Title
Effect of treatment and diet on body weight after breast cancer diagnosis: the women's healthy eating and living (WHEL) study perspective

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Author
Saquib, Abu Taiyab M. N.

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Effect of treatment and diet on body weight after breast cancer diagnosis:

The Women’s Healthy Eating and Living (WHEL) Study perspective.

A dissertation submitted in partial satisfaction of the requirements for the degree

Doctor of Philosophy

in

Public Health (Epidemiology)

by

Abu Taiyab M. N. Saquib

Committee in charge:

University of California, San Diego

Dr. John P. Pierce, Chair
Dr. Gerry Boss
Dr. Loki Natarajan
Dr. Cheryl Rock

San Diego State University

Dr. Ming Ji
Dr. Richard Shaffer

Outside Community Member

Dr. Bette Caan

2007
The dissertation of Abu Taiyab M. N. Saquib is approved, and it is acceptable in quality and form for publication on microfilm:

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Chair

University of California, San Diego

San Diego State University

2007
DEDICATION

To my parents,

Md. Akbar Hossain

&

Fatema Nargis,

who always have prioritized their children’s education

over their earthly comfort,


to

Nazneen Hossain Lucky,

Aklima Hossain Dola,

and

Jesmin Hossain Dipti

who anyone would love to have as sisters,

and


to

Laura Margaret Gibney,

without whose inspiration and support I would not be here today.
And when your Lord said to the angels: “Verily, I am going to place generations after generations on earth.” They said: “Will you place therein those who will make mischief therein and shed blood,--while we glorify You with praises and thanks and sanctify you” He said:” I know that which you do not know.”

--- Al-Baqarah (2:30)
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Research paper II has been submitted to ‘Health Education and Behavior’ and is currently under review. The dissertation author was the primary investigator and the first author and Dr. Cheryl L Rock, Dr. Loki Natarajan, Ms. Shirley Flatt, Ms. Vicky A Newman, Dr. Cynthia A Thomson, Dr. Bette Caan, and Dr. John P Pierce were the co-authors of this paper.

Research paper III has been submitted to ‘Nutrition and Cancer’ and is currently under review. The dissertation author was the primary investigator and the first author and Dr. Loki Natarajan, Dr. Cheryl L Rock, Ms. Shirley Flatt, Dr. Lisa Madlensky, Ms. Sheila Kealey, and Dr. John P Pierce were the co-authors of this paper.

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VITA

1996  Bachelor of Medicine and Surgery (MBBS). University of Dhaka, Bangladesh.


PUBLICATIONS


ABSTRACT OF THE DISSERTATION

Effect of treatment and diet on body weight after breast cancer diagnosis:

The Women’s Healthy Eating and Living (WHEL) Study perspective.

by

Abu Taiyab M. N. Saquib

Doctor of Philosophy in Public Health (Epidemiology)

University of California, San Diego, 2007

San Diego State University, 2007

Dr. John P. Pierce, Chair

The dissertation’s three research papers examined the following issues in breast cancer survivors (a) the effect of adjuvant therapy on significant relative weight gain after cancer diagnosis and whether those participants gaining weight return to pre-cancer weight during follow-up, (b) the effect of dietary intervention on weight over time, and (c) the role of dietary energy density on weight over time. The data came from a large, multi-site trial that randomized 3088 women, followed them for 6 years, and encouraged its intervention participants to consume a high fiber and low fat diet. At baseline and at follow-up visits weight and height were measured, dietary intake was assessed by 24-hour dietary recall and validated with plasma carotenoids concentrations, and
demographic and physical activity data were obtained through questionnaire. Cancer stage and treatment modalities were obtained by medical record review.

Paper I was cohort in design and included 3088 participants. Weight gain of $\geq 5\%$ body weight following cancer diagnosis was considered significant. Chemotherapy was significantly associated with weight gain and Tamoxifen was not. Tamoxifen did not modify the effect of either chemotherapy or its different regimens on weight gain. Weight gain occurred irrespective of types or regimens of chemotherapy. Only 10% of participants returned to their pre-cancer weight at the follow-up visits.

Paper II included 1510 overweight and obese participants and analyzed data adopting randomized design. Intervention participants consumed significantly more fruit, vegetables, and fiber, and less energy from fat than controls during follow-up. Body weight and obesity incidence did not differ between study groups at any follow-up visit.

Paper III utilized randomized design to analyze data and included 3088 participants. Dietary energy density among intervention participants, irrespective of calculation method, decreased significantly compared to controls and was maintained over the follow-up period. Total energy intake or physical activity did not vary between the groups. Weight change between study groups was significant, albeit small, by one year and not afterwards.

Return to initial weight following weight gain is unlikely. Dietary modification or dietary energy density reduction alone is not sufficient to promote long-term weight loss in a free-living population.
General Introduction:

Research Papers I, II, and III (references included)
In the past decade, medical science has observed a significant improvement in breast cancer therapy. With the advent of newer generations of adjuvant drugs, the majority of breast cancer patients will be disease-free 10 years post-diagnosis, irrespective of cancer type [1, 2]. For these disease-free women, obesity and weight gain have been thought to pose health risks and have consequences comparable to women in the general population, i.e. susceptibility to chronic diseases such as diabetes, stroke and heart disease, as well as lower self-esteem and a poor body image [3-5]. Further, heavier women are at greater risk for breast cancer, particularly if they are postmenopausal [6-8]. Obesity and weight gain may be even more consequential for women who have previously had breast cancer. A number of studies have found associations between weight gain and risk of cancer recurrence [9] and survival [10], though contrary evidence also exists [11, 12]. In one study women who gained above a median 5.9 kg were 1.5 times more likely to experience a relapse of breast cancer and were 1.6 times more likely to die [9].

One factor reported to be associated with weight gain in breast cancer patients following diagnosis is the use of adjuvant therapy – an incidental finding in the beginning [13] but later supported in numerous studies [9, 14-16] with little dissent [17]. Weight gain in most studies ranged from 2.5 to 6.2 kg [9, 14-16, 18], though in a few gains greater than 10 kg were also reported [19, 20]. It has been debated whether this weight gain was the effect of therapy or of the disease itself, given reports of weight gain in patients who did not receive chemotherapy. The magnitude of weight gain in the latter patients was, however, far smaller than in the chemotherapy-treated patients [21].
Despite abundant research and the insights those studies collectively provide into the possible mechanisms of weight gain during chemotherapy, – including an increase in hunger [22, 23] and dietary intake [14, 24], a decrease in physical activity [25-28], drug induced premature menopause [29], a lowered resting metabolic rate [30, 31], and the dose and duration of chemotherapy [26, 32, 33] – there are several limitations in the literature. First, weight gain reported following adjuvant therapy has consistently been ‘absolute’ [9, 13-17]; by not accounting for the initial body weight, it has not been possible to assess the proportion of women who had a clinically meaningful weight gain (e.g. a 5-10% increase in relative weight) [34-36]. Second, many of the studies did not have an appropriate control group; hence, it was impossible to assess whether weight gain resulted from chemotherapy or from the disease itself [19, 31, 37]. Third, most of the studies had a brief follow-up period, in which patients were monitored for weight change only during chemotherapy or 6 months to 1 year afterward [25, 29, 30, 38]. Fourth, some studies were unable to control for the potential confounders between the relationship of chemotherapy and weight gain [19, 31, 37]. Fifth, few studies examined whether weight gain varied by the type of chemotherapy used; those which did were constrained in their analyses by a small sample size [32, 33]. Sixth, the evidence that adjuvant therapy is associated with weight gain is not as convincing for anti-estrogen Tamoxifen as it is for anti-neoplastic chemotherapy, due to the existence of studies with conflicting results [20, 39-45]. Seventh, no study has examined whether in patients who have had chemotherapy certain characteristics – demographic or tumor related – are more likely to be associated with weight gain than others. The latter information would help health care providers to identify high-risk patients and warn them of their greater risk of weight gain. A further
limitation of the literature is that we do not know whether the increased weight gain in breast cancer patients during treatment is a transient or a permanent phenomenon due to the absence of long-term follow-up data.

Strategies that would help breast cancer patients manage their weight are warranted, in light of the evidence of weight gain during chemotherapy. Body weight is determined by the balance between energy intake and energy expenditure; the manipulation of either or both of these factors is central to weight gain and obesity [46, 47]. One way to reduce energy intake is to decrease dietary energy density, which for any food is the amount of energy exerted per unit of weight (g). The reduction of dietary energy density can be achieved either by increasing the proportion of fiber-rich food or decreasing the proportion of fatty food. If food intake volume remains more or less constant, a reduction of dietary energy density will automatically cause a reduction of total energy intake. The energy content of fiber-rich food such as fruit and vegetables is low. Further, fruit and vegetables increase gastric distension and increase the sensation of fullness. Results from feeding studies also suggest that dietary fiber can promote increased satiety, possibly because of prolongation of the intestinal phase of nutrient processing and absorption [48-50].

Whether a diet that is high in fruit and vegetables and/or low in fat can produce weight loss in the long term in a ‘free-living’ population has been tested in a number of dietary intervention trials; weight change among the intervention participants in these trials ranged from weight loss to no change to actual weight gain [51-58]. The variation in weight change observed in these trials was likely the product of variations in dietary intakes and/or physical activity. It is also possible that some of the variation was due to
differences in the age and body mass index (BMI) distribution of participating cohorts; current age and BMI are strong predictors of weight change during adulthood [59-62], yet none of these trials reported age and BMI specific results. It is important to note that other than the WHEL study, none of these clinical trials had breast cancer survivors as their study population.

Though the hypothesis that a reduction of dietary energy density would result in weight loss has been tested in a number of feeding trials [63, 64], it has not been tested in an ad-libitum setting, where study participants are free to eat at their will. Feeding trials are limiting for they are usually shorter in duration (a few days to a few weeks), include motivated participants who want to lose weight, and provide their study participants overtly or covertly manipulated test meals.

This study’s three research papers examine the following issues in breast cancer survivors: (a) the effect of adjuvant therapy on significant relative weight gain after cancer diagnosis and whether those participants gaining weight return to pre-cancer weight during follow-up, (b) the effect of dietary intervention on weight over time, and (c) the role of dietary energy density on weight over time.

The data for these papers came from the Women’s Healthy Eating and Living Study (WHEL). This is a large, multi-site, clinical trial designed to examine the efficacy of dietary intervention – i.e. increased consumption of fruits, vegetables, and fiber and reduced consumption of energy from fat – in reducing the risk of breast cancer recurrence. The WHEL study randomized 3088 breast cancer survivors, 1537 to the intervention group and 1551 to the comparison group. Patients were randomized by age, stage of cancer, and clinical site. To be included in the study women had to be 18 - 70 years old
at the time of cancer diagnosis, have had primary, operable, invasive stage I-III breast
cancer within 4 years of study entry, undergone mastectomy or lumpectomy followed by
radiotherapy, and not have experienced cancer recurrence. Dietary intake, physical
activity and body weight were among the factors assessed at baseline, 12 months, 24 or
36 months (50% sample at each point), 48 months, and 72 months. The study will
continue until the end of 2006.
References for General Introduction: Research Papers I, II, and III.


Research Paper I (references included)

Weight Gain and Recovery of Pre-Cancer Weight after Breast Cancer Treatments:

Evidence from the Women’s Healthy Eating and Living (WHEL) Study.
Abstract

Purpose: To examine predictors of weight gain following breast cancer diagnosis and subsequent return to pre-cancer weight.

Objectives: To determine (1) the associations of anti-neoplastic chemotherapy and/or, Tamoxifen® therapy on weight change following breast cancer diagnosis, (2) whether chemotherapy modified the effect of specific demographic and tumor characteristics on weight gain, (3) the proportion and characteristics of women who gained significant weight on chemotherapy and returned to their pre-cancer weight during follow-up.

Subjects and Methods: Participants were 3088 breast cancer survivors, aged 27-74 years. Weight was measured at baseline and years 1 through 6; pre-cancer weight was self-reported. Cancer stage and treatment modalities were obtained by medical record review; demographic and physical activity data were obtained from questionnaires. Weight gain of ≥ 5% body weight following cancer diagnosis was considered significant.

Results: Chemotherapy was significantly associated with weight gain (OR=1.65, 95% CI=1.12, 2.43) and Tamoxifen® was not (OR=1.03, 95% CI=0.71, 1.51). Tamoxifen® did not modify the effect of either chemotherapy or its different regimens on weight gain. Both types (anthracycline: OR=1.63, p-value=0.01, non-anthracycline: OR=1.79, p=0.003) and all regimens of chemotherapy (AC: OR=1.55, p-value=0.01, CAF: OR=1.83, p=0.003, CMF: OR=1.76, p=0.004) were associated with weight gain but the associations were not different from one another. Only 10% of participants returned to their pre-cancer diagnosis weight at the follow-up visits; the degree of initial gain (p for trend <0.0001) predicted that return.

