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Fatigue reduction diet in breast cancer survivors: a pilot randomized clinical trial

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Abstract

Purpose—Fatigue is a prevalent and burdensome effect of breast cancer. Fatigue has been linked to chronic inflammation, and diets high in antioxidant nutrients have been associated with lesser prevalence and severity of fatigue. Studies are needed, however, to test if antioxidant-rich diets could improve fatigue.

Methods—Pilot, randomized, trial conducted between January 2014 and April 2015, to investigate if a 3-month diet rich in fruit, vegetables, whole grains, and omega-3 fatty acid-rich foods, named the fatigue reduction diet (FRD), improved fatigue and sleep compared to an attention control, named the general health curriculum (GHC). 30 stage 0 to III breast cancer survivors, who had completed cancer treatments, were randomized: 15 receiving the FRD and 15

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Authors' Contributions Dr. Zick made substantial contributions to conception and design, data analysis and interpretation of data, and acquisition of data; was involved in drafting the manuscript revising the manuscript critically for important intellectual content and gave final approval of the version to be published. Dr. Djuric made substantial contributions to conception and design, data analysis, and interpretation of data, was involved in revising the manuscript critically for important intellectual content and gave final approval of the version to be published. Dr. Colacino made substantial contributions to conception and design, data analysis and interpretation of data, and he was involved in revising the manuscript critically for important intellectual content and gave final approval of the version to be published. Ms. Brash, Surnow, Khabir, Cornellier, and Mr. Ren made substantial contributions to acquisition of data, and were involved in revising the manuscript critically for important intellectual content and gave final approval of the version to be published.

Conflicts of interest Drs. Zick, Djuric and Colacino and Ms. Cornellier, Surnow and Khabir declare that they have neither financial nor non-financial competing interest to disclose nor do they have any conflicts of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

the GHC. Primary outcome was change in fatigue, as measured by the brief fatigue Inventory, from baseline to 3 months analyzed using linear mixed models. Secondary analyses were changes in sleep quality, serum carotenoids, and fatty acids.

Results—From baseline to 3-month fatigue improved by $44 \pm 39\%$ in FRD compared to $8 \pm 34\%$ in GHC ($p = 0.01$); sleep quality improved by 2.5 ± 3.3 points in FRD, and diminished by 0.9 ± 2.3 in GHC ($p = 0.03$); serum total carotenoids ($p < 0.01$), β -cryptoxanthin ($p = 0.02$), lutein ($p = 0.05$), zeaxanthin ($p = 0.01$), lycopene ($p = 0.05$), omega-3 fatty acids ($p < 0.01$), and ratio of omega-3:omega-6 fatty acids ($p = 0.02$) were significantly increased, and percent saturated fatty acids were decreased ($p = 0.04$) in FRD; γ -tocopherol was significantly increased in GHC ($p = 0.03$), and there was a significant visit by group difference for α -carotene between the study groups ($p = 0.05$).

Conclusions—The FRD intervention improved fatigue and sleep in breast cancer survivors compared to the GHC. FRD diet could provide a non-toxic treatment strategy for persistent fatigue.

Keywords

Cancer-related fatigue; Sleep quality; Breast cancer survivor; Diet, omega-3 fatty acids; Fruits; Vegetables; Whole grains; Carotenoids

Background

Persistent fatigue is one of the most prevalent and burdensome late-term effects of breast cancer treatment [41, 44]. Even ten years after the completion of their breast cancer treatment, as many as one-third of breast cancer survivors experience moderate-to-severe persistent fatigue [10, 31, 38]. Persistent fatigue also often co-occurs with depression [26, 33, 45], poor sleep [3], and decreased quality of life [53], and some research suggest that more severe fatigue is independently associated with shorter times to breast cancer recurrence and shorter overall survival [29].

The etiology of persistent fatigue is currently unknown; however, research suggests that peripheral pro-inflammatory markers including cytokines and C-reactive protein (CRP) are consistently elevated in fatigued breast cancer survivors [8, 9, 20, 48]. This increased inflammation in the periphery can lead to a cascade of inflammatory response throughout the brain [22, 54] potentially causing CNS-induced sickness behavior in which fatigue plays a predominant role [35, 40]. It has been posited that diets high in antioxidants and other specific micronutrients could help to counter the elevated inflammatory state and thus help to alleviate fatigue. In several observational studies in breast cancer survivors, higher quality diets [27, 32]; diets high in fiber, lower in total fat [30], and high in fruits and vegetables [1]; and those high in omega-3 fatty acids relative to omega-6 fatty acids [2] were associated with a lower likelihood of having persistent fatigue in breast cancer survivors [2]. Likewise, we found that diets high in fatty fish, nuts and seeds, whole grains, and vegetables (in particular green leafy vegetables and tomatoes) were associated with both a lower chance of having fatigue and less severe fatigue in adult cancer survivors, and cancer survivors reporting no-fatigue had significantly higher intakes of certain antioxidant nutrients [55]. All

these studies are, however, cross-sectional and thus cannot determine if diet is improving fatigue or if higher diet quality is simply associated with other healthy behaviors such as increased exercise or achieving and maintaining a normal body weight, both of which are known to improve persistent cancer-related fatigue.

