Influence of a Diet Very High in Vegetables, Fruit, and Fiber and Low in Fat on Prognosis Following Treatment for Breast Cancer:

The Women's Healthy Eating and Living (WHEL) Randomized Trial

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Abstract

Context—Evidence is lacking that a dietary pattern high in vegetables, fruit, and fiber and low in total fat can influence breast cancer recurrence or survival.

Objective—To assess whether a major increase in vegetable, fruit, and fiber intake and a decrease in dietary fat intake reduces the risk of recurrent and new primary breast cancer and all-cause mortality among women with previously treated early stage breast cancer.

Design, Setting, and Participants—Multi-institutional randomized controlled trial of dietary change in 3088 women previously treated for early stage breast cancer who were 18 to 70 years old at diagnosis. Women were enrolled between 1995 and 2000 and followed up through June 1, 2006.

Intervention—The intervention group (n=1537) was randomly assigned to receive a telephone counseling program supplemented with cooking classes and newsletters that promoted daily targets of 5 vegetable servings plus 16 oz of vegetable juice; 3 fruit servings; 30 g of fiber; and 15% to 20% of energy intake from fat. The comparison group (n=1551) was provided with print materials describing the "5-A-Day" dietary guidelines.

Main Outcome Measures—Invasive breast cancer event (recurrence or new primary) or death from any cause.

Results—From comparable dietary patterns at baseline, a conservative imputation analysis showed that the intervention group achieved and maintained the following statistically significant differences vs the comparison group through 4 years: servings of vegetables, +65%; fruit, +25%; fiber, +30%, and energy intake from fat, −13%. Plasma carotenoid concentrations validated changes in fruit and vegetable intake. Throughout the study, women in both groups received similar clinical care. Over the mean 7.3-year follow-up, 256 women in the intervention group (16.7%) vs 262 in the comparison group (16.9%) experienced an invasive breast cancer event (adjusted hazard ratio, 0.96; 95% confidence interval, 0.80–1.14; *P*=.63), and 155 intervention group women (10.1%) vs 160 comparison group women (10.3%) died (adjusted hazard ratio, 0.91; 95% confidence interval, 0.72–1.15; *P*=.43). No significant interactions were observed between diet group and baseline demographics, characteristics of the original tumor, baseline dietary pattern, or breast cancer treatment.

Conclusion—Among survivors of early stage breast cancer, adoption of a diet that was very high in vegetables, fruit, and fiber and low in fat did not reduce additional breast cancer events or mortality during a 7.3-year follow-up period.

Trial Registration—clinicaltrials.gov Identifier: NCT00003787

Considerable evidence from preclinical studies indicates that plant-derived foods contain anticarcinogens.[1] A comprehensive review of the literature found that a diet high in vegetables and fruit probably decreases breast cancer risk and that a diet high in total fat possibly increases risk.[2] However, evidence of an association between a diet high in vegetables and fruit and low in total fat and prevention of cancer progression has been mixed in epidemiological studies. [3–17] An interim analysis of data from the Women's Intervention Nutrition Study (WINS), which assessed the effect of a dietary intervention designed to reduce fat intake on relapse-free survival in breast cancer patients,[18] found that the intervention was associated with a marginally statistically significant improvement in relapse-free survival. To our knowledge, no other clinical trials investigating dietary change and breast cancer survival have been reported.

The Women's Healthy Eating and Living (WHEL) Study was a randomized trial assessing whether a dietary pattern very high in vegetables, fruit, and fiber and low in fat reduces the risks of recurrent and new primary breast cancer and all-cause mortality among women with previously treated early stage breast cancer. The study was based on the recommendations of a national committee of experts called to respond to a 1993 challenge grant from a private philanthropist who believed that the role of diet in preventing cancer progression deserved scientific study to enable cancer survivors to make decisions without having "to rely on folklore, rumor and hearsay."[19]

METHODS

Details of the study design, eligibility criteria, randomization procedures, and dietary intervention have been reported previously.[20,21] In brief, we compared 2 dietary patterns: an intervention group that was intensively counseled to adopt a dietary pattern very high in vegetables, fruit, and fiber and low in fat[21] and a comparison group advised to follow the 5-A-Day diet.[22,23] The study tested primary hypotheses of whether the intervention dietary pattern was associated with (1) a longer breast cancer event–free interval and (2) increased overall survival among women previously treated for early stage breast cancer. Based on the 6 epidemiological studies that had been published at the time of the trial design, we estimated the likely effect size of this multicomponent diet.[20] Following Lachin and Foulkes,[24] we determined that a sample size of 3000 would have 82% power to detect a 19% reduction in additional breast cancer events in the intervention group (expected comparison group rate=24%) and a 24% reduction in all cause mortality (expected comparison group rate=15%).

Participants

Participants were enrolled at 7 study sites between 1995 and 2000. Eligibility criteria included diagnosis of a primary operable invasive breast carcinoma categorized using American Joint Committee on Cancer (edition IV) criteria as stage I ($\geq$1 cm), stage II, or stage IIIA within the past 4 years; age at diagnosis between 18 and 70 years; treatment with axillary dissection and total mastectomy or lumpectomy followed by primary breast radiation; no current or planned chemotherapy; no evidence of recurrent disease or new breast cancer since completion of initial local treatment; and no other cancer in the past 10 years. Eligible women were randomly assigned to either the study dietary pattern or the comparison group (FIGURE 1). The institutional review boards at the 7 clinical sites approved the study protocol and consent forms, and all participants provided written informed consent.

