

Meta-analysis: Dietary Fat Intake, Serum Estrogen Levels, and the Risk of Breast Cancer

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Background: There is compelling evidence that estrogens influence breast cancer risk. Since the mid-1980s, dietary fat intervention studies have been conducted to investigate the effect of fat intake on endogenous estrogen levels. To further our understanding of the possible relationship between dietary fat and breast cancer, we conducted a meta-analysis of dietary fat intervention studies that investigated serum estradiol levels, and we reviewed the nature of the evidence provided by prospective analytic studies of fat consumption and breast cancer risk. **Methods:** A computerized search of the English language literature on estrogen/estradiol and dietary fat intervention studies published from January 1966 through June 1998 was conducted using the MEDLINE® database. Pooled estimates were derived from the change in estradiol levels associated with fat reduction from 13 studies. Analyses were conducted separately for premenopausal and postmenopausal women and in both groups combined. **Results and Conclusions:** Statistically significant reductions in serum estradiol levels of -7.4% (95% confidence interval [CI] = -11.7% to -2.9%) among premenopausal women and -23.0% (95% CI = -27.7% to -18.1%) among postmenopausal women were observed, with an overall -13.4% (95% CI = -16.6% to -10.1%) reduction observed. The greatest reductions occurred in two studies in which dietary fat was reduced to 10%–12% of calories compared with 18%–25% of calories in the other studies. A statistically significant reduction in estradiol levels of -6.6% (95% CI = -10.3% to -2.7%) remained after exclusion of these two studies. Review of prospective analytic epidemiologic studies that allowed for dietary measurement error suggests

that the possibility that reducing fat consumption below 20% of calories will reduce breast cancer risk cannot be excluded. **Implications:** Dietary fat reduction can result in a lowering of serum estradiol levels and such dietary modification may still offer an approach to breast cancer prevention. [J Natl Cancer Inst 1999;91:529–34]

Dietary fat has been the major focus in the search for dietary causes of breast cancer, but its importance remains controversial (1,2). Although a combined analysis of 12 case-control studies did find a statistically significant positive association between fat intake and risk (3), it has been argued that case-control studies of this issue can lead to spurious associations (4,5). Prospective cohort studies, in which diet is assessed before the diagnosis of disease, are superior in this regard. In a combined analysis of seven cohort studies of fat intake and breast cancer risk, Hunter et al. (6) concluded there is “no evidence of a positive association between . . . fat intake and risk of breast cancer” and “no reduction in risk even among women whose energy intake from fat was less than 20 percent of total energy intake.” However, in these studies, less than 2% of subjects had fat intake less than 20% and only 6% had intake between 20% and 25% (6). As we discuss below, these figures are likely to be substantial overestimates, and the assertion concerning the effect of an intake of less than 20% calories may not be valid (6).

The lack of support of a fat-breast cancer association from prospective epidemiologic studies contradicts the overwhelming support for such an association from international correlational studies (2,7). Until around 1970, there existed about a sixfold difference in breast cancer rates between the low rates in Asia and the high rates in U.S. whites (8,9). This large variation in risk was not due to underlying genetic differences, since the rates of breast cancer in Asian migrants to the United States have shifted substantially toward those of U.S. whites, and the rates in Japanese-Americans are now some 70% of the rates in U.S. whites (10). In recent years, women living in urban areas of Japan have also experienced a great increase in their breast cancer incidence

(11,12); concurrent with this increase has been an extraordinary change in their dietary habits. In the early 1950s, fat comprised only some 8% of the calories in the typical Japanese diet, but by the late 1980s, fat consumption was some 32% of calories (13,14), approaching the typical U.S. level.

As reviewed by Welsch (15), reduction in fat consumption can lower mammary tumor incidence in rodents. In some animal studies (16–18), the incidence of mammary tumors plateaued at about 20% of calories from fat.

If a threshold effect of fat can be extended to breast cancer in humans, it may help explain the lack of association between fat and breast cancer usually reported in studies conducted in Western populations, most of whom have fat intake substantially above 20% calories from fat. Thus, sorting out the role of fat in the lower range (i.e., <20% of calories) in humans remains a priority.