To determine if diet quality, independent of weight loss, could improve persistent cancer-related fatigue, we tested the hypothesis that a three-month randomized pilot clinical trial of a fatigue reduction diet (FRD) high in fruits, vegetables, whole grains and omega-3 rich foods (fatty fish, nuts, and seeds) compared to an attention control named the general health curriculum (GHC), which was focused on education about general health topics, could decrease persistent cancer-related fatigue and improve sleep quality. We also examined the ability of the FRD compared to the attention control group to increase serum concentrations of carotenoids and omega-3 fatty acids, while decreasing serum concentrations of omega-6 fatty acids, and if these changes in serum nutrients were associated with changes in either fatigue or sleep quality.

Methods

Subjects and eligibility

The study was approved by the University of Michigan Institutional Review Board, and written informed consent was obtained from all participants. Participants were recruited between January 2014 and April 2015 from the University of Michigan Breast Cancer Clinics (Ann Arbor, Michigan), the surrounding community or from participants of a completed study in fatigued breast cancer survivors, who had indicated that they were willing to be contacted for future studies. Eligible participants were women 18 years of age and older with a body mass index (BMI) between 18.5 and 35 kg/m², and with a diagnosis of local regional breast cancer (stage 0-IIIa), who had completed all cancer-related treatments, except for hormonal therapy and Herceptin, at least one year previously. Eligible women also had to report persistent fatigue starting on or after their cancer diagnosis and score ≥ 4 on the brief fatigue inventory (BFI) and have a low fruit and vegetable intake of less than 5.5 servings per day, not including potatoes and iceberg lettuce. Women who had a diagnosis of untreated anemia, hypo-, or hyper-thyroid; who were supplementing with omega-3 fatty acids; on medically prescribed diets; who were pregnant; wanting to become pregnant or lactating; and planning on starting or stopping any chronic supplements or medications within six weeks prior to or throughout the study were ineligible to participate. All women were asked to maintain their typical exercise program and were considered ineligible if they were planning on stopping or starting a new exercise routine during the course of the study.

Study design, blinding, randomization, allocation, and study visits

A 3-month randomized, parallel, pilot clinical trial comparing the FRD to a general health curriculum (GHC) was conducted. Because of the nature of the intervention, study staff was not able to be blinded; however, all data analyses were conducted in a blinded fashion. The randomization code was computer-generated in blocks of size 6 by the study biostatistician. Study personnel, who had no contact with participants or study data, placed the

randomization assignments in sequentially numbered opaque envelopes. Upon randomization, the next number in the sequence was chosen, and the envelope opened indicating treatment assignment.

There were three in-person research visits: screening, baseline, and 3-month (end of treatment), and six telephone counseling visits: weeks 1, 2, 3, 4, 6, 8, 10, and 12. Seven-day diet records were asked to be completed the week before the baseline and 3-month visits. BFI, Pittsburgh sleep quality index (PSQI), weight, height, sociodemographic, clinical characteristics, concomitant medications, and fasting blood samples (obtained from the arm) were collected at baseline and at the 3-month visit. Three unannounced 24-h dietary recalls, one each on Tuesday, Thursday, and Sunday, were conducted during the 3 months of the study. Study visits were conducted at the Michigan Clinical Research Unit (MCRU) at the University of Michigan (Ann Arbor).

Interventions

Both the FRD and the GHC employed individualized counseling using the theoretical framework of Bandura's social cognitive theory [5, 13], and with the exception of the baseline and 3-month visits, which were conducted inperson, were delivered using six brief 15-minute telephone counseling (once per week for the first 4 weeks and then once every other week) by a MCRU registered dietitian (for the FRD) or a study staff member (for the GHC). The FRD maintained a woman on a diet with her baseline caloric intake (isocaloric diet) and replaced some of her calories with the following foods on a daily basis:

(1) At least half of grain intake from whole grains; (2) five servings of vegetables (one leafy green, one tomato, and one yellow or orange); (3) two servings of fruit (one high in vitamin C); (4) one serving of fatty fish and (5) one serving of omega-3 fatty acid-rich nuts, seeds, or their associated oils (two servings of nuts or seeds for vegetarians). The counseling for this diet used participant daily self-monitoring checklists to help participants achieve goal intakes for the target foods. The checklists were mailed or faxed to the dietitian before the telephone counseling session and discussed.

For the control arm, we employed an attention control, which we named the GHC. The GHC sessions were matched in amount of time spent (~15 min), frequency (8 sessions), and method of delivery to those in the FRD arm. The 8 GHC topics were: (1) oral health, (2) healthy eyesight, (3) over-the-counter and prescription drug disposal, (4) healthy skin and hair, (5) cell phones and health, (6) hearing loss, (7) colorectal cancer screening, and (8) preventing colds and flu. None of the GHC topics contained dietary information.

