Dietary fat reduction and breast cancer outcome: results from the Women’s Intervention Nutrition Study (WINS)\(^1\text{--}^4\)

George L Blackburn and Katherine A Wang

ABSTRACT
Given that existing epidemiologic data on the correlation between dietary fat and breast cancer have been mixed, the Women’s Intervention Nutrition Study was launched in 1987. This randomized clinical trial of 2437 women between the ages of 48 and 79 y with early-stage breast cancer tested the hypothesis that dietary fat reduction would increase the relapse-free survival rate. The study determined that low-fat dietary interventions can influence body weight and decrease breast cancer recurrence. Results showing a differential effect of diet on hormone-receptor-positive and -negative disease suggest that metabolic mechanisms involving insulin and insulin-like growth factor-1 may be involved in tumorigenesis. The results of the Women’s Intervention Nutrition Study may therefore contribute to knowledge of the role of insulin resistance in cancer risk. *Am J Clin Nutr* 2007;86(suppl):878S–81S.

KEY WORDS  Breast cancer, dietary fat, adjuvant therapy, Women’s Intervention Nutrition Study, WINS, metabolic syndrome, insulin resistance

INTRODUCTION
The increase in overweight and obesity in the past few decades is well documented. Larger portion sizes (1), the availability of high-fat and high-calorie food options (2, 3), and a lack of physical activity (4) all contribute strongly to the epidemic of obesity. Strikingly, two-thirds of the adult population in the United States is now overweight or obese (5).

Paralleling the recent rise in obesity, metabolic syndrome has also become more common; an estimated 47 millions US residents have metabolic syndrome, and the age-adjusted prevalence is 23.7% (6). Insulin resistance, the pathophysiology of metabolic syndrome, is a common result of obesity. Leading to an increase in insulin and insulin-like growth factor-1 (IGF-1), insulin resistance activates a cascade that ultimately promotes cell proliferation and inhibits programmed cell death.

Fortunately, it appears that lifestyle interventions, including both diet and physical activity, can reverse metabolic syndrome, insulin resistance, and insulin’s tumorigenic effect. Because overweight and obesity—both preventable conditions—contribute to 14–20% of cancer-related mortality (7), the American Cancer Society’s top recommendation for cancer prevention is to maintain a healthy weight throughout life (8). With such mixed results from cohort and observational studies, a randomized controlled trial was in order. Several other randomized trials have recently been completed investigating the links between diet and breast cancer, and the Women’s Intervention Nutrition Study (WINS) shows a comparable reduction in fat intake (14–17).

THE WOMEN’S INTERVENTION NUTRITION STUDY
Given the evidence suggesting the role of a healthy diet in preventing tumorigenesis, WINS was designed to investigate the effects of dietary fat reduction on breast cancer recurrence (18, 19). Launched in 1987, this randomized trial assigned 2437 women between the ages of 48 and 79 y with stage I or II disease to either a dietary intervention (n = 975) or a control (n = 1462) group. The trial provided an intensive dietary intervention for the diet group, and the control group received minimal dietary counseling; the primary endpoint was relapse-free survival. To be eligible, women were required to meet several criteria, including the following: completely resected unilateral invasive breast carcinoma, baseline caloric intake from fat of ≥20%, and adjuvant systemic therapy appropriate to their condition (eg, women with estrogen-receptor-positive tumors must have daily tamoxifen, chemotherapy optional; women with estrogen-receptor-negative tumors must have chemotherapy). At baseline, there were no significant differences between the groups in age, tumor size, nodal status, histologic tumor type, systemic treatment chemotherapy regimen, estrogen receptor status, or progesterone receptor status.

On the basis of the results of pilot studies (20, 21), WINS researchers developed an intensive, individualized, low-fat dietary intervention with a target of 15% of energy from fat. The pilot study results indicated that subjects would achieve a reduction to about 20% of energy from fat, which would be sufficient

\(^1\) From the Beth Israel Deaconess Medical Center (GLB and KAW) and Harvard Medical School (GLB), Boston, MA.

\(^2\) Presented at the 8th Postgraduate Nutrition Symposium “Metabolic Syndrome and the Onset of Cancer,” held in Boston, MA, March 15–16, 2006

\(^3\) Supported by the Center for the Study of Nutrition Medicine, R01-CA55504-17 NCI Low-Fat Diet in Stage II Breast Cancer: Outcome Trial, S Daniel Abraham Chair in Nutrition Medicine at Harvard Medical School, and the Harvard Center for Healthy Living.