There is overwhelming evidence that estrogen levels are a critical determinant of breast cancer risk (19,20). Women in Asia at low risk for breast cancer have been shown consistently to have lower urinary and blood levels of estrogens than Caucasian women at high risk for this disease (20,21). Strong support for a role of postmenopausal estrogens and risk of breast cancer was recently reported by Hankinson et al. (22) using the Nurses' Health Study. In a pooled analysis of six prospective studies on endogenous estradiol levels and breast cancer risk, postmenopausal women who subsequently developed breast cancer showed a 15% higher mean concentration of serum estradiol than women who did not (23). Similar differences in mean estradiol levels were seen in a pooled analysis of 16 case-control studies (23).

Since the mid-1980s, dietary fat inter-

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vention studies have been conducted to investigate the effect of fat intake on endogenous estrogen levels. The assumption is that lowered estrogen levels could be regarded as likely to lead to lower breast cancer risk. We have conducted a quantitative review of published studies of the effect of dietary fat intervention studies on serum estradiol levels in premenopausal and postmenopausal women.

MATERIALS AND METHODS

Identification of studies. We identified studies by a computerized search of the MEDLINE® English language literature on estrogen/estradiol and dietary fat intervention studies published from January 1966 through June 1998. We also reviewed the reference lists of the relevant publications to identify additional studies. We included only intervention studies that specified the level of fat consumed during the intervention period and the duration of the study and presented endogenous estrogen levels prior to and during (or at the completion of) the intervention or the percent change in endogenous estrogen level before and during intervention. We did not include dietary fat intervention studies that were conducted among women with breast cancer (24–26) or that investigated the effect on estrogen levels of different types of fats consumed (27). The former group of studies was excluded in the present analysis because of potential confounding by adjuvant chemotherapy and treatment-related weight changes (24–26). Thus, our pooled analysis included 10 studies with data on premenopausal women (28–37) and four studies with data on postmenopausal women (35,38–40). Although Crichton et al. (38) presented results on premenopausal women, we excluded these data in our analysis because we could not determine for certain the endogenous estradiol levels at baseline and during the intervention period from the figures or the text of this paper. However, we have included results on postmenopausal women from this study (38), because the change in estradiol levels, that we calculated by extrapolating the results presented in the figures, was compatible with the results these investigators described in the text.

Statistical analyses. For each study, we took either the reported ratio of estradiol level after the low-fat diet to the level at baseline or we calculated this ratio using the estradiol levels reported at baseline and after dietary intervention. To calculate the standard error of this ratio, we used either the 95% confidence intervals (CIs) from the reports (31,34,38), the reported *P* value (33), or the standard deviation (or standard error of the mean) of the baseline and treatment estradiol levels (28–30,32,35–37,39,40). The measurements (ratio and standard errors) were expressed in natural logarithms. Assuming that the log ratio is approximately normally distributed, the estimated standard errors were used to obtain a 95% CI for the log ratio that then was exponentiated to calculate the corresponding CI for the ratio. To summarize the effect of interest, summary estimates of the log ratios in estradiol levels were first described using fixed-effects models (42). Heterogeneity was assessed by visual inspection of the graphic plot of data and by the heterogeneity test described by DerSimonian and Laird (43).

Analyses were conducted separately for premenopausal and postmenopausal women and in both groups combined. Relevant information (i.e., sample size, study duration, timing of blood specimen collection, dietary goals in terms of percent calories in fat and intake of fiber, and body weight before and after dietary change) regarding each of the intervention studies is described in Table 1. Study-specific estimates of the ratio of serum estradiol levels are shown in Fig. 1, ordered, from top to bottom, by decreasing percent of fat calories during intervention by menopausal status. The average ratio and the corresponding CI are denoted, respectively, by a square and line through the square. A summary average of the ratio using all 14 studies combined is shown as a triangle, whereas the summary average calculated after exclusion of the two most extreme studies (37,40) (see below) is shown as a circle. All reported *P* values were derived from two-sided statistical tests.

