We read with interest the article by Chlebowski et al. (1), in which the authors investigated the effect of a dietary intervention designed to reduce fat intake in women with resected early-stage breast cancer receiving conventional cancer...
management. After approximately 5 years of follow-up, women in the dietary intervention group had a 24% lower risk of relapse than those in the control group (hazard ratio = 0.76; 95% confidence interval = 0.60 to 0.98). Exploratory analyses suggested a differential effect of the dietary intervention based on hormonal receptor status such that there was a stronger effect for dietary fat reduction on breast cancer recurrence in women with hormone receptor–negative cancers than in women with hormone receptor–positive cancers. Saphner et al. (2) found that, when compared with estrogen receptor (ER)–negative status, a positive ER status was associated with a lower peak hazard of recurrence in the first 5 years but a higher hazard of recurrence from years 5–12. This means that the ER-negative recurrences occur more frequently in early follow-up and ER-positive recurrences occur more frequently in later follow-up. Because more recurrences are observed in ER-positive patients between 5 and 12 years, it seems possible that the differential effect of the dietary intervention on hormonal receptor status may be reduced after longer follow-up of these patients.

Chlebowski et al. (1) recently reported an interim analysis of the Women’s Intervention Nutrition Study trial and concluded that a reduction in dietary fat intake may influence relapse-free survival following breast cancer. This effect was observed mainly in the subgroup of patients with previously diagnosed hormone receptor–negative tumors. The accompanying Editorial (2) noted that the study’s conclusion is contrary to much of the literature and raised the possibility that the analysis may have been confounded by either the higher frequency of mastectomy or greater weight loss in the intervention group.

However, a simpler explanation for the observed result could be differences between study arms in the completeness of the interim efficacy data. The authors note that 84% of the intervention group and 89% of the control subjects were successfully contacted in the 12 months before the analysis closeout date. This 5% lower outcome ascertainment rate in the intervention group was nearly double the absolute difference in study outcomes reported between the two groups. The authors did not comment on whether this differential follow-up varied by body mass index, surgery status, or hormone receptor status of the initial tumor. It is not clear that the intent-to-treat approach used by the authors would account for this potentially critical loss to follow-up.

That this suggestive finding is contrary to findings of several observational cohort studies but in line with the large Women’s Health Initiative randomized trial of incident breast cancer, as noted by Thiebaut et al. (2), emphasizes the importance of controlled randomized trials to furthering the knowledge base. A more definitive result would have been achieved in this trial with better evidence that the effect of the dietary intervention had been maintained. The authors used a completers-only analysis when presenting the level of change achieved in the trial in table 3. An impressive 40% between-group difference in energy from fat was reported at the 12-month study assessment. However, differential assessment rates make it difficult for the reader to ascertain how well this difference was maintained. At the 3-year assessment, information was obtained from 67% of the intervention group and 74% of control subjects. At the 5-year assessment, information was reported for only 39% of the intervention group compared with 44% of the control group. If even modest proportions of nonresponders were no longer following the intervention, the indicated intervention effect for both dietary pattern and weight would need to be reduced substantially.

References


Notes

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Response

We agree with Altundag and Kurt that estrogen receptor (ER)–negative breast cancers are more likely to recur early and that longer follow-up could alter the differential dietary effect we observed. However, after an average follow-up of more than 8 years, the Women’s Health Initiative trial evaluating the influence of a similar dietary change on breast cancer incidence also saw evidence of effect in hormone receptor–negative cancers (1). In a recent update of the Women’s Intervention Nutrition Study (2), we continued to see the largest effect on relapse-free survival in the ER- and progesterone receptor–negative subgroup (hazard ratio of 0.46,
95% confidence interval = 0.26 to 0.80) for relapse–free survival influence of dietary modification versus control group randomization. By protocol design, definitive analyses addressing this issue with 3 years of follow-up after completion of recruitment will be available later this year (3).

We agree with Pierce et al. that maintaining a lifestyle intervention is difficult but suggest, based on our experience (1–3), that it will be difficult to achieve greater adherence in any clinical trial setting. Finally, it is extremely unlikely that a 5% difference in recent contact between groups could explain our results, because such an explanation assumes that all those not contacted had relapsed. In addition, in the hormone receptor–negative subgroup, early rather than late separation for relapse-free survival events was seen and such early events would not be influenced by a small difference in the proportion of participants with contacts late in the follow-up period.

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References


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