Study outcome measures

We used the BFI [36] to assess severity and impact of fatigue in cancer patients. The BFI is validated in cancer patients, and it correlates highly with other fatigue measure [39]. It has a Cronbach alpha exceeding 0.95 [6]. The BFI has 9 items, each measuring a different aspect of fatigue, and is calculated from the mean of all completed items giving a 0-10 score. Clinically-relevant fatigue scores are defined as mean BFI scores of ≥ 4 [36].

The 19-item PSQI was used to assess sleep quality. The PSQI evaluates sleep interferences over the past month. The PSQI yields seven component scores and a global score, and the global PSQI score has an alpha coefficient of 0.81 [6]. In the general US population, a global PSQI score of ≤ 5 indicates poor sleep quality [15].

To assess dietary intakes at baseline and 3 months, 7-day food records and 24-h recalls were analyzed using the University of Minnesota Nutrition Data System Research software (Nutrition Coordinating Center, University of Minnesota, version 2014; <http://www.ncc.umn.edu/>).

Adherence to dietary goals was assessed using the daily food check lists and serum fatty acids and carotenoids. Fasting blood samples were stored at -70°C until analysis. Analytical methods for both serum fatty acids and carotenoids have both been reported previously in detail. In brief, carotenoids were extracted with hexane and quantified using high-pressure liquid chromatography, and serum fatty acids were measured as fatty acid methyl ester by gas chromatography [24].

Statistical analysis

Descriptive statistics for baseline sociodemographic and clinical characteristics were analyzed between groups using an independent sample *t* test for continuous measures or Pearson's Chi-square for categorical variables. To investigate the change through time both within and between groups for BFI, PSQI, changes in dietary measures, e.g., green leafy vegetable intake, BMI, calories, serum fatty acids, and serum carotenoids we conducted an intent-to-treat (ITT) analysis using linear mixed models (LMM). For each LMM, a random subject intercept was included to account for subject clustering, and fixed effects were visit, group, and the interaction term (visit by group). The models for BFI and PSQI were also controlled for the fixed effects of baseline age and BMI, while the serum fatty acids and carotenoids were further controlled for the fixed effects of smoking and analytical batch. Smoking status, BMI, and the analytical batch that the fatty acid and carotenoids were analyzed in were added to the models as these variables have been shown to impact the variability in these measures in other studies [18, 49].

Normality of the residuals derived from the LMM was assessed using the Shapiro—Wilk test and *q-q* plots. For non-normal results, a Box—Cox transformation was utilized [12]. A square root transformation was used for serum α -carotene, β -carotene, β -cryptoxanthin, lutein, total carotenoids, and PSQI. The other carotenoids, tocopherols, and fatty acids required no transformation. Associations between changes in concentrations of serum nutrients and changes in fatigue and sleep quality from baseline to 3 months were investigated using pairwise correlations for the FRD group (Spearman rank correlation coefficient for variables with non-normal distributions and Pearson correlation coefficients for all other variables).

In all analyses, a *p* value of ≤ 0.05 was considered statistically significant except for correlations between change in serum nutrients and change in fatigue and sleep quality between baseline and the 3-month visits where a *p* value of ≤ 0.10 was considered significant. As this was a pilot trial with a small sample size, we allowed for the larger *p*

value of 0.10 when examining the serum correlations to allow for hypothesis generation. All tests were two-sided.

Our power analysis was based on detecting a time-by-group interaction term in the mixed effects regression model for BFI, our primary outcome measure. At baseline, both diet arms are assumed to have a mean BFI of 6. At the 3-month follow-up, the control arm was assumed to reduce the average BFI value to 5, whereas the FRD was assumed to experience a reduction of three points, bringing the mean BFI down to 3. The between-subject variance was assumed to be 4, and the intra-subject correlation is taken to be 0.3, a moderate value. These assumed values are estimates based on our pilot data [55]. For this configuration, the power for detecting a significant time-by-group interaction is 0.89 with a sample size of 15 per diet arm and a 5% level of significance.

Results

Screening, enrollment, and withdrawals

We screened 50 women of whom 30 were enrolled in the study with 15 randomized to the GHC and 15 to the FRD group. Twenty-nine of the 30 participants were evaluable for the primary outcome of change in BFI from baseline through month 3. All study visits were completed by 100% of women in the GHC group, and 93% in the FRD. Figure 1 documents exclusions and reasons for discontinuing the interventions.

Sociodemographic and clinical characteristics

There were no significant differences between study groups at baseline by any sociodemographic or clinical characteristics (Table 1). Despite no significant differences in baseline age or BMI between groups, the women in the GHC group were on average 4 years younger than the women in the FRD group and the participants in the GHC group had a 2-point lower BMI. Participants were mainly white ($n = 28$, 93%) and none self-reported as Hispanic. Mean baseline fatigue was 5.5 ± 1.2 , baseline PSQI was 7.2 ± 3.6 and baseline BMI was 28.2 ± 3.8 . The participants' ages ranged from 47 to 81 years with the average age being 62.4 ± 9.7 years. Women had been diagnosed with breast cancer on average 7.4 ± 3.9 years before enrollment into the study; the majority were postmenopausal at the time of their breast cancer diagnosis ($n = 16$, 53%), and most women had estrogen receptor-positive breast cancer ($n = 24$, 80%).

