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A comparison of two dietary instruments for evaluating the fat–breast cancer relationship

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Background Previous research suggests food diaries may be more efficient than food frequency questionnaires (FFQ) in detecting a dietary fat–breast cancer relationship. We assessed this further using 4 day food records (FRs) and FFQs in a large sample.

Methods Participants were from the non-intervention group of the dietary modification component of the Women's Health Initiative Clinical Trial: 603 breast cancer cases and 1206 controls matched on age, clinic, and length of follow-up. Relative risks (RRs) were estimated using unconditional logistic regression, adjusted for confounders and for the selection into the trial of women with an FFQ report exceeding 32% calories from fat. Direct comparison of the statistical power of the two instruments used the standardized log RR. An alternative analysis after removing subjects with missing covariate data was also conducted.

Results The RR estimate for breast cancer in the top quintile of total fat intake, adjusted for confounders and total energy, was 1.82 (P for trend 0.02) for the FR but 0.67 for the FFQ (P for trend 0.24). Following adjustment for selection, estimates were 2.09 (P for trend 0.008) for the FR (alternative: 2.54, P for trend 0.006) and 1.71 (P for trend 0.18) for the FFQ (alternative: 1.24, P for trend 0.41). Similar results were seen for fat subtypes, particularly unsaturated fats. Comparisons showed higher statistical power for the FR than the FFQ (e.g. total fat, $P = 0.08$: alternative $P = 0.01$).

Conclusions Alternative instruments, such as FRs, may be preferable to FFQs for evaluating diet–disease relationships in cohort studies. The results support a positive association between dietary fat and breast cancer.

Keywords Breast cancer, dietary fat, food frequency questionnaire, multiple-day food record

The results of case–control studies, international comparisons, and laboratory experiments in animals generally support a positive association between fat consumption and the incidence of breast cancer.[1] Conversely, pooled analysis of several cohort studies, which are free from some of the biases that potentially affect case–control studies, has not found such an association.[2] A major problem besetting studies relating a woman's fat consumption to her risk of breast cancer is that of dietary measurement error.[3] Case–control and cohort studies employ self-reporting techniques for measuring dietary intake. For reasons of logistics and cost the reporting instrument most commonly used has been the food frequency questionnaire

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(FFQ).[4] Little is known about the magnitude and nature of errors in reporting fat intake through an FFQ, and there has been much discussion about whether such errors could have led to the failure of the cohort studies to find a fat–breast cancer association.[5,6]

In 2003, Bingham *et al*.[7] reported the results of a comparison of two instruments, an FFQ and a quantitative 7 day diary, both completed by a cohort of 13 070 women, on which the fat–breast cancer association hypothesis was tested. They found a statistically significant positive association [relative risk (RR) 1st vs 5th quintile = 1.79, *P* for trend = 0.05] between total fat intake and breast cancer incidence using the 7 day diary but not using the FFQ (RR 1st vs 5th quintile = 1.31, *P* for trend = 0.52). A similar result was found for saturated fat intake. This suggested that the 7 day diary, being associated with less error than the FFQ for nutrients studied,[8] may be more powerful than the FFQ in detecting this diet–disease relationship. However, the study was based on a relatively small number of breast cancer cases (168).[9]

In this paper we report a similar study of the association of dietary fat and breast cancer, comparing two dietary instruments, an FFQ and a 4 day food record (FR), in a larger cohort comprising the control group of the dietary modification (DM) arm of the Women's Health Initiative (WHI) randomized trial.

Methods

Participants

The design and recruitment methods of the overall WHI are described in detail elsewhere.[10,11] The DM component of the WHI is a randomized controlled trial (RCT) of a low-fat dietary pattern high in fruits, vegetables, and grains.[12]

The WHI included post-menopausal women aged 50–79 years, recruited from areas surrounding 40 clinical centres established primarily at major academic health centres in 24 states and the District of Columbia. Recruitment areas included urban, suburban, and rural populations. Though not a probability sample, enrolment of racial/ethnic minority groups proportionate to the population was a high priority of the programme and 17.5% of the clinical trial participants were from minority groups.[11]

Women entered the trial during 1993–98. Briefly, recruitment was primarily based on mass mailing using population-based lists of women in the desired age range who were living in proximity to one of the 40 WHI clinical centres across the US. Women could express interest in either the DM component of the WHI clinical trial or the hormone therapy component, or both. Among the women invited, who were generally representative of US women, a total of 373 092 initiated screening by responding to the invitation.

Those women who expressed interest were then contacted by telephone to ascertain eligibility. Prior to the first screening visit, women received information in the mail including a cover letter, a bag for their medications and dietary supplements, instructions to prepare for a fasting blood collection, and several self-administered questionnaires, including an FFQ. At the first visit, the FFQ and other questionnaires were reviewed, anthropometric measurements were taken, and informed consent obtained.

Of the 373 092 women screened 53 139 women provided consent for the DM trial and met a 32% or greater energy from fat criterion based on a food frequency assessment. The latter requirement was intended to enrol a group having a relatively high fat intake and, thereby, increase the difference in percentage energy from fat between women randomized to the dietary intervention and control groups. This screening raised the mean percentage energy from fat intake from ~32% to ~35%. Approximately 42% of those who expressed interest in the DM were excluded because of the fat intake criterion.

An additional 7304 women were excluded based on nutritionist judgement, participant reconsideration, or on the basis of additional eligibility criteria, including the exclusion of women with previous or existing breast or colon cancer, or invasive cancer of any type within the past 10 years; women who reported extremes of energy intakes (<600 or 5000+kcal); had dietary needs incompatible with the intervention programme (e.g. celiac disease); ate 10 or more meals per week outside the home; could not complete a 4 day FR; or had type I diabetes mellitus or any gastrointestinal conditions that contraindicated a high-fibre diet.