\(^4\) Reprints not available. Address correspondence to GL Blackburn, Beth Israel Deaconess Medical Center, Center for the Study of Nutrition Medicine, Feldberg 880, East Campus, 330 Brookline Avenue, Boston, MA 02215, E-mail: gblackbu@bidmc.harvard.edu.
for the study’s purposes. The goal was not to lose weight (subjects did not receive weight-reduction counseling or information) but rather to reduce fat intake. Subjects received counseling from registered dietitians who had received centralized training for the protocol and in topics including motivational interviewing. Counseling was delivered over 8 biweekly individual sessions, followed by individual sessions every 3 mo. Additional monthly group sessions were instituted to reinforce behavior changes. In contrast, after a baseline visit, women in the control group had contact with dietitians only every 3 mo.

Because no accepted best practices currently exist to measure dietary fat intake, fat intake was self-reported by the subjects (22). At baseline, the intervention and control groups both consumed ≈30% of their calories from fat (29.6 ± 7.1%, or 56.3 ± 23.2 g fat, and 29.2 ± 6.7%, or 57.3 ± 24.4 g fat, respectively). After 12 mo, fat intake was successfully reduced in the intervention group to an average of 20.3 ± 7.8% of calories from fat (33.3 ± 17.0 g fat). Meanwhile, the control group made only a slight reduction in fat gram intake, to 29.2 ± 8.2% of calories from fat (51.3 ± 24.4 g fat). The intervention group maintained this fat reduction for >5 y (dietary versus control group difference of 18.0 ± 21.9 fat grams per day at 12 mo and 19.0 ± 24.0 fat grams per day at 60 mo respectively; P < 0.001).

Reducing fat brought about larger changes in diet without compromising nutrient intake (23). For instance, women in the intervention group significantly decreased their consumption of fats, oils, and sweets and were able to make healthier choices; the percentage of subjects consuming fruit such as apples, pears, and bananas increased. Moreover, analysis of serum fatty acid concentrations showed that the group not only lowered their total fat intake but also improved their fatty acid profile (ie, saturated fats were reduced and essential fatty acid concentrations were retained) by switching to vegetable oil use.

Although weight loss was not a stated goal of the study, after 60 mo, body weight was significantly lower (P = 0.005) in the intervention group than among women in the control group, who on average gained weight (P < 0.02 with 3-y weights; x ± SD: 71.3 ± 15.5 and 73.1 ± 15.5 kg for the intervention and control groups, respectively). This body weight change points to a high probability that women in the intervention group successfully adapted to a low-fat diet plan.

The results supported the initial hypothesis that dietary fat reduction improves relapse-free survival in postmenopausal women with primary early-stage resected breast cancer receiving standard cancer management. After a median follow-up of 60 mo, relapse-free survival was 24% higher in the intervention group than in the control group.

Additionally, when subgroups were analyzed, it appeared that the dietary intervention had a greater effect on relapse-free survival in women with hormone-receptor-negative (estrogen, progesterone, or both) disease than in women with receptor-positive disease; the relapse-free survival rate was 42% greater than in the control group, corresponding to a relapse-free survival rate of 9.5% after 8 y. This finding agrees with similar findings by the Women’s Health Initiative and in the Nurse’s Health Study (14, 24). Although this finding should be investigated further, a dietary effect based on estrogen-receptor-negative disease would provide a therapeutic option for those women who do not benefit from the therapies such as aromatase inhibitors (25–27), trastuzumab (28–30), and adjuvant chemotherapy (31) that are more effective in certain subgroups (eg, women with estrogen-receptor-positive tumors).

### INSULIN RESISTANCE AND CANCER

As has been noted before, breast cancer is likely mediated by factors other than sex hormones. The risk of breast cancer cannot be fully explained by changes in estrogen and other sex hormone concentrations if the results of WINS show that diet may have a stronger effect on estrogen-receptor-negative cancers. Other mechanisms may involve adipokines or factors such as insulin resistance, IGF-1, and inflammatory biomarkers.

Insulin resistance, the pathophysiology of metabolic syndrome, is a common result of obesity (32). As excess adipose tissue accumulates, adipocytes display increased lipolytic activity and an increased release of free fatty acids (33). Along with a reduction of tumor necrosis factor-α and adiponectin release, these changes lead to insulin resistance and compensatory hyperinsulinemia (34).

Chronically elevated concentrations of insulin may lead to tumor growth (35); insulin resistance has specifically been linked to breast cancer development (36, 37). Elevated insulin activates a cascade that eventually leads to an increase in IGF-1. Insulin’s method of action may be through direct signaling to insulin receptors or by affecting hormone metabolism, that is, by affecting IGF-1, the IGF-1 receptor, or sex hormones such as androgens, progesterone, and estrogens (38). Because IGF-1 and insulin are both believed to be growth factors, the combined effect of these changes is to down-regulate normal apoptosis and promote cell division (39, 40).