Change in calories, BMI, and dietary intake

There was no significant change in BMI between the baseline and the final visit for either group ($p = 0.70$). Nor was there any significant change in calories in the FDR group ($p = 0.50$). There was a significant decrease in calories between the baseline and the 3-month visit in the GHC group (-188 calories, $p < 0.01$). All targeted food groups in the FRD, with the exception of non-citrus fruits, were significantly increased (all $p < 0.01$) roughly twofold between the baseline and 3-month visit, while no foods had changed in the GHC group (as shown in Table 2).

Change in fatigue and sleep quality

In our adjusted models, the BFI decreased from baseline by 2.4 ± 2.0 points between baseline and the 3-month visit in the FRD group compared to a decrease of 0.77 ± 1.8 in the GHC group ($p < 0.01$). This represents an average % decrease of $44 \pm 39\%$ in FRD group and an $8 \pm 34\%$ decrease in the GHC group ($p = 0.01$, Table 3). The global PSQI score decreased by 2.5 ± 3.3 points between baseline and the 3-month visit in FRD group, while it increased by 0.9 ± 2.3 in the GHC group ($p = 0.03$). At the 3-month visit, the global PSQI score had decreased by 3.9 ± 2.8 in the FRD and 0.8 ± 2.0 ($p = 0.02$) in those women with baseline global PSQI scores of ≥ 5 ($N = 23, 77\%$) (Table 3).

Serum nutrient concentrations

Table 4 shows serum nutrient levels by visit and study groups. In the adjusted analyses serum total carotenoids ($p < 0.01$), β -cryptoxanthin ($p = 0.02$), lutein ($p = 0.05$), zeaxanthin ($p = 0.01$), lycopene ($p = 0.05$), percent omega-3 fatty acids ($p < 0.01$), and the ratio of omega-3 to omega-6 fatty acids ($p = 0.02$) were significantly increased, and percent saturated fatty acids were decreased ($p = 0.04$) between baseline and the 3-month visit in the FRD group. The only nutrient change in the GHC group was γ -tocopherol, which was significantly increased ($p = 0.03$). There was also a significant visit by group difference for α -carotene between the study groups ($p = 0.05$), increasing in the FRD group, while decreasing or staying approximately the same in the GHC group.

Correlations between changes in serum nutrients, fatigue, and sleep quality

Change in fatigue was significantly inversely associated with both changes in omega-3-to-omega-6 fatty acid ratio (Pearson $r = -0.45$, $p = 0.09$) and percent eicosapentaenoic acid (EPA, Pearson $r = -0.49$, $p = 0.07$). No changes in serum nutrients were significantly correlated with changes in sleep quality in the FRD group (Table 5). There was no significant correlation between either baseline fatigue and sleep quality (Pearson $r = 0.20$, $p = 0.30$) or change in fatigue and change in sleep quality between baseline and the 3-month visit in the FRD group (Pearson $r = 0.16$, $p = 0.59$).

Feasibility of fatigue reduction diet and general health curriculum

Based on the daily food check lists, participants meet their daily food goals for vitamin C-rich fruit $92 \pm 12\%$, other fruit $94 \pm 7\%$, green leafy vegetables $78 \pm 19\%$, deep yellow or orange vegetables $84 \pm 15\%$, tomatoes $92 \pm 8\%$, other vegetables $73 \pm 25\%$, whole grains $73 \pm 22\%$, and omega-3 rich foods $79 \pm 16\%$. Phone counseling sessions ranged from 6 to 30 min with the average phone counseling time being 14.5 ± 4.1 min.

Discussion

A 3-month whole foods dietary intervention compared to an attention control was able to significantly improve persistent cancer-related fatigue by over 44% compared to only 8% in the attention control group. In addition, women randomized to the dietary intervention also experienced a significant improvement of nearly 50% in sleep quality, while women in the control group experienced no change or a slight decrease in their sleep quality. These findings were achieved independent of weight change as neither group had a significant

difference in weight during the study. Decreases in fatigue, between the baseline and 3-month visits, were also significantly inversely associated with increases in both serum EPA and the omega-3-to-omega-6 omega fatty acid ratio.

Our research builds on prior studies in a number of important ways. All other studies have only been able to investigate the association between diet and fatigue prevalence and severity. These cross-sectional studies were not able to explore if differences in diet quality or nutrient content were causal in nature or instead just associated with other healthy behaviors known to decrease persistent fatigue in cancer survivors such as exercising or maintaining a healthy weight, and these other behaviors could explain the association between fatigue and diet quality [23, 37]. We also assessed the impact of diet on sleep, which none of the previous studies had investigated despite strong associations between sleep disruptions and persistent fatigue in breast cancer survivors [42]. This study also adds to the literature by showing that improving diet quality outside of weight loss or calorie restriction could be a viable option to improve burdensome symptoms and thus improve quality of life in breast cancer survivors. While the goal of achieving and maintaining a healthy weight is the ideal, many breast cancer survivors find losing weight particularly challenging. Improving diet quality offers a possibly more achievable goal as demonstrated by the high level of adherence in our study.