Conclusion: Chemotherapy was associated with clinically meaningful weight gain, and a return to initial weight following weight gain was unlikely.
Introduction

There is considerable evidence that higher levels of adiposity at breast cancer diagnosis, estimated through the body mass index (BMI), are associated with poorer prognosis [1-3]. Many women gain weight post diagnosis, particularly pre-menopausal women, and some evidence suggests that this gain may also be associated with worse prognosis [4, 5], although the association is not consistent [6, 7]. Weight gain is a major concern of breast cancer survivors [8] but few studies report data on long-term patterns of weight change in this population.

Weight gain in breast cancer patients has been associated with anti-neoplastic chemotherapy in the majority of studies [4, 9-14], although there are a few notable exceptions [15, 16]. Further, adjuvant therapy with Tamoxifen® could also lead to weight increase, although the causal effect is much less certain [17-24]. Some of the inconsistencies could be the result of methodological issues [8, 25-29] such as inadequate sample [8, 27], inadequate control for confounders [25] or lack of a control group [8, 25, 26]. Another issue is that weight gain reported by studies has been consistently ‘absolute.’ By not accounting for the initial body weight, it is not possible to assess the proportion of women who had a clinically meaningful weight gain [30-32] (e.g. a 5-10% increase in relative weight).

Weight gain is expected when energy intake exceeds energy expenditure and is frequently described among breast cancer patients in relation to a reduction in physical activity [33-36] or relatively higher energy consumption during treatment [37-39]. Conditions that reduce resting metabolic rate [25, 40, 41] such as loss of lean body mass are also associated with weight gain. Women in general gain weight as they transition
through menopause [42] but breast cancer patients are at particular risk as treatments frequently result in a premature chemically induced menopause [33, 34].

There is little longitudinal data describing the proportion of women who are able to reestablish and maintain their pre-breast cancer body weight following completion of treatment, or factors that influence body weight in this population over time. In this study, we examine factors associated with weight gain following cancer diagnosis in participants enrolled in the Women’s Healthy Eating and Living (WHEL) study (n = 3088). These women, aged between 18 and 70 years at time of diagnosis, were all identified as having breast cancer in the United States between 1991 and 2000.

The objectives of the present study were to determine (1) the associations of chemotherapy and/or Tamoxifen® use with significant relative weight gain, (2) whether weight gain varied by the types or regimens of chemotherapy used, (3) whether chemotherapy use influenced the associations of age and stage at cancer diagnosis, pre-cancer BMI, and race with weight gain (4) the proportion of women who gained weight in association with chemotherapy and returned to their pre-cancer weight in the subsequent follow-up visits, and (5) the characteristics that were associated with return to pre-cancer weight.

**Materials and Methods**

**Population**

Study participants were women previously treated for breast cancer and part of the Women’s Healthy Eating and Living (WHEL) study (N=3088)—an ongoing, multi-site clinical trial designed to determine the efficacy of a dietary intervention in reducing breast cancer recurrence and death. The WHEL study protocol has been described in
detail elsewhere [43]. WHEL study participants were aged 18-70 years at the time of cancer diagnosis; had completed initial treatment for primary, operable, and invasive stage I, II, or IIIA breast carcinoma within 4 years of study entry; were not receiving or scheduled for chemotherapy at the time of study entry, and with no evidence of cancer recurrence since completion of initial treatment. Enrollment in another dietary trial, pregnancy, receiving estrogen replacement therapy, and presence of life threatening medical conditions or diseases were key exclusion criteria. All participants were scheduled for clinic visits at 12 months and 48 months. An additional clinic visit was scheduled randomly for either 24 or 36 months.

For the present study, data from a total of 2972 participants were used to assess the association between chemotherapy or Tamoxifen® use and weight gain (anti-estrogen use could not be ascertained for 80 participants; 36 women were prescribed an anti-estrogen other than Tamoxifen®). Another 72 participants were excluded (n=2900) to examine the association of weight gain with types of chemotherapy used (49 were prescribed both anthracycline and non-anthracycline chemotherapy, and data were missing for another 23). Forty-one women were further excluded (N=2859) from analysis that explored the effect of specific chemotherapy regimen (AC: adriamycin and cyclophosphamide, CAF: cyclophosphamide, adriamycin, and fluorouracil, or CMF: cyclophosphamide, methotrexate, and fluorouracil) on weight gain (23 received non-anthracycline other than CMF; 18 received anthracycline regimen not in the form of AC or CAF).

A total of 3045 participants were used to assess interactions between chemotherapy use and age, race, BMI, and stage of cancer at diagnosis in predicting
weight gain (pre-cancer weight data were missing for 43 women). Proportions of participants that returned to pre-cancer weight during follow-up visits (both ever and at specific follow-up time) were first calculated for all participants who gained weight following cancer diagnosis (N=1362), and then for each category of chemotherapy use (yes: N=1031, no: N=331). Of 1031 participants who gained weight on chemotherapy, 868 (163 women had missing weight data for all follow-up visits) were used to determine characteristics that were associated with return to pre-cancer weight.

**Measurements**

Weight and height were measured following a standard General Clinical Research Center protocol during clinic visits. Percent weight change between pre-cancer diagnosis and study entry was calculated as \( \frac{(\text{baseline weight} - \text{pre-cancer weight})}{\text{pre-cancer weight}} \times 100 \) and was categorized into gain (≥ 5% gain) and no gain (<5% gain).

Information on age and stage of cancer at diagnosis and on treatment received was obtained from reviewing patients’ medical records. In the analysis, age at cancer diagnosis was categorized into 5-year age groups (<44, 45-49, 50-54, 55-59, 60-64, and 65-71 years). Stage of cancer was categorized as the following: stage I or II or IIIA. Treatment modality variables were categorized as: chemotherapy use (yes/no), Tamoxifen® use (yes/no), types of chemotherapy (anthracycline vs. non-anthracycline), and chemotherapy regimen (AC, CAF, CMF). A participant was considered to have received anthracycline chemotherapy if her therapy included either doxorubicin (adriamycin) or daunorubicin or epirubicin or idarubicin [44]. Similarly, if a participant was not prescribed any of these medications, she was considered to have received non-anthracycline chemotherapy.
Standard questionnaires administered at baseline ascertained demographic characteristics and weight history. Patients reported their weight at baseline, one year prior to cancer diagnosis (pre-cancer weight), and weight pattern throughout adult life. Body mass index was calculated as weight (kg)/height (m)$^2$ and was categorized as underweight (<18.5), normal (18.5-24.9), overweight (25-29.9), obese class-I (30-34.9), and obese class-II ($\geq 35$) [45]. Height at study entry was used to calculate pre-cancer body mass index (BMI). A woman’s adult weight history was considered stable if she reported that her weight throughout adult life, except during pregnancy, stayed within 4.5 kg of her reported weight at study entry. Demographic variables used included race/ethnicity (non-Hispanic white, African American, Asian American, Hispanic, and others), education (college-graduate vs. non-graduate), smoking (current, past, and never), alcohol intake (none, 0-19 gm/day, and $\geq 20$ gm/day), and menstrual status (pre-menopausal, peri-menopausal, post-menopausal).

Physical activity was determined from the Personal Habits questionnaire developed for Women’s Health Initiative [46], expressed as metabolic equivalents (Mets) per week [47], and assessed at each clinic visit. Energy intake was estimated from a set of four 24-hour dietary recalls administered over the telephone using the Minnesota Nutrition Data System (version 2.91, 1996, University of Minnesota, Minneapolis, Minn).

Informed written consent was obtained from all study participants. The Human Subjects Committee of the University of California at San Diego and all participating institutions approved the procedures for the study.
Statistical analyses

Descriptive statistics were calculated for all variables used in this study; and data distributions were examined for normality.

Multiple logistic regressions were employed to examine the associations of chemotherapy use, Tamoxifen®, or types of chemotherapy with significant relative weight gain between pre-cancer diagnosis and study entry. Four different models were explored where the dependent variable was kept the same, and the exposure variables were allowed to vary. The first model tested the associations of weight gain with chemotherapy use and Tamoxifen® use, and the second model with types of chemotherapy (anthracycline vs. non-anthracycline). The third model examined the effect of specific chemotherapy regimens (AC, CAF, or CMF) on weight gain, and the fourth model explored whether that varied by Tamoxifen® use.

Covariates considered as potential confounders in the above models included age and stage at cancer diagnosis and pre-cancer BMI, education history, menstrual status, smoking status, physical activity, total energy intake, and alcohol consumption at baseline, adult weight history and time elapsed between cancer diagnosis and study entry. Variables associated in the univariable analysis at a level of p<0.25 were considered for inclusion in the final models. A forward selection procedure was used to select the most parsimonious model in which a variable was considered a confounder if it changed the regression coefficient of the exposure variable by more than 10%.

In the next step, the associations of age and stage of cancer at diagnosis, pre-cancer BMI, and race/ethnicity with significant weight gain were determined separately—using logistic regression—for chemotherapy users and non-users. The
corresponding odds ratios and the confidence intervals of the predicting variables were then compared across the categories of chemotherapy use to identify the presence of an interaction, if any.

The proportions of women who gained significant weight but had returned to their pre-cancer weight during follow-up visits (both ever and at a specific follow-up time) were calculated first for all participants and then for each category of chemotherapy use (yes/no). Subsequently, a series of t-tests compared corresponding proportions between chemotherapy users and nonusers for significant difference.

Finally, a logistic regression model explored the association of characteristics with return to pre-cancer weight in the follow-up visits. The same procedures of model building, as described earlier, were followed. Finally, mean weights of various categories of pre-cancer BMI (normal, overweight, obese class 1 and II) over the study period were plotted to explain the result of the logistic regression.

**Results**

The 3088 women were 27 to 74 years of age at study entry (means age 53.2, standard deviation [SD] = 9.0). The mean BMI was 27.3 (SD = 6.1); 57% were overweight or obese. Although mostly non-Hispanic white (85%), the cohort also included a small but varied group of minority women (African American: 4%, Asian American: 3%, and Hispanic: 5%, other ethnicities: 3%). Well-educated (college graduate: 54%) and predominantly employed (72%), 69% of the WHEL women were also married. Only a small percentage (5%) was diagnosed with either stage IIIA cancer or was currently smoking. Approximately one-quarter (28%) of all women reported having stable weight throughout their adult lives, and 32% reported no alcohol consumption. The mean energy
intake, physical activity, and time elapsed between cancer diagnosis and study entry were 1717 kcal/day (SD=407), 868 Mets/week (SD=879), and 23.7 months (SD=12.5), respectively (data not shown).

Most women had received either chemotherapy (70%) or antiestrogen therapy (67%); 24% were treated with Tamoxifen® alone, and 5.7% (N=177) received treatment other than chemotherapy or Tamoxifen. The majority (64%) of participants who received chemotherapy were prescribed anthracycline-based chemotherapy. The predominant regimen of choice for anthracycline-based chemotherapy was AC (66%), followed by CAF (32%). Virtually all of the non-anthracycline agents were received in the form of CMF (97%) (data not shown).

Women who received chemotherapy were 65% more likely to have gained significant weight than women who did not receive either chemotherapy or Tamoxifen® (OR=1.65, 95% CI 1.12, 2.43). Tamoxifen® was not associated with significant weight gain (OR=1.03, 95% CI 0.71, 1.51). It did not modify the effect of either chemotherapy use (OR=1.65 vs. OR=1.69) or specific chemotherapy regimen on weight gain (model 4, Table 1). Weight gain was associated with chemotherapy, irrespective of type (anthracycline: OR=1.63, 95% CI=1.11, 2.38; non-anthracycline: OR=1.79, 95% CI=1.22, 2.63) or regimen (CAF: OR=1.83, 95% CI =1.20, 2.79; AC: OR=1.55, 95% CI=1.05, 2.29, and CMF: OR=1.76, 95% CI= 1.20, 2.59).

No differential effect was observed by chemotherapy use for the associations of age and stage of cancer at diagnosis, pre-cancer BMI, and race with weight gain (Table 2). Older age at cancer diagnosis and the higher pre-cancer BMI was associated with less likelihood of gaining weight. In addition, being an African-American increased the risk
of gaining weight while being an Asian-American decreased it, although differences in these subgroups attained statistical significance among chemotherapy users only (African-American OR=1.81, 95% CI= 1.15, 2.86; Asian-American OR=0.55, 95% CI= 0.34, 0.92) (Table 2).

The highest proportion of participants that returned to pre-cancer weight at any follow-up visit was less than 5% (at 4-year follow-up), and only 10% returned to pre-cancer weight over the course of follow-up visits. There was no difference in return to pre-cancer weight by chemotherapy use, either ever during follow-ups (p=0.8) or at specific follow-up time (p-values for year 1, year 2/3, year 4, and year 6 were 0.9, 0.4, 0.3, and 0.3 respectively (Figure 1).

The greater the initial gain in body weight with treatment, the less the likelihood of returning to pre-cancer weight during follow-up; in fact, a strong decreasing trend (p-for trend< 0.0001, data not shown) was observed across the quartiles of initial weight gain.