This led to the randomization of 48 835 participants. These women were randomly assigned 40% (n = 19 541) to a low-fat eating pattern intervention, and 60% (n = 29 294) to a control group who were not asked to make dietary changes. Of those randomized to the trial, 38% had a college degree or higher, 39% reported a family income of $50 000 and above, and 38% had a body mass index (BMI) of 30.0 kg/m^2 or higher.[12]

Participants included in our analyses were in the control arm of the DM trial (n = 29 294). Staff at the WHI Clinical Coordinating Center (CCC) frequency matched two controls for every case of invasive breast cancer, with matching on age (50–59, 60–69, 70–79), clinic, and length of follow-up (±12 months) resulting in a sample of 603 cases and 1206 controls, that together comprise a case–control design nested within the prospective cohort. The median length of follow-up in the study was 83 months at the time of choosing the matched controls.

The 4 day food record

During the second screening visit, participants were given a 4 day FR booklet[13] and were instructed how to complete the records accurately, using a 15 min videotape and 15–30 min of personal instruction by certified staff. Between the second and third screening visits, participants completed the FR on four alternate days, thus including at least one weekend day. At the third screening visit, the FRs were reviewed for completeness by certified staff and incomplete food descriptions or missing portion sizes were queried and resolved with the participant. The FR booklets were archived at the clinical centres and mailed to the CCC in 2004 for the current analyses, where the Nutrition Assessment Shared Resource of the Fred Hutchinson Cancer Research Center electronically coded the FRs using version 34 (released in 2004) of the University of Minnesota Nutrient Data System for Research software (Nutrition Coordinating Center, Minneapolis, MN).

The food frequency questionnaire

The WHI FFQ was designed by a dietary assessment working group composed of WHI scientists[13] and was based on instruments developed and tested in other studies.[14–17] It incorporated many of the modifications to standard questionnaires that had been suggested by previous research to improve estimation of fat intake.[18] The main section asked for frequency of intake in the

past 3 months of 122 foods or food groups, with frequency questions ranging from 'never or less than once per month' to '2+ per day' for foods and '6+ per day' for beverages. Portion size was defined as small, medium, and large compared with a stated medium portion. There were 19 adjustment questions, which asked for specificity on typical intake of a variety of items, with a focus on fat content. In addition, there were four summary questions on usual intake of fruits, vegetables, and fat added to foods and used in cooking. Instructions for self-administration included directions and examples on the questionnaire, and an additional page with instructions and portion size pictures. The University of Minnesota Nutrition Coding Center nutrient database (Nutrition Coordinating Center, Minnesota, MN), Version 30 (released in 2002) was used to derive the FFQ nutrient database.[19]

The WHI FFQ has been compared with four 24 h recalls and 4 day food diaries in a study of 113 participants.[13] This study showed that, compared with the reference instruments, the WHI FFQ had similar energy-adjusted fat correlations ($r = 0.6$) to commonly used FFQs.[20–23] This suggests that the WHI FFQ performs similarly to other FFQs in the field.

Statistical analysis

Participants completed a questionnaire at baseline on demographic, health, and lifestyle characteristics, including the following non-dietary factors that were considered as potential confounders of the dietary variables: race, marital status, parity, age at first birth, post-menopausal hormone use, family history of breast cancer, age at menarche, age at menopause, height, BMI, alcohol consumption, history of biopsy for benign breast disease, physical activity, years of education, and smoking status. In developing a parsimonious statistical model, the following variables were included in models as they were statistically significantly associated with disease (at the conventional 5% level) and changed the risk estimates for total fat in the FR or FFQ models by 10% or more; post-menopausal hormone use (current/former, never), family history in a first-degree relative (yes/no), and biopsy for benign breast disease (yes/no). Some final analyses were repeated including age at first birth, parity, BMI, and physical activity to check that their omission had not influenced the results.

Unconditional logistic regression adjusted for matching variables was used in the main analysis, as results were very similar to those from conditional logistic regression analyses. Missing values were present in hormone use (1 participant), family history (88 participants), and breast biopsy (201 participants). Of the 201 with missing breast biopsy, 194 had entered the study early at a time when the baseline questionnaire did not contain this question. In our main analysis we dealt with the missing values by adding an extra 'missing' category to the variable in question. To further check, we ran an alternative analysis in which we excluded the 'early' participants and adjusted for the remaining missing values using the Horvitz–Thompson method.

A variety of statistical models relating to breast cancer were examined. Separate analyses were performed for total, saturated, polyunsaturated, and monounsaturated fats. Each type of fat was examined across quintiles of fat intake, with adjustment for total energy (Standard model) or for non-fat energy (Partition model).[24] Also, the relationship of breast cancer to quintiles of energy-adjusted fat (Residual model) was examined. Tests for trend across quintiles were conducted using the median values of the quintiles as continuous variables. Besides these quintile models, a 'Standard model' using continuous values of (log transformed) fat and energy was also applied.

Other models were also examined, including the same models as were used by Bingham *et al*. [see Table 1 in Ref. (7)], but are not reported here, as their results were very similar to those of the models presented in this paper.

The above analyses are those typically used in nutritional epidemiological studies. However, as mentioned above, participants were selected into the study on the basis of the percentage energy from fat reported on their FFQ, with all those reporting <32% being excluded. This 'truncation' of the sample causes a downward bias in all the RRs estimated. The bias arises from the fact that the selection variable, percentage energy from fat, is associated with the exposures of interest (e.g. FFQ total fat intake in quintiles) and also potentially with the outcome, breast cancer. The stronger these two associations are the greater will be the selection bias. Truncation will also change the range of intakes reported in the sample, with further impact on the estimated RRs between quintiles. Because the selection is based on the FFQ, the association between the selection variable and FFQ exposures of interest could be particularly strong. One would therefore expect greater selection bias in the case of RRs estimated from the FFQ. The selection also reduces the variance in reported fat intake and, thus, indirectly inflates the standard errors of the estimated RRs for the two instruments; again the effect is expected to be stronger for the FFQ than for the FR.

We, therefore, adjusted for this selection with two goals in mind. First we obtain unbiased estimates of RRs (which we call selection-adjusted RRs) for breast cancer based on either of the two instruments, so as to provide a proper evaluation of the fat–breast cancer association. Second, we calculate unbiased estimates of standardized log RRs for the two instruments, so as to provide a fair comparison of their power to detect a fat–breast cancer association in a non-truncated study. These standardized log RRs are estimated as the ratio of the selection-adjusted log RR to its selection-adjusted standard error and are directly related to the statistical power. Division by the selection-adjusted standard error is necessary to account for both the different range of values reported on the two instruments and the differential effect of selection on this range. The principal assumption used in these correction procedures is that log transformed reported intakes for fat, type of fat, and energy are normally distributed. Approximate normal distributions for these quantities have been observed in other studies[5,26] and contexts. Further details of the statistical method of selection-adjustment are given in Appendix 1.

