Commentary: Fat and breast cancer: time to re-evaluate both methods and results?

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International comparisons, comparisons within countries, time trends within countries, case–control studies, and animal studies are all consistent with a positive relationship between incidence of breast cancer and fat consumption. Cohort studies are normally considered free of the bias that potentially affect case–control studies, but, in contrast to expectations that a relationship would be confirmed, reports of pooled cohort data show no relation between total or types of fat intake and breast cancer risk. In a summary of the prospective studies relating fat to breast cancer risk, it was concluded that there was moderate evidence to conclude that total fat in adult life ‘does not influence’ the risk of breast cancer independently of BMI, and in another summary in which evidence from both case–control and prospective studies was used, the evidence of increased risk was classified as ‘possible’. However, concerns about the accuracy of dietary assessment methods used in the epidemiology of cancer continue to be raised. Measurement error of diet is a major problem when examining associations between diet and disease endpoints such as cancer. Studies in which biomarkers have been used as the reference method for assessing dietary intake indicate that the degree of error associated with the food frequency questionnaires (FFQ) is considerably larger than previously estimated, which may explain the earlier negative findings of existing cohort studies of diet and cancer. Quantitative 7 day diaries of all food and drink consumed by cohort participants are associated with less error. We previously used biomarkers to assess the accuracy of different techniques of measuring diet and, consequently, incorporated several into our cohort study in the Norfolk arm of the European prospective Investigation of cancer (EPIC). When using a method, which had previously been shown to be more accurate using biomarkers, the 7 day food diary, the hazard ratio for breast cancer for each quintile increase of energy adjusted fat was strongly associated with saturated fat intake. In the same women, there was no association with breast cancer risk and saturated fat measured using the simpler FFQ usually used in most other prospective studies and all of those in the pooled analysis. The top level of saturated fat consumption (mean total fat 92 g or 42% total energy) was associated with a 2-fold increase in breast cancer risk using the food diary estimates compared with the bottom quintile, whereas there was no significant elevation when intakes were assessed using the FFQ. Associations between fat and breast cancer may, therefore, have been substantially attenuated using the FFQ, as has been suggested from previous studies of measurement error in which biomarkers have been used to establish the ‘true’ intake independently of the dietary assessment method.

This finding, although based on a small sample of 168 cases and four matched controls, prompted a reanalysis of stored data from a larger cohort comprising the control arm of the Women’s Health Initiative randomized trial (WHI). Findings from 603 cases and 1206 controls are reported in this issue. As in the earlier study, the RR estimate for breast cancer in the top quintile of fat intake compared with that in the lower quintile was significant (RR 2.54, P trend 0.006), whereas the RR estimate from the FFQ was not (RR 1.24, P trend 0.41). The association was stronger for total rather than saturated fat intake. In the earlier report, the association with saturated fat was stronger than that with total fat but the differences between saturated, monounsaturated, and polyunsaturated fat were not significant.

Where does this finding leave the evidence concerning fat intake and breast cancer? It could be argued that the effects of fat, either total or saturated, are relatively small, even if measured more accurately from food records in prospective studies. A pooled analysis from nine prospective studies has shown that estradiol and other circulating endogenous sex hormones have well established and strong associations with risk of breast cancer. When compared across quintiles, the HR for breast cancer associated with fat from both studies in EPIC Norfolk and the WHI using food records is of the same order as those of circulating estradiol in post-menopausal women (Figure 1). Both these studies adjusted for weight and height. The effect of fat on post-menopausal breast cancer risk from these prospective studies using better methodology cannot be dismissed as small. Both these studies suggest that a reduction in fat intake should be recommended in order to reduce the risk of breast cancer. Furthermore, since a comparatively low fat diet is consumed by a substantial proportion, one-fifth, of these women in the UK and USA, it should not in theory be difficult or unpleasant to achieve for the majority.

However, reducing average fat intake in the whole population to as low as 17% energy may not be easy. Total fat intake has declined by ~40% in the UK since the 1970s, but total energy intake has declined in addition. Hence fat as a percentage of total intake has only declined by ~4% in women from 39% in 1986 to 35% in 2000 in response to a public health consensus that a reduction in fat, especially saturated fat, would reduce risks of coronary heart disease and...
subsequent efforts by the food industry to reduce fat levels in
food products in the UK. As it has taken 14 years to
achieve only a 4% population average reduction in fat in
women, a further 15% reduction to the lowest risk level would
take some time.