Dietary Intervention

The intensive intervention was delivered primarily by telephone counseling, supplemented with 12 cooking classes in the first year and monthly newsletters throughout the study. Trained counselors[21] followed a computer-assisted protocol that was based on social cognitive theory[25] and had 3 phases of decreasing intensity. During the first phase (3–8 calls in 4–6 weeks), counselors focused on building self-efficacy to implement the study targets, which consisted of daily intake of 5 vegetable servings plus 16 oz of vegetable juice, 3 fruit servings, 30 g of fiber, and 15% to 20% of energy intake from fat. Phase 2 (through 5 months) focused on self-monitoring and dealt with barriers to adherence. Phase 3 (through study completion) focused on retaining motivation for the study dietary pattern and preventing setbacks. During the first year of the intervention, participants received an average of 18 counseling calls, attended an average of 4 of 12 offered cooking classes, and received 12 study newsletters. By 4 years, a key point for assessing long-term effect, these participants had received an average of 31 calls and 48 newsletters.

Women randomized to the comparison group were provided with print materials (from the US Department of Agriculture[26] and the National Cancer Institute[22,23]) describing a diet with a recommended daily intake of 5 servings of vegetables and fruit, more than 20 g of fiber, and less than 30% total energy intake from fat. The comparison group attended an average of 1 of 4 offered cooking classes in the first year and received 24 newsletters tailored to the comparison group during the first 4 years.

Data Collection

Dietary Assessment—Dietary intake was assessed by sets of 4 prescheduled 24-hour dietary recalls conducted by telephone on random days over a 3-week period, stratified for weekend vs weekdays.[20] These dietary recalls were scheduled for all participants at baseline, 1 year, 4 years, and 6 years and on 50% random samples at 6, 24, and 36 months. We report data for participants completing follow-up assessments. We also conducted additional analyses as follows: for participants who did not complete follow-up assessments we imputed estimates by assuming that they changed dietary intake in a manner similar to comparison group respondents, using the expectation maximization algorithm in SAS software, version 9.1 (SAS Institute Inc, Cary, North Carolina).[27] As previously described,[20] dietary assessors completed a training program and used the multipass software-driven recall protocol of the Nutritional Data System software (NDS-R, 1994–2006, University of Minnesota, Minneapolis). To assess overall adherence, we developed an adherence score.[20] A completely adherent participant would score 600 points: 300 points reflected vegetable consumption and the remaining 300 points were divided equally among fiber, fruit, and energy from fat.

Other Data Collection—We collected a detailed family history of cancer at baseline and used the mutation prevalence tables from Myriad Genetic Laboratories (Salt Lake City, Utah) [28] to classify families with at least a 10% risk of a *BRCA1/2* mutation as high-risk. Clinic visits conducted at baseline, 1 year, 2 or 3 years (randomly determined), 4 years, and 6 years included measured weight and venipuncture. Separated blood samples were stored in cryovials in −80° C freezers for later analysis. Participants were mailed a set of study questionnaires to complete and bring to each clinic visit, including a health status questionnaire with questions on recent physician visits and 2 questionnaires used in the Women's Health Initiative: the Personal Habits Questionnaire,[29] which included a 9-item measure of physical activity validated for our study[30] and from which we calculated metabolic equivalent task minutes per week,[31] and the Thoughts and Feelings Questionnaire,[32] which included measures of psychosocial functioning. Each participant self-reported race/ethnicity as 1 of 8 categories.

Assessment of Study Outcomes

Primary study end points were (1) the combined outcome of invasive breast cancer recurrence or new primary breast cancer and (2) death due to any cause. Recurrences were further classified as local/regional or distant metastasis. Carcinoma in situ was not counted as a study outcome. The breast cancer event–free interval was defined as the time from date of enrollment to development of a new breast cancer event. Follow-up time was censored at the time of the participant's death, at the last documented staff contact date, or at the study completion date (June 1, 2006).

During semiannual telephone interviews, clinical site staff queried study participants regarding the occurrence of outcome events, any hospitalization, or new or existing medical diagnoses. Any report of a breast cancer event or death triggered a confirmation interview and collection of medical records and/or death certificates. Two independent oncologists reviewed the medical records (pathology reports and physician notes) to confirm reported recurrences. In cases of disagreement, the coordinating center pathologist adjudicated the outcome. Finally, we searched the National Death Index using Social Security number, name, and date of birth.

Statistical Analysis

Participants were randomly assigned to the intervention or comparison group using a random permuted-block design stratified by tumor stage, age, and clinical site. The allocation of participants was conducted by the clinical site coordinator running the study's randomization computer program, which automatically stamped the assigned study group in the database. An independent data and safety monitoring committee conducted a blind review of potential post-randomization exclusions.[20]

Baseline group comparisons of demographic, anthropometric, clinical, and dietary measures were conducted with 2-sided *t* tests, rank-sum tests, or χ^2 tests. We based the primary analysis of disease-free survival on the intention-to-treat principle using time-to-event methods. A 2-sided log-rank test was performed with *P*<.041 considered statistically significant (to account for interim analyses undertaken at the request of the data and safety monitoring committee). Both unadjusted and adjusted hazard ratios were computed. We fit a Cox model stratified by stage, age, and clinical site.

The frequencies of antiestrogen therapy use and bilateral oophorectomies differed marginally between study groups at baseline; therefore, these covariates were also included in the model. However, the antiestrogen therapy variable did not satisfy the proportional hazards assumption; hence, the analysis was stratified by this covariate.[33] Thus, the final model was stratified by stage of initial tumor, age at randomization, clinical site, and antiestrogen use and was adjusted for oophorectomy status.