No statistical adjustments for the effect of dietary measurement error on the RRs are attempted in this paper, mainly because there is insufficient information regarding errors in reporting fat intake. The possible influence of measurement error on our results will be addressed in the Discussion section. All statistical tests are two-tailed and conducted at the 5% significance level. No statistical adjustments are made for the multiple analyses that we have conducted. As mentioned in the Introduction section, our analyses are guided by previous hypotheses generated from the study by Bingham *et al*. and are confirmatory rather than exploratory.

Table 1 Distribution of potential risk factors and associated relative risks (RR) of breast cancer among cases and controls in the non-intervention group of the diet modification arm of the Women's Health Initiative (WHI)

Risk Factor	Cases (n = 603)	Controls (n = 1206)	RR[a]	95% CI
Race				
White[b]	528	1020	1.00	
African American	37	100	0.65	0.42–1.01
Other/unknown	38	86	0.79	0.49–1.27
Marital status				
Married[b]	388	797	1.00	
Previously married	176	357	1.01	0.81–1.26
Never married	38	47	1.66	1.06–2.58
Number of births				
0[b]	85	125	1.00	
1	49	116	0.62	0.41–0.96
2	151	275	0.82	0.58–1.14
⩾3	314	689	0.67	0.49–0.91
Age (years) at first birth[c]				
<20	74	134	1.33	0.94–1.88
20–24[b]	211	484	1.00	
25–29	135	279	1.21	0.91–1.61
⩾30	60	93	1.43	0.97–2.11
Hormone usage[d]				
Never	350	836	1.00	
Current/past user	253	369	1.70	1.38–2.10
Family history (first-degree relative)				
No	462	979	1.00	
Yes	117	163	1.51	1.16–1.96
Biopsy for benign breast disease				
No	367	853	1.00	
Yes	161	226	1.69	1.33–2.15
Smoking status				
Never	272	606	1.00	
Past	288	527	1.24	1.01–1.52
Current	33	70	1.05	0.68–1.62
Age (years) at menarche				
⩽13[b]	484	943	1.00	
14	71	142	0.98	0.72–1.33
15	29	71	0.81	0.52–1.25
⩾16	19	48	0.78	0.45–1.34
P-value for trend			$P = 0.21$	
Age (years) at menopause				
⩽40[b]	72	158	1.00	
41–45	83	182	0.97	0.65–1.43
46–50	169	386	0.96	0.68–1.35
51–52	90	154	1.28	0.87–1.89
⩾53	157	249	1.33	0.94–1.90
P-value for trend			$P = 0.01$	
Physical activity[e]				
No activity	111	204	1.00	
Some activity	236	477	0.91	0.69–1.20
2–3 episodes/week	101	200	0.91	0.65–1.28
⩾4 episodes/week	89	206	0.80	0.56–1.13
P-value for trend			$P = 0.23$	
Height (cm)				
⩽157.3[b]	129	244	1.00	
157.4–161	120	245	0.92	0.67–1.25
161.1–163.8	98	233	0.80	0.58–1.10
163.9–168	145	254	1.08	0.80–1.46
⩾168.1	109	226	0.91	0.66–1.25
P-value for trend			$P = 0.98$	
BMI (kg/m^2)				
⩽23.97[b]	108	242	1.00	
23.98–26.26	118	239	1.11	0.80–1.53
26.27–29.43	123	241	1.14	0.83–1.58
29.44–33.01	119	240	1.12	0.81–1.53
⩾33.02	133	240	1.25	0.91–1.71
P-value for trend			$P = 0.21$	
Alcohol (grams from FFQ)				
0[b]	239	458	1.00	
0.39 to <1.0	70	149	0.90	0.65–1.24
1.0 to <2.3	68	149	0.88	0.64–1.22
2.3 to <6.2	70	149	0.90	0.66–1.23
6.2 to <12.4	72	149	0.93	0.68–1.29
⩾12.4	80	149	1.02	0.75–1.39
P-value for trend			$P = 0.90$	
Years of education				
High school or less	20	49	1.00	
High school graduate/GED	78	208	0.94	0.52–1.69
Some post-high school	226	492	1.18	0.68–2.05
College graduate or higher	275	451	1.57	0.90–2.74
P-value for trend			$P < 0.001$	

In models as single variables.

[a] Relative risk and 95% confidence interval (95% CI), matched on age, centre and follow-up time. For some variables, the number of observations does not equal 1809 (603 cases and 1206 controls) because of missing values.

[b] Referent category.

[c] Restricted to parous women.

[d] Oestrogen and progesterone usage status (baseline questionnaire).

[e] Episodes per week of moderate and strenuous activity of at least 20 min (baseline questionnaire).

Results

Table 1 shows the distribution of a variety of putative risk factors for breast cancer among cases and controls. Statistically significant associations were seen for hormone use, family

history and biopsy for benign breast disease, age at menopause, and education.

Table 2 shows the median intakes in each quintile reported by control group women on the FR and FFQ, and provides a background for understanding the RR estimates that are presented in later tables. For total fat and subtypes of fat, the FR intake estimates were lower than those for the FFQ. These differences are partly attributable to measurement error in the FFQ and FR, and partly to the exclusion from the trial of those with lower FFQ-reported percentage energy from fat.

RRs unadjusted for selection into the study are shown in Table 3. Analyses of four types of fat (total, saturated, polyunsaturated, and monounsaturated) using three models (Standard, Residual, and Partition) are shown. Statistically significant trends in these models are seen for total, polyunsaturated, and monounsaturated fat when using the FR, but no such trends are seen when using the FFQ. The same pattern is observed when relating risk to reported fat intake measured on a log-transformed continuous scale (Table 4). Similar results were obtained using the models employed by Bingham *et al*.[7] (data not shown). In addition, further adjustment for age at first birth/parity, age at menarche, age at menopause, BMI, physical activity, marital status, education, and smoking did not alter substantially the relative risk estimates.