The primary aim of the WHI was to establish whether a
low-fat diet would reduce the risk of breast cancer, and the
difficulties of reducing population average intakes of fat are
illustrated in this trial. A total of 48 835 women were
randomized to either a low fat or comparison group and
followed for over 8 years. Enormous efforts were made to
achieve a reduction in intake to 20% fat, with the intervention
group of 19 541 women receiving 18 group sessions in the first
year, and quarterly maintenance sessions thereafter, with each
group consisting of 8–15 women led by a specially trained and
certified nutritionist. Given the logistics of this exercise it is
unsurprising that the costs of the trial as a whole were $415M
over 8 years.

In the WHI, those who had the highest intake of fat at
baseline had the greatest reduction in risk; a reduction in
intake from greater than 37% energy to an average of 24%
energy as fat was associated with an HR of 0.78 (0.64–0.95), a
22% reduction in risk. Overall in the WHI, however, there was
only a 9% reduction in risk, which narrowly escaped
significance (HR 0.91; CI 0.83–1.01). This was almost certainly
because relatively few of the women overall met the dietary
 targets of 20% of energy from dietary fat, only 31.4% at year 1
and 14.4% at year 5. The results of the WHI trial do not,
therefore, provide a basis for the JAMA media release that this
‘large study shows low at diet has little effect on reducing risk

Figure 1 Hazard ratios for breast cancer by quintile of free and total oestrogen and of fat intake. Relative risks for breast cancer by quintiles. Adjusted for weight, height, parity, menopausal status, HRT, and non-fat energy. Adjusted for duration of follow-up, age, region, HRT, family history, breast biopsy, energy. Further adjustment for BMI did not alter risk estimates substantially.

Figure 2 Dietary Intake of Fat and Risk of Developing Breast Cancer: Comparison of EPIC Norfolk and WHI observation hazard ratios across quintiles of dietary intake of fat with WHI intervention trial intakes of fat. Circles: WHI B = Baseline % energy fat, T = Target % energy fat, C = Comparison % energy fat, I = intervention % energy fat, 9% reduction in incidence compared with baseline.
of breast cancer nor for the results being interpreted as unimpressive by US government media releases. Although the aim was to reduce fat intake to 20% of total energy, at Year 3, only a reduction to 27% of total energy was achieved. Furthermore intake of fat in the comparison arm also fell, so that in the intervention arm the projected 14% reduction in incidence, which would have given a study power of 86% at \( P < 0.05 \), was not achieved. Figure 2 shows that the actual reduction in risk of 9% (two-thirds of the 14% projected reduction in risk) at this level of fat reduction is in line with what would have been predicted from the risks found in both the observational component of the WHI and the EPIC Norfolk studies.

Do we need further evidence that fat intake needs to be reduced in order to reduce the current high levels of post-menopausal breast cancer? At present there are only three prospective studies (all of which have used a food record to assess diet)\(^{11,13,19} \) that have shown a positive effect of fat on post-menopausal breast cancer risk, all of which are comparatively small compared with cohorts that have used FFQ methodology. This position should change at least in the UK now that several smaller mature cohorts are about to pool resources and form a UK consortium of 100,000 participants for whom prospective food diaries are available for analysis, with MRC support.\(^{20} \) The substantial numbers of cases that will arise within a comparatively short time will allow further examination of the hypothesis that failure to demonstrate strong association with diet and cancer may have resulted from the use of methodology associated with large measurement error within homogeneous populations.\(^{21} \)

The lack of a clear mechanism whereby fat increases post-menopausal breast cancer risk also requires further investigation. Although the effects of fat are presumed to affect risk via an effect on sex hormone levels, in the WHI analysis in a subgroup of 300 women, there was only a marginal evidence of a fall in estradiol at year 1, and the significant effects on SHBG levels were probably brought about by the significant changes in weight in the intervention arm. Other mechanisms, particularly why a reduction in fat should be associated with a reduction in risk of ER+ and PR− tumours, require investigation.\(^{12} \)

References