The a priori analysis plan[20] included fitting a Cox proportional hazards model to evaluate the effect of the intervention on key covariates. These included stage of disease (classified as I, II, or III), age at randomization (<55 years vs ≥55 years), hormone receptor characteristics of initial tumor, body mass index, and years from diagnosis to randomization. Product terms between randomization assignment and indicator variables for covariate categories were included in Cox regression models. Interactions between randomization group and each covariate were formally tested for significance with likelihood ratio tests. The results are presented as hazard ratios and 95% confidence intervals.

In additional analyses, we examined possible interactions between study group and the baseline dietary factors targeted by the intervention (vegetable, fruit, fiber, and fat intakes) to address whether the effects of the dietary intervention might vary by baseline intake level.

Analyses were conducted in the statistics software package R, version 2.3.1 (R Foundation, Vienna, Austria; http://www.r-project.org) or SAS, version 9.1.

RESULTS

Recruitment and Baseline Characteristics

Study staff screened 7572 potential participants and randomized 3107 between March 1995 and November 30, 2000 (Figure 1). There was no difference in postrandomization exclusions by study group (9 vs 10). The final study sample included 1537 women in the dietary intervention group and 1551 in the study comparison group.

The study end date was June 1, 2006. Number and frequency of reported physician visits did not differ significantly between groups at any point during the study. We confirmed vital status on the study end date (Figure 1) for 95% of the intervention group and 96% of the comparison group. Breast cancer status was confirmed for 96% of the intervention group and 97% of the comparison group.

Randomization achieved highly comparable groups (TABLE 1) with regard to demographics (ie, age, minority status, and education), breast cancer characteristics (ie, stage, grade, nodal involvement, hormone receptor status, time from breast cancer diagnosis to randomization, and eligibility for *BRCA1/2* testing), and treatment (ie, surgery and radiation). Slight imbalances were observed between groups in bilateral oophorectomy, antiestrogen use, and chemotherapy treatment, all of which favored an intervention effect; however, no between-group difference was observed in the percentage of women who received at least 1 of these therapies (intervention, 93.6%; comparison, 92.3%; *P*=.12). Fourteen percent of women self-identified as minority race/ethnicity, and these were fairly equally divided among African Americans, Hispanics, and Asian Americans.[20]

Dietary Changes Between Groups

In analyses of dietary change, only participants without a study end point at the time of assessment were included. A high proportion of women completed the dietary assessments (TABLE 2). At baseline, no between-group differences were observed in in-takes of vegetables, fruit, or fiber or energy intake from fat, with both groups consuming a daily mean of more than 7 servings of vegetables and fruit. No between-group differences were observed in measured mean body weight or in energy intake.

In the comparison group, consumption of vegetables, fruit, or fiber changed only modestly over the 6 years following randomization, while relative energy intake from fat increased 13%, reflecting an identified secular trend (J.P.P., V.A.N., L.N., et al, unpublished data, May 2007). In the intervention group, the dietary pattern changed substantially and a large (*P*<.001) between-group difference was achieved and maintained for each dietary target across the 6 years of the intervention. From no difference at baseline, the overall adherence score was 91% higher in the intervention group at 6 months and remained 61% higher than the comparison group at 6 years. Details of changes in dietary targets are presented elsewhere (J.P.P., V.A.N., L.N., et al, unpublished data, May 2007). Using the more conservative imputed data approach,[27] at 1 year, the intervention group had increased average total vegetable and fruit intake to 12 servings/d. This change in total vegetable and fruit intake reflected a major increase in vegetable intake, averaging 7.8 vegetable servings/d at 1 year and remaining relatively high at 6 servings/d at the 4-year follow-up.

At 4 years, relative differences in mean intake between study groups were +65% for vegetable servings, +25% for fruit servings, +30% for fiber, and −13% for energy intake from fat. All differences were statistically significant at *P*<.001. Total plasma carotenoid concentration, a biomarker of vegetable and fruit intake, was 73% higher in the intervention group than the comparison group at 1 year and 43% higher at 4 years, differences that were statistically significant (*P*<.001). In addition, a subsample study identified changes in plasma triacylglycerol and high-density lipoprotein cholesterol concentrations that were specific to the intervention group, supporting self-reported changes in carbohydrate and fat intakes.[34] Study groups differed by less than 80 kcal/d in energy intake and by less than 1 kg in body weight at any study point.

Breast Cancer Event-Free Survival

During the study, 518 participants had a breast cancer event (TABLE 3), representing 256 participants (16.7%) in the intervention group and 262 participants (16.9%) in the comparison group. The disease-free survival curves were virtually identical across groups (FIGURE 2). The unadjusted hazard ratio is presented in Figure 2. The hazard ratio after adjustment for antiestrogen use, oophorectomy status, and stratification factors (including tumor stage, clinic site, and age) at baseline was 0.96 (95% confidence interval, 0.80–1.14; *P*=.63). The likelihood ratio test statistics for group interactions with age, body mass index, physical activity, energy

intake, characteristics of the original tumor (including hormone receptor status), and years from diagnosis to study entry were not significant (TABLE 4). Furthermore, hazard ratios for intervention effects within covariate strata were not significant (Table 4).