RESULTS

Table 1 summarizes the dietary fat intervention studies. Subjects served as their own control in all studies but one (31); baseline hormone levels were measured and were compared with measurements obtained after varying periods of dietary intervention. In the studies conducted among premenopausal women, subjects changed from a high-fat (29%–46% of fat calories) to a low-fat (12%–25% of fat calories) diet typically for 2 or 3 months. During the intervention period, fat intake was 21%–25% of calories in five studies (28–32), 18%–20% in four (33–36), and 12% in one (37). As part of the intervention design, four studies (28,33,34,36) showed increases of approximately 30 g of fiber per day, while in six studies (29–32,35,37), fiber intake showed increases of 2–9 g per day.

In the studies with data on postmenopausal women, the intervention period ranged from 3 weeks (40) to 5 months (39). During the intervention period, calories from fat was 24% in one study (38), 18%–20% in two (35,39), and 10% in a fourth (40). Fiber intake increased by 2 g per day in one study (35), was 35–45 g per day (per 1000 kcal) as part of the intervention protocol in a second (40) (baseline fat and fiber intakes were not presented), and was not presented in two (38,39).

Serum estradiol levels decreased by at least 5% in seven (29–34,37) of the 10 studies in premenopausal women; results reached statistical significance in two studies (30,37). One study showed a change (28) of less than 2% and two showed slight statistically nonsignificant increases (35,36). In postmenopausal

women, three (38–40) of the four studies showed a reduction in serum estradiol levels; results were statistically significant in two (39,40). One study (35) showed a small statistically nonsignificant increase.

Fig. 1 shows our calculated estimates of the percent change in estradiol levels and the corresponding 95% CIs. We found a pooled estimate of a change in estradiol level of –7.4% (95% CI = –11.7% to –2.9%) among premenopausal women and of –23.0% (95% CI = –27.7% to –18.1%) among postmenopausal women; the overall percent change was –13.4% (95% CI = –16.6% to –10.0%). The two studies (37,40) in which the fat intake was reduced to 12% or less showed the largest percent reductions. We repeated our pooled estimate calculations for studies in which the calories from fat was 18%–25% by excluding these two most extreme studies (37,40). This analysis showed a pooled estimate of a change in estradiol level of –6.7% (95% CI = –11.1% to –2.1%) among premenopausal women and –6.2% (95% CI = –13.1% to –1.3%) among postmenopausal women. The percent change in premenopausal and postmenopausal women combined was –6.6% (95% CI = –10.3% to –2.7%).

Fig. 1 is indicative of heterogeneity of the effects of fat on estradiol levels, with the studies with the lowest percent calories from fat (37,40) evidently the most discrepant (test for heterogeneity, $\chi^2_{13} = 126.3$; $P < .0001$). Heterogeneity was markedly reduced after exclusion of the latter two studies ($\chi^2_{11} = 24.4$) but remained statistically significant ($P = .01$). Using the random-effects model (43), which accounts for heterogeneity across the remaining 12 studies while still estimating a mean effect, changed the estimate of effect from –6.6% to –6.8% but the result was no longer statistically significant (95% CI = –13.2% to 0.1%).

DISCUSSION

In this review of 13 dietary fat intervention studies, percent calories from fat intake changed to 18%–25% in 11 studies (28–36,38,39), while two studies (37,40) showed changes to 10% and 12% during the intervention period. We found in all studies combined that serum estradiol levels decreased statistically significantly (–13.4%) in premenopausal and postmenopausal women together and separately in premenopausal (–7.4%) and

Table 1. Summary of dietary fat intervention studies in premenopausal and postmenopausal women, ordered by percent calories from fat during dietary intervention*

