

Dietary Fat, Serum Estrogen Levels, and Breast Cancer Risk: a Multifaceted Story

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The hypothesis that dietary fat may increase the risk of breast cancer by increasing the availability of estrogen and related sex steroids has been explored in basic, epidemiologic, and dietary-intervention studies for many years. In this issue of the Journal, Wu et al. (1) clearly describe the debate regarding the dietary fat and breast cancer hypothesis (2,3) and have contributed to the debate by the use of meta-analysis to quantify the combined effect of fat in dietary intervention studies that have examined the influence of fat reduction on various serum estrogen levels. Their analysis focuses on dietary fat and serum estradiol, a reasonable starting point in attempting to summarize the complex interactions of diet with sex steroids. The dietary intervention studies included in the meta-analysis generally examined the effect of reducing dietary fat intake to 18%–25% of total energy in comparison with various “control” diets of 35%–40% energy from fat. However, in interpreting the results of these studies, a number of issues must be considered: 1) the changes that occur in other dietary components in association with dietary fat reduction, 2) the effect of other dietary components on serum estrogens, and 3) measurement error for both diet and serum estrogens.

With respect to the first issue, examination of Table 1 in the article by Wu et al. (1) and descriptions of the diets in the controlled dietary studies that they analyzed reveals a well-known phenomenon. Dietary fat reduction can be accompanied by changes in other dietary components—including total calories, fiber, carbohydrates, fruits and vegetables, carotenoids and other micronutrients—that may also alter sex steroid metabolism and serum estrogen levels (4,5). For example, in five of 13 studies in this meta-analysis, the intervention protocol included markedly increased amounts of dietary fiber. Some of the dietary protocols were based on Asian diets, others on vegetarian, or on the National Health Lung and Blood Institute Step II diet for cholesterol reduction. Finally, the approach to dietary intervention varied from providing counseling to change the diet, with assessment of intake by self-report, to metabolic ward studies where women were fed a defined diet and intake was recorded from trays. While many studies have included isocaloric high-fat control diets in an effort to avoid differential weight gain or loss during intervention and control periods, a number of low-fat dietary intervention studies have reported modest weight losses or avoidance of weight gain in intervention periods compared with weight gain in control periods. The domino effect that change in one dietary parameter has on other diet and related parameters demonstrates the difficulty of isolating the effect of a single dietary factor on a chronic disease, particularly when multiple dietary factors are hypothesized to be involved, often by similar mechanisms.

With respect to the second issue, a number of dietary components have been examined for a possible effect on estrogen metabolism. Studies (4,5) of dietary fiber suggest that increases in fiber are inversely associated with levels of serum estradiol and other estrogens. More recently, dietary and supplement in-

terventions have examined the effect of a variety of “phytoestrogenic” compounds, such as genistein and related soy products, for their possible estrogenic effect. The effect of these compounds varies by dose and compound and is generally ascribed to their dose-dependent activity as estrogens or antiestrogens. Severe energy restriction has long been known to alter hormonal metabolism; however, the effect of modest decreases in energy commonly seen in low-fat dietary interventions is less well understood (6). One of the mechanisms by which dietary fat is presumed to reduce estrogen levels is by lowering overall energy intake and consequently reducing adipose tissue storage and production of hormones. Among premenopausal and postmenopausal women, increased overall and central adiposity is associated with increased levels of bioavailable estrogen, and, in the case of postmenopausal women, with increased breast cancer risk.

Some dietary intervention studies attempt to control for the confounding effect of energy and weight change by maintaining isocaloric conditions. However, low-fat diets that are high in fiber appear to have substantially different metabolic effects compared with isocaloric diets high in fat and low in fiber in terms of effects on weight and hormone metabolism. In addition, the variability of an individual’s response to any specific dietary alteration is a well-recognized phenomenon (7) and may explain, in part, the apparent lack of response to dietary fat reduction found in some studies (8,9). Finally, alcohol, while not commonly included in controlled dietary studies of nutrients, has been found to increase risk for breast cancer in a number of epidemiologic studies (10) and is hypothesized to alter hormone metabolism (11).

With respect to the third issue, we will focus on measurement error and compatibility issues in diet and serum estrogen studies. Key issues to consider in comparing changes in serum estradiol include types of assays, lab variability, menopausal status of study participants, and, for premenopausal and perimenopausal women, timing of blood specimen collection relative to the menstrual cycle. Radioimmunoassays are the current standard for serum hormone measurement but were not commonly used in some of the earlier controlled dietary studies. Intraindividual and interindividual variability in laboratory measurement of serum hormones (12) has led to the use of a single reference laboratory performing assays for large-scale dietary intervention studies, such as the Women’s Health Intervention. Furthermore, estrogen levels decline markedly with menopause, often to the limits of