Overall Mortality

There were 315 deaths reported within the study period, with 155 (10.1%) in the intervention group and 160 (10.3%) in the comparison group (Figure 2). More than 80% of all deaths were due to breast cancer (Table 3). The treatment-associated hazard ratio was 0.91 (95% confidence interval, 0.72–1.15; *P*=.43) after adjusting for antiestrogen use, bilateral oophorectomy, and stratification factors. The likelihood ratio test statistics for the group interactions with age, body mass index, physical activity, energy intake, characteristics of the original tumor (including hormone receptor status), and years from diagnosis to study entry were not statistically significant, nor were significant effects of the intervention on mortality observed for any subgroups of women classified by major covariates (TABLE 5).

Group Effects by Baseline Quartiles of Dietary Intake

Within each quartile of the targeted dietary components, the intervention group achieved significant change from baseline (TABLE 6). However, there was no evidence of a consistent pattern of an intervention effect for either breast cancer events or mortality according to any baseline diet subgroup, and the findings that are statistically significant in 2 of the 40 compared strata are what one might expect due to chance.

COMMENT

In this randomized trial of a dietary intervention to achieve a substantial change to a diet very high in vegetables, fruit, and fiber and low in fat, the risk of developing additional breast cancer events and survival were not altered in women previously treated for early stage disease. No significant benefit in recurrence was observed overall among population subgroups characterized by demographic characteristics, baseline diet, or initial tumor types. Although breast cancer mortality rates in the United States declined during the study period,[35] the similarity in survival patterns between the WHEL Study groups suggests that continued follow-up would not alter the study results.

It is unlikely that our results were materially affected by bias in assessing the main study end points. Follow-up of participants was nearly complete and did not differ between study groups, and we considered only reports of recurrence and new primary tumors that were validated by medical record review. We observed large and sustained between group differences in vegetable and fruit intake, as assessed by self-report and plasma carotenoid concentrations, a biomarker of vegetable and fruit intake. We also observed significant differences in fiber and fat intake. Although weight has been associated with health outcomes, we observed less than a 1-kg difference in average weight between WHEL Study groups at any time point. While psychosocial factors have been linked with health outcomes, we found no between-group differences for depression, social support, or quality of life during year 1, when the intervention was most intense.[36] Therefore, we believe that our investigation provides an adequate test of whether the study dietary pattern (very high in vegetables, fruit, and fiber and low in fat) provided an added benefit over the dietary pattern of the comparison group women.

Many WHEL Study participants had likely changed their dietary pattern since receiving a diagnosis of breast cancer[37]; 75% were consuming at least 5 servings of vegetables and fruit a day at randomization, an intake that is considerably higher than that observed in other populations of breast cancer survivors.[38,39] However, we observed little evidence of recurrence benefit in the quartile of the intervention group that was consuming less than 5 daily

servings of vegetables and fruit at baseline, despite a major change in dietary pattern that was specific to the intervention group. Previously, in longitudinal analyses of the comparison group only, we observed a possible threshold effect on recurrence for low levels of baseline plasma carotenoid concentration[13] and also that a baseline combination of 5 fruits and vegetables a day and physical activity equivalent to walking at a moderate pace for 30 minutes, 6 d/wk, was associated with lower mortality.[14] However, in this analysis of data from the randomized trial, a major increase over the 5-a-day dietary pattern was not associated with reduced breast cancer events or mortality.

We suggest caution in applying our findings to groups of women other than those represented in our study, which was confined to women who had already completed initial therapy for breast cancer and excluded women with diagnoses after age 70 years and those with stage 1 tumors smaller than 1 cm. Also, only 14% of our study population was self-identified as from African American, Hispanic, and Asian American racial/ethnic groups.

Our finding that reducing dietary fat intake did not benefit breast cancer outcomes appears at odds with the interim analyses from the Women's Intervention Nutrition Study (WINS), which concluded that reducing dietary fat intake was marginally associated with longer relapse-free survival of breast cancer patients, an effect most noted in the subgroup with estrogen-negative tumors. However, differential follow-up between intervention and comparison groups may have influenced the WINS finding.[40] Furthermore, the reduced body weight observed only in the intervention group might partially account for the improved relapse-free survival in WINS. [41] In addition, although WINS reported an 8% to 9% between-group difference in energy intake from fat maintained through 5 years, they reported a higher rate of missing dietary intake data in the intervention group. At the 3-year point, data were available for 67% of the intervention group vs 74% of the comparison group. At 5 years, data were available for 39% of the intervention group and 44% of the comparison group. If even moderate proportions of nonresponders increased their fat intake, the between-group effect could well be less than the absolute 4% difference that we observed. Finally, it is important to note that the women enrolled in WINS differed from those in the WHEL trial regarding prognosis following the original diagnosis, age, and treatment regimen.

Although the WHEL Study's intervention diet focused mainly on increasing vegetable, fruit, and fiber intake, there was a significant between-group difference in fat intake. However, this difference may not have been sufficient to test the dietary fat hypothesis adequately. Unlike the changes observed for intakes of vegetables, fruit and fiber, the smallest dietary fat change was made by participants in the quartile that was furthest from the study target at baseline. Nonetheless, our analyses did not suggest an effect across quartiles of fat intake at baseline, nor did our results indicate an intervention effect in subgroups defined by hormone receptor status, as was seen in WINS.

The absence of an observed effect on breast cancer events or all-cause mortality over a 7.3-year follow-up period in this study does not rule out the possibility of improved longer-term survivorship within this cohort. We did not explore the possibility that increased exercise and weight loss might benefit breast cancer survivors. Finally, our study did not address whether consuming the high–vegetable/fruit/fiber and low-fat diet of our study intervention early in life would alter risk of primary breast cancer.