Study, year of publication (reference No.)	No. of subjects/ duration of intervention†	Day of blood collection‡	Methods of diet change and frequency of diet counseling	Measure of dietary compliance	% fat calories		Fiber, g/day		Weight, kg	
					Before§	During	Before	During	Before	During
Premenopausal women										
Woods et al., 1989 (28)	17/8–10 wk	Days 4–7	Metabolic meals	Meal trays checked after each meal	40	25	12	40	60.4	NSSC
Hagerty et al., 1988 (29)	6/1 mo†	Follicular	Metabolic meals	NA	46§	25§	17	19	60.3	59.0
Rose et al., 1987 (30)	16/3 mo	Days 17–20	Fat portion exchange list-diet plan	4-d food diaries—monthly	35	21	14	16	59.4	58.0
Boyd et al., 1997 (31)	112/24 mo	Not timed in relation to cycle	Food exchange, visits: 1 mo to y 1, 1/3 mo to y 2	3-d food records—at each visit	34	21	16	19	60.8	60.8
Williams et al., 1989 (32)	15/2 mo	Days 21–26	Individualized diet plan; weekly meetings	24-h diet recall, 7 d weighed inventory of foods eaten—mo 2, assess lipid profiles	37	21	22	28	64.2	61.1
Goldin et al., 1994 (33)	48/2 mo	Days 4–7	Metabolic meals	Meal trays checked after each meal	40	20	12	40	58.5	NSSC
Woods et al., 1996 (34)	21/2 mo	Days 4–7	Metabolic meals	Meal trays checked after each meal	40	20	12	42	65.1	NSSC
Ingram et al., 1987 (35)	18/2 mo†	Mid-luteal	Individualized diet plans	Seven 24-h food records	40§	18§	19	21	61.3	62.2
Schaefer et al., 1995 (36)	22/8–10 wk	Days 3–7	Metabolic meals	Weekly meetings to assess compliance, assess lipid profiles	40	18	12	40	Body mass index = 22.2¶	Body mass index = NSSC
Bagga et al., 1995 (37)	12/3 mo	Follicular	Metabolic meals	4-d food records monthly; assess lipid profiles	29	12	19	28	61.7	59.7
Postmenopausal women										
Crichton et al., 1992 (38)	19/1 mo	Weekly	Fat exchanges weekly visits	7-d diet diary—wk 4	38	24	NA	NA	64.1	62.7
Prentice et al., 1990 (39); Henderson et al., 1990 (41)#	73/3–5 mo	NA	Part of the WHT study; extensive counseling	4-d food records assess lipid profile	37	20	NA	NA	69.6	66.2
Ingram et al., 1987 (35)	15/2 mo	NA	Individualized diet plans	Seven 24-h food record	40	18	19	21	62.7	62.1
Heber et al., 1991 (40)	13/3 wk	NA	Metabolic meals-at Pritikin Longevity Center	Assess lipid profiles	NA	<10	NA	34–45	84.9	82.3

*NA = not available, NSSC = no statistically significant changes; WHT = Women's Health Trial.

†Duration of low-fat intervention phase of crossover study design.

‡For premenopausal women, in relation to menstrual cycle. Estradiol comparisons in Fig. 1 are based on measurements of specified days of blood collection.

§Before or during intervention. In these two studies, half of the subjects were randomly chosen to begin the high-fat diet (before) and half to begin the low-fat diet (during).

|| $P < .05$ before and during intervention.

¶Body mass index = weight in kg/(height in m)².

#Supplemental material to (39).

postmenopausal women (–23.0%). Statistically significant, but smaller reductions in serum estradiol levels were found when we restricted the analysis to the 11 studies in which fat calories changed to 18%–25%.

We have no explanation for the increase in estradiol levels found in two studies (35,36) that had the largest reduction in percent calories from fat intake and in which fat intake was 18% of calo-

ries from fat. The CIs were wide in one of these studies (36) but not in the second (35).

Two studies (37,40) differ from the other dietary fat intervention studies in that the level of fat intake was much lower (10%–12% of fat calories) than in the other studies (18%–25% of fat calories). These diets were similar in fat content to that of traditional low-fat-consuming Asian women (see below). The

largest reductions in estradiol levels were also found in these two studies (37,40).