Results for models using nutrient densities were very similar to those of the Residual model. For example, for total fat, using the FR, the RRs in quintiles 2–5 for the density model were 1.34, 1.27, 1.55, and 1.59 (trend test, $P = 0.005$) compared with 1.43, 1.39, 1.53, and 1.72 (trend test, $P = 0.002$) for the Residual model. For the FFQ, the RRs were 0.85, 1.03, 0.98, and 1.08 (trend test, $P = 0.39$) for the density model compared with 0.99, 0.99, 1.11, and 1.14 (trend test, $P = 0.28$) for the Residual model.

RRs adjusted for selection into the study are shown in Table 5. Note that, unlike earlier tables, these RRs apply to quintiles for the base population, without the screening-related truncation. The adjustment has a strong effect on the RRs in the models for total fat, reversing negative trends for the FFQ into positive ones in the Standard (adjusting for total energy) and Partition models (adjusting for non-fat). The confidence limits were wide for the adjusted FFQ RRs in the Residual model for total fat, because the adjustment involved re-assigning individuals to adjusted residual quintiles, and only 15 individuals were assigned to the first quintile for the FFQ. However, apart from these effects, the impact of selection-adjustment was rather modest, and the same patterns seen in the unadjusted analysis were observed after adjustment. In particular, the estimated RRs for saturated, polyunsaturated, and monounsaturated fats did not change substantially after the adjustment, and the *P*-values for trend remained similar for total fat and all fat subtypes. Adjustment for selection had almost no impact on the RRs estimated from the continuous models (third column of Table 6).

Direct comparison of the instruments' power to detect a fat–breast cancer association was made through an adjusted standardized log RR (see Appendix for details). These are shown for the various continuous models in the final column of Table 6. The estimated standardized log RR was larger for the FR than for the FFQ for all types of fat, and although none of the differences reached the formal two-sided 5% criterion for statistical significance, they were nevertheless close.

An alternative analysis for handling missing data, explained in the Methods section, yielded similar, but stronger, trends to those reported above. For each type of fat, the adjusted RRs were stronger for the FR and weaker for the FFQ. For total fat,

Table 2 Median reported fat intake and fat density by quintiles in the control group

	Q1 median	Q2 median	Q3 median	Q4 median	Q5 median
FR total fat (g/day)	37.8	50.3	61.2	72.4	93.0
FFQ total fat (g/day)	42.1	57.5	69.5	85.7	118.9
FR% total fat	24.6	29.8	32.7	36.2	41.5
FFQ% total fat	33.2	35.6	37.6	40.5	45.0
FR saturated fat (g/day)	11.2	16.2	20.0	24.1	31.8
FFQ saturated fat (g/day)	13.7	19.1	24.0	29.9	42.5
FR% saturated fat	7.3	9.3	10.8	12.3	14.2
FFQ% saturated fat	10.4	11.9	13.0	14.3	16.6
FR polyunsaturated fat (g/day)	7.2	9.9	12.3	15.2	20.8
FFQ polyunsaturated fat (g/day)	8.1	11.6	14.5	18.2	25.8
FR% polyunsaturated fat	4.5	5.6	6.5	7.6	9.7
FFQ% polyunsaturated fat	5.7	6.9	7.9	8.9	11.0
FR monounsaturated fat (g/day)	14.0	19.0	23.3	27.6	36.1
FFQ monounsaturated fat (g/day)	15.1	21.1	25.6	31.8	44.3
FR% monounsaturated fat	9.0	11.0	12.4	14.0	16.3
FFQ% monounsaturated fat	11.9	13.0	14.0	15.1	16.9

Table 3 Relative risks[a] (95% confidence limits in brackets) for breast cancer in quintiles of total fat intake, estimated according to different statistical models, unadjusted for selection criteria

Type of fat	Model	Q1	Q2	Q3	Q4	Q5	*P* for Trend
	FR fat + log energy	1.00	1.35 (0.95–1.91)	1.28 (0.87–1.89)	1.66 (1.10–2.51)	1.82 (1.12–2.98)	0.02
	FFQ fat + log energy	1.00	0.88 (0.61–1.29)	0.88 (0.55–1.38)	1.03 (0.60–1.77)	0.67 (0.33–1.37)	0.24
	FR residual + log energy	1.00	1.43 (1.03–2.0)	1.39 (0.99–1.95)	1.53 (1.09–2.13)	1.72 (1.23–2.39)	0.002
	FFQ residual + log energy	1.00	0.99 (0.72–1.36)	0.99 (0.72–1.36)	1.11 (0.81–1.52)	1.14 (0.83–1.56)	0.28
	FR fat + log non-fat	1.00	1.29(0.92–1.80)	1.19 (0.85–1.68)	1.50 (1.06–2.13)	1.57 (1.09–2.27)	0.02
	FFQ fat + log non-fat	1.00	0.93 (0.66–1.32)	0.96 (0.65–1.42)	1.17 (0.76–1.81)	0.80 (0.47–1.38)	0.44
Saturated	FR fat + log energy	1.00	1.08 (0.77–1.53)	1.18 (0.83–1.69)	1.05 (0.71–1.56)	1.44 (0.92–2.25)	0.12
	FFQ fat + log energy	1.00	1.08 (0.76–1.55)	0.97 (0.64–1.48)	1.01 (0.62–1.64)	0.88 (0.48–1.63)	0.48
	FR residual + log energy	1.00	0.87 (0.62–1.21)	1.24 (0.91–1.70)	1.14 (0.83–1.57)	1.13 (0.82–1.56)	0.17
	FFQ residual + log energy	1.00	1.13 (0.63–1.54)	0.92 (0.67–1.27)	1.05 (0.77–1.43)	0.94 (0.68–1.29)	0.59
	FR fat + log non-fat	1.00	1.07 (0.77–1.50)	1.16 (0.82–1.64)	1.03 (0.71–1.49)	1.40 (0.93–2.09)	0.12
	FFQ fat + log non-fat	1.00	1.09 (0.76–1.54)	0.97 (0.65–1.45)	1.01 (0.64–1.60)	0.89 (0.51–1.56)	0.48
Polyunsaturated	FR fat + log energy	1.00	1.13 (0.80–1.60)	1.42 (1.00–2.02)	1.59 (1.09–2.32)	1.67 (1.10–2.53)	0.01
	FFQ fat + log energy	1.00	0.93 (0.66–1.30)	0.96 (0.67–1.38)	1.13 (0.76–1.69)	1.10 (0.68–1.77)	0.47
	FR residual + log energy	1.00	1.31 (0.95–1.81)	1.00 (0.71–1.40)	1.40 (1.01–1.93)	1.45 (1.05–2.00)	0.03
	FFQ residual + log energy	1.00	1.00 (0.73–1.37)	0.92 (0.67–1.27)	1.01 (0.73–1.38)	1.07 (0.78–1.47)	0.65
	FR fat + log non-fat	1.00	1.12 (0.80–1.59)	1.40 (0.99–1.98)	1.56 (1.09–2.25)	1.62 (1.10–2.40)	0.01
	FFQ fat + log non-fat	1.00	0.92 (0.66–1.29)	0.95 (0.67–1.36)	1.12 (0.76–1.64)	1.08 (0.69–1.70)	0.49
Monounsaturated	FR fat + log energy	1.00	1.33 (0.94–1.89)	1.58 (1.09–2.29)	1.46 (0.97–2.20)	1.96 (1.23–3.13)	0.01
	FFQ fat + log energy	1.00	1.07 (0.74–1.56)	1.14 (0.73–1.77)	1.42 (0.85–2.40)	1.46 (0.75–2.84)	0.22
	FR residual + log energy	1.00	1.62 (1.16–2.25)	1.49 (1.07–2.09)	1.59 (1.13–2.22)	1.69 (1.21–2.37)	0.006
	FFQ residual + log energy	1.00	1.18 (0.86–1.64)	1.21 (0.87–1.66)	1.12 (0.80–1.55)	1.42 (1.03–1.95)	0.06
	FR fat + log non-fat	1.00	1.31 (0.93–1.84)	1.54 (1.08–2.20)	1.41 (0.96–2.07)	1.86 (1.22–2.84)	0.008
	FFQ fat + log non-fat	1.00	1.07 (0.74–1.53)	1.12 (0.74–1.71)	1.40 (0.86–2.29)	1.43 (0.77–2.63)	0.21