In conclusion, during a mean 7.3-year follow-up, we found no evidence that adoption of a dietary pattern very high in vegetables, fruit, and fiber and low in fat vs a 5-a-day fruit and vegetable diet prevents breast cancer recurrence or death among women with previously treated early stage breast cancer.

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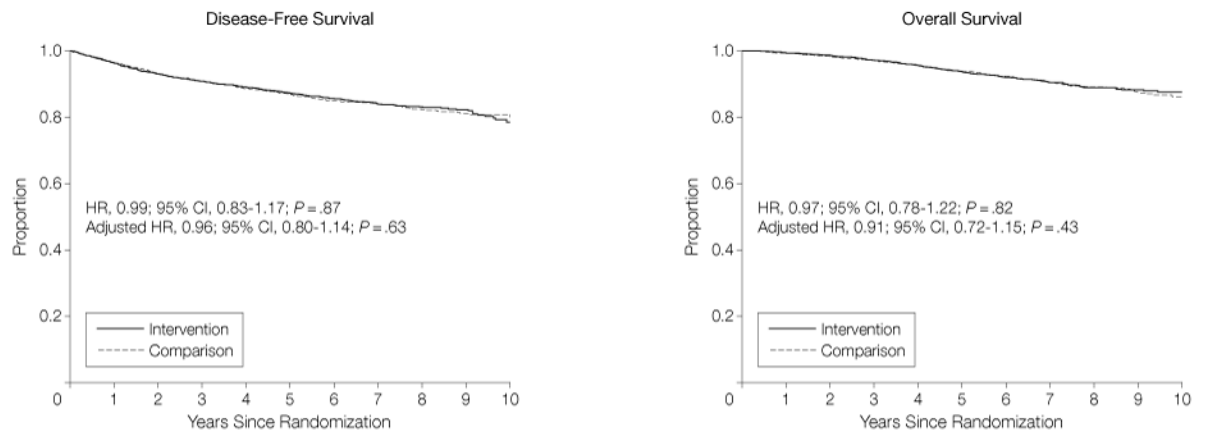
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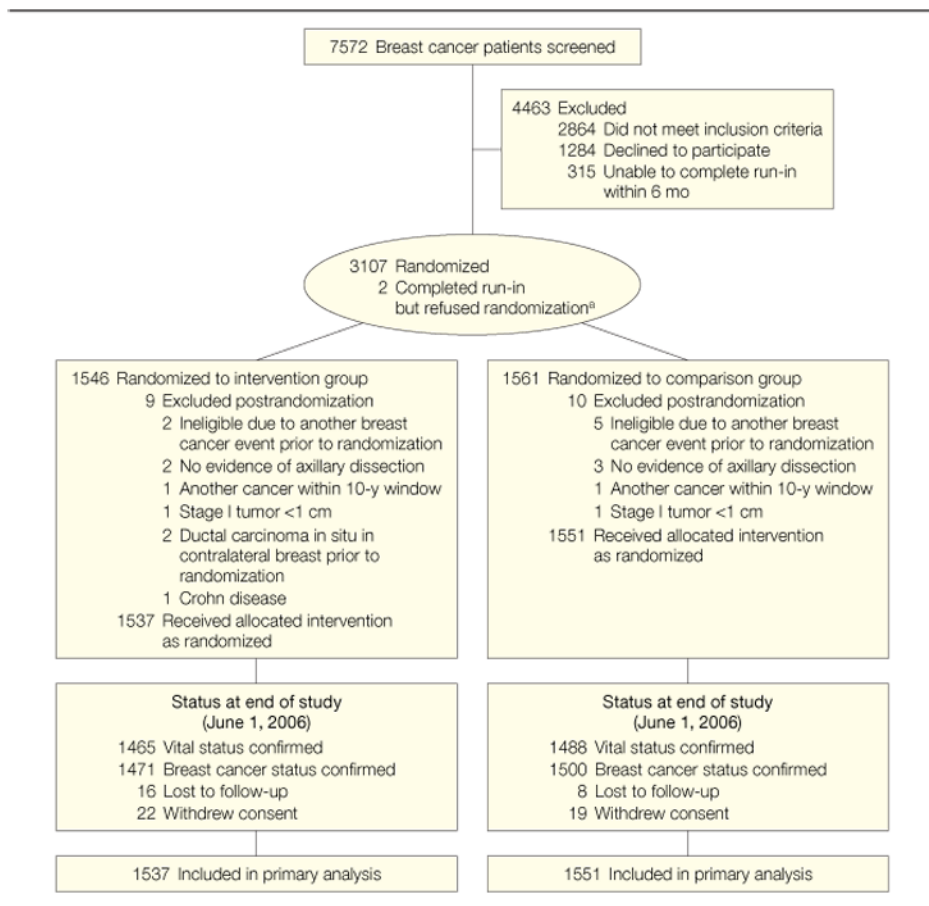
Figure 1.
Participant Flow

Figure 2.
Kaplan-Meier Estimates of Disease-Free Survival and All-Cause Mortality by Diet Group

Table 1.