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detection by laboratory assays (4). Wu et al. (1) avoid the problems of attempting to compare markedly different absolute values in their meta-analysis by calculating a ratio of postintervention estradiol levels compared with baseline. They have similarly stratified each intervention on the basis of the menopausal status of the participants. However, they have not been able to address, in comparing results, whether premenopausal women had ovulatory cycles because the information was not always available. In menstruating women, breast epithelial proliferation has been shown to be most active during the luteal phase (approximately days 20–23) of the menstrual cycle, presumably in response to the very high levels of estradiol, and perhaps progesterone, that occur at that time. However, timing the blood collection to capture this peak in estradiol requires repeat measurements to capture the luteinizing hormone surge at the late follicular period. Because of the difficulty of timing this measurement and the marked variability in estradiol during this period, many studies collect blood in the early follicular phase (days 3–7) of the menstrual cycle. As long as the periods of blood collection are similar for the baseline and intervention phases of the study, they can be compared within a study. One notable exception to this standard is the Canadian Diet and Breast Cancer Prevention Study reported by Boyd et al. (13), in which estradiol was measured in blood collected annually and not timed in relation to the menstrual cycle.

In attempting to compare the effect of dietary fat reduction on serum estradiol levels, sources of measurement error and other factors influencing comparability for both dietary fat and serum estradiol must be considered. As is well known, dietary measurement is subject to substantial error that can have a profound impact on assessment of the association between an exposure and a disease outcome. This has important implications for the design of nutritional studies and for their analysis and interpretation. Errors in measuring dietary intake based on metabolic meals can be substantially smaller and have different structures compared with those associated with self-reported intake based on a 24-hour recall or multiple-day food record. Increasing evidence suggests that, in addition to random within-person variation, records/recalls are likely to be also flawed with systematic, person-specific biases, so that for any individual, the average of multiple replicate assessments may not converge to her/his true usual nutrient intake (14). Seven of the 13 studies in the Wu et al. meta-analysis comprised studies based on metabolic meals; the remainder used food records/recalls to assess the intake of fat and other dietary nutrients. This fact alone may be responsible for at least some of the heterogeneity that was present in their analysis.

Given the marked variability in the protocols of the studies considered by Wu et al. (1), it is not surprising that their statistical analysis, based on a simple fixed-effects model, has demonstrated highly statistically significant heterogeneity among the studies. Exclusion of the two most extreme studies, in which fat intake was reduced to 12% or less, reduced heterogeneity at the cost of discarding potentially interesting information on the association of a very low-fat diet with reduction of serum estradiol. Unfortunately, heterogeneity among the remaining 11 studies was still statistically significant. Wu et al. also presented results applying a random-effects model, more appropriate to this situation. Application of this model did not change materially the estimate of a mean effect but produced a statistically nonsignificant result. The last part of the paper by Wu et al. reviews the

nature of the evidence provided by prospective analytic studies of fat intake and breast cancer risk. They observe that the failure to detect the association between fat and breast cancer may be due to a possible threshold effect of energy from fat, starting at or below the 20% of total energy level. In this case, too few women in the reported studies would fall into this category when allowance is made for dietary measurement error in the food-frequency questionnaires (FFQs) used in analytic epidemiologic studies. Their argument is based on the estimated attenuation factor of 0.28 for percent energy from fat in the pooled analysis of seven cohort studies reported by Hunter et al. (15). This attenuation factor is the slope of the regression line for the estimated true, usual fat intake plotted against reported fat intake based on a FFQ. The estimate calculated by Wu et al. (1) is based on the standard regression calibration approach (16), which assumes that a reference instrument in a validation study, such as food record/recall, is unbiased and contains only random within-person error uncorrelated with error in a FFQ. As noted above, this assumption does not seem to be warranted by the results of recent studies that used such biomarkers as doubly-labeled water and urinary nitrogen to measure intakes of total energy and protein, respectively. Assuming that fat intake follows this pattern, accommodation for the resulting person-specific biases in dietary assessment instruments (14) may lead to a significantly smaller estimated attenuation factor (i.e., a larger attenuation effect due to measurement error) than estimated by Wu et al. This would make their argument about the lack of power in analytic studies to estimate a potentially important effect of low-fat diet on breast cancer risk even stronger.

The meta-analysis by Wu et al. is a first effort to attempt to quantify the potential effect of dietary fat reduction on serum estradiol levels. The strong correlations between diverse dietary components that many speculate to have similar effects on serum estradiol limit our ability to identify an independent effect of a single dietary factor. Future studies might contribute to this debate by including more complete descriptions of dietary changes, by rigorous attention to the timing of blood specimen collection relative to the menstrual cycle in premenopausal women, and by more detailed measurement of changes in body weight and composition with these changes in diet. Given the highly controlled nature of metabolic ward studies, it may be helpful to examine the effect of these studies in a separate meta-analysis, in addition to analysis of their combined effects with those studies conducted in the free-living state. In future meta-analyses, it may add to our understanding of the effect of dietary intervention on serum estradiol levels to consider a statistical model that includes the effect of covariates, such as intakes of fat, fiber, and total energy, and perhaps such as weight. Not only would this enable us to quantify different effects of dietary factors and, hopefully, to substantially reduce heterogeneity, but also to adjust the results for measurement error in dietary assessment methods.

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