[a] Adjusted for the following baseline variables: duration of follow-up, age at entry to study (in 5-year age groups), clinical centre region (North-East, South, Mid-West, West), hormone use (never, ever), family history (missing, no, yes), and breast biopsy (missing, no, yes).

Table 4 Log relative risks[a] for breast cancer in the continuous model, unadjusted for selection criteria

Type of fat	Model	Log relative risk[a]	*P*
Total	FR log fat + log energy	0.79	0.003
	FFQ log fat + log energy	0.39	0.37
Saturated	FR log fat + log energy	0.29	0.15
	FFQ log fat + log energy	−0.09	0.75
Polyunsaturated	FR log fat + log energy	0.50	0.005
	FFQ log fat + log energy	0.08	0.68
Monounsaturated	FR log fat + log energy	0.72	0.002
	FFQ log fat + log energy	0.59	0.11

[a] Adjusted for the following baseline variables: duration of follow-up, age at entry to study (in 5-year age groups), clinical centre region (North-East, South, Mid-West, West), hormone use (never, ever), family history (missing, no, yes), and breast biopsy (missing, no, yes). The exponent of the value gives the RR for a change in 1 unit of fat intake on the natural logarithmic scale, i.e. for a 2.7-fold increase in fat intake. For example the value of 0.79 for total fat based on the FR represents an estimated RR of 2.20 for a 2.7-fold increase in total fat intake.

the fourth and fifth quintile RRs adjusted for total energy and corrected for selection were: for the FR, 1.86 and 2.54 (*P*-value for trend = 0.006) and for the FFQ, 1.06 and 1.24 (*P*-value for trend = 0.41), respectively. For saturated fat, these adjusted RRs for the fourth and fifth quintiles were 1.33 and 1.79 for the FR (*P*-value for trend = 0.06) and 1.01 and 0.85 for the FFQ (*P*-value for trend = 0.49). In addition, parallel comparisons with those of Table 6 revealed statistically significant advantages in the standardized log RR of the FR over the FFQ for total fat and all sub-types of fat examined (*P*-values of 0.01, 0.02, 0.03, 0.02 for total, saturated, polyunsaturated, and monounsaturated fats, respectively).

Discussion

Our study is able to address two important questions in nutritional epidemiology: the methodological question of whether or not FRs have more power to detect diet–disease relationships than FFQs, and the specific question of whether or not there is an association between dietary fat intake and breast cancer incidence.

The dietary fat–breast cancer relationship has been a topic of controversy for >20 years, with positive associations seen in animal studies, international comparisons, and case–control studies, but no associations seen in most cohort studies. Each of these study designs has its strengths and weaknesses. Animal studies require a hazardous extrapolation across species, and international comparisons may be influenced by unmeasured

Table 5 Relative risks[a] (95% confidence limits in brackets) for breast cancer in quintiles of total fat intake, estimated according to different statistical models, adjusted for selection criteria