Baseline Characteristics of WHEL Study Participants by Study Group[a]

Characteristics	Intervention (n = 1537)	Comparison (n = 1551)
Age at study entry, mean (SD), y	53.3 (8.9)	53.0 (9.0)
College graduate	853 (55.5)	820 (52.9)
Race/ethnicity		
White	1306 (85.0)	1328 (85.6)
African American	61 (4.0)	57 (3.7)
Hispanic	87 (5.7)	78 (5.0)
Asian American	46 (3.0)	50 (3.2)
Mixed/other	37 (2.4)	38 (2.5)
Cancer stage at diagnosis		
I	585 (38.1)	606 (39.1)
II	876 (57.0)	867 (55.9)
IIIA	76 (4.9)	78 (5.0)
Nodal status[b]		
Negative	879 (57.2)	896 (57.8)
1–3 positive nodes	436 (28.4)	448 (28.9)
> positive nodes	221 (14.4)	207 (13.4)
Hormone receptor status[b]		
ER+/PR+	955 (62.1)	948 (61.1)
ER+/PR−	197 (12.8)	169 (10.9)
ER−/PR+	52 (3.4)	77 (5.0)
ER−/PR−	300 (19.5)	319 (20.6)
Initial treatment		
Mastectomy	812 (52.8)	801 (51.6)
Breast-sparing surgery	725 (47.2)	750 (48.4)
Radiation	937 (61.0)	962 (62.0)
Adjuvant chemotherapy	1095 (71.2)	1064 (68.6)
Ever antiestrogen use	1067 (69.4)	1012 (65.3)
Tumor grade		
I (well differentiated)	239 (15.6)	245 (15.8)
II (moderately differentiated)	620 (40.3)	620 (40.0)
III (poorly differentiated)	551 (35.9)	557 (35.9)
Unspecified	127 (8.3)	129 (8.3)
Prior bilateral oophorectomy	223 (14.6)	177 (11.4)
Time from diagnosis to randomization, mean (SD), mo	23.6 (12.5)	23.5 (12.5)
Baseline eligibility for *BRCA* testing	132 (8.6)	123 (7.9)

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

[a]Data are expressed as No. (%) of participants unless otherwise indicated. There were no significant between-group differences in baseline characteristics based on χ^2 test for categorical variables or t test for continuous variables, except for ever antiestrogen use ($P = .03$) and prior bilateral oophorectomy ($P = .01$).

[b]Numbers do not total 3088 because of missing data.

Table 2.

Dietary Pattern and Body Weight by Group[a]

	Baseline	6 mo	12 mo	24 mo	36 mo	48 mo	72 mo
Intervention group							
Eligible sample, No.	1537	738	1463	715	676	1355	1308
Response rate, %	99.9	91.3	88.3	85.5	84.8	83.0	77.9
Comparison group							
Eligible sample, No.	1551	765	1484	699	713	1363	1313
Response rate, %	99.8	96.9	93.0	90.6	89.5	88.6	86.2
Total vegetable servings/d							
Intervention	3.9 (0.05)	8.4 (0.13)	7.8 (0.09)	7.1 (0.13)	6.6 (0.13)	6.4 (0.09)	5.8 (0.09)
Comparison	3.8 (0.05)	3.9 (0.07)	3.9 (0.05)	3.7 (0.07)	3.7 (0.07)	3.7 (0.05)	3.6 (0.05)
Total fruit servings/d							
Intervention	3.5 (0.05)	4.4 (0.08)	4.2 (0.06)	3.9 (0.08)	3.8 (0.09)	3.6 (0.06)	3.4 (0.07)
Comparison	3.4 (0.05)	3.6 (0.08)	3.4 (0.05)	3.3 (0.08)	2.9 (0.07)	2.8 (0.05)	2.6 (0.05)
Fiber, g/d							
Intervention	21.1 (0.21)	30.9 (0.40)	29.0 (0.28)	27.6 (0.41)	26.1 (0.42)	25.2 (0.29)	24.2 (0.30)
Comparison	21.2 (0.20)	21.4 (0.30)	21.0 (0.22)	20.5 (0.30)	20.0 (0.30)	19.3 (0.21)	18.9 (0.24)
Energy from fat, %							
Intervention	28.5 (0.18)	21.2 (0.26)	22.7 (0.20)	24.5 (0.29)	25.4 (0.32)	27.1 (0.24)	28.9 (0.25)
Comparison	28.7 (0.18)	27.8 (0.27)	28.4 (0.19)	29.2 (0.30)	30.6 (0.30)	31.4 (0.22)	32.4 (0.22)
Adherence score[b]							
Intervention	286 (3)	574 (7)	533 (6)	485 (8)	461 (8)	435 (6)	396 (6)
Comparison	283 (3)	301 (5)	292 (4)	282 (5)	268 (5)	262 (3)	246 (3)
Energy intake, kcal/d							
Intervention	1719 (10)	1619 (14)	1603 (10)	1592 (15)	1523 (15)	1552 (11)	1538 (11)
Comparison	1717 (11)	1615 (15)	1605 (11)	1606 (15)	1601 (16)	1574 (11)	1559 (12)
Body weight, kg							
Intervention	73.5 (0.42)	NA[c]	73.0 (0.45)	74.2 (0.71)	73.9 (0.73)	74.2 (0.51)	74.1 (0.54)
Comparison	73.3 (0.43)	NA[c]	73.8 (0.47)	74.0 (0.68)	74.9 (0.74)	74.1 (0.50)	73.7 (0.53)

[a] Data are expressed as mean (SE) unless otherwise indicated.

[b] Adherence score was calculated as 30 points for each vegetable or fruit serving (excluding white potatoes, juice, and iceberg lettuce); 10 points for each ounce of vegetable juice; 5 points for each percentage point of energy from fat below 40% to a maximum of 100 points for 20% energy from fat; and 7.7 points for each gram of fiber per 1000 kcal above 5 g/1000 kcal. Perfect adherence was 600 points.