Discussion

Chemotherapy use but not Tamoxifen® was significantly associated with weight gain in this study. Tamoxifen® use did not modify the effect of either chemotherapy, in general, or specific chemotherapy regimens, in particular, on weight gain. Weight gain across subcategories of age, race, BMI, and stage of cancer did not vary by chemotherapy use. Only a small percentage (10%) of these breast cancer survivors returned to their pre-cancer weight during follow-up; the degree of initial weight gain following chemotherapy was inversely related to likelihood of return to pre-cancer diagnosis weight.
Studies of chemotherapy and breast cancer-associated weight gain have been
criticized for their analytical approach and potential measurement error. First, studies
frequently chose absolute weight gains that ranged from 2.5 to 6.2 kg as outcome [4, 9-
14]. While this gain can be statistically significant, it may not always be of clinical
importance. Relative weight gain is a better measure in that it considers the potential
confounding by initial body weight. A number of studies suggest that a 5-10% change in
body weight is clinically meaningful [30-32]. Second, numerous studies only include
chemotherapy-treated women and reported weight gain at the end of treatment [25, 27,
36, 48, 49]. Hence it is not possible to rule out—in the absence of an appropriate control
group who did not receive chemotherapy—that similar weight change would have
occurred regardless of treatment. Finally, a number of studies, particularly the ones that
reported no gain in association with chemotherapy, provided univariable analysis of
weight gain [25, 36]. These studies may have been unable to adjust for confounders due
to small sample size. Control for various confounders relevant for weight change, such as
age, BMI, race, education, energy intake, and physical activity, are essential before
making such inference [50]. This analysis tried to overcome these potential concerns by
adopting relative weight gain instead of absolute gain as its primary study outcome, by
comparing weight gain in chemotherapy treated patients to those characteristics of a
comparison group, and by presenting multi-variable as opposed to univariable analysis
only. Our results, with a larger sample size and more sophisticated analytical approaches,
showed a significant association between weight gain and chemotherapy use in women
diagnosed with early stage breast cancer.
Limited evidence has also been reported regarding weight gain associated with various types or regimens of chemotherapy. Use of anthracycline-based chemotherapy, in one such study, did not predict weight gain [49]. Among the participants in the present study, use of either anthracycline or non-anthracycline based chemotherapy was found to be associated with significant weight gain. Choice of the comparison groups—non-anthracycline in one [49] and no chemotherapy in this study—may be responsible for the apparently conflicting results. Although weight gain with CMF regimen [24-26] is well known, three studies [8, 15, 27] in which women were treated primarily with AC regimen did not demonstrate weight gain over the treatment period; small sample [8, 27] and selection bias [15] may have influenced these findings. The results of the present study showed that significant weight gain occurred irrespective of chemotherapy regimen used (AC, CAF, or CMF) and no particular regimen was associated with a greater weight gain than the others. The difference in odds ratios observed for various types or regimens of chemotherapy were more likely a random variation around a common odds ratio, as their respective 95% confidence intervals widely overlapped one another. Hence, our data does not support the published research suggesting that weight gain is less with AC regimen because it uses fewer agents [5, 51], has shorter duration of treatment [52], and is administered intravenously [53].

The study design issues described above may also contribute to the conflicting results found in the research regarding the effect of Tamoxifen® on weight gain. Studies that reported significant weight gain with Tamoxifen® were constrained by short follow-up period [18], small sample size [19], and absence of a control group [19, 20]. On the other hand, studies that reported no weight gain with Tamoxifen® [17, 21-24] are not
without criticism either. In one such study [21], women who did not receive any chemotherapy gained the most weight (3.4 kg), a factor that may underlie the failure to find a difference. Using a better design and an adequate sample size, the WHEL data support existing evidence suggesting that Tamoxifen® use is not associated with significant weight gain in breast cancer patients. Despite the fact that many breast cancer patients currently receive both chemotherapy and Tamoxifen®, there is a paucity of evidence evaluating how this treatment regimen influences weight gain. One prospective study that included 100 women treated with either CMF or FEC chemotherapy supported our findings, reporting no significant difference in weight gain by Tamoxifen® use [24].

Our findings relating age and pre-cancer body weight to weight gain are also supported by current evidence. In studies of the general population, adult women tend to gain weight until approximately age 55 years, and then begin to stabilize and subsequently lose weight thereafter [30, 54, 55]. This pattern is consistent with the findings in the present study, where older women (≥ 55 at diagnosis) were less likely to gain weight than their younger counterparts (<55 at diagnosis). Our study also corroborates findings from several studies that have reported that weight at diagnosis is inversely related to subsequent weight gain [6, 7, 50, 55]. Unlike Chlebowski et al. [5] who reported significant weight gain regardless of breast cancer stage, the present study found that having a stage II or stage IIIA cancer was associated with a reduced likelihood of weight gain.

The WHEL study intervention neither advised nor proscribed an energy-restricted diet, nor did it encourage participants to increase physical activity levels. Thus, the finding that only 10% of the WHEL study participants returned to their pre-cancer weight
over the study period, after an initial gain, seems reasonable. The few studies that gathered long-term follow-up weight data in women who had been diagnosed and treated for breast cancer support this notion. One study showed that without intervention some women did not return to their pre-treatment weight [4]. In other cases, women continued to gain weight even after completion of treatment [8, 14].

This study found that the likelihood of losing weight is independently related and inversely proportional to the degree of initial gain. The observation that overweight or obese women at pre-cancer diagnosis were more successful in returning to their pre-cancer weight than their normal weight counterparts (Table 3), however, requires clarification. First, the mean percent weight gain following chemotherapy decreased with increasing pre-cancer body mass index categories (normal: 13%, overweight: 12%, obese class I & II: 11%; data not shown). Second, body weight among the obese (both class I & II) fluctuated over time compared to other BMI categories (Figure 2). Hence the result should not be interpreted that overweight or obese women were more likely to lose weight, but rather that they gained less than normal weight women following diagnosis and that their weight was less stable. Likewise, employment at baseline was strongly correlated with age, education, and marital status (data not shown), and hence the finding that being employed at baseline decreased the likelihood of returning to pre-cancer weight should not be interpreted as an independent determinant.

The population under study was mostly white, well-educated, and predominantly employed. Hence the results reported in this study should be interpreted with caution and may not be generalizable to the population of breast cancer survivors. In addition, chemotherapeutic and estrogen modulation agents have evolved since the 1990s, when
the vast majority of these women were diagnosed and completed initial treatments. These factors could have significant implications for current issues related to weight change in breast cancer patients. Although baseline and follow-up visit weights were measured in the clinic, data on pre-cancer weight was self-reported. It is unlikely, however, for two reasons, that this self-reported pre-cancer weight influenced the reported effect of chemotherapy on weight gain. First, the study participants were unaware of the study hypothesis at the time of data collection, and hence unlikely to report their weight differentially by chemotherapy use. Second, research supports that self reported weight is a good measure of actual weight [56]. In this study the correlations between self-reported pre-cancer weight and measured baseline weight and between self-reported and measured baseline weight were 0.90 and 0.98 respectively. Another potential limitation of the present study is that we lacked information on steroid use during chemotherapy treatment. Steroids are known to be potent stimulators of weight gain, and chemotherapy regimens that included steroids have been found to be associated with greater weight gain [16, 28].

This study supports the existing evidence that women who have been treated for breast cancer with chemotherapy gain weight. Our data indicate that weight gain is likely to occur, irrespective of types or regimens of chemotherapy chosen, and that gains are similar across these treatments. Our findings support the notion that Tamoxifen® is not associated with weight gain. Finally, this study found that after an initial weight gain a return to pre-cancer weight is unlikely, and thus identifies the need for research to examine whether specific dietary and/or exercise interventions could help promote healthy weight management.
Acknowledgements

The dissertation author was the primary investigator and the first author and Ms. Shirley Flatt, Dr. Loki Natarjan, Dr. Cynthia A Thomson, Dr. Wayne Bardwell, Dr. Betty Caan, Dr. Cheryl L Rock, and Dr. John P. Pierce were the co-authors of this paper. This study was initiated with the support of the Walton Family Foundation and continued with funding from NCI grants CA 69375 and CA 72092. Some of the data were collected from General Clinical Research Centers, NIH grants M01-RR0070, M01-RR0079, and M01-RR00827. The authors thank Sheila Kealey and Christine Hayes for their editorial support.
Table 1.1. Association between breast cancer chemotherapy modalities and weight gain in the Women’s Healthy Eating and Living (WHEL) study (N=2972)

<table>
<thead>
<tr>
<th>Models&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th>N (%)</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No chemo+ No Tamoxifen®</td>
<td>177(6.0)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen® only</td>
<td>716(24.0)</td>
<td>1.03</td>
<td>0.71, 1.51</td>
<td>0.80</td>
</tr>
<tr>
<td>Chemotherapy only</td>
<td>794(26.7)</td>
<td>1.65</td>
<td>1.12, 2.43</td>
<td>0.01</td>
</tr>
<tr>
<td>Tamoxifen® +chemotherapy</td>
<td>1285(43.3)</td>
<td>1.69</td>
<td>1.16, 2.47</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Model 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthracycline only</td>
<td>1277(44.0)</td>
<td>1.63</td>
<td>1.11, 2.38</td>
<td>0.01</td>
</tr>
<tr>
<td>Non-anthracycline only</td>
<td>730(25.1)</td>
<td>1.79</td>
<td>1.22, 2.63</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Model 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AC only</td>
<td>847(29.6)</td>
<td>1.55</td>
<td>1.05, 2.29</td>
<td>0.01</td>
</tr>
<tr>
<td>CAF only</td>
<td>412(14.4)</td>
<td>1.83</td>
<td>1.20, 2.79</td>
<td>0.003</td>
</tr>
<tr>
<td>CMF only</td>
<td>707(24.7)</td>
<td>1.76</td>
<td>1.20, 2.59</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Model 4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AC only</td>
<td>279(9.7)</td>
<td>1.55</td>
<td>1.00, 2.41</td>
<td>0.05</td>
</tr>
<tr>
<td>AC+ Tamoxifen®</td>
<td>568(19.6)</td>
<td>1.56</td>
<td>1.04, 2.34</td>
<td>0.03</td>
</tr>
<tr>
<td>CAF only</td>
<td>181(6.3)</td>
<td>1.86</td>
<td>1.14, 3.03</td>
<td>0.01</td>
</tr>
<tr>
<td>CAF + Tamoxifen®</td>
<td>231(8.1)</td>
<td>1.81</td>
<td>1.14, 2.87</td>
<td>0.01</td>
</tr>
<tr>
<td>CMF only</td>
<td>296(10.4)</td>
<td>1.60</td>
<td>1.04, 2.46</td>
<td>0.03</td>
</tr>
<tr>
<td>CMF + Tamoxifen®</td>
<td>411(14.4)</td>
<td>1.89</td>
<td>1.25, 2.85</td>
<td>0.002</td>
</tr>
</tbody>
</table>

<sup>1</sup>For each model reference category: No chemotherapy + No Tamoxifen®; percents were calculated with denominator for model 1=2972, model 2=2900, and model 3 or 4=2859.

<sup>2</sup>Models were adjusted for pre-cancer diagnosis age and body mass index, education, smoking status, adult weight history, menstrual history, energy intake, alcohol intake at baseline, and time between pre-cancer diagnosis and study entry.