Type of fat	Model	Q1	Q2	Q3	Q4	Q5	*P* for Trend
	FR fat + log energy	1.00	1.48 (0.94–2.33)	1.64 (1.06–2.54)	1.96 (1.22–3.15)	2.09 (1.21–3.61)	0.008
	FFQ fat + log energy	1.00	1.16 (0.72–1.85)	1.15 (0.65–2.02)	1.56 (0.79–3.08)	1.71 (0.70–4.18)	0.18
	FR residual + log energy	1.00	1.11 (0.72–1.72)	1.23 (0.79–1.92)	1.30 (0.88–1.94)	1.58 (1.08–2.33)	0.007
	FFQ residual + log energy	1.00	1.26 (0.28–5.69)	1.22 (0.28–5.33)	1.16 (0.27–4.93)	1.43 (0.33–6.25)	0.30
	FR fat + log non-fat	1.00	1.40 (0.90–2.16)	1.50 (1.01–2.22)	1.73 (1.16–2.57)	1.73 (1.14–2.63)	0.009
	FFQ fat + log non-fat	1.00	1.11 (0.71–1.72)	1.05 (0.65–1.70)	1.38 (0.80–2.37)	1.40 (0.72–2.70)	0.24
Saturated	FR fat+ log energy	1.00	1.21 (0.79–1.86)	1.29 (0.85–1.95)	1.07 (0.69–1.66)	1.51 (0.94–2.43)	0.20
	FFQ fat + log energy	1.00	1.12 (0.70–1.80)	1.09 (0.66–1.81)	1.19 (0.67–2.11)	1.00 (0.49–2.02)	0.95
	FR residual + log energy	1.00	0.82 (0.55–1.24)	1.24 (0.88–1.74)	1.14 (0.81–1.61)	1.17 (0.85–1.62)	0.11
	FFQ residual + log energy	1.00	0.95 (0.62–1.45)	1.02 (0.68–1.53)	0.94 (0.63–1.39)	0.99 (0.68–1.44)	0.99
	FR fat + log non-fat	1.00	1.20 (0.78–1.83)	1.27 (0.85–1.89)	1.05 (0.69–1.59)	1.47 (0.96–2.25)	0.19
	FFQ fat + log non-fat	1.00	1.12 (0.71–1.78)	1.09 (0.68–1.77)	1.20 (0.70–2.03)	1.01 (0.53–1.90)	0.95
Polyunsaturated	FR fat + log energy	1.00	1.00 (0.67–1.51)	1.43 (0.95–2.14)	1.27 (0.83–1.95)	1.74 (1.06–2.84)	0.01
	FFQ fat + log energy	1.00	0.89 (0.60–1.32)	0.90 (0.60–1.36)	0.94 (0.59–1.52)	1.02 (0.57–1.83)	0.79
	FR residual + log energy	1.00	1.37 (0.92–2.03)	1.19 (0.81–1.74)	1.40 (0.96–2.04)	1.56 (1.05–2.33)	0.03
	FFQ residual + log energy	1.00	0.95 (0.61–1.49)	0.89 (0.58–1.36)	0.90 (0.57–1.42)	1.03 (0.66–1.61)	0.76
	FR fat + log non-fat	1.00	0.99 (0.66–1.49)	1.41 (0.95–2.10)	1.25 (0.82–1.89)	1.68 (1.06–2.68)	0.01
	FFQ fat + log non-fat	1.00	0.89 (0.60–1.32)	0.90 (0.60–1.35)	0.94 (0.60–1.49)	1.02 (0.59–1.77)	0.77
Monounsaturated	FR fat + log energy	1.00	1.27 (0.78–2.07)	1.63 (1.09–2.45)	1.58 (0.99–2.51)	1.96 (1.11–3.45)	0.02
	FFQ fat + log energy	1.00	1.06 (0.68–1.64)	1.03 (0.62–1.72)	1.41 (0.77–2.59)	1.39 (0.64–3.01)	0.25
	FR residual + log energy	1.00	1.11 (0.70–1.76)	1.69 (1.16–2.47)	1.66 (1.16–2.38)	1.46 (1.01–2.11)	0.03
	FFQ residual + log energy	1.00	0.95 (0.45–2.03)	1.16 (0.57–2.40)	1.08 (0.52–2.23)	1.27 (0.62–2.63)	0.13
	FR fat + log non-fat	1.00	1.25 (0.77–2.03)	1.60 (1.09–2.35)	1.52 (0.99–2.36)	1.87 (1.12–3.12)	0.02
	FFQ fat + log non-fat	1.00	1.05 (0.68–1.62)	1.02 (0.62–1.67)	1.39 (0.79–2.46)	1.36 (0.67–2.76)	0.23

[a] Adjusted for the following baseline variables: duration of follow-up, age at entry to study (in 5-year age groups), clinical centre region (North-East, South, Mid-West, West), hormone use (never, ever), family history (missing, no, yes), and breast biopsy (missing, no, yes).

confounders. The cohort design reduces (but does not eliminate) the impact of confounders, and is clearly stronger than the case–control design, effectively eliminating bias arising from differential recall of diet between breast cancer cases and controls. However, the cohort design rests heavily on the quality of the dietary reporting by participants, which is strongly influenced by the assessment method used. Most cohort studies to date have used some form of FFQ. The strongest design, the RCT, is expensive and time consuming and can be used for only a few select questions. The WHI includes an RCT, which has just been completed,[25] that evaluates the impact of a low fat, high fruits, vegetables, and fibre dietary pattern on breast cancer incidence. The results of the trial are discussed towards the end of this section.

The data from our study demonstrate an association between dietary fat intake as reported on a 4 day FR and breast cancer incidence, with statistically significant relationships found for total fat, polyunsaturated fat, and monounsaturated fat, after appropriate adjustment for confounders. The association is seen both in the analyses unadjusted for selection into the study, and also after statistical adjustment for selection, with little change in the estimated RRs. It is also seen in a range of statistical models, both categorical and continuous. This is, to our knowledge, the largest cohort study (with over 600 cases of breast cancer) to have demonstrated such an association.

The women in our cohort were not completely representative of the US population in that they were self-selected volunteers who were found eligible to participate in the WHI DM trial, who were more obese, less likely to be smokers, and had lower rates of hypertension than nationally representative samples of the population.[12] Many large nutritional epidemiology cohort studies carry the same limitations having selection characteristics that differ somewhat from the general population. However, it has not been demonstrated that such characteristics create serious biases in the relative risks for nutrient intakes that derive from these studies. Women entering the study were selected according to their reported intake of energy from fat on the baseline FFQ. Because this selection criterion was precisely defined we were able to make statistical adjustments for this, as described in the Methods and Results sections.