[c] Data for body weight are not applicable (NA) because it was not measured at 6 months.

Table 3.

Study Events

Study Outcomes	No. of Events	
	Intervention	Comparison
Confirmed breast cancer event	256	262
Local	35	28
Regional	10	10
Distal	168	189
New primary	43	35
Confirmed deaths	155	160
Breast cancer	127	135
Other cancer	12	15
Heart disease	2	5
Other	14	5

Table 4.

Intervention Effects on Additional Breast Cancer Events by Baseline Clinical and Demographic Characteristics

| | No./Total | | | |
	Intervention	Comparison	HR (95% CI)[a]	P Value[b]
Age at randomization, y				
<55	167/908	161/917	1.05 (0.84–1.30)	.35
≥55	89/629	101/634	0.89 (0.67–1.18)	
Cancer stage at diagnosis				
I	50/585	55/606	0.94 (0.64–1.38)	
II	178/876	182/867	0.97 (0.79–1.19)	.74
IIIA	28/76	25/78	1.19 (0.69–2.04)	
Hormone receptor status[c]				
ER+/PR+	140/955	145/948	0.95 (0.76–1.20)	
ER+/PR−	37/197	32/169	0.97 (0.60–1.56)	.85
ER−/PR+	11/52	18/77	0.89 (0.42–1.88)	
ER−/PR−	64/300	62/319	1.14 (0.80–1.61)	
Time from diagnosis to randomization, y				
≤1	59/352	65/350	0.88 (0.62–1.26)	
>1 to 2	83/488	90/508	0.95 (0.71–1.28)	.50
>2 to 3	64/375	52/372	1.26 (0.87–1.82)	
>3 to 4	50/322	55/321	0.90 (0.61–1.32)	
Tumor differentiation				
I (well differentiated)	20/239	22/245	0.90 (0.49–1.65)	
II (moderately differentiated)	94/620	100/620	0.93 (0.70–1.24)	.75
III (poorly differentiated)	121/551	114/557	1.09 (0.85–1.41)	
Unspecified	21/127	26/129	0.83 (0.47–1.48)	
No. of positive nodes[c]				
0	93/879	117/896	0.80 (0.61–1.06)	
1–3	83/436	69/448	1.25 (0.91–1.72)	.07
4–6	39/116	31/115	1.29 (0.80–2.06)	
≥7	41/105	45/92	0.75 (0.49–1.15)	
Tumor size, cm[c]				
0 to <2	82/752	88/769	0.94 (0.70–1.28)	
2 to <3	88/421	86/441	1.09 (0.81–1.47)	
3 to <4	30/174	41/160	0.62 (0.39–1.00)	.22
4 to <5	21/79	20/72	0.90 (0.49–1.67)	
≥5	35/109	27/106	1.32 (0.80–2.18)	
Body mass index[d]				
<25	107/652	112/678	0.99 (0.76–1.29)	
25 to <30	81/475	68/480	1.22 (0.88–1.69)	.17
≥30	68/410	82/393	0.79 (0.57–1.09)	
Physical activity, MET-min/wk[c]				
≤210	68/397	66/350	0.90 (0.64–1.27)	
211–615	62/368	71/383	0.91 (0.64–1.27)	.56
616–1290	65/375	54/374	1.22 (0.85–1.74)	
>1290	49/351	60/387	0.88 (0.60–1.28)	
Energy intake, kcal/d[c]				
≤1430	63/377	73/396	0.89 (0.64–1.25)	
1431–1680	59/384	64/386	0.90 (0.63–1.28)	.69
1681–1980	64/390	54/379	1.16 (0.81–1.66)	
>1980	70/383	70/386	1.04 (0.75–1.45)	

Abbreviations: CI, confidence interval; ER, estrogen receptor; HR, hazard ratio; MET, metabolic equivalent task; PR, progesterone receptor.

[a] Hazard ratios of group effect were derived from Cox model stratified by covariate categories.

[b] P values based on likelihood ratio test for group X covariate interaction.

[c] Numbers do not total 3088 because of missing data.

[d] Calculated as weight in kilograms divided by height in meters squared.

Table 5.

Intervention Effects on All-Cause Mortality by Baseline Demographic and Clinical Characteristics