<sup>3</sup>Significant gain: ≥ 5% gain between pre-cancer and study entry.
Table 1.2. Associations between select demographic and cancer clinical characteristics and significant weight gain in the Women’s Healthy Eating and Living (WHEL) study (N=3045)

<table>
<thead>
<tr>
<th>Significant weight gain&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Chemotherapy ‘Yes’ (N=2133)</th>
<th>Chemotherapy ‘No’ (N=912)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR 95%CI p-value</td>
<td>OR 95%CI p-value</td>
<td></td>
</tr>
<tr>
<td>Pre-cancer BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>1.48, 0.68, 3.21, 0.32</td>
<td>2.02, 0.58, 7.03, 0.27</td>
</tr>
<tr>
<td>18.5-24.9</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>25-29.9</td>
<td>0.92, 0.75, 1.14, 0.45</td>
<td>0.95, 0.68, 1.32, 0.74</td>
</tr>
<tr>
<td>30-34.9</td>
<td>0.68, 0.50, 0.91, &lt;0.01</td>
<td>0.68, 0.44, 1.07, 0.10</td>
</tr>
<tr>
<td>≥ 35</td>
<td>0.39, 0.27, 0.56, &lt;0.0001</td>
<td>0.32, 0.16, 0.62, &lt;0.01</td>
</tr>
<tr>
<td>Pre-cancer age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26-44</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>45-49</td>
<td>0.91, 0.73, 1.14, 0.40</td>
<td>0.94, 0.55, 1.61, 0.83</td>
</tr>
<tr>
<td>50-54</td>
<td>1.00, 0.77, 1.29, 0.99</td>
<td>0.68, 0.40, 1.15, 0.15</td>
</tr>
<tr>
<td>55-59</td>
<td>0.68, 0.50, 0.93, 0.01</td>
<td>0.59, 0.34, 0.98, 0.04</td>
</tr>
<tr>
<td>60-64</td>
<td>0.71, 0.47, 1.05, 0.09</td>
<td>0.51, 0.30, 0.87, 0.01</td>
</tr>
<tr>
<td>≥ 65</td>
<td>0.75, 0.41, 1.39, 0.36</td>
<td>0.49, 0.27, 0.86, 0.01</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Black</td>
<td>1.81, 1.15, 2.86, 0.01</td>
<td>1.35, 0.60, 3.08, 0.47</td>
</tr>
<tr>
<td>Asian</td>
<td>0.55, 0.34, 0.92, 0.02</td>
<td>0.43, 0.17, 1.13, 0.09</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.94, 0.65, 1.37, 0.75</td>
<td>1.84, 0.89, 3.81, 0.10</td>
</tr>
<tr>
<td>Others</td>
<td>1.19, 0.67, 2.12, 0.56</td>
<td>0.74, 0.27, 1.84, 0.52</td>
</tr>
<tr>
<td>Stage of cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>II</td>
<td>0.79, 0.64, 0.97, 0.03</td>
<td>1.09, 0.79, 1.52, 0.59</td>
</tr>
<tr>
<td>IIIA</td>
<td>0.77, 0.53, 1.13, 0.19</td>
<td>*</td>
</tr>
</tbody>
</table>

<sup>1</sup>Models were also adjusted for time between pre-cancer diagnosis and study entry.
<sup>2</sup>Significant weight gain defined as >5% gain between pre-cancer diagnosis and study entry. (mean = 23.7 months)
BMI: Body Mass Index; * Unstable estimate because of sparse cell
Table 1.3. Associations\(^1\) between select demographic characteristics and ever returning to pre-cancer body weight in the Women’s Healthy Eating and Living (WHEL) study (N=868)

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-cancer BMI (kg/m(^2))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>1.08</td>
<td>0.13, 8.90</td>
<td>0.63</td>
</tr>
<tr>
<td>18.5-24.9</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-29.9</td>
<td>1.99</td>
<td>1.16, 3.41</td>
<td>0.01</td>
</tr>
<tr>
<td>30-34.9</td>
<td>3.90</td>
<td>2.03, 7.51</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥ 35</td>
<td>6.31</td>
<td>2.55, 14.00</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Percent weight gain by study entry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (5-7.7%)</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2 (7.8-11.4%)</td>
<td>0.83</td>
<td>0.49, 1.40</td>
<td>0.49</td>
</tr>
<tr>
<td>Q3 (11.5-16.8%)</td>
<td>0.23</td>
<td>0.11, 0.45</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Q4 (≥ 16.9%)</td>
<td>0.15</td>
<td>0.07, 0.33</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pre-cancer age (in years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26-44</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45-49</td>
<td>0.74</td>
<td>0.41, 1.32</td>
<td>0.31</td>
</tr>
<tr>
<td>50-54</td>
<td>0.86</td>
<td>0.46, 1.62</td>
<td>0.64</td>
</tr>
<tr>
<td>55-59</td>
<td>0.53</td>
<td>0.23, 1.22</td>
<td>0.14</td>
</tr>
<tr>
<td>60-64</td>
<td>0.44</td>
<td>0.16, 1.24</td>
<td>0.12</td>
</tr>
<tr>
<td>≥ 65</td>
<td>0.16</td>
<td>0.02, 1.24</td>
<td>0.08</td>
</tr>
<tr>
<td>Employment at study entry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.45</td>
<td>0.26, 0.77</td>
<td>0.003</td>
</tr>
<tr>
<td>Smoking at study entry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>0.67</td>
<td>0.42, 1.07</td>
<td>0.09</td>
</tr>
</tbody>
</table>

\(^1\)Model was adjusted for pre-cancer BMI, percent weight gain between cancer diagnosis and study entry, pre-cancer age, and smoking and employment status at baseline.

Q: Quartile
**Figure 1.1.** Proportion of participants who returned to their pre-cancer diagnosis weight after gaining significant body weight following diagnosis; results showed after stratification by chemotherapy use; p-values presented compared percentages between chemotherapy and non-chemotherapy user at indicated time points; N=1362.
**Figure 1.2.** Mean body weight over the study period: stratified by pre-cancer body mass index (kg/m²) categories (normal: 18.5-24.9, overweight: 25-29.9, obese class-I: 30-34.9, obese class-II: ≥ 35); Study time points: pre-breast cancer (PBC), study entry (Base), follow-up (Years 1 through 6) in the Women’s Healthy Eating and Living (WHEL) study, N=868.
References for Research Paper I


Research Paper II (references included)

Does a Healthy Diet Help Weight Management among the Overweight and the Obese?
Abstract

A randomized dietary intervention trial over 4 years examined diet, weight, and obesity incidence (BMI ≥ 30 kg/m^2) differences between study groups. Participants were 1510 breast cancer survivors with BMI ≥ 25 kg/m^2 at entry. Dietary intake was assessed yearly by telephone; weight and height were measured at clinic visits. Intervention participants consumed more fruit, vegetables, and fiber, and less energy from fat than controls during follow-up—cross-sectionally (p<.0001) and longitudinally (p<.0001); weight did not differ between study groups at any follow-up visit; significant weight change difference was observed between groups only in the first year (p<.0001). Diet and weight results remained unchanged after stratifying by age and BMI. No difference in obesity incidence was found during follow-up (p> 0.1) among overweight members of either study group. Without specific efforts to reduce total energy intake, dietary modification does not reduce obesity or result in long-term weight loss.
Introduction

As the prevalence of obesity among Americans continues to rise (Kuczmarski, Flegal, Campbell, & Johnson, 1994; Swinburn, Caterson, Seidell, & James, 2004), the impetus to promote weight management among the overweight and obese is increasingly important, because obesity is associated with greater risk for chronic diseases, (Brown, Brauner, & Minnotte, 1993; Li & Stovall, 1998) mortality (Chlebowski et al., 1986), and psychological distress (Knobf, Mullen, Xistris, & Moritz, 1983). Weight control is particularly of clinical relevance among breast cancer survivors, where co-morbidities such as elevated glucose, insulin, and cardiovascular diseases are common (Goodwin et al., 2002; Yu & Rohan, 2000).

Manipulating the energy density of diet has been an area of intensive interest: studies have examined replacing energy-dense high-fat food with fiber-rich food such as fruit and vegetables and whole grains as an approach to reduce the risk of both chronic disease and obesity (Rolls, Ello-Martin, & Tohill, 2004; Tohill, Seymour, Serdula, Kettel-Khan, & Rolls, 2004). Current data suggest that people typically eat consistent amount (volume) of food on day-to-day basis (Bell, Castellanos, Pelkman, Thorwart, & Rolls, 1998; Kral, Roe, & Rolls, 2002). Hence, reducing a diet’s energy density should theoretically reduce total energy intake, which in turn should help maintain an energy balance that is favorable to weight management (Duncan, Bacon, & Weinsier, 1983; Golay et al., 1996; Reaven, 1997). However, whether such dietary modification can produce the desired effect on weight in an ad-libitum conditions remains inconclusive (Djuric et al., 2002; Howard et al., 2006; Lanza et al., 2001; Maskarinec, Chan, Meng, Franke, & Cooney, 1999; Rock et al., 2001; Singh et al., 2002; Smith-Warner et al.,
weight change among intervention participants in these studies range from ‘weight loss’ (Howard et al., 2006; Lanza et al., 2001; Singh et al., 2002) to ‘no change’ (Maskarinec et al., 1999; Rock et al., 2001; Smith-Warner et al., 2000; Zino et al., 1997) to ‘weight gain’ (Djuric et al., 2002). The variation in weight change observed was likely the product of variations in dietary intake and physical activity. But it is also possible that some of that variation was due to the difference in the age and body mass index (BMI) distribution of the participating cohorts. Current age and BMI are strong predictors of weight change during adulthood (Ball, Crawford, Ireland, & Hodge, 2003; Lahmann, Lissner, Gullberg, & Berglund, 2000; Williamson, 1993; Williamson, Kahn, Remington, & Anda, 1990), yet none of these studies reported age and BMI specific results.

The suggestion that a diet high in fruit and vegetables might reduce the incidence of obesity came from a number of large-scale cohort studies with long-term follow up data (He et al., 2004; Newby et al., 2003). Clinical trials (Epstein et al., 2001; Singh, Niaz, & Ghosh, 1994) that reported similar findings are of limited value for a number of reasons, such as restriction of energy intake in intervention subjects, choice of a vegetarian population, and short duration of follow-up.

This report investigates energy density in a subgroup of participants in the Women’s Healthy Eating and Living (WHEL) Study, a large-scale clinical trial (n=3088) with long-term follow-up data (6 years), that is testing the effect of a diet high in vegetables, fruit, and fiber, and low in fat on risk for recurrence and survival in women with a history of breast cancer. Energy intake and weight loss were not WHEL Study objectives. This report considers WHEL participants who were either overweight or
obese at study entry, and investigates the relationship between dietary intake and body weight for up to 4 years of follow-up. This study compares the intervention and control groups at baseline and follow-up periods for the following variables (1) mean consumption of fruit and vegetables, fiber, and percent energy from fat, as well as body weight; (2) mean dietary intakes and body weight after stratifying by baseline age and BMI, (3) changes in dietary intake and body weight, and (4) the incidence of obesity in overweight control and intervention group participants.

**Materials and Methods**

**Population**

This study investigates a subgroup of participants in the Women’s Healthy Eating and Living (WHEL) Study—an ongoing, multi-site clinical trial designed to determine the efficacy of a dietary intervention on reducing breast cancer recurrence and death. The WHEL Study protocol has been described in detail elsewhere (Pierce et al., 2002).

WHEL Study participants who were either overweight (BMI=25-29.9 kg/m²) or obese (BMI ≥ 30 kg/m²) at baseline (n=1760) were eligible for inclusion in the present study. Of this sample, 250 participants (14%) lacked data on body weight beyond baseline because of recurrence, death, or voluntary non-participation. The present analyses considers the remaining 1510 women (control=760, intervention=750) for whom dietary intake and weight data were available at 4 years post-randomization.

Of 1510 women, 838 were overweight at study entry (control=423, intervention=415), and formed the sample for examining obesity incidence during follow-up periods (years 1, 2 or 3, and 4).
Dietary assessment

Dietary intake was assessed through a set of four 24-hour dietary recalls. Trained dietary assessors conducted these recalls over the telephone on randomly selected days, stratified for weekend vs. weekdays, over a 3-week period. Dietary recalls were administered to the participants at study entry and then annually thereafter for 4 years (split sample (50%) at years 2 and 3). The Minnesota Nutritional Data System software was used to collect and estimate dietary intakes (NDS version 4.01, 2001, University of Minnesota, Minneapolis, MN).

A number of strategies were in place to maximize the accuracy of dietary recall data (Newman et al., 2005). Dietary assessors had completed a training program that included standardized data collection, proper interview technique, and efficient use of dietary analyses software. Participants were trained, before study enrollment, to estimate serving sizes with food models, measuring cups, and spoons, and were provided with two-dimensional food models for reference during recalls. In addition, NDS used a multi-pass method that improved recall accuracy by prompting assessors to obtain detail data about type, amount, and preparation method of food eaten.

Participants in the intervention group were encouraged to maintain a dietary pattern that included a daily consumption of at least 5 vegetable servings, 16 ounces of vegetable juice (or equivalent vegetable servings), 3 fruit servings, 30 grams of fiber (18g/1000 kcal), and 15-20% energy from fat. Telephone counseling, monthly cooking classes and newsletters were the principal methods to promote dietary change in the intervention participants. Control group participants received print materials that included dietary guidelines from the U.S. Department of Agriculture (USDHHS, 1995) and the
National Cancer Institute (NCI, 1995) and a bimonthly cohort maintenance newsletter, general health, and nutrition information unrelated to the intervention group’s dietary goal.

**Exposure variables**

Intake of total fruit and vegetables (servings/day/1000kcal): a vegetable serving was defined as ½ cup cut-up fresh or cooked vegetable or 1 cup raw leafy green vegetable or equivalent amounts provided by multi-ingredient dishes; a fruit serving was ½ cup of cut-up fresh or cooked fruit or ¼ cup of dried fruit or 1 medium piece fresh fruit; fruit juice, iceberg lettuce, white potatoes, and legumes were not included in the computation of daily total fruit and vegetables intake, (2) Intake of total fiber (grams/day/1000 kcal): total fiber included both soluble and insoluble fiber; and (3) percent energy from fat/day: (energy obtained from daily intake of total fat / total daily energy intake) x100.

**Outcome variable**

Weight and height were measured—with the participants wearing light clothing and no shoes—during clinic visits (baseline, years 1, 2 or 3, and 4) scheduled in the WHEL Study. BMI was calculated as weight (kg)/height (m$^2$). A woman was considered obese if her BMI was ≥ 30 kg/m$^2$.