In common with other associations discovered in nutritional epidemiology cohort studies, the associations that we have found may be explained by the presence of unmeasured confounders, by residual confounding (particularly with energy or non-fat energy) in the multivariate modelling resulting from dietary measurement error, or by the presence of a real

Table 6 Log relative risks[a] (log RR) for breast cancer in the continuous model, and standardized log relative risk parameters for FR and FFQ, adjusted for selection criteria; standard errors (SE) and *P*-values (*P*) estimated by the bootstrap method

Model	Instrument	Log RR adjusted for selection[a]	Standard error of log RR adjusted for selection[b]	Standardized log RR adjusted for selection[b]
Log total fat and log energy	FR	0.79 ($P = 0.003$)	0.24 (SE = 0.006)	3.32 (SE = 1.16)
	FFQ	0.39 ($P = 0.37$)	0.31 (SE = 0.012)	1.24 (SE = 1.33)
	Difference			$P = 0.08$
Log saturated fat and log energy	FR	0.31 ($P = 0.11$)	0.18 (SE = 0.005)	1.68 (SE = 1.06)
	FFQ	0.03 ($P = 0.91$)	0.25 (SE = 0.008)	0.14 (SE = 1.17)
	Difference			P = 0.17
Log polyunsaturated fat and log energy	FR	0.51 ($P = 0.006$)	0.17 (SE = 0.004)	3.02 (SE = 1.08)
	FFQ	0.13 ($P = 0.56$)	0.17 (SE = 0.005)	0.77 (SE = 1.29)
	Difference			$P = 0.07$
Log monounsaturated fat and log energy	FR	0.71 ($P = 0.002$)	0.20 (SE = 0.006)	3.47 (SE = 1.14)
	FFQ	0.52 ($P = 0.16$)	0.29 (SE = 0.011)	1.82 (SE = 1.30)
	Difference			$P = 0.16$

[a] Adjusted for the following baseline variables: duration of follow-up, age at entry to study (in 5-year age groups), clinical centre region (North-East, South, Mid-West, West), hormone use (never, ever), family history (missing, no, yes), and breast biopsy (missing, no, yes). The exponent of the value gives the RR for a change in 1 unit of fat intake on the natural logarithmic scale, i.e. for a 2.7-fold increase in fat intake. For example the value of 0.79 for total fat based on the FR represents an estimated RR of 2.20 for a 2.7-fold increase in total fat intake.

[b] Estimates of what the standard error of the log relative risk and the standardized log relative risk would have been if the selection criterion had not been used to select participants into the study: (standardized log RR in a study with no selection) = (log RR adjusted for selection)/(std. error log RR in a study with no selection).

relationship between dietary fat and breast cancer. The first two explanations cannot be completely ruled out. We have adjusted for the known important risk factors for breast cancer and the observed association has remained, but it is in the nature of observational epidemiology that other unsuspected confounders could be present. For a strong effect of residual confounding from total energy or non-fat energy, the multiplicative factor that governs the proportion of total energy or non-fat energy effects attributed to the fat effect[26] would need to be large, or the effects themselves would be required to be strongly associated with breast cancer. Data from the OPEN study indicate that these multiplicative factors are quite small,[27] but a strong relationship between total energy or non-fat energy and breast cancer risk cannot be excluded. Though not conclusive, the presence of a real relationship between dietary fat and breast cancer seems to us a reasonable interpretation of the findings.

Previous analyses have also indicated an association between breast cancer risk and total fat intake, but in contrast to our findings, those analyses showed elevated risks particularly related to saturated fat.[1,7,28] Using the FR, we observed an elevated, but not statistically significant increased risk for saturated fat, and statistically significant increased risks for total, polyunsaturated and monounsaturated fat intakes. However, we do not regard our lack of statistical significance for saturated fat as a qualitatively different result. Reported intakes of different types of fat are often highly correlated, which, together with measurement error, make it extremely difficult to disentangle the effect of one type of fat from another.[29] In our study the correlations between total fat and different types of fat (saturated, polyunsaturated, and monounsaturated) were all >0.8, both for the FFQ and the FR. Correlations between monounsaturated fat and the other two types of fat were also high (0.83 and 0.90 for the FFQ, and 0.76 and 0.84 for the FR). Furthermore, our alternative analysis for handling missing data yielded a stronger association between saturated fat and breast cancer incidence.

In an effort to understand our findings for different fat subtypes, we attempted to evaluate food sources of monounsaturated and saturated fat in these data. Unfortunately, this was not possible with the NDS-R software. We were able to reanalyse nationally representative dietary intake data (US Department of Agriculture 1994–1996 Continuing Survey of Food Intake by Individuals)[30] for dietary food sources of fat subgroups among women aged 50–79 years. Some foods contributed heavily to both saturated and monounsaturated fats (beef 10% of the saturated fat intake and 10% of the monounsaturated fat intake, oils/salad dressings/mayonnaise 8 and 14%, sweet baked goods 5 and 8%, respectively); while others such as cheese (10%), milk (8%), frozen desserts (6%) and butter (6%) contributed mainly to saturated fat, and others contributed mainly to monounsaturated fat such as margarine (9%) and other fats (shortening, lard, etc.) (5%). It remains unclear whether any particular food group was driving our observed monounsaturated fat association, and further work is required before the contributions of the different fat subtypes to breast cancer risk can be disentangled.

That the association was demonstrated using an FR and not an FFQ appears qualitatively similar to the result by Bingham *et al*. However, it must be understood that the selection of the women into our study according to their FFQ reported percentage energy from fat creates a bias against the FFQ that must be removed before fair comparisons can be made. The statistical significance of the RRs for the FR together with the non-significance of the selection-adjusted RRs for the FFQ seen in Table 5 does not in itself allow the conclusion that the FR is the more powerful instrument. More relevant to the direct comparison of the two instruments is the relative size of the RRs in Table 5 (as opposed to their significance) and also the comparison of the standardized log relative risks in Table 6.

In this respect we see a uniform pattern where the values are larger for the FR than for the FFQ. The increase in standardized log RR for the FR over that of the FFQ in Table 6 is close to conventional statistical significance for total and polyunsaturated fats. In an alternative analysis for handling missing data, this increase reached statistical significance for all types of fat considered. Thus our results provide direct, although not conclusive, evidence that the FR is a more powerful instrument than the FFQ for detecting fat–breast cancer associations. Together with the results by Bingham *et al*., they suggest a possible reason for the failure to detect such associations in previous cohort studies, given that those studies used FFQs. Day *et al*.[31] in a comparison of a 7 day diary with an FFQ reported finding less error with the diary, although this finding was disputed.[32] A large study using biomarkers of energy and protein intake has shown that intakes reported on an FFQ have weaker correlations with true intake than the corresponding intakes reported on 24 h recalls.[27] Thus it seems plausible that the difference in results seen in our study using the FR and FFQ is not a chance event, but one due to the different properties of the instruments.