Our findings are consistent with previous observational studies that found higher quality diets [27, 32], as well as diets high in fiber [30], fruits, and vegetables [1], omega-3 fatty acids relative to omega-6 fatty acids [2] were associated with a lower likelihood and less severe persistent fatigue in breast cancer survivors. In contrast to our study, which emphasized at least two servings per day of omega-3 fatty acid-rich foods, and thus encouraged targeted fat consumption, one study found that diets high in fat were associated with increased fatigue [30]. Fat consumption in this study, however, was investigated as one group and not broken down into different types of fat. As such, fats which could have a potential negative impact on fatigue such as saturated fats were grouped with fats such as omega-3 polyunsaturated fatty acids (omega-3 PUFAs), which are associated with lower likelihood of fatigue. This combining of types of fat could obscure the association between fatigue and various types of fat. This same study also did not find an association between fruit and vegetable consumption and fatigue [30]. Unlike our study, fruit and vegetable intake was combined, and mean intake was 2.7 servings per day, which is lower than the 3.5 servings per day in our participants at baseline.

Previous research has suggested supplementation of omega-3 fatty acids may be a strategy to reduce fatigue in breast cancer survivors [2]. Our results, however, suggest a dietary approach versus a supplemental approach may be a more successful strategy. For instance, our results found that the ratio of omega-3 to omega-6 fatty acids appeared as an important correlation of fatigue improvement, not just an increase of omega-3 fatty acids by themselves. To achieve meaningful changes in fatty acid ratios, it may be necessary to decrease the levels of omega-6 in the diet while simultaneously increasing the levels of omega-3 fatty acids. Also, changes in serum fatty acids were associated with only some of the decrease in fatigue and none of the improvement in sleep quality suggesting that other nutrients are involved in bringing about changes in these symptoms. Indeed, recent research

investigating the relationship between sleep and diet found that numerous other nutrients including lower levels of calcium, vitamin C, and selenium were associated with disrupted sleep [28], and that in postmenopausal women, a lower diet quality, but not individual foods, was associated with shorter sleep duration [51].

The FRD method of using brief telephone counseling and written food exchange lists appears to be a feasible intervention for breast cancer survivors. The self-reported 7-day food records and daily food check lists both demonstrated significant increases in daily intake of target foods, and these differences were objectively confirmed by significant increases in serum levels of carotenoids and omega-3 fatty acids. We also found that all of the serum carotenoids categories increased indicating that we were able to impact the intake of a wide variety of vegetables and fruits. The increases in lycopene, β -cryptoxanthin, and zeaxanthin are particularly encouraging as other dietary intervention studies that focused on increasing fruit and vegetable intakes were unable to impact the levels of these carotenoids [7, 16, 24, 34]. As higher levels of β -cryptoxanthin, lycopene, and zeaxanthin are associated with lower breast cancer recurrence [25, 50, 52], the ability of the FRD to increase these nutrients has potential positive implications beyond control of symptoms in breast cancer survivors. Further, these dietary changes were achieved through a brief telephone delivered dietary counseling sessions. This approach could prove to be cost-effective.

Our work suggests several areas for additional research including exploration of the mechanisms through which this dietary intervention was associated with decreasing persistent cancer-related fatigue and improved sleep quality. Also a better understanding of how specific constituent parts (increased leafy green vegetables, whole grains, etc.) of the FRD intervention may have facilitated decreased fatigue and improved sleep quality. A likely mechanism through which the FRD is working is by decreasing chronic inflammation and modulating immune activation [11, 46], and in particular, decreasing circulating inflammatory biomarkers CRP, Interleukin-6 (IL-6), and interleukin 1 receptor antagonist (IL-1RA), which are associated with fatigue in cancer patients [21, 43, 47, 56]. We have previously reported that individuals who eat diets high in antioxidant micronutrients [19], or have high intake of whole foods including fish, fruits, and vegetables, similar to the FRD, have significantly lower concentrations of circulating inflammatory biomarkers [4, 14, 17].

Our study has several limitations. First, we had a small sample size, which could overestimate the effect size of the intervention. The intervention, however, was designed to focus on feasibility, adherence, and to establish a preliminary effect of the FRD. While we posited that the FRD would work through anti-inflammatory mechanisms, future studies will be needed to explore if this is true or if other mechanisms are important. Third, we were unable to measure other phytochemicals present in the FRD that could have been responsible for improving fatigue and sleep. Nonetheless, we did have serum measures, which were found in high levels in our targeted food groups, and that have been shown to have significant impacts on both fatigue and sleep. Also, we were unable to explore the impact of diet on symptoms such as hot flashes or arthralgias, which are prevalent in breast cancer survivors and can also cause poor sleep and fatigue.

This study also had several strengths including an attention control group that was matched for the frequency and duration of contacts in the dietary intervention. This is especially important for subjective patient reported outcomes such as fatigue where participating in a study independent of an intervention can lead to significant improvements in symptoms. Other strengths of this study include objective measures of dietary adherence in addition to patient reported intakes and a very high completion rate with only one participant withdrawing from the study.