**Covariates**

Information on age and stage of cancer at the time of diagnosis, and treatment modalities was obtained from patients’ medical records. Standard questionnaires administered at baseline ascertained demographic and weight history. BMI was categorized as overweight (25-29.9 kg/m$^2$), obese class-I (30-34.9 kg/m$^2$), and obese
class-II (≥35 kg/m²) (WHO, 1998). Other potential co-variables examined in this analysis included race/ethnicity, education, marital status, employment status, smoking habit, alcohol intake, menstrual history, adult weight history (stable vs. not stable), and time elapsed between cancer diagnosis and study entry (in months).

Informed written consent from study participants was collected in the original WHEL Study. The Human Subjects Committee of the University of California, San Diego, and all participating institutions approved the procedures for the present study.

**Statistical Analyses**

Descriptive statistics were calculated (means and standard deviations for continuous variables and frequencies for categorical variables) for all variables included in the analyses.

The control and the intervention group were compared for participants’ baseline characteristics to validate randomization. Demographic, behavioral, cancer, and treatment related variables, thought to be potential confounders of the relationship between dietary intake and weight, were examined in this respect.

Participants with missing weight data at all follow-up time points were calculated as a whole and then separately by study groups; they were compared against each other for attrition frequency. Participants with missing data were also compared to participants with complete data on key variables such as age, BMI, and cancer stage.

Mean daily intake of fruit and vegetables, total fiber, and percent energy from fat, as well as mean body weight, were calculated and graphed for the control and intervention participants, both at baseline and at follow-up (years 1-4). Corresponding means at specific follow-up times were compared against each other to discern group
difference, if any. Daily total energy consumption was taken into account while calculating mean fruit and vegetable servings and total fiber intake. The same analyses were rerun after stratification by baseline age (<55 vs. ≥55 years) and BMI (overweight, obese class-I, and obese class-II). For stratified analyses, body weight at year 2 and 3 (split (50%) sample) were considered together to ensure adequate sample size in each of the categories.

A mixed effect model ascertained group by time interaction. Mixed effect models are the best option available for such analyses given the correlations among repeated measurements within a participant and the ability of this model to handle random missing values. To find a suitable covariance structure, correlations and variances over time were examined for each variable modeled. Although the correlation between any two time points varied little, and the variances over time remained steady, both of which favored compound symmetry as the choice of covariance structure, each model was run with the same fixed effect but different covariance structure such as toeplitz, unstructured, and autoregressive. The model that had the smallest Akaike’s Criterion (AIC) value was considered the best and was chosen.

Since a significant difference in weight change was observed between control and intervention groups only in the first year of follow-up despite sustained dietary changes in the intervention group, secondary data analysis, using a linear regression model, was carried out to ascertain which of the dietary changes might be associated with the weight change.
Finally, incidence of obesity at follow-up (years 1, 2 or 3, and 4) was calculated for those who were overweight at study entry, first for all participants and then separately for each study group. The corresponding incidences of all specific follow-up visits were then compared by T-test to ascertain any difference by randomization status.

Results

The mean age of the 1510 women who were either overweight or obese at baseline was 54.4 years (range: 28-74 years, standard deviation [SD] = 9.0). The mean BMI was 30.9 (SD=5.2); 56% were overweight, 26% were obese class-I, and 18% were obese class-II. Although mostly non-Hispanic white (83%), the cohort also included a small but varied group of minority women (African American: 5%, Asian: 3%, and Hispanic: 6%, other ethnicities: <3%). Highly educated (48% college graduate) and predominantly employed (71%), 70% of the participants were also married. Fewer than 5% were diagnosed with stage IIIA cancer or were currently smoking. Approximately one third of the participants reported no alcohol consumption, and only 9% reported having stable weight throughout their adult lives. The mean energy intake was 1746 kcal/day (SD=426) and time between cancer diagnosis and study entry was 24.9 months (SD=12.2) (data not shown).

Comparison of various demographic, behavioral, cancer, and treatment related characteristics between the control (n=760) and the intervention participants (n=750) showed that the randomization was successful. Tamoxifen use was marginally significantly higher in the intervention group (p-value=0.06) (Table 1).
At study entry, consumption of fruit and vegetables, total fiber, and percent energy from fat was similar in both groups. At baseline, the control group reported consuming approximately 5 servings of fruit and vegetables, 20 grams of fiber, and 30% energy from fat; these values remained relatively unchanged during follow-up. Intervention group participants were consuming significantly more fruit and vegetables, total fiber, and lower percent energy from fat during follow-up (p <0.0001) than they were at baseline (Figure 1a, 1b, and 1c). No difference in mean body weight was observed between the groups, either at baseline or at follow-up (Figure 1d).

The difference in mean dietary intakes between the study groups at follow-up remained significant, irrespective of baseline age and BMI categories, except for the percent energy from fat in the obese class-II. In that category, the percent energy from fat among the intervention participants declined significantly in the first year; but started to increase thereafter, and by the end of follow-up there was no difference between the groups. In the control group, mean weight increased monotonically with each follow-up measurement in younger women (<55 years, mean weight: 83.2 (base), 84.0 (year 1), 84.8(year 2/3), and 84.8(year 4)) and decreased in older women (≥55 years, mean weight: 82.7 (base), 82.4 (year 1), 82.3(year 2/3), and 82.1(year 4)). Among intervention participants, mean weight increased in younger women (<55 years, mean weight: 83.7 (base), 83.6 (year 1), 85.2 (year 2/3), and 85.6 (year 4)) and remained stable in older women (≥55 years, mean weight: 81.0 (base), 80.3 (year 1), 81.2 (year 2/3), and 81.5 (year 4)) by the end of follow-up (data not shown).

Table 2 includes the longitudinal weight and diet data analyses using mixed effects models. Significant differences were observed between the groups over time in
their changes of reported fruit and vegetables, total fiber, and percent energy from fat intake \((p\) for group by time interaction: <0.0001). Significant difference in change of body weight occurred between the groups in the first year of follow-up only \((p\) for group by time interaction: 0.001), and not at subsequent follow-up times.

Secondary analyses showed that weight change at 1-year follow-up was strongly but inversely associated with a change in total fiber \((p <0.0001)\) and moderately but proportionately with a change in percent energy from fat \((p <0.01)\); change in fruit and vegetable intake was not found to be associated with weight change (Table 3).

The incidence of subsequent obesity among women who were overweight at study entry was 10.6%, 14.3%, and 18.6% at year 1, 2 or 3, and 4 respectively. Obesity incidence did not vary by study group at any follow-up time \((p\) for year 1, 2/3, and 4 were 0.9, 0.1, and 0.3 respectively) (Figure 2).

**Discussion**

In this dietary intervention of women with a history of breast cancer, overweight or obese participants assigned to the intervention arm significantly changed their diets by increasing their fruit, vegetable, and fiber intake, and by decreasing their percent energy consumed from fat. Participants maintained these changes over the study follow-up period. The dietary intakes in the control group remained unchanged over the course of the study. Differences in dietary intake between the groups were shown to be independent of baseline age and BMI. Mean body weight did not vary between the study groups, either at baseline or at follow-up time points. A significant difference in weight change was observed between the groups in the first year of follow-up only, and not afterwards. Secondary data analysis indicated that weight decrease in the first year was associated
strongly with an increase in total fiber intake and moderately with a decrease in percent energy from fat and not with an increase in fruit and vegetable intake. Finally, significantly different dietary intakes between the overweight control and intervention participants did not translate into difference in the incidence of obesity.

The clinical trial with data most comparable to that in the present study is the Polyp Prevention Trial (PPT) (Lanza et al., 2001). Both of these trials were a multi-center randomized trial, had similar dietary goals (daily 5-8 servings of fruit and vegetables, <20% of energy from fat, and approximately 30 g/d of fiber for the PPT), had large enrollments, and followed their participants for the same length of time (4 years). The intervention participants of the present study, as in the PPT (Lanza et al., 2001), significantly increased their fruit, vegetable, and total fiber intake and decreased their percent energy from fat compared to the control group, and maintained that difference throughout the study follow-up period. However, by the end of follow-up, weight differed between study groups in PPT but it did not between the corresponding groups in the present analyses. Although the weight change among the control group in both trials was very similar (PPT: mean=0.31 kg, WHEL subgroup: mean=0.55 kg), the intervention participants in PPT lost a small amount of weight on average (mean= -0.65 kg) whereas their counterparts in the present study actually gained a small amount of weight over time (mean=1.3 kg). The variations of results in body weight between these two trials may be explained by a number of factors.

Unlike the WHEL Study, the PPT included men, but weight data were not presented separately for gender. Hence, it is not known whether women in the PPT experienced weight change that was any different from that in men. Hormonal
differences and the onset of menopause in women may lead to different weight change patterns in adult men and women (Santoro & Chervenak, 2004). A difference in age distribution between study cohorts might explain the difference in weight change between studies. Adult women generally gain weight until 55 years of age and typically lose weight thereafter (Williamson, 1993). PPT participants were considerably older than this WHEL Study subgroup (mean age: 61(PPT) vs. 54 years). Finally, differences in dietary intake may have played a role. Although the mean increase of fruit and vegetable intake over time was similar between the intervention groups of these two studies (PPT=1.5-2.0 servings/1000kcal, WHEL subgroup =1.86 servings/1000kcal), the mean increase of total fiber intake and decrease of percent energy from fat were considerably higher in PPT (fiber: 7-8 g/kcal; fat: 10%) than in the WHEL subgroup (fiber: 4.6 g/kcal; fat: 3.4%).

In other diet trials (Djuric et al., 2002; Maskarinec et al., 1999; Smith-Warner et al., 2000; Zino et al., 1997) that focused on increasing fruit and vegetable intake where weight loss was not a study objective, weight did not differ by study groups and intervention participants did not lose weight. In fact, in one trial (Djuric et al., 2002), participants in the high fruit and vegetable intake group actually gained on an average of 6 pounds compared to a mean loss of 5 pounds in the low-fat intake group. If fruit and vegetable intake is increased without decreasing total energy intake, weight gain is a plausible result. Also, a fruit and vegetable rich diet is not always low in energy density: the form of fruit and vegetable, cooking method, and the additional foods consumed also influence energy density of the overall diet (Rolls et al., 2004; Tohill et al., 2004).
The diet intervention trials that reported a change in weight associated with an increase in fruit and vegetable intake also reported a significant increase in total fiber intake and a decrease in percent energy from fat (Howard et al., 2006; Lanza et al., 2001). Hence it became impossible to partition the effect of each of these factors on the reported weight change. The Women’s Health Initiative (WHI) trial (Howard et al., 2006) followed 48,835 post-menopausal participants for 7.5 years and showed that an increase in total fiber intake and decrease in percent energy from fat were associated with weight loss, while fruit and vegetable intake did not influence weight loss. The WHEL Study subgroup showed a significant weight loss only in the first year of follow-up. As with the WHI, weight loss in the first year was associated strongly with an increase in total fiber intake and modestly but proportionately with a decrease in percent energy from fat, but not with an increase in fruit and vegetable intake (Table 3). Indeed, weight change is much more commonly associated with total fiber intake than it is with fruit and vegetable intake (Gropper & Acosta, 1987; Henry, Stout, & Love, 1978; Howarth, Saltzman, & Roberts, 2001; Tuomilehto, Voutilainen, Huttunen, Vinni, & Homan, 1980; Vido, Facchin, Antonello, Gobber, & Rigon, 1993; Walsh, Yaghoubian, & Behforooz, 1984).

The present study offers a number of valuable insights by examining stratified diet and weight data by baseline age and BMI categories. Dietary change in intervention participants occurred in each level of age and BMI except for percent energy from fat in the obese class-II. Nevertheless, body weight did not differ between the groups in any of these instances. In both groups, older women (≥55 years) generally had a higher fruit and vegetable intake, lower total fiber intake, and lower intake of energy from fat than younger women (<55 years). Also, fruit and vegetable intake and total fiber intake were
lower and percent energy from fat higher as the baseline BMI increased. Intervention participants, irrespective of age and BMI categories, changed their diet the most in the first year of follow-up. Afterwards, the dietary differences between the groups decreased as the follow-up time increased. Finally, the age-stratified weight among the control group corroborated known trends (Williamson, 1993): mean weight monotonically increased in the <55 years age group and decreased in ≥55 years age group as follow-up time progressed (data not shown).