| | No./Total | | | |
	Intervention	Comparison	HR (95% CI)[a]	P Value[b]
Age at randomization, y				
<55	84/908	85/917	0.99 (0.74–1.34)	.85
≥55	71/629	75/634	0.95 (0.69–1.32)	
Cancer stage at diagnosis				
I	33/585	32/606	1.07 (0.66–1.73)	
II	102/876	107/867	0.94 (0.71–1.23)	.90
IIIA	20/76	21/78	0.96 (0.52–1.77)	
Hormone receptor status[c]				
ER+/PR+	79/955	84/948	0.92 (0.68–1.26)	
ER+/PR−	25/197	20/169	1.03 (0.57–1.85)	.88
ER−/PR+	7/52	10/77	1.08 (0.41–2.83)	
ER−/PR−	44/300	42/319	1.13 (0.74–1.73)	
Time from diagnosis to randomization, y				
≤1	46/352	47/350	0.97 (0.64–1.45)	
>1 to 2	51/488	58/508	0.90 (0.62–1.32)	.72
>2 to 3	34/375	28/372	1.28 (0.77–2.11)	
>3 to 4	24/322	27/321	0.86 (0.50–1.49)	
Tumor differentiation				
I (well differentiated)	13/239	7/245	1.80 (0.72–4.52)	
II (moderately differentiated)	58/620	64/620	0.90 (0.63–1.28)	.32
III (poorly differentiated)	75/551	74/557	1.04 (0.75–1.43)	
Unspecified	9/127	15/129	0.62 (0.27–1.42)	
No. of positive nodes[c]				
0	58/879	67/896	0.89 (0.62–1.26)	
1–3	48/436	39/448	1.27 (0.83–1.94)	.20
4–6	21/116	19/115	1.09 (0.59–2.03)	
≥7	28/105	35/92	0.64 (0.39–1.05)	
Tumor size, cm[c]				
0 to <2	42/752	51/769	0.83 (0.55–1.26)	
2 to <3	59/421	50/441	1.27 (0.87–1.85)	
3 to <4	17/174	28/160	0.53 (0.29–0.96)	.13
4 to <5	13/79	12/72	0.94 (0.43–2.06)	
≥5	23/109	19/106	1.21 (0.66–2.22)	
Body mass index[d]				
<25	57/652	61/678	0.97 (0.67–1.38)	
25 to <30	48/475	44/480	1.11 (0.74–1.67)	.70
≥30	50/410	55/393	0.86 (0.59–1.27)	
Physical activity, MET-min/wk[c]				
≤210	43/397	47/350	0.80 (0.53–1.22)	
211–615	45/368	45/383	1.04 (0.69–1.58)	.81
616–1290	36/375	35/374	1.02 (0.64–1.63)	
>1290	25/351	27/387	1.01 (0.58–1.73)	
Energy intake, kcal/d[c]				
≤1430	44/377	48/396	0.95 (0.63–1.43)	
1431–1680	32/384	40/386	0.77 (0.49–1.23)	.62
1681–1980	34/390	31/379	1.08 (0.66–1.75)	
>1980	45/383	40/386	1.17 (0.77–1.79)	

Abbreviations: CI, confidence interval; ER, estrogen receptor; HR, hazard ratio; MET, metabolic equivalent task; PR, progesterone receptor.

[a] Hazard ratios of group effect were derived from Cox model stratified by covariate categories.

[b] P values based on likelihood ratio test for group X covariate interaction.

[c] Numbers do not total 3088 because of missing data.

[d] Calculated as weight in kilograms divided by height in meters squared.

Table 6.

Intervention Effects on Additional Breast Cancer Events and All-Cause Mortality by Baseline Quartiles of Dietary Intake

Variables by Baseline Quartile[a]	No. of Participants at Baseline (Difference, %)[b]	Breast Cancer Events[c]		Deaths[c]	
		No.	HR (95% CI)[d]	No.	HR (95% CI)[d]
Vegetables and fruit, servings/d					
≤4.94	772 (+60)	152	0.97 (0.71–1.34)	88	0.75 (0.49–1.14)
4.95–6.74	771 (+52)	122	1.23 (0.86–1.75)	76	1.25 (0.80–1.97)
6.75–8.92	768 (+53)	144	0.93 (0.67–1.30)	83	1.28 (0.83–1.98)
>8.92	770 (+54)	99	0.83 (0.56–1.24)	67	0.76 (0.47–1.23)
Vegetables, servings/d					
≤2.55	772 (+82)	162	1.13 (0.83–1.54)	101	1.05 (0.71–1.55)
2.56–3.54	770 (+75)	127	0.98 (0.70–1.39)	67	0.85 (0.52–1.38)
3.55–4.80	769 (+74)	118	0.85 (0.59–1.22)	76	0.85 (0.54–1.33)
>4.80	770 (+68)	110	0.97 (0.67–1.40)	70	1.19 (0.74–1.90)
Fruit, servings/d					
≤1.76	771 (+40)	139	1.02 (0.73–1.42)	85	0.75 (0.49–1.15)
1.77–2.93	771 (+21)	129	1.02 (0.72–1.44)	77	1.02 (0.65–1.60)
2.94–4.38	772 (+27)	126	1.11 (0.78–1.58)	77	1.60 (1.02–2.51)
>4.38	767 (+27)	123	0.81 (0.57–1.16)	75	0.76 (0.48–1.19)
Fiber, g/d					
≤15.6	771 (+40)	135	0.97 (0.70–1.36)	83	0.69 (0.45–1.07)
15.7–19.9	772 (+33)	132	1.07 (0.76–1.51)	83	1.12 (0.72–1.72)
20.0–25.2	769 (+28)	131	1.07 (0.76–1.51)	87	1.36 (0.89–2.08)
>25.2	769 (+28)	119	0.83 (0.58–1.20)	61	0.80 (0.48–1.34)
Fat, % of energy per d					
≤23.8	782 (−17)	106	0.72 (0.49–1.06)	59	0.73 (0.44–1.22)
23.9–28.6	768 (−13)	149	1.27 (0.92–1.76)	91	1.61 (1.06–2.45)
28.7–33.4	766 (−15)	122	0.86 (0.60–1.23)	78	0.73 (0.46–1.14)
>33.4	765 (−10)	140	1.13 (0.81–1.58)	86	0.98 (0.64–1.49)

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Seven participants (4 in comparison group and 3 in intervention group) were missing baseline dietary data.

[b] Percentage relative difference in mean dietary intake ([intervention − control]/control) between intervention and comparison groups at 4 years.

[c] Likelihood ratio test for group × diet quartile interactions was not significant at $P < .05$ level for any diet component (except energy from fat and mortality; $P = .04$).

[d] Hazard ratios were derived from Cox model stratified by quartiles of dietary intake.