Conclusions

A dietary intervention (the FRD rich in fruits, vegetables, whole grains, and omega-3 fatty acid-rich foods) delivered via brief phone counseling sessions significantly decreased fatigue and improved sleep quality over the course of 3 months compared to an attention control in persistently fatigued breast cancer survivors.

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Abbreviations

FRD	Fatigue reduction diet
GHC	General health curriculum
RD	Registered dietitian
HEI-2010	Healthy eating index
BFI	Brief fatigue inventory
PSQI	Pittsburgh sleep quality index
BMI	Body mass index
EPA	Eicosapentaenoic acid
CRP	C-reactive protein
LMM	Linear mixed models
CNS	Central nervous system
ITT	Intent-to-treat
MCRU	Michigan Clinical Research Unit
IL-6	Interleukin-6
IL-1RA	Interleukin 1 receptor antagonist

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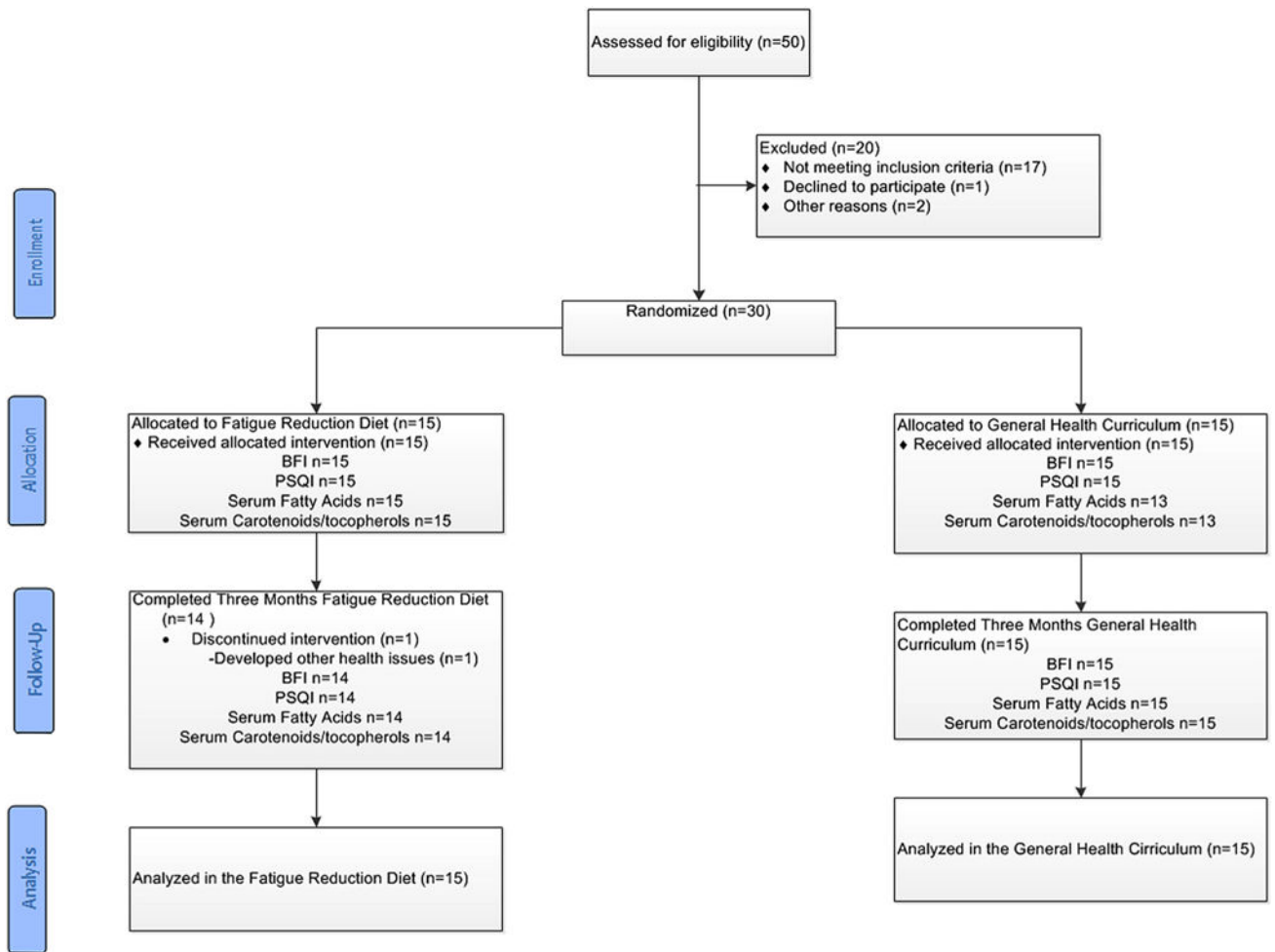