The notion that an increased fruit and vegetable consumption may reduce the incidence of obesity is based on data from both epidemiological studies (He et al., 2004; Newby et al., 2003) and clinical trials (Epstein et al., 2001; Singh et al., 1994). Despite the advantage of superiority in design, the results of the clinical trials in question may not be extrapolated to a broader U. S. population. One trial (Singh et al., 1994) was conducted in a population in which being a vegetarian is the norm. Participants were also required to restrict their daily energy intake (Epstein et al., 2001), were followed for shorter duration (6 months (Singh et al., 1994) to 1 year (Epstein et al., 2001)), and were small in number (Epstein et al., 2001) (n=27). Of the epidemiological studies (He et al., 2004; Newby et al., 2003; Togo, Osler, Sorensen, & Heitmann, 2004) that examined the relationship between fruit and vegetable intake and obesity, the Nurses Health Study (NHI) (He et al., 2004) is the largest. In that study, women in the highest quintile of fruit and vegetable intake change had a 24% lower risk of becoming obese in 12 years compared to women in the lowest quintile of change. It is possible, however, that these two groups of women were so dissimilar from one another, both in observed and unobserved attributes, that the difference in fruit and vegetable consumption (median: 9.3
vs. 2.6 servings/d) was simply a correlate of that dissimilarity. In the present study, with limited confounding due to study design, the incidence of obesity was similar in control and intervention groups, and other studies, both cohort (Togo et al., 2004) and clinical trials (Rock et al., 2001), also support this finding. Finally, even if we assume that no residual confounding existed in the NHI, the difference of fruit and vegetable intake between top and bottom quintiles was more than double the difference reported between the groups of the present study (6.7 vs. 3.0 servings/day).

This study has strengths as well as limitations. The first and foremost of the strengths is its clinical trial design, whereby randomization theoretically distributes all attributes of the study participants, both measured and unmeasured evenly between the groups. The only difference was that one group received a dietary intervention and the other did not. Hence the findings that the dietary differences between the groups were not associated with any difference in weight or obesity incidence were most probably unconfounded. Although tamoxifen usage was slightly higher in the intervention group, it is unlikely that it influenced body weight; most studies (Day et al., 1999; Fisher et al., 1996; Kumar et al., 1997; Lankester, Phillips, & Lawton, 2002) including in WHEL Study (Saquib et al., In process), have found that tamoxifen use is not associated with weight change. Unlike many other studies that use self-reported weight and height (He et al., 2004; Newby et al., 2003; Togo et al., 2004), this study used measured body weight and height. Hence, the accuracy of outcome measures was higher. Although systematic underreporting of dietary intake is common among the obese (Caan et al., 2000); it should not be of concern in this WHEL Study subgroup, for the obese were distributed evenly between the groups due to randomization. Finally, although it is possible that
intervention participants reported their diet differently than the controls, it itself is not likely to account for the dietary difference reported between study groups for plasma levels of various carotenes, biomarkers of fruit and vegetables consumption, were also found to have increased significantly among intervention participants by one year of follow-up (Pierce et al., 2006). Further, accurate dietary assessment cannot be assumed, and all methodologies have well-known limitations.

This WHEL Study subgroup differed in their dietary practices from their age and year matched cohort in the U.S. general population (GP) (USDHHS, 2000). For example, the frequency of participants that consumed 3 servings of fruit and vegetables (WHEL subgroup: 69% vs. GP: 49%) and <30% energy from fat (WHEL subgroup: 58% vs. GP: 33%) were higher among WHEL participants—indicators suggestive of higher health consciousness. In addition, WHEL participants were overwhelmingly white, highly educated, and predominantly employed. Hence the results reported in this study may not be generalizable to the population at large. Finally, it is not known what impact missing follow-up data could have had on the study results. Participants whose data were missing were comparatively younger and heavier and were more likely to have stage IIIA cancer. This study was, however, about discerning group differences and so the concern was whether attrition rate varied between the groups, which it did not (control: 13%, intervention: 15%) (data not shown).

In conclusion, the present study adds to the evidence that without a specific goal of energy restriction, an increase in consumption of fruit and vegetables may not promote weight loss in free living people.
Acknowledgements

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**Table 2.1.** Comparison of baseline characteristics between the control and the intervention groups: The Women’s Healthy Eating and Living (WHEL) study; N=1510.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control (n=760)</th>
<th>Intervention (n=750)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54.5 ± 8.4</td>
<td>54.4 ± 8.4</td>
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</tr>
<tr>
<td>Body mass index (kg/m²)</td>
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<td>Time elapsed since cancer diagnosis (months)</td>
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<td>24.5 ± 12.2</td>
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<td>≥ 65</td>
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<td>Body mass index categories</td>
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<td>55.3</td>
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<tr>
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<td>70.0</td>
<td>69.6</td>
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Table 2.1 (cont’d)

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<th>Intervention (n=750)</th>
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<td>mean ± sd</td>
<td>mean ± sd</td>
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<td>0-19 gm/d</td>
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<tr>
<td>Using at study entry</td>
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Mean and standard deviation for continuous variables and frequency for categorical variables are presented.
Table 2.2. Longitudinal data analyses; the Women’s Healthy Eating and Living (WHEL) study.
<table>
<thead>
<tr>
<th>Group</th>
<th>Fruit &amp; Vegetables (servings/day/1000 kcal)</th>
<th>Total Fiber (g/day/1000 kcal)</th>
<th>Percent Energy from Fat</th>
<th>Body Weight (kilogram)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>p</td>
<td>β</td>
<td>p</td>
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<tr>
<td>Int†</td>
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<td>0.33</td>
<td>0.06</td>
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<tr>
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</tr>
<tr>
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<td>&lt;.0001</td>
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<td>&lt;.0001</td>
</tr>
<tr>
<td>Year 2</td>
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<td>0.45</td>
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</tr>
<tr>
<td>Year 3</td>
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<td>0.002</td>
<td>0.51</td>
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<tr>
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<td>&lt;.0001</td>
</tr>
</tbody>
</table>

*N=1510, Participants with baseline body mass index <25 kg/m² and no weight data at all follow-up visits have been excluded in the analyses.

†Int: Intervention; β= Beta coefficient; p=p-value.
Group (ref= control); Time (ref= baseline)
Table 2.3. Adjusted associations* of dietary changes with weight change† in the first year of follow-up. The Women’s Healthy Eating and Living (WHEL) study, N=1510.

<table>
<thead>
<tr>
<th>Age (years)</th>
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<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>20-44</td>
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<tr>
<td>45-54</td>
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<td>55-64</td>
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<table>
<thead>
<tr>
<th>Body mass index‡</th>
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<th>p-value</th>
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<tbody>
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<td>25-29.9</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>29.9-34.9</td>
<td>-0.18(0.29)</td>
<td>0.54</td>
</tr>
<tr>
<td>≥35</td>
<td>-0.69(0.33)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Race/ethnicity</th>
<th>Coefficient estimate (SE)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>0.04(0.54)</td>
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<tr>
<td>Asian</td>
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<tr>
<td>Hispanic</td>
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<td>0.73</td>
</tr>
<tr>
<td>Other</td>
<td>2.64(0.78)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fruit and vegetables (servings/day)</th>
<th>Coefficient estimate (SE)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-0.01(0.05)</td>
<td>0.81</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Energy from fat, %</th>
<th>Coefficient estimate (SE)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.05(0.02)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fiber (gram/day)</th>
<th>Coefficient estimate (SE)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-0.08(0.02)</td>
<td>&lt;0.0001</td>
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</tbody>
</table>

* Model is also adjusted for randomization status and change in total energy intake from baseline to year one; r-square=0.07.
†Change for consumption of fruit and vegetables, fiber, energy from fat, and body weight was calculated by taking the difference between baseline and year one follow-up value.
‡Measured as weight kg/height (m²).
SE: standard error
Figure 2.1 (a, b, c, d).

Mean consumption of fruit and vegetables, total fiber, and percent energy from fat and mean body weight in the control and in the intervention group over the study period: The Women’s Healthy Eating and Living (WHEL) study; N=1510. Participants with baseline body mass index <25 kg/m² and no weight data at all follow-up visits have been excluded in the analyses.
Figure 2.2

Incidence of obesity in the control and in the intervention group over the study period. The Women’s Healthy Eating and Living (WHEL) study; N=838. Only the overweight (24.99<BMI<29.99 kg/m²) at baseline were included in the analyses; error bar = standard deviation.
References for research paper II


Research Paper III (references included)

The impact of a long term reduction in energy density of the diet

on body weight within a randomized diet trial
Abstract

We examined the effect of change in dietary energy density on body weight in participants of a randomized trial in which the intervention group markedly increased fruit and vegetables intake while reducing energy intake from fat. Participants were 3088 breast cancer survivors, aged 26-74 years, with a mean body mass index (BMI) of 27.3 kg/m² (SD=6.3) at baseline. Dietary intake was assessed by 24-hour dietary recalls and validated with plasma carotenoids concentrations. Weight and height were measured at baseline and at follow-up (years 1 and 4). Energy density of the diet was calculated using six different methods. Dietary energy density among intervention participants, irrespective of calculation method, decreased significantly compared to controls and was maintained over the follow-up period in both cross-sectional ($p < 0.0001$) and longitudinal (group by time interaction $p < 0.0001$) analyses. Total energy intake or physical activity did not vary between the groups. Intervention group had a small but significant weight loss at one year (group by time interaction $p < 0.0001$) but there was no between-group weight difference at 4 years. Reducing energy density of diet without a reduction in total energy intake is not sufficient to promote long-term weight loss in a free-living population.
Introduction

Fiber, water, and fat are the three most important determinants of energy density of the diet. Although much depends on preparation methods, fruit and vegetables, in general, are low in energy density due to their high fiber and water content. It has been observed that the volume of an individual’s dietary intake remains more or less constant, which has led to the hypothesis that people may regulate their food intake based on volume rather than total energy. Accordingly, replacing energy-dense high-fat food with much less energy dense fiber-rich food such as vegetables and fruit should result in a reduction of energy intake and weight loss.

Various cross-sectional studies have found that individuals who eat high-energy-dense foods consume more energy and are relatively heavier than those who consume proportionately greater amounts of low-energy-dense foods. Energy density of the diet has been manipulated in a number of feeding studies, and results of those studies have suggested that a decrease in energy density is associated with weight loss. However, the results of these feeding studies may not be generalizable to free living populations because they are characterized by short duration, target participants motivated to lose weight, and can exert control over the type of food available.

Ad-libitum randomized trials that have encouraged participants to increase their fruit and vegetable intake and/or decrease their fat intake have had mixed results in terms of the amount of validated dietary change as well as weight change. None of these trials reported the energy density of the diets in the intervention and control groups, and thus it is possible that those studies that did not observe a weight change may not have achieved a significant change in dietary energy density.
In this analysis, we investigate the relationship between change in energy density of the diet and body weight in the Women’s Healthy Eating and Living (WHEL) study, a large-scale randomized diet intervention trial (n=3088) that closely monitored dietary pattern, physical activity, and weight change over a 6-year period \(^{24}\). Participants in the WHEL Study intervention group significantly increased their fruit, vegetable, and fiber intake \(^{25,26}\), a pattern characterizing a low-energy density diet. A number of different methods have been proposed for measuring energy density \(^{27}\) and the WHEL Study has the necessary data to test each method of calculation. In this study, we compare dietary energy density between the intervention and the control groups at study entry and demonstrate the reported association between energy density of the diet and body weight using cross-sectional data. Then, we investigate the relationship of change in energy density of the diet to change in weight between study groups up to 4 years post-randomization.

**Materials and Methods**

**Population**

Study participants were women previously treated for breast cancer and enrolled in the Women’s Healthy Eating and Living (WHEL) Study (n=3088)—an ongoing, multi-site clinical trial designed to determine the efficacy of a dietary intervention in reducing breast cancer recurrence and death. The WHEL Study protocol has been described in detail elsewhere \(^{24}\). Briefly, participants were aged 18-70 years at the time of cancer diagnosis; had completed initial treatment for primary, operable, and invasive stage I, II, or IIIA breast carcinoma within 4 years of study entry; were not receiving or scheduled for chemotherapy at the time of study entry, and with no evidence of cancer
recurrence since completion of initial treatment. Enrollment in another dietary trial, pregnancy, receiving estrogen replacement therapy, and presence of life-threatening medical conditions or diseases were key exclusion criteria.

This analysis used baseline, 1-year, and 4-year follow-up data. All women enrolled in the WHEL Study were eligible for the present study. Dietary data at baseline, 1 year, and 4 years were available for 3088, 2670, and 2328 women respectively; 453 participants (14%) lacked data on body weight at both follow-up assessments because of recurrence, death, or voluntary non-participation.

Dietary intervention

Participants in the intervention group were encouraged to maintain a dietary pattern that included a daily consumption of at least 5 vegetable servings, 16 ounces of vegetable juice (or equivalent vegetable servings), 3 fruit servings, 30 grams of fiber (18 g/1000 kcal), and 15-20% energy from fat. Telephone counseling, monthly cooking classes, and newsletters were the principal methods to promote dietary change in the intervention participants. Control group participants received print materials that included dietary guidelines from the U.S. Department of Agriculture and the National Cancer Institute and a bimonthly cohort maintenance newsletter with general health and nutrition information unrelated to the intervention group’s dietary goals.

Dietary assessment

Dietary intake was assessed through a set of four 24-hour dietary recalls. Trained dietary assessors conducted these recalls by telephone on randomly selected days, stratified for weekend vs. weekdays, over a 3-week period. Dietary recalls were administered to the participants at study entry and at year 1 and at year 4. The Nutrition
Data System for Research (NDS-R) software was used to collect and estimate dietary intakes (NDS-R version 6.0, 2006, University of Minnesota, Minneapolis, MN). NDS-R included more than 18,000 food codes, including many ethnic foods and over 8,000 brand-name products.

