The relation between dietary fat and breast cancer incidence and survival remains one of the most controversial hypotheses in nutritional epidemiology, with mostly observational studies showing rather inconsistent results (1–3). In this ongoing debate, results of a pertinent intervention trial are potentially highly informative. In this issue of the Journal, Chlebowski et al. (4) report interim results of the Women’s Intervention Nutrition Study (WINS), a low-fat dietary intervention trial among women diagnosed with breast cancer. The WINS findings, however, raise several concerns that complicate drawing etiologic conclusions about dietary fat and breast cancer as well as making definitive recommendations for survivors.

Results of the interim analysis (4) suggest a benefit of dietary fat reduction on relapse-free survival: the log-rank test was of borderline statistical significance ($P = .07$), and exploratory multivariable Cox regression analysis showed a statistically significant decrease in the risk of relapse in the group assigned to the low-fat dietary eating plan ($P = .03$). A key concern is whether the improved survival could have been confounded by the higher frequency of mastectomy in the intervention group than in the control group, given that a recent pooled analysis (5) showed that breast-conserving therapy was associated with a greater risk of locoregional recurrence than mastectomy. The authors note that adjustment for the surgical procedure did not eliminate the outcome advantage observed in women randomly assigned to the low-fat dietary eating plan. Moreover, among WINS patients who underwent lumpectomy, those in the intervention group also experienced lower ipsilateral breast recurrence (11 events out of 624, compared with 31 out of 1018 in the control group) [tables 2 and 4, (4)]. A post hoc covariate adjustment, however, is not as inferentially strong as an analysis that is based on baseline equivalence across the two groups. The treatment imbalance thus lends a note of uncertainty to the overall findings.

A second key concern is the greater weight loss among dietary intervention, as opposed to control group, participants. As in other trials whose participants lost weight as a result of adopting a low-fat dietary pattern (6–8), it is difficult to disentangle the role of dietary fat reduction from that of weight loss on the improved relapse-free survival seen in the dietary intervention group of WINS. On average, women in the intervention group lost 4.6 pounds after the first year, whereas women in the control group gained 0.6 pound (4). Throughout follow-up, women in the intervention group tended to maintain their weight, whereas those in the control group gained an additional 1.1 pounds (9), resulting in the final 6-pound difference between the two groups. Because increased adiposity has been identified as a negative prognostic factor for recurrent disease and survival after breast cancer diagnosis (10), the apparent benefit of dietary fat reduction in the intervention group could partly result from the weight loss.

The molecular pathology findings in WINS raise a third concern. Unexpectedly, subgroup analyses showed that dietary fat reduction was most beneficial in women diagnosed with either estrogen receptor–negative (ER−) or progesterone receptor–negative (PR−) breast cancer (4). This result may be of clinical relevance and suggests a possible adjuvant therapy for hormone receptor–negative breast cancer patients. However, this finding needs confirmation because it may have arisen by chance—the stratified analysis was unplanned—or may reflect residual confounding. On this latter point, it would be useful to know whether the intervention–control group difference in mastectomy versus lumpectomy was more pronounced among ER− patients.

Other studies of breast cancer prognosis have not provided much evidence of a differential effect of fat intake on survival after breast cancer diagnosis depending on the hormone receptor status of the tumor, except for one study, in which associations were confined to ER+ cancers (11). The pertinent evidence on the relation of dietary fat to hormone receptor status–specific incident breast cancer is also both sparse and inconsistent. In the Women’s Health Initiative (WHI) randomized controlled dietary modification trial, a low-fat dietary pattern (that included increased vegetable, fruit, and grain consumption) was associated with a statistically significant reduction of incidence of PR−, but not ER−, breast cancer (1). Among observational prospective studies, the Iowa Women’s Health Study (12) did not show any statistically significant association between dietary fat and incidence of any type of breast cancer, whereas the direct association between animal fat intake and breast cancer found in the Nurses’ Health Study II (13) was confined to ER+ and PR+ tumors.

Despite these concerns, the WINS results contribute to the ongoing debate on whether dietary fat affects breast carcinogenesis. The other major trial dealing with the fat–breast cancer hypothesis, the WHI trial (1), produced a suggestive result of a beneficial effect of low-fat dietary patterns on invasive breast cancer incidence (log-rank test $P = .07$). With a shorter than planned follow-up (average 8.1 instead of 9 years) and only 14.4% of women in the intervention group who reported reaching the dietary target of 20% of energy from fat, the WHI trial had limited

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... statistical power to detect a projected reduction in breast cancer incidence in the intervention group compared with the control group (1). The reduction in power could be even more profound should women in the intervention and control groups report their diet differentially. The continuing follow-up of both trials may bring more definitive answers.

Evidence from numerous observational epidemiologic studies on the fat–breast cancer hypothesis remains controversial. The inconsistent results may, at least partially, be explained by possible biases due to dietary measurement error as well as confounding. In general, retrospective case–control studies of incident breast cancer have supported a positive relation with dietary fat (14); many prospective cohort studies have failed to show such an association (13,15), although a few recent ones have done so (2,13,16,17). A recent meta-analysis provided evidence for a weak direct association between fat intake and breast cancer in case–control and cohort studies combined (18). In cohort studies that adjusted for energy intake, highest versus lowest categories of total fat intake were associated with a statistically significant 13% increased risk of breast cancer (18).

Nor do observational studies relating dietary fat to survival after breast cancer diagnosis provide strong evidence for a direct association (11,19–21). Some studies did find a statistically significant increased risk of recurrence or mortality with high-fat diets, but the association did not remain after adjustment for energy intake or tumor characteristics. Findings from several ongoing, yet-unpublished, large-scale cohort studies, including the European Prospective Investigation into Cancer and Nutrition (22) and the National Institutes of Health–AARP Diet and Health Study (23), may bring new evidence to bear on the association between fat and breast cancer incidence and survival.

The WINS results have important implications for the future of lifestyle trials involving interventions in diet, body size, or physical activity. WINS demonstrates, as did the Dietary Approaches to Stop Hypertension (DASH) (24) and Diabetes Prevention Program (DPP) (25) trials, that it is feasible to implement complex, demanding interventions involving even combinations of nutritional factors in large numbers of people over an extended period of time. WINS participants apparently achieved fat reduction and weight loss by the end of the first year and were able to maintain both throughout the 5-year follow-up (4). Some lifestyle trials may not fully achieve the intended treatment group dietary or other lifestyle differences—the WHI being a prominent example (1)—but even partial intervention success may provide informative evidence. We may be seeing, however, that intervention success is more readily achieved in trials—WINS, DASH, and DPP, for example—among highly motivated individuals with a previously diagnosed medical condition (breast cancer, hypertension, and diabetes, respectively). Some recent trials, such as the DPP, which focused on weight loss and included both dietary and physical activity interventions, achieved a greater than expected benefit in terms of weight loss and management of diabetes (25). The lifestyle intervention group of DPP experienced improved clinical outcomes, fewer adverse side effects, and greater cost-effectiveness than the control group, which underwent conventional drug therapy for diabetes (26).

Lifestyle trials are expensive and logistically challenging. Nevertheless, WINS demonstrates that such trials can be successfully conducted and yield valuable evidence to complement that derived from observational epidemiology and basic science. The totality of this evidence will help us better understand the fat–breast cancer connection and ultimately provide more definitive public health recommendations.

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