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Original Research

# Feasibility of Investigational Procedures and Efficacy of a Personalized Omega-3 Dietary Intervention in Alleviating Pain and Psychoneurological Symptoms in Breast Cancer Survivors

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ABSTRACT

*Background:* Breast cancer survivors (BCS) are at risk for psychoneurological symptoms (PNS) and inflammation for years following cancer treatment. Fish, particularly salmon, provides a rich source of omega-3 long chain fatty acids (omega-3LC), which has an anti-inflammatory effect. However, the benefit of omega-3LC on PNS is not well-known.
*Aims:* This study evaluated the feasibility and the initial efficacy of a personalized meal plan with dietary omega-3LC in reducing PNS.
*Methods:* A prospective, randomized controlled trial design ($n = 46$) was used to evaluate the feasibility of a personalized meal plan using two omega-3LC dose levels (high and low omega-3LC) in reducing PNS including pain, depression, fatigue, sleep, and stress.
*Results:* The recruitment rate was 4.9% with overall retention rate of 74% and 67.1% adherence to personalized meal plan and dietary procedures. Of participants who completed the investigation, 94% completed fish adherence logs and consumed ≥70% of the assigned quantity of fish. Saliva collection was 97.8% at baseline and 100% at follow-up. BCS in the high omega-3LC group had a significant decrease in pain ($p < .01$), perceived stress ($p < .05$), sleep ($p < .001$), depression ($p < .001$), and fatigue ($p < .01$) over the course of intervention. There were trends of PNS improvement in the low omega-3LC group but the differences did not reach statistical significance.
*Conclusion:* Our results support the feasibility of our investigational design, procedures, and intervention. The outcomes provide preliminary support for an expanded research effort using fish as a source of omega-3LC and personalized dietary planning as a vehicle for symptom self-management in BCS.


## Introduction

As of 2019, more than 3.8 million US women had a history of breast cancer (BC), comprising the largest group of cancer survivors (DeSantis et al., 2019). Due to BC and/or its treatment, many women experience a myriad of distressing symptoms, e.g., pain, fatigue, depression, and sleep disturbance, referred to herein as psychoneurological symptoms (PNS) (Starkweather et al., 2013). The reported prevalence rates of PNS include pain (84%), sleep disturbance (78%), fatigue (51%), and depression (32%); these symptoms are elevated in BC survivors (BCS) compared with national averages among American adults (Hamood et al., 2018; Lee et al., 2020; Schreier et al., 2019). Furthermore, PNS can persist for years during/after the treatment, leading to significant decreases in productivity and quality of life (Ganz et al., 2011; Gwede et al., 2008; Reinertsen et al., 2010; Roiland & Heidrich, 2011).

Risk factors for PNS in BCS are complex (Starkweather et al., 2013). An inflammatory etiology of PNS has been repeatedly reported in BCS, including chronically elevated inflammatory mediators (Bouchard et al., 2016; Bower et al., 2009; Jasionowska et al., 2019; Liu et al., 2012; Lyon et al., 2008; Minton et al., 2014; Starkweather, 2010). Proinflammatory cytokines of particular interest from the standpoint of cytokine dysregulation include interleukin-1(IL-1), IL-2, IL-6, tumor-necrosis factor (TNF), and C-reactive protein (CRP) (Glaser & Kiecolt-Glaser, 2005; Starkweather, 2017). Convincing evidence has demonstrated that both psychoneurological factors, e.g., depressive symptoms and situational perceived stress augment pro-inflammatory cytokine pro-

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duction, suggesting that stress-related changes have broader health implications (Glaser & Kiecolt-Glaser, 2005). Lifestyle modification, such as combination of diet and exercise have shown effectiveness in reducing inflammatory load (Arikawa et al., 2018) and PNS (Ruiz-Vozmediano et al., 2020). However, limited evidence has been reported on the effect of diet alone in PNS improvement in BCS (Zick et al., 2017).

The omega-3 long chain fatty acid (omega-3LC) is known to have anti-inflammatory functions that downregulate the inflammatory cascade (George et al., 2010; He et al., 2009). Increased omega-3LC consumption has been associated with reduced inflammation, as evidenced by reduced CRP and PNS in BCS (Alfano et al., 2012; Martinez et al., 2019; Zick et al., 2017) and other populations (Duran et al., 2019; He et al., 2009; Sanchez-Villegas et al., 2018). Feedings comprised of omega-3LC rich fish oil effectively relieved neuropathic pain by reducing thermal hypersensitivity and mechanical allodynia compared with controls in a rat model (Unda et al., 2020). A lower ratio of dietary omega-3LC to omega-6 long chain fatty acid (omega-6LC) is associated with more inflammation and fatigue in BCS (Alfano et al., 2012). Diets laden with processed foods and corn oil, resulting in high circulating omega-6LC, reduce the availability of omega-3LC due to direct competition for biosynthetic enzymes between the two pathways (Calder, 2016). Omega-3LC is capable of partly inhibiting many aspects of inflammation including leucocyte chemotaxis, adhesion molecule expression and leucocyte-endothelial adhesive interactions, production of key eicosanoids including prostaglandins and leukotrienes from omega-6LC and production of pro-inflammatory cytokines (Calder, 2017; Gupta et al., 2016; Norris & Dennis, 2012). Additionally, this delicate balance impacts the type of fatty acids incorporated into membrane phospholipids of neural and peripheral cells influencing structure, function, cell signaling, communication, and gene expression (Casares et al., 2019; Lauritzen et al., 2016).