A number of strategies were used to maximize the accuracy of dietary recall data. Dietary assessors completed a training program that included standardized data collection, proper interview technique, and efficient use of dietary analysis software. Participants were trained, before study enrollment, to estimate serving sizes with food models, measuring cups and spoons, and were provided with two-dimensional food models for reference during recalls. In addition, assessors used a multi-pass method that improved recall accuracy by prompting to obtain detailed data about type, amount, and preparation method of foods eaten.

Calculation of energy density of the diet

A participant’s dietary energy density (kcal/g) (1 kcal = 4.18 kJ) for any particular day is determined by estimating total energy intake (kcal) for that day and dividing it by the total amount (g) of food and/or beverages reported being consumed on that day. Energy density values of the set of four days were averaged to derive a mean dietary energy density value for each participant. As there appear to be significant day- to-day variations of beverage intake within individual respondents, we focused on the estimate from ‘food only’ sources, i.e. excluding all beverages. However, we present estimates using all six different combinations of food and beverages. These are: (a) food only, (b) food + alcohol, (c) food + juice, (d) food + milk, (e) food + milk + juice, and (f)
food + energy-containing beverages. As previously recommended, water and energy-free beverage are not considered in these calculations.\(^8,27\)

Alcohol included alcoholic beverages such as beer, wine, and liquor. Both fruit and vegetables juices were considered in calculating juice intake. Milk and various dairy food beverages constituted milk intake. Energy-free beverages and very low-energy beverages [\(<5\, \text{kcal/100 g}\) (1 kcal = 4.18 kJ), such as diet soda, coffee, and tea, were excluded among the energy-containing beverages. Energy density values were normally distributed for each of the calculation methods.

**Physical activity assessment**

Physical activity was determined from the Personal Habits questionnaire developed for Women’s Health Initiative\(^{31}\), expressed as metabolic equivalents (METs) per week\(^{32}\), and assessed at each clinic visit. This questionnaire has been calibrated with the standard physical activity recall\(^{33}\) and validated with an accelerometer reading\(^{34}\).

**Ascertainment of body weight**

Weight and height were measured—with the participants wearing light clothing and no shoes—during clinic visits (baseline, year 1, and year 4) scheduled in the WHEL Study. Body mass index (BMI) was calculated as weight (kg)/height (m\(^2\)).

**Covariates**

Standard questionnaires administered at baseline ascertained demographic characteristics. Potential co-variables examined included age (<44, 45-54, 55-65, and ≥ 65 years), race/ethnicity (non-Hispanic white, African-American, Hispanic, Asian-American, and other), BMI (<25, 25-29.9, and ≥ 30 kg/m\(^2\)), total fruit and vegetables (servings/d), and percent energy intake from fat.
Validation of dietary intake with biomarkers

Plasma carotenoids are well-known biomarkers of fruit and vegetable intake. The WHEL Study measured plasma carotenoids at baseline and at follow-up visits and has published plasma carotenoids measurement procedures and baseline to 1-year results [25]. In this analysis, we examined total plasma carotenoids concentrations in a 27% random sample at baseline, 1 year, and 4 years. The variable total plasma carotenoids is the sum of the individual carotenoid separated and quantified (α-carotene, β-carotene, β-cryptoxanthin, lycopene, and lutein plus zeaxanthin) using high-performance liquid chromatography methodology [25]. The mean day-to-day coefficient of variation for total plasma carotenoids was less than 7%.

Informed written consent from study participants was collected in the WHEL Study. The Human Subjects Committee of the University of California, San Diego, and all participating institutions approved the study procedures.

Statistical Analyses

We compared energy density of the diet obtained from the six different methods described above and estimated the level of observed difference between study groups at baseline, 1 year and 4 years from each method.

To assess covariates of energy density, mean baseline values for the ‘food only’ calculation were determined for categories of age, race/ethnicity, and BMI. For any one variable, one-way ANOVA was used to compare mean values of different categories against a referent category. Next, participants were grouped into tertile of baseline dietary energy density. Mean values of total energy intake, physical activity, and body weight were calculated for each tertile and were compared against one another after setting the
lowest tertile as referent. Bar charts of group-specific dietary energy density, total energy intake, physical activity, and body weight were constructed at baseline and at 1 and 4 years of follow-up. We used t-tests to compare the corresponding values between the intervention and the control group for any time point.

Finally, mixed effect models were used to assess change in energy density, total plasma carotenoids, total energy intake, physical activity, and body weight over the study follow-up period; they are the best option available for such analyses given the correlations among repeated measurements within a participant and the ability of this model to handle random missing values. To find a suitable covariance structure, correlations and variances over time were examined for each variable modeled. Each model was run with the same fixed effect but different covariance structure such as toeplitz, unstructured, and autoregressive; the model that had the smallest Akaike’s Criterion (AIC) value was considered the best and was selected for use.

All calculations were performed using SAS version 8.2 (Cary NC: SAS Institute). All statistical tests were two-tailed with an alpha level of 0.05.

**Results**

The 3088 women in the WHEL study were successfully randomized into two groups with no significant differences in any of the key variables for this study. Women were 27 to 74 years of age at study entry (mean age 53.2, standard deviation [SD] = 9.0). The mean BMI was 27.3 (SD = 6.3); 57% were overweight or obese. Although predominantly non-Hispanic white (85%), the cohort also included a small but varied group of minority women (African American: 4%, Asian-American: 3%, Hispanic: 5%, other ethnicities: 3%). Well-educated (college graduate (54%) and
predominantly employed (72%), 69% of the WHEL women were also married. Only a small percentage (5%) was diagnosed with either stage IIIA cancer or was currently smoking. Approximately one-quarter (28%) of all women reported having stable weight throughout their adult lives, and 32% reported no alcohol consumption. The mean energy intake and physical activity were 1717 kcal/d (SD=407) and 868 METs/week (SD=879), respectively (data not shown). Further, there was no significant difference in mean dietary energy density between the intervention and the control participants at baseline, irrespective of determination method (Table 1).

Using the ‘food only’ method of measuring of energy density of the diet, at study entry, energy density was inversely associated with categories of age (1.58, 1.51, 1.44, and 1.40 for <44, 45-54, 55-64, and ≥ 65 years respectively; p for trend: <0.0001) and was directly associated with BMI (1.42, 1.51, and 1.57 for <25, 25-29.99, ≥ 30 kg/m² respectively; p for trend: <0.0001). Asian-American participants reported the highest intake of fruit and vegetables and the lowest energy intake from fat, making the energy density of their diets significantly lower than any other racial/ethnic group (1.48, 1.66, 1.54, 1.32, and 1.48 for non-Hispanic white, African-American, Hispanic, Asian-American, and Others respectively) (data not shown). There were strong linear trends (p <0.0001) across the tertiles of energy density, with energy intake and body weight having strong positive associations and physical activity having a strong negative association. Participants in the highest tertile of energy density reported, on average, total energy intake that was approximately 300 kcal/d (1 kcal = 4.18 kJ) higher and physical activity that was 450 METs/week lower than participants in the lowest tertile; mean body weight differed by 6.5 kg between these two tertiles (Table 2).
A significant difference in energy density of the diet was found between the study groups at both follow-up time points (p-values <0.0001); at one year, the intervention group reported consuming a diet that was 25% less energy dense (25%, 24%, 22%, 28%, 23%, and 25% for ‘food only’, ‘food + alcohol’, ‘food + energy beverage’, ‘food + juice’, ‘food + milk’, and ‘food + juice + milk’ methods respectively) than the control group. At year 4, this difference was still highly significant but had declined to 15% (16%, 15%, 18%, 15%, 14%, and 16% for ‘food only’, ‘food + alcohol’, ‘food + energy beverage’, ‘food + juice’, ‘food + milk’, and ‘food + juice + milk’ methods respectively) (data not shown). The multivariate analysis (Table 3) shows that these study group differences in energy density were statistically significant at both the 1 year and 4 year time points (p-value for group by time interaction <0.0001). The biomarker for vegetable/fruit intake, total plasma carotenoids, confirmed the study group differences for fruit and vegetable intake; in the 27% random sample, there was a 66% difference between groups at 12 months assessment period and a 39% difference at 48 months assessment period. Further, in the control group, these carotenoids values remained relatively stable (averaging 2% and 7% increase at 1 and 4 years, respectively).

The mean data for energy intake, physical activity, and body weight for study groups at baseline and both follow-up periods are presented in Figure 1 and Table 3. At baseline, the intervention group had a very slightly higher mean weight than the control group (+0.2%). At the 12 month time point, the control group had increased by 0.69 kg whereas the intervention group had decreased by 0.03 kg, so that the mean weight in the intervention group was 0.7% lower than the control. The multivariate analysis identified this as statistically significant (group by time interaction: <0.0001). At the 4 year time
point, both groups had gained weight and the mean weight for the intervention group was
0.7% higher than the control group. The multivariate analysis did not identify this as
statistically significant (group by time interaction: 0.23).

Reported energy intake was essentially the same at both baseline and 1 year time
points and there was a non-significant 1.4% difference between groups at 4 year time
point. At baseline, the intervention group undertook 6% less physical activity than the
control group. While both groups reported some increase in physical activity, the
intervention group was 3.6% lower than the control group at 1 year and 0.3% lower at
year 4. This change in physical activity was borderline significant at the 4 year time point
(group by time interaction: 0.04).

Discussion

The WHEL randomized trial achieved a major difference in dietary pattern
between the study groups\textsuperscript{26} that has been validated using plasma carotenoids
concentrations as a biomarker of vegetable and fruit intake\textsuperscript{25}. The change in dietary
pattern in the intervention group resulted in a large difference in the energy density of the
diet, regardless of how this energy density was calculated. Although there was evidence
of some decline in the intervention effect through 4 years, there were still large and
statistically significant differences between the study groups in energy density of the diet
at that time point. Thus, the study provides an opportunity to test the hypothesis that a
change in energy density will be associated with weight change.

In this study, the development of a 25% between group differences in energy
density of the diet at one year was associated with small (0.7%) difference in weight in
the hypothesized direction. However, maintenance of this low-energy density dietary
pattern through 4 years was not associated with a maintained lower weight in the intervention group. Although the 12-month weight difference was statistically significant, it did not reach a level that would be considered clinically meaningful. Accordingly, this evidence does not support the hypothesis that a major reduction in the energy density of the diet will independently result in a reduction in body weight.

A key component of the energy density hypothesis is the assumption that people who change to a low-energy density dietary pattern will regulate their food intake by volume rather than by total energy. This did not appear to occur in this population. Although the intervention group increased their vegetable and fruit intake substantially, there was no evidence that they changed their total energy intake at either the one-year or four-year time-point.

These results are different from those in the only other trial in the literature that examined a longitudinal association between energy density of the diet and body weight. However, that study only enrolled overweight and obese participants and the intervention focused on the amount as well as the type of food consumed to achieve a weight loss goal. That focus on the volume of food to be consumed means that the study could not truly address whether a change in energy density necessarily results in a change in the volume of food eaten.

All dietary studies need to address measurement error. Although low-energy reporting is more common among overweight, among smoker, among black, among younger, and among those who want to lose weight, it should not be of concern in the present study, for these attributes were distributed evenly between the groups due to randomization. A more important issue is whether intervention participants were more
prone to bias in reporting their food intake. Difficulties and challenges to change
behavior and then to maintain that behavioral change for a considerable period have been
acknowledged. Also, intervention group participants may feel pressure to fulfill the
dietary goals. It is not known how these two factors—one being the challenges to change
behavior, the other being a desire to be seen as following study protocol—may have
influenced accuracy of dietary assessment. A number of studies actually report higher
frequency of low-energy reporting in the intervention group, and the trend is more
prevalent among men than among women. Lastly, although the days of the dietary
recalls were selected randomly, to ensure maximum participation, all participants knew
the date and timing of telephone interview beforehand. The foreknowledge of the
interview dates may have influenced participants, especially those in the intervention
group, to consume differently in the preceding 24 hours. While the possibilities of
differential dietary reporting between groups are acknowledged, they themselves are not
likely to account for the dietary difference observed between study groups: total plasma
carotenoids—a biomarker of fruit and vegetables consumption—increased significantly
among intervention participants throughout the follow-up period but remained unchanged
in the control group (Table 3).

This study has a number of strengths. The first and foremost is its clinical trial
design, whereby randomization theoretically distributes all attributes of the study
participants, both measured and unmeasured, evenly between the groups. The only
difference was that one group received a dietary intervention and the other did not. Hence
the findings that the dietary energy density difference between the groups was not
associated with a difference in weight was most probably un-confounded. Unlike many
other studies that used self-reported weight and height \(^{44-46}\), this study used measured body weight and height. Hence, the accuracy of outcome measures was higher. Finally, the cross-sectional associations of dietary energy density described in this report are consistent with findings from previous studies \(^{10,11,27,47}\).