A concern in interpreting the effect of dietary fat reduction on blood estrogen levels is the possible effect of other dietary factors. Reductions in serum estradiol levels have been associated with increases in fiber intake while the percent calories from fat remained unchanged (44,45). However, the fiber–estrogen association is complex; it may depend on

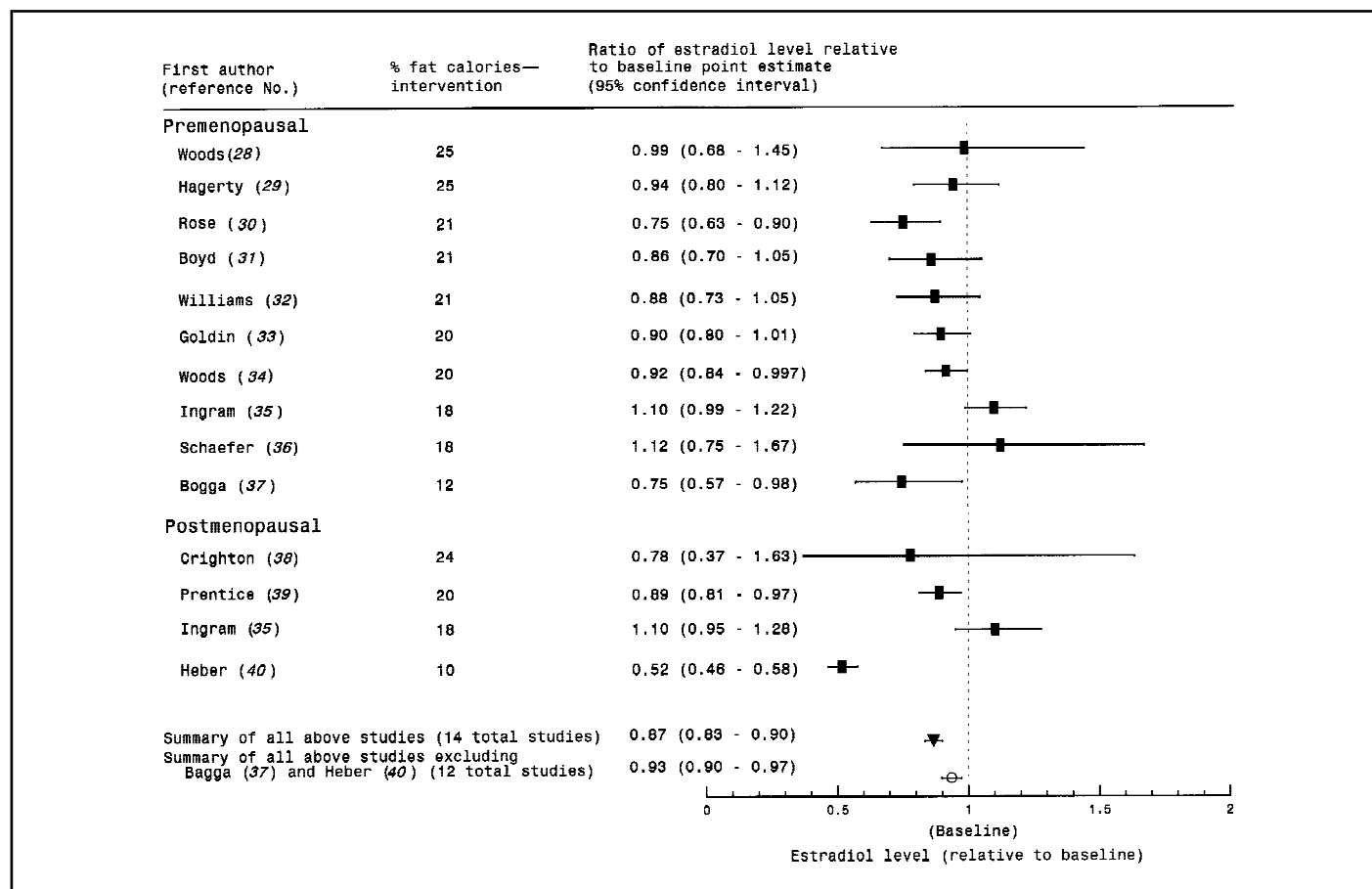


Fig. 1. Calculated ratios (95% confidence intervals [CIs]) of serum estradiol levels relative to baseline levels. Each study-specific point estimate is plotted as a square and its 95% CI is denoted by a line through the square. The point estimate for all studies combined is represented by an inverted triangle. The point estimate for all studies combined excluding the studies by Bagga et al. (37) and Heber et al. (40) is denoted by a circle. The baseline level is represented by 1 and a dotted line extends upward from the baseline in the figure. We found a pooled estimate of a change in estradiol level of -7.4% (95% CI = -11.7% to -2.9%) among premenopausal women and of -23.0% (95% CI = -27.7% to -18.1%) among postmenopausal women; the overall percent change was -13.4% (95% CI = -16.6% to -10.0%). The two studies (37,40) in which the fat intake was reduced to 12% or less showed the largest percent reductions. We repeated our pooled estimate calculations for studies in which the calories from fat was 18%–25% by excluding these two most extreme studies (37,40). This

analysis showed a pooled estimate of a change in estradiol level of -6.7% (95% CI = -11.1% to -2.1%) among premenopausal women and -6.2% (95% CI = -13.1% to -1.3%) among postmenopausal women. The percent change in premenopausal and postmenopausal women combined was -6.6% (95% CI = -10.3% to -2.7%). Fig. 1 is indicative of heterogeneity of the effects of fat on estradiol levels, with the studies with the lowest percent calories from fat (37,40) evidently the most discrepant (test for heterogeneity, $\chi^2_{13} = 126.3$; $P < .0001$). Heterogeneity was markedly reduced after exclusion of the latter two studies ($\chi^2_{11} = 24.4$) but remained statistically significant (two-sided $P = .01$). Use of the random-effects model (43), which accounts for heterogeneity across the remaining 12 studies while still estimating a mean effect, changed the estimate of effect from -6.6% to -6.8% but the result was no longer statistically significant (95% CI = -13.2% to 0.1%).