Although the benefits of omega-3LC have a recognized value in clinical practice, further education is necessary in delineating between the different forms of omega-3 fatty acid and associated food sources. In brief, omega-3 fatty acids are a class of fatty acids that includes the the shorter chained linolenic acid and the omega-3LC's which include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Although omega-3 fatty acids of different chain lengths are available in the diet, the dietary sources are different for the shorter chained linolenic acid compared with the omega-3LC's (DHA and EPA), and associated food sources are commonly misunderstood. The shorter chained linolenic acid obtained from flaxseed, soy, and canola serves as a metabolic precursor in the eventual production of omega-3LC. Although EPA and DHA can be produced endogenously from linolenic acid, metabolic conversion is limited (Calder, 2016). Hence, fish and/or fish-based oils contain omega-3LC and consuming these sources bypasses the necessity for metabolic conversion. For this reason, foods containing omega-3LC are classified as "preformed" sources. Salmon is an excellent source of omega-3LC, providing 476-618 mg of DHA per 3-ounce cooked portion, while also relatively low in contaminants compared with other larger fish species (USDA, 2016).

Increased consumption of omega-3LC, and specifically more fish, is encouraged as a component of the Nutrition and Physical Activity Guidelines for Cancer Survivors (Rock et al., 2012). The guidelines emphasize that nutrients should be obtained through dietary sources, not supplements unless consumed under medical supervision (Rock et al., 2012). Specifically, a personalized planning approach improves adherence with dietary guidelines in BCS (Greenlee et al., 2016). Current guidelines point to a minimum consumption of fish of 8-12 ounces of low mercury fish per week (U.S. Food and Drug Administration, 2017). The two intervention groups in this investigation fall within these guidelines for fish consumption. Given concerns of low fish consumption in BCS, further work is necessary in understanding how low versus high range consumption is associated with inflammation and PNS symptom (Alfano et al., 2012).

Based upon existing literature, a critical gap exists regarding the effectiveness of a personalized high or low omega-3LC (via fish consumption groupings) dietary plan in mitigating inflammation and PNS in BCS (Greenlee et al., 2016; Siegel et al., 2016; Ventura et al., 2013). The purpose of this study was to evaluate the feasibility and initial efficacy of a personalized dietary plan, including increased omega-3LC intake via fish consumption, in mitigating the impact of PNS in BCS. Aspects of feasibility critical to successful project implementation, recruitment, adherence, PNS, and salivary sample collection procedures were evaluated in addition to preliminary analyses of the efficacy of our intervention.

## Methods

### *Study Design*

This study used a prospective, randomized controlled trial design (ClinicalTrials.gov Identifier: NCT04293874) with a Phase I personalized meal plan and a Phase II omega-3LC dietary intervention. Randomization to high omega-3LC or low omega-3LC groupings (wild-caught Alaskan salmon; high = 12 ounces/week, 2040 mg omega-3LC; low = 6ounces/week, 1020 mg, Fig. 1) was accomplished using an assignment schedule created using GraphPad Prism version 7.00 for Windows, GraphPad Software, La Jolla California USA. Fish consumption levels of the low and high groups are based on current guidelines pointing to a minimum consumption of fish, 8-12 ounces of low mercury fish per week (U.S. Food and Drug Administration, 2017).

### *Participants and setting*

After institutional review board (IRB) approval, participants were enrolled through a large cancer institute in the northeast region of the United States. Letters detailing eligibility criteria and investigational procedures were mailed to BCS who had previously been treated in the center. Potential participants were encouraged to call the study phone line for more information. Initial meetings were arranged if interested individuals met the eligibility criteria: 6-24 months post-treatment for early-stage BC (stage I to IIIA), no diagnosis of dementia or active psychosis, 30-75 years of age, and had no evidence of cancer recurrence. The recruitment window post treatment was chosen based on existing literature pointing to elevation in inflammatory cytokines for up to 5 years following treatment (Seruga et al., 2008). The post treatment window starting at 6 months through 2 years captures the earliest component of this timeframe where PNS are most likely to be experienced (Starkweather et al., 2017). The age range was chosen based upon previous reports of elevated PNS and inflammatory markers in early stage BCS of a similar age range (Starkweather et al., 2017).