In conclusion, the intervention efforts utilized in this randomized trial achieved a major reduction in the energy density of the diet in the intervention group and provides evidence that such a change in dietary pattern, without being associated with a change in the energy balance (total energy intake versus expenditure), is not sufficient to result in a meaningful change in weight in free-living individuals. As a strategy to specifically reduce total energy intake, a focus on reducing the energy density of the diet may be a useful component of weight management. However, changing this characteristic of the diet out of the context of aiming to reduce energy intake to promote weight loss does not appear to result in reduced energy intake and consequent weight loss.

**Acknowledgements**

The dissertation author was the primary investigator and the first author and Dr. Loki Natarajan, Dr. Cheryl L Rock, Ms. Shirley Flatt, Dr. Lisa Madlensky, Ms. Sheila Kealey, and Dr. John P Pierce were the co-authors of this paper. This study was initiated with the support of the Walton Family Foundation and continued with funding from NCI grant CA 69375. Some of the data were collected from General Clinical Research Centers, NIH grants M01-RR00070, M01-RR00079, and M01-RR00827. The authors thank Christine Hayes for her editorial support.
Table 3.1. Comparison of energy density\(^1\) of the diet by randomization status at baseline; energy density was calculated with six different methods. The Women’s Healthy Eating and Living (WHEL) Study (n=3082).

<table>
<thead>
<tr>
<th>Group</th>
<th>Control (n = 1547)</th>
<th>Intervention (n = 1535)</th>
<th>Significance(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SEM(^3)</td>
<td>Mean ± SEM(^3)</td>
<td>(p-value)</td>
</tr>
<tr>
<td>Food only</td>
<td>1.49 ± 0.01</td>
<td>1.48 ± 0.01</td>
<td>0.3</td>
</tr>
<tr>
<td>Food + Alcohol</td>
<td>1.46 ± 0.01</td>
<td>1.44 ± 0.01</td>
<td>0.3</td>
</tr>
<tr>
<td>Food + Juice</td>
<td>1.38 ± 0.01</td>
<td>1.37 ± 0.01</td>
<td>0.4</td>
</tr>
<tr>
<td>Food + Milk</td>
<td>1.36 ± 0.01</td>
<td>1.36 ± 0.01</td>
<td>0.7</td>
</tr>
<tr>
<td>Food + Energy beverages(^2)</td>
<td>1.40 ± 0.01</td>
<td>1.38 ± 0.01</td>
<td>0.1</td>
</tr>
<tr>
<td>Food + Juice + Milk</td>
<td>1.28 ± 0.01</td>
<td>1.27 ± 0.01</td>
<td>0.7</td>
</tr>
</tbody>
</table>

\(^1\) 24 Hour dietary recalls were used to obtain dietary information via telephone interview. Food included both solid and liquid food; Alcohol included beer, wine, and liquor; Juice included both fruit and vegetable juice; Milk included milk and other dairy food beverages.

\(^2\) Energy beverages included any beverage that provides > 5 kcal/100 g (1 kcal = 4.18 kJ).

\(^3\) SEM: standard error of the mean.

\(^4\) T-tests were employed to examine group differences.
Table 3.2. Energy intake, physical activity, and body weight by tertile of energy density of the diet calculated at baseline; n=3082

<table>
<thead>
<tr>
<th>Energy density (Food only)</th>
<th>Bottom Tertile &lt;1.30 kcal/g</th>
<th>Middle Tertile 1.30 – 1.61 kcal/g</th>
<th>Top Tertile ≥1.62 kcal/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SEM²</td>
<td>1570 ± 10.7</td>
<td>1704 ± 11.5 b</td>
<td>1874 ± 13.7 c</td>
</tr>
<tr>
<td>Total energy intake (kcal¹/day)</td>
<td>1086 ± 29.3</td>
<td>895 ± 29.4 b</td>
<td>633 ± 22.9 c</td>
</tr>
<tr>
<td>Physical activity (METs/week)³</td>
<td>70.3 ± 0.48</td>
<td>72.9 ± 0.52 b</td>
<td>77.0 ± 0.55 c</td>
</tr>
</tbody>
</table>

Reference: Bottom tertile; values with different superscript letters are significantly different (p<0.05);
¹1 kcal = 4.18 kJ.
²SEM: standard error of the mean.
³METs: Metabolic Equivalent Tasks. Sum of METs assigned as: 2 METs per minute of casual strolling, 3 METs per minute of mild activity or average walking, 4 METs per minute of fast walking, 5 METs per minute of moderate walking, 6 METs per minute of very fast walking, 8 METs per minute of strenuous activity.
**Table 3.3.** Changes in energy density, total energy intake, physical activity, and body weight over the study follow-up period; The Women’s Healthy Eating and Living (WHEL) Study.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Group</th>
<th>Baseline Mean ± SEM(^2)</th>
<th>Year 1-Baseline Mean ± SEM(^2)</th>
<th>Year 4-baseline Mean ± SEM(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy density</td>
<td>Control</td>
<td>1.49 ± 0.01</td>
<td>-0.03 ± 0.01</td>
<td>0.05 ± 0.01</td>
</tr>
<tr>
<td>(Food only)</td>
<td>Intervention</td>
<td>1.48 ± 0.01</td>
<td>-0.35 ± 0.01***</td>
<td>-0.22 ± 0.01***</td>
</tr>
<tr>
<td>Total plasma carotenoids</td>
<td>Control</td>
<td>2.47 ± 0.04</td>
<td>-0.07 ± 0.03</td>
<td>-0.10 ± 0.04</td>
</tr>
<tr>
<td>(µmol/L)</td>
<td>Intervention</td>
<td>2.40 ± 0.03</td>
<td>1.59 ± 0.05***</td>
<td>0.94 ± 0.06***</td>
</tr>
<tr>
<td>Energy intake</td>
<td>Control</td>
<td>1716 ± 10.5</td>
<td>-118 ± 10.4</td>
<td>-152 ± 11.2</td>
</tr>
<tr>
<td>(kcal(^1)/day)</td>
<td>Intervention</td>
<td>1718 ± 10.2</td>
<td>-117 ± 11.0</td>
<td>-171 ± 12.2</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Control</td>
<td>892 ± 23.0</td>
<td>63.4 ± 20.8</td>
<td>25.7 ± 24.4</td>
</tr>
<tr>
<td>(METs/week(^3))</td>
<td>Intervention</td>
<td>843 ± 22.5</td>
<td>79.4 ± 20.0</td>
<td>72.3 ± 26.7*</td>
</tr>
<tr>
<td>Body weight</td>
<td>Control</td>
<td>73.4 ± 0.4</td>
<td>0.69 ± 0.11</td>
<td>1.42 ± 0.20</td>
</tr>
<tr>
<td>(kg)</td>
<td>Intervention</td>
<td>73.6 ± 0.4</td>
<td>-0.03 ± 0.12***</td>
<td>1.76 ± 0.23</td>
</tr>
</tbody>
</table>

Mixed effect models were used to examine difference of change between groups from baseline. P-values (*<0.05 **<0.01 ***<0.0001) were computed for testing group by time interaction for each variable.

\(^1\) 1 kcal = 4.18 kJ.

\(^2\) SEM: standard error of the mean.

\(^3\) METs: Metabolic Equivalent Tasks. Sum of METs assigned as: 2 METs per minute of casual strolling, 3 METs per minute of mild activity or average walking, 4 METs per minute of fast walking, 5 METs per minute of moderate walking, 6 METs per minute of very fast walking, 8 METs per minute of strenuous activity.
Figure 3.1 (a, b, c, and d)

Mean energy density (food only), energy intake, physical activity, and body weight in the control and in the intervention group over the study period: The Women’s Healthy Eating and Living (WHEL) Study; 1 kcal = 4.18 kJ.
References for Research Paper III


10. de Castro JM: Dietary energy density is associated with increased intake in free-living humans. *J Nutr* **134**:335-41, 2004
11. Kant AK, Graubard BI: Energy density of diets reported by American adults: association with food group intake, nutrient intake, and body weight. *Int J Obes* (Lond) **29**:950-6, 2005


29. NCI: Action guide for healthy eating. Bethesda, MD, National Cancer Institute, 1995, pp NIH publication no. 95-3877


General Discussion:

Research Papers I, II, and III (references included)
This study’s analysis of data from the Women’s Healthy Eating and Living (WHEL) Study supported previous studies’ findings [1-6] of weight gain in breast cancer patients on chemotherapy. It also showed that the magnitude of such weight gain was clinically meaningful [7-9], something previous studies had not examined [1-6]. The study further contributed to the literature by demonstrating that significant relative weight gain occurred irrespective of type or regimen of chemotherapy and that the magnitudes of gain according to type or regimen were not significantly different from one another. Previously, only a few studies had examined whether weight gain varied by type of chemotherapy and those studies produced mixed results [10-12].

Clear consensus has also not existed in the literature as to whether use of anti-estrogen Tamoxifen [13-20] is associated with weight gain. This analysis of the WHEL data found, like a number of the previous studies, that Tamoxifen was not associated with weight gain [13, 17-20]. Further, as with the only previous study [20] examining the interaction effect between Tamoxifen and type of chemotherapy in causing weight gain, no interaction effect was found in WHEL subjects.

The present study also explored factors that might define a high-risk population for weight gain among chemotherapy patients. It did so by examining separately for breast cancer survivors who had chemotherapy and those who did not, associations between weight gain and demographic characteristics such as age and race, physical characteristics (BMI) and cancer stage. The associations did not vary according to chemotherapy use.
The results of the present study are convincing because it had access to extensive and elaborate medical records on treatment and tumor characteristics, used measured as opposed to self-reported weight, followed participants and collected data on dietary practices and physical activity over a considerable period of time, and used a sample large enough to allow it to control for potential confounders. The study, nonetheless, has limitations. It could not control for steroid use – a potent stimulator of temporary weight gain [21]– and it used a cohort of breast cancer survivors that was highly educated and under-representative of minorities; hence, the sample was not representative of breast cancer survivors in general.

The participants in the WHEL Study were instructed to neither restrict their caloric intake nor lose weight. In this context, it seems reasonable that only 10% of those breast cancer survivors who had gained significant relative weight (≥ 5%) by study entry ever returned to their pre-cancer weight during follow-up (6 years). Research indicates that once weight is gained the human body accommodates itself physiologically to the new weight. Without motivation and active intervention, it does not return to the initial weight [22, 23].

The creation of an environment in which the body experiences chronic energy deficit is mandatory to lose weight [24]. Energy deficit, in theory, can be achieved either by reducing energy intake or by increasing energy expenditure or by both measures simultaneously. Results from clinical intervention studies demonstrate that changes in energy intake may have a greater impact on body weight than exercise alone [25, 26] – a surrogate of total energy expenditure – though there are studies that suggest exercise can be as effective as diet for precipitating weight loss [27]. Weight loss through chronic
energy deficit works in the short term but frequently fails in the long term [24, 28]. The reason is that when the body is subjected to chronic energy deficit it triggers various physiologic compensatory mechanisms such as hunger and thirst to overcome the deficit. A strong motivation is needed to deny the body fulfillment of its desire. Vigilance regarding body weight and conscious control of eating behavior – with a change of dietary habit and/or physical activity – are crucial in achieving long-term weight loss [29].

The weight change observed between WHEL study groups over the follow-up period can be explained by energy intake and physical activity. Intervention participants reported a significant increase in their consumption of fruit and vegetables and a significant reduction in consumption of fat during follow-up. As a result, dietary energy density decreased substantially in the intervention group. Total energy intake did not, however, vary between the study groups during the same period of time. In addition, no definitive pattern of physical activity change was observed between the groups. It should be noted, however, that there are certain limitations in using physical activity as a surrogate of total energy expenditure. In most studies, including the present one, physical activity data are self-reported; hence, a certain degree of misreporting is likely. In addition, physical activity is a poor maker of total energy expenditure as it accounts for only 20% of it [25, 27, 30]; the lion’s share is determined by resting metabolic rate (70%) and, to a much smaller extent (10%), by the thermal effect of food [31]. Since weight loss was not an incentive for participating in this trial, the women in the intervention group probably did not make a conscious decision to change either their caloric intake or physical activity, even though they made the dietary changes encouraged by the
intervention. This was reflected in their weight over time. Body weight did not differ between study groups at any time during the four-year follow-up period. Although a significant difference in weight change was observed in the first year of follow-up, the magnitude of that weight change was so small as to make it of more statistical than clinical significance.

In conclusion, results from the study’s analyses show that an increase in consumption of fruit and vegetables and a decrease in consumption of energy from fat – the result being a decrease in dietary energy density – by itself, is not sufficient to result in a meaningful weight loss in a normal living population. As a strategy to specifically reduce total energy intake, a focus on reducing the energy density of the diet may be a useful component of weight management. However, changing this characteristic of the diet out of the context of aiming to reduce energy intake to promote weight loss does not appear to result in reduced energy intake and consequent weight loss.
References for Discussion: Research Papers I, II, and III