Fig. 1.
Consort flow diagram BCRT

Table 1

Sociodemographic and clinical characteristics at baseline

	Fatigue reduction diet (<i>n</i> = 15)	General health curriculum (<i>n</i> = 15)
Demographics		
Age (mean years) ± SD	64.4 ± 10.0	60.4 ± 9.35
Race <i>n</i> (%)		
White	14 (93)	14 (93)
Clinical characteristics		
BFI (mean ± SD)	5.4 ± 1.1	5.6 ± 1.3
PSQI (mean ± SD)	6.8 ± 3.9	7.5 ± 3.4
BMI (mean ± SD)	27.2 ± 3.8	29.2 ± 3.6
Stage of cancer <i>n</i> (%)		
Stage 0 ^a	1 (7)	5 (33)
Stage 1	4 (27)	3 (20)
Stage 2	7 (47)	4 (27)
Stage 3	2 (13)	2 (13)
Unknown	1 (7)	0 (0)
Estrogen receptor status		
Yes	12 (80)	12 (80)
No	3 (20)	2 (13)
Unknown	0 (0)	1 (7)
Menopausal status ^b		
Premenopausal	3 (21)	7 (47)
Perimenopausal	2 (14)	1 (7)
Postmenopausal	9 (64)	7 (47)
Time since cancer diagnosis in years (mean ± SD) ^c	7.4 ± 3.8	7.5 ± 4.1
Treatments (were received) <i>n</i> (%) ^c		
Surgery	15 (100)	15 (100)
Chemotherapy	11 (73)	8 (53)
Radiation	12 (86)	11 (73)
Hormone therapy	12 (80)	10 (67)

Percentages may not add up to 100% because participants can receive multiple treatments or diagnoses *BFI* brief fatigue inventory, *BMI* body mass index, *PSQI* Pittsburgh sleep quality index

^aStage 0 includes ductal carcinoma in situ (DCIS) and Lobular carcinoma in situ (LCIS)

^bMenopausal status at the time of initial breast cancer diagnosis

^cTime since “cancer diagnosis” was calculated from on-study date and date of diagnosis in years

Table 2

Change in dietary measures

Measures	Fatigue reduction diet <i>N</i> = 15		General health curriculum <i>N</i> = 15	
	Mean ± SD		Mean ± SD	
	Baseline	3 months	Baseline	3 months
Calories per day	1608 ± 381	1665 ± 359	1788 ± 313	1600 ± 330 ^a
BMI	27.2 ± 3.8	27.2 ± 3.9	29.2 ± 3.9	29.1 ± 3.6
Fruit excluding citrus ^d	0.9 ± 0.5	1.3 ± 0.7	1.0 ± 0.9	0.7 ± 0.5
Citrus	0.2 ± 0.2	0.8 ± 0.6 ^a	0.4 ± 0.3	0.5 ± 0.6
Vegetables ^c	2.8 ± 0.8	5.7 ± 1.9 ^a	1.9 ± 1.0	2.0 ± 0.9
Leafy green ^c	0.5 ± 0.6	1.2 ± 0.7 ^a	0.3 ± 0.4	0.3 ± 0.4
Yellow/orange ^c	0.3 ± 0.4	0.6 ± 0.5 ^a	0.1 ± 0.1	0.1 ± 0.2
Tomatoes ^c	0.4 ± 0.3	1.2 ± 0.7 ^a	0.4 ± 0.3	0.4 ± 0.2
Other ^c	1.0 ± 0.5	2.1 ± 1.5 ^a	1.0 ± 0.6	1.0 ± 0.5
Fish servings per day ^d	0.6 ± 0.9	1.5 ± 1.5 ^b	0.8 ± 0.9	0.6 ± 0.7
Nuts and Seeds servings per day	0.7 ± 0.7	1.4 ± 1.0 ^b	0.9 ± 1.0	0.9 ± 1.2
Whole Grains servings per day ^c	1.2 ± 0.8	2.3 ± 0.9 ^a	1.2 ± 0.7	1.3 ± 1.1

^aSignificantly ($p < 0.01$) different from baseline to 3 months for that study arm from mixed linear regression models

^bSignificantly ($p < 0.05$) different from baseline to 3 months for that study arm from mixed linear regression models

^cA significant ($p = 0.01$) group-by-time interaction from mixed linear regression models

^dA significant ($p = 0.05$) group-by-time interaction from mixed linear regression models

Table 3

Fatigue and sleep measures by treatment group and visit

Measures	Fatigue reduction diet <i>N</i> = 15		General health curriculum <i>N</i> = 15	
	Mean ± SD		Mean ± SD	
	Baseline	3 months	Baseline	3 months
Brief fatigue inventory ^a	5.4 ± 1.1	3.0 ± 2.2 ^a	5.6 ± 1.3	4.9 ± 1.6
PSQI ^d total score (all) ²	6.8 ± 3.9	3.9 ± 2.1	7.5 ± 3.4	8.5 ± 3.4
PSQI ^d total score ^b				
Greater than or equal to 5	8.3 ± 3.3	3.9 ± 2.4 ^c	8.8 ± 2.6	9.5 ± 3.3