### *Procedure*

There were a total of three in-person visits including the following: (1) the initial meeting providing phase I intervention of personalized meal planning; (2) 3 weeks later the second meeting at the beginning of the phase II intervention, when participants were provided omega-3LC-rich fish (according to their randomized groupings), which was consumed for a 6-week interventional period; and (3) 9 weeks following the baseline visit, at

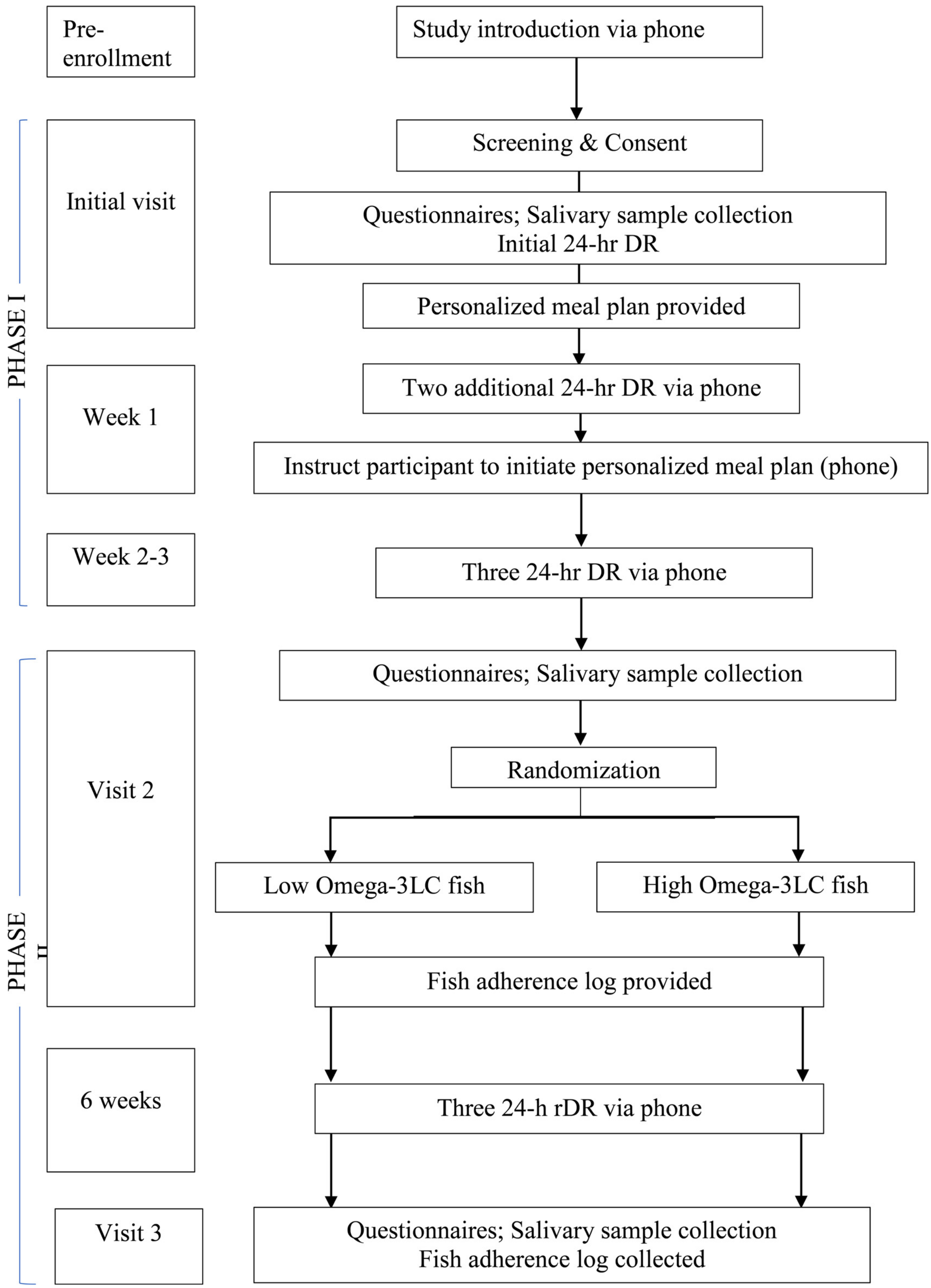


**Figure 1.** Study procedure diagram.

the end of phase II interventional period. Self-reported questionnaires specific to PNS were collected at each of the in-person visits. Phone interviews were used to conduct repeated 24-hour dietary recalls (24-hour DR) in order to assess dietary intake and adherence at baseline and following initiation of both phase I and phase II interventions. Each 24-hour DR was averaged based on 3 days of dietary consumption, and these averaged DR were collected at three timepoints: (1) baseline; (2) 3 weeks following the baseline visit, beginning phase II; and (3) 9 weeks following the baseline visit, the end of phase II). Additionally, salivary samples were collected at the initial and third visits to assess inflammatory cytokines.

*Phase I*

At the initial visit, a personalized meal plan was formulated by the research team members trained in nutrition immediately af-