the specific type of fiber (i.e., an effect of wheat but not of oat or corn bran) (44) and both the duration and amount of wheat bran supplementation (45). In five of the studies reviewed here (28,33,34,36,40), as part of the intervention protocol, reduction in dietary fat was accompanied by a large increase in all sources of fiber (i.e., grain, legume, vegetable, and fruit). Among the other studies (29,31,32,35,37) that presented information on fiber intake, intake remained low (<20 g per day) (29–31) or moderate (21–29 g per day) (32,35,37). Reductions in estradiol level were found in studies with low (30,31), medium (32,37), and high (33,34,40) fiber intake (Table 1). The separate effects of fiber and fat intake were formally

evaluated in one study (33); both macronutrients were found to have independent effects on serum estrogen levels. In this study, fat reduction was associated with more pronounced reductions in free estradiol and total estrone levels, while fiber increase appeared to produce a greater reduction in total estradiol; however, both had comparable reducing effects on estrone sulfate (33). The effects of fiber intake on estrogen levels clearly warrant further investigation.

Reduction in dietary fat intake was also accompanied by significant reductions in body weight in some studies (30,32,37–40) but not in others (28,29,31,33–36). Reductions in serum estradiol levels were found in all six studies that

reported significant reductions in body weight and in four of the seven studies that found no significant changes in body weight (Table 1). Investigators in two studies (39,40) noted that the individual reductions in estradiol levels in their studies were not related to weight loss. In two other studies (33,34) that found substantial reductions in serum estradiol levels in association with dietary fat reduction, the body weight of study subjects was maintained during the intervention period. Publication bias is unlikely to explain the present findings but this source of bias cannot be precluded with certainty.

