
Meta-analysis							
	Boyd et al 2003 (20)	Meta-analysis of 14 prospective studies, 7 of which are included in Smith-Warner et al 2001	8735	10 studies food frequency questionnaires 4 studies food record, recall or diet history	Highest versus lowest tertile, quartile or quintile of fat, various models	1.11 (0.99, 1.25)	1.15 (1.02, 1.30)
Individual studies since 2003							
	Löf et al 2007 (21)	Swedish women' lifestyle and health cohort	974	Food frequency questionnaire	Highest versus lowest quintile of fat, adjusted for energy	1.02 (0.72, 1.45)	1.12 (0.69, 1.81)
	Thiébaut et al 2007 (18)	National Institutes of Health-AARP Diet and Health Study	3501	Food frequency questionnaire	Highest versus lowest quintile of percent energy from fat, adjusted for energy	1.11 (1.00, 1.26)	1.18 (1.06, 1.31)
	Sieri et al 2008 (22)	European Prospective Investigation into Cancer and Nutrition	7119	Mostly food frequency questionnaires	Highest versus lowest quintile of percent energy from fat, adjusted for energy	1.04 (0.96, 1.13)	1.10 (1.01, 1.19)
Studies with food records and food frequency questionnaires							
	Freedman et al 2006 (5)	Women's Health Initiative USA, non-intervention group	603	Food record	Highest versus lowest quintile of fat, adjusted for energy	2.09 (1.21, 3.61)	1.51 (0.94, 2.43)
				Food frequency questionnaire		1.71 (0.70, 4.18)	1.00 (0.49, 2.02)
	Current study	Pooled analysis of 4 British prospective studies	657	Food record	Highest versus lowest quintile of percent energy from fat, adjusted for energy	0.93 (0.68, 1.26)	0.80 (0.59, 1.09)
				Food frequency questionnaire		0.85 (0.62, 1.14)	0.82 (0.61, 1.11)
Randomized controlled trials							
	Prentice et al 2006 (23)	Women's Health Initiative	1727	Intervention trial	Low-fat dietary pattern intervention versus control	0.91 (0.83, 1.01)	Not applicable
	Martin et al 2011 (24)	Canadian dietary intervention trial	220	Intervention trial	Low-fat dietary pattern intervention versus control	1.19 (0.91, 1.55)	Not applicable