An important consideration in selecting dietary assessment instruments for future large cohort studies is that the FFQ is less expensive and more convenient. FRs themselves are ~10–25 times more expensive than FFQs [personal communications from the Fred Hutchinson Cancer Research Center and Westat, Inc.]. In the WHI, such costs included intensive training of participants, review of records by trained staff, coding and analysis. However, not all the FRs in a cohort study need be coded and analysed, since results can be obtained from cases and matched controls in a nested case–control design. FRs are known to have other drawbacks. Foremost among these is the respondent burden and reaction to completing them. Respondents tend to vary from their usual intakes when asked to record, underreport total energy, and record with declining quality over time,[33–35] although, in a prospective study it is reasonable to expect that cases and controls are equally impacted by these biases. It is also worth noting that, despite these drawbacks, the selection-adjusted total energy intake (1642 kcal) estimated from the FR was slightly higher than that on the FFQ (1592 kcal), possibly indicating slightly less underreporting on the FR. Further consideration of what is the most appropriate instrument for such studies is needed.

This study was conducted in the control group of the WHI DM trial of a low-fat eating pattern. Principal results of the randomized comparison in this trial were reported very recently[25] and showed a reduction in breast cancer risk in the intervention group that did not quite attain conventional statistical significance. The estimated RR (hazard ratio) between the intervention and comparison group was 0.91 with a 95% confidence interval of 0.83–1.01. Assuming the intervention group consumed ~9.5% calories from fat per day less than the comparison group (they reported, on average, consuming 25.5 and 35% calories from fat, respectively), applying our results from the continuous model for the FR (Table 6) to this difference in intake would predict a relative risk between the two groups of ~0.78, a reduction in risk of 22% compared with the 9% reduction observed in the trial. (The predicted relative risk of 0.78 is obtained by multiplying the log relative risk for total fat of 0.79 by the logarithm of 25.5/35 and exponentiating the result.) However, our cohort study was based on baseline reported dietary intakes that are thought to reflect long-term intake. The WHI DM trial estimated the effect of short-term dietary change and was designed under the assumption that breast cancer risk would decline linearly over time with the intervention achieving its maximum effect after 10 years. If we take our estimate of 22% reduction as that maximum effect, then one would expect an average risk reduction over the first 8 years of the trial to be $26\% \times 0.4 = 8.8\%$, an estimate very close to the observed 9.1%. Thus, our results, particularly those based on FRs, point in the same direction as the main result of the randomized comparison.

In summary, our results support a positive association between dietary fat and breast cancer and suggest that the detection of important diet–disease relationships in epidemiological studies is sensitive to the type of dietary assessment instrument used. Additional evaluation of dietary assessment strategy is clearly warranted, as alternative self-report instruments (dietary records or multiple 24 h recalls) may be preferable to the FFQ.

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Appendix 1

Method of estimating selection-adjusted relative risks and selection-adjusted standard errors

(a) Adjustment of the relative risk estimates

Suppose we are interested in the relative risk related to a continuous variable F (for example, log reported intake of total fat or fat subtype, either by FFQ or FR) and that there are confounders X that need to be adjusted for. We, therefore, want to estimate the logistic regression parameter β_2 in the model

$$\text{logit}[\Pr(Y = 1|X, F)] = \beta_0 + \beta_1 X + \beta_2 F. \quad (1)$$

This model is for the general (unselected) population, but the WHI data is from a selected population, where all the participants satisfy the condition that log FFQ percentage calories from fat, which we will denote by C, is greater than log (32). If we analyse the data from this sample we will obtain a biased estimate of β_2 because of the selection.

Our method to obtain an unbiased estimate of β_2 is to add an extra variable C_R into the regression model above, where $C_R = C-(\alpha_0 + \alpha_1 X + \alpha_2 F)$ is the residual from regressing C on X and F in the unselected healthy population. The new regression model now includes the selection variable C, but in a version of C (C_R) that is uncorrelated with X or F. According to the theory by Gail *et al.*,[36] the estimates of the parameters in the logistic regression model, including β_2, will be very nearly unbiased in large samples.

To execute this method, we have to estimate (α_0, α_1, and α_2), and use them to estimate C_R. In order to do this we assume that

in the general healthy population log FFQ percentage calories from fat (C) is distributed normally conditional on F and X. With F as log intake of total fat (or fat subtype) from the FFQ or FR, this assumption agrees well with previous experience. Under this assumption the distribution of C in the truncated population can be written as a function of the parameters α_0, α_1, and α_2, and the parameters may then be estimated by maximum likelihood in the control group. When F represents quintiles of fat intake, then some further computations are required, made under the extra assumption that log continuous fat intake is normally distributed. Details are available from the corresponding author.

In simulations of the standard energy adjustment model for continuous variables, this estimation method performed exceedingly well, resulting in unbiased estimates with hardly any increase in standard errors over the naive model.

(b) Adjustment of the standard errors of the relative risk estimates

The aim here is to obtain an estimate of the standard error that would have been obtained in a study of relative risk in the general population without any selection according to FFQ percentage calories from fat. This standard error of the log relative risk is proportional to the inverse of the variance in the general healthy population of F conditional on X. When F is the log of FFQ or FR fat intake on a continuous scale, then as above, it appears reasonable to assume that C and F are jointly normally distributed in that population conditional on X. Under this assumption it is possible to estimate quite simply the conditional variance of F, mentioned above. This is done by considering separately the regression within the controls of the truncated sample of: (i) F on C and X, and the regression of the healthy general population of (ii) C on X. These models are written as:

$$F = \gamma_0 + \gamma_1 X + \gamma_2 C + \upsilon, \quad \text{(i)}$$

$$C = \eta_0 + \eta_1 X + \omega. \quad \text{(ii)}$$

Then the conditional variance of F given X is given by $\mathrm{var}(\upsilon) + \gamma_2^2 \mathrm{var}(\omega)$. The parameters γ_2 and var (υ) are estimated directly from the truncated sample, and var (ω) is estimated by likelihood methods, as above, knowing the form of the truncated distribution of C given X.

More details on these methods are available from the corresponding author.

Appendix 2

List of WHI investigators

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