Dietary intervention through a low-fat diet, therefore, would be expected to restore insulin sensitivity and reverse insulin’s tumor-promoting effects. The metabolic profiles of a subset of WINS participants were examined for the effect of a low-fat diet on insulin resistance. A subgroup of 53 women from 3 clinical sites had serum insulin and lipid profiles evaluated at baseline and after 2 y (Table 1; 41). Of those subjects with initial insulin resistance, after 1 y women in the intervention group saw their fasting insulin decrease by 18 ± 34 μU/mL; in comparison, fasting insulin of women in the control group decreased by only 13.8 ± 47 μU/mL. Although not quite statistically significant, these results predict that elevated insulin concentrations (a marker of insulin resistance) may be influenced by dietary fat reduction. There were no significant differences between the treatment groups over time and no time × treatment interactions, and no significant differences were seen between the insulin-resistant and non-insulin-resistant subgroups.

Even modest weight loss can restore insulin sensitivity, which in turn affects the action of tumor promoters like IGF-1. This supports other landmark studies such as the Diabetes Prevention Program (42, 43), in which weight loss was the primary determinant of reduced risk of diabetes, and the Women’s Health Initiative. In a subset of participants of the Women’s Health Initiative, 2996 postmenopausal women with no prior cancer history, researchers saw that both increased physical activity and decreased caloric intake independently predicted lower insulin concentrations (44). Shulman’s work on the mechanisms of insulin resistance also shows that insulin sensitivity improves considerably after weight loss (45).
CONCLUSIONS

The pathophysiology of metabolic syndrome, insulin resistance, is affected by lifestyle patterns such as diet and physical activity. The results of WINS show that, by effecting modest weight loss through a low-fat diet, the body’s metabolism is altered so as to reduce risk of breast cancer recurrence.

WINS, one of the first randomized controlled trials to demonstrate the effect of dietary intake on breast cancer recurrence, will undoubtedly influence future research in this area. The study’s strengths, such as the randomized design, defined breast cancer management and outcome ascertainment, and standardized dietary intervention delivered by registered dietitians far outweigh its limitations, such as the dependence on self-reported dietary information. For instance, WINS showed that even a small reduction in fat intake can affect tumorigenesis. Epidemiologic studies would not have been able to demonstrate such an effect because of the difficulty of finding subjects with such low dietary fat intake in a natural setting.

The lifestyle intervention resulting in dietary fat reduction increased relapse-free survival in a population of mostly postmenopausal breast cancer patients. Furthermore, WINS showed that dietary fat intake can be successfully reduced in a free-living population (23). Although it is likely that counseling with a trained dietitian will be necessary to replicate these results in a clinical setting, the low-fat dietary intervention resulted in a marked improvement in the fatty acid profile as measured by lower proportions of saturated fats and higher proportions of polyunsaturated fats. In the wake of the Women’s Health Initiative reports that a low-fat diet had only a small effect on mediating breast cancer risk, these results are particularly important.

The weight loss of the WINS participants in the intervention group was a critical component of the dietary intervention and demonstrated the efficacy of the provided counseling. Participants in the Women’s Health Initiative, who attained a 25–28%–fat diet, could not reach the same risk reduction as did the WINS participants, who achieved a 20%-fat diet. Furthermore, documentation of dietary changes, including amounts of “good” and “bad” fats, were essential to the success of WINS but were not included in the Women’s Health Initiative.

It is possible that the weight change, and not only the dietary fat reduction, played a role in the results of WINS (46–48). Similarly, changes in the intake of other nutrients besides fats in the intervention group might have influenced the risk of breast cancer recurrence. These possibilities should be explored in the future.

Exploratory analyses also suggest a greater dietary effect in patients with estrogen-receptor-negative disease. Future avenues of research might explore this differential effect on estrogen-receptor-positive subjects and subjects and provide further treatment options for breast cancer patients. Given the success of WINS, further study is warranted of other lifestyle interventions that are designed to improve breast cancer outcomes. For instance, McAuley et al’s (49) recent research on a subset of the postmenopausal women participating in the Women’s Health Initiative shows that low physical activity is linked with higher amounts of estrogens, which is in turn linked with a higher risk of breast cancer. Research on lifestyle interventions including diet and physical activity on breast cancer risk continues to return promising results.

The contributions of the authors were as follows—GLB: one of the original investigators of WINS and participated in study design, data collection, data analysis, and writing of the manuscript, and KAW: participated in the writing and editing of the manuscript, conducted a literature search, and compiled the reference library. None of the authors had a personal or financial conflict of interest.

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