^a A significant ($p < 0.01$) group-by-time interaction from mixed linear regression models adjusted for; baseline age and BMI

^b A significant ($p < 0.05$) group-by-time interaction from mixed linear regression models adjusted for; baseline age and BMI

^c Significantly ($p < 0.01$) different from baseline to 3 month for that study arm from mixed linear regression models adjusted for baseline age and BMI

^d *PSQI* Pittsburgh sleep quality index; *PSQI* 5 is considered someone who has poor sleep quality

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Table 4

Serum concentrations of fatty acids, carotenoids, and tocopherols by treatment group and study visit

Nutrients	Fatigue reduction diet <i>N</i> = 15 Mean ± SD		General health curriculum <i>N</i> = 15 Mean ± SD	
	Baseline	3 months	Baseline	3 months
Serum carotenoids				
Total carotenoids	465 ± 255	694 ± 454 ^b	439 ± 316	459 ± 384
α-Carotene (ng/mL) ^a	50 ± 53	83 ± 85	40 ± 26	41 ± 29
β-Carotene (g/mL)	99 ± 139	169 ± 179	97 ± 141	86 ± 100
β-Cryptoxanthin (ng/mL)	107 ± 79	154 ± 162 ^b	92 ± 76	134 ± 243
Lutein (ng/mL)	121 ± 66	155 ± 121 ^b	104 ± 75	96 ± 55
Zeaxanthin (ng/mL)	27 ± 17	34 ± 26 ^c	24 ± 16	25 ± 17
Lycopene (ng/mL)	61 ± 47	99 ± 86 ^b	83 ± 46	76 ± 49
Serum tocopherols				
α-Tocopherol (lg/mL)	8.8 ± 3.7	8.5 ± 4.2	7.6 ± 3.8	7.7 ± 3.5
γ-Tocopherol (lg/mL)	0.8 ± 0.4	0.7 ± 0.3	0.7 ± 0.3	0.8 ± 0.3 ^b
Serum fatty acids				
SFA (%)	36.2 ± 3.8	34.3 ± 2.5 ^b	36.5 ± 4.1	36.1 ± 4.9
MUFA (%)	24.2 ± 2.6	23.5 ± 2.7	22.8 ± 4.3	21.9 ± 3.8
N6 PUFA (%)	35.2 ± 3.6	36.3 ± 3.7	35.5 ± 5.8	36.1 ± 6.5
N3 PUFA (%)	4.5 ± 1.1	5.8 ± 1.5 ^c	5.3 ± 1.3	5.9 ± 1.3
N3/N6 fatty acid ratio	0.13 ± 0.04	0.16 ± 0.05 ^b	0.15 ± 0.04	0.16 ± 0.03

SFA saturated fatty acid, MUFA monounsaturated fatty acid, PUFA polyunsaturated fatty acid, N6 omega-6 fatty acid, N3 omega-3 fatty acid

^aA significant ($p < 0.05$) group-by-time interaction from mixed linear regression models adjusted for batch; baseline age, BMI, and smoking status

^bSignificantly ($p < 0.05$) different from baseline to 3 months for that study arm from mixed linear regression models adjusted for batch; baseline age, BMI, and smoking status

^cSignificantly ($p < 0.01$) different from baseline to 3 months for that study arm from mixed linear regression models adjusted for batch; baseline age, BMI, and smoking status

Table 5

Correlations in changes in serum nutrients with changes in fatigue and sleep quality

	Fatigue	Sleep quality
Serum fatty acids		
SFA (%)	-0.42	-0.11
MUFA (%)	-0.08	-0.23
N6 PUFA (%)	0.43	0.18
N3 PUFA (%)	-0.22	0.32
N3/N6 fatty acid ratio	-0.45^a	0.25
DHA (%)	-0.22	0.46
EPA (%)	-0.49^a	0.36
Serum carotenoids		
Total carotenoids	-0.06	0.12
α-Carotene (ng/mL)	-0.01	0.08
β-Carotene (ng/mL)	-0.20	0.15
β-Cryptoxanthin (ng/mL)	-0.04	-0.27
Lutein (ng/mL)	0.18	-0.25
Zeaxanthin (ng/mL)	0.22	-0.18
Lycopene (ng/mL)	-0.19	0.42
Serum tocopherols		
α-Tocopherol (lg/mL)	-0.05	0.05
γ-Tocopherol (lg/mL)	-0.15	-0.29

SFA saturated fatty acid, *MUFA* monounsaturated fatty acid, *PUFA* polyunsaturated fatty acid, *N6* omega-6 fatty acid, *N3* omega-3 fatty acid, *DHA* docosahexaenoic acid, *EPA* eicosapentaenoic acid

^aA significant ($p < 0.10$) from bivariate correlations; Pearson correlation coefficients for zeaxanthin, total lycopene, γ-tocopherol, α-tocopherol, DHA, EPA, SFA, MUFA, N6 PUFA, N3 PUFA, and N3/N6 PUFA; Spearman correlation coefficients for α-carotene, β-carotene, β-cryptoxanthin, lutein, and total carotenoids