The WHI joins MRFIT: a revealing look beneath the covers

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In the early 1990s, much debate surrounded a proposal to conduct the most expensive study ever to test the hypothesis that a low-fat diet would reduce the risks of breast cancer, coronary heart disease, and other major diseases in women (1, 2). Although the existing data from prospective studies on dietary fat intake and breast cancer did not support an important relation, the primary argument against putting so many resources into such a study was that the hypothesis would probably not be tested due to difficulty in maintaining for many years an adequate difference in fat intake between the intervention and control groups. The background for this concern was the experience of the Multiple Risk Factor Intervention Trial (MRFIT), which found no significant effect on coronary disease of an intervention that combined reduction of serum cholesterol by diet, smoking cessation, and treatment of hypertension (3). The differences in changes in these risk factors between the treatment and placebo groups were far less than planned, rendering the findings uninterpretable; the authors concluded that they believed in the original hypotheses, despite the lack of significant outcomes. Thus, the MRFIT study failed to provide an adequate test of the hypothesis because of poor adherence. Although the proposed dietary fat reduction trial was not funded by the peer review process, after an extensive lobbying effort it was launched as the Women’s Health Initiative (WHI). After 8 y of follow-up, the dietary intervention had no significant effect on rates of breast cancer, total cancer, coronary heart disease, a composite of major chronic disease, or total mortality (4, 5). Consistent with the original concerns, the reported difference in fat intake between the intervention and control groups was 8% of energy, substantially less than the planned difference of 14%.

In this issue of the Journal, the article by Howard et al (6) provides valuable additional data from the WHI showing that the dietary intervention, which “intended to reduce fat and increase vegetables, fruit, and grains;” had no overall effects on plasma LDL or HDL cholesterol or triglycerides. This finding is remarkable because a large literature, including many cross-sectional analyses, controlled feeding studies, and longer-term randomized trials, shows that replacing dietary fat with carbohydrate increases plasma fasting triglycerides and reduces HDL-cholesterol concentrations (7–9). By using the results of a large meta-analysis of controlled feeding studies (7), the predicted increase in triglycerides with the reduction in fat reported by Howard et al at year 3 would have been 18.4 mg/dL, which is significantly larger than the difference between groups observed by Howard et al (3.8 mg/dL; 95% CI: −3.3, 10.9 mg/dL). For HDL cholesterol, the predicted difference is −3.4 mg/dL, which is also incompatible with Howard et al’s observed difference of −0.67 mg/dL (95% CI: −1.5, 0.2 mg/dL). The authors provide no compelling reason as to why their findings appear to refute a vast literature. One possible explanation raised is that the effects of fat reduction on these blood lipid fractions may only be transient. However, this was refuted earlier by other studies, including the pilot to the WHI and the year-long study by Knopp et al (8, 9). One possibility might be that a large increase in fruit, vegetables, whole grains, and protein counterbalanced the adverse effects of fat reduction on HDL cholesterol and triglycerides. However, the changes in those dietary factors were very small. A more plausible explanation, not considered by the authors, is that women in the intervention group overreported their compliance with fat reduction. Such overreporting of adherence would be consistent with other dietary intervention studies that compared reported diet with objective biomarkers of diet (10), including in the WHI in which the difference in reported energy intake between the intervention and control groups was greater than for measured energy intake (11). Although we do not have another biomarker to assess compliance with fat reduction in the WHI, overreporting of compliance with fat reduction appears to be the most likely explanation for the findings.

The findings of Howard et al (6) also provide some methodologic insights relevant to the rationale for the WHI. A primary argument for investing so greatly in the dietary fat and breast cancer hypothesis was that the unpromising results from prospective epidemiologic studies, showing that dietary fat intake did not predict breast cancer incidence, could have been due to errors in measuring fat intake by food-frequency questionnaire (2). However, in the present report, dietary fat assessed by food-frequency questionnaire strongly predicted changes in LDL and HDL cholesterol, although not in triglycerides. We have earlier found that percentage of energy from dietary fat assessed by food-frequency questionnaire predicts serum triglycerides and HDL cholesterol in women (12), as would be expected from controlled feeding studies. Thus, the blood lipid data provided by Howard et al suggest that food-frequency questionnaires used

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in observational epidemiologic studies actually provide a stronger test of the dietary fat and breast cancer hypotheses than does an intervention study such as the WHI, which could not sustain a difference in the key exposure, total fat intake. Howard et al (6) conclude that the WHI diet, combined with increased physical activity, may be used by persons who choose to restrict calories by reducing fat intake to achieve weight loss. If one assumes that the reported reduction in fat intake was real, the lack of effect of this diet on risk factors and on disease outcomes should lead us to discard this diet as a recommended intervention because effective alternatives exist. Specifically, replacement of carbohydrate or saturated fats with unsaturated fats improves cardiovascular risk factors (7, 13) and reduces risks of coronary heart disease (14). Why recommend a diet documented to have no health benefits? The lack of benefit on risks of cancer or cardiovascular disease from replacing dietary fat with carbohydrate, at least during midlife or later, comes not just from the WHI but also from many controlled feeding studies and prospective cohorts (15).

By failing to achieve the planned contrast in diet between the intervention and control groups, the WHI joins MRFIT as huge investments that did not really test the hypotheses that they were designed to address. The failure was not the result of inexperienced investigators; these trials were conducted by our very best research teams who invested enormous efforts to achieve their goals. This experience suggests that we may not be able to evaluate many dietary hypotheses using decade-long randomized trials that require changes in eating behavior. When long-term trials are started, their continuation should be contingent on documentation of adherence to dietary goals, whenever possible with objective biomarkers.

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REFERENCES
8. West CE, Sullivan DR, Katan MB, Halfkamps IL, van der Torre HW. Boys from population with high-carbohydrate intake have higher fasting triglyceride levels than boys from populations with high-fat intake. Am J Epidemiol 1990;131:271–82.