The effect of dietary fat on serum estradiol levels from our pooled analyses

can be compared with the differences in serum estradiol levels reported in studies that have evaluated estradiol levels of Asian and white women (20,21). Studies conducted among premenopausal and postmenopausal women in Japan (46), China (47,48) and recent southeast Asian migrants to Hawaii (49) have found that serum estradiol levels were some 30%–70% lower in Asians than in whites of comparable age and menopausal status. Information on intake of dietary fat was available in only one of these studies (49). In this study, premenopausal Asian and Caucasian women consumed, respectively, 22% and 40% of calories from fat. The corresponding fat intake was 19% and 38% among postmenopausal women (49). Thus, levels of fat intake among Caucasian and Asian women in this study resembled, respectively, the level of dietary fat intake at baseline and during intervention in the fat intervention studies we have reviewed here. The larger difference in estradiol levels between Asian and Caucasian women compared with the results obtained in the short-term dietary intervention studies may be related to the cumulative effects of dietary fat intake.

The 7% to 13% reduction in estradiol levels in our pooled analyses is certainly in the range of difference (15%) that has been reported in serum estradiol levels for women who developed breast cancer compared with those who did not (23). Prentice et al. (39) calculated that a 17% reduction in estradiol concentration could explain the fivefold international gradient in breast cancer risk between populations having dietary fat intakes similar to those levels consumed before and during dietary intervention, as reviewed above. On this basis (39), analytic studies on dietary fat and breast cancer risk that are truly investigating the effect of a 20% calories from fat diet should be able to detect a reduction in breast cancer risk. It may be that the failure to detect this in analytic cohort studies (6) is due to too few persons having a fat intake as low as 20% when allowance is made for measurement error in measuring fat intake. The cohort studies combined by Hunter et al. (6) all had associated calibration substudies to enable them to be able to predict 'true' nutrient intake from the measurements made with a food-frequency questionnaire (FFQ). These studies take a sample of each cohort and record 'true' nutrient intakes over a number of days and, on this

basis, estimate separate (for each cohort) calibration equations of the form $f_i = a + b \times f_q$, where f_i is the estimated true intake based on the intake f_q determined from the FFQ. The effect on the estimated (logistic) regression of disease incidence on nutrient intake is to change the regression coefficient from β to β/b (50,51). Hunter et al. (6) reported that the effect of this on the studies they analyzed was to increase the breast cancer relative risk per 25 g of (calorie-adjusted) fat from 1.02 to 1.07. We can, therefore, estimate the average b from the equation $0.02/b = 0.07$, i.e., approximate average $b = 0.28$. Since calorie-adjusted fat consumption is closely related to percent calories from fat, we can use this b to draw tentative conclusions about the effect of measurement error on estimates of risk associated with percent calories from fat. A b of 0.28 means that an observed difference of FFQ-based percent calories from fat of 20%, say, is truly a difference of only $(0.28 \times 20\%) = 5.6\%$.

The "20 percent" figure in the statement by Hunter et al. (6) that there is "no reduction in risk even among women whose energy intake was less than 20 percent of total energy intake" does not appear to have been corrected for measurement error. From the results given by Hunter et al. (6), it is not possible to directly estimate what this 20 percent figure translates into in terms of true percent calories from fat. However, it is highly likely that it translates into a figure much greater than 20%. From calibration studies we have performed, the average 'true' percent calories from fat is reasonably close to the average FFQ-derived percent calories from fat. If this is true for the studies analyzed by Hunter et al. (6), then the 20 percent figure will translate roughly into $(35\% - [35\% - 20\%] \times 0.28) = 30.8\%$, where we estimate the average percent calories from fat in the cohort studies as 35%. That is, the statement concerning the '20 percent' figure may be more applicable to a '30 percent' figure, and, in this case, the analytic cohort studies provide no data on the effects of a very low-fat (<20% calories from fat) diet.

The above argument is, of course, hypothetical, since the actual corrected results from the papers included in the meta-analysis by Hunter et al. (6) were not presented. Although we believe our argument is reasonable and the tentative conclusions we have drawn are likely to be true, the actual corrected results from

the papers included in the meta-analysis need to be presented.

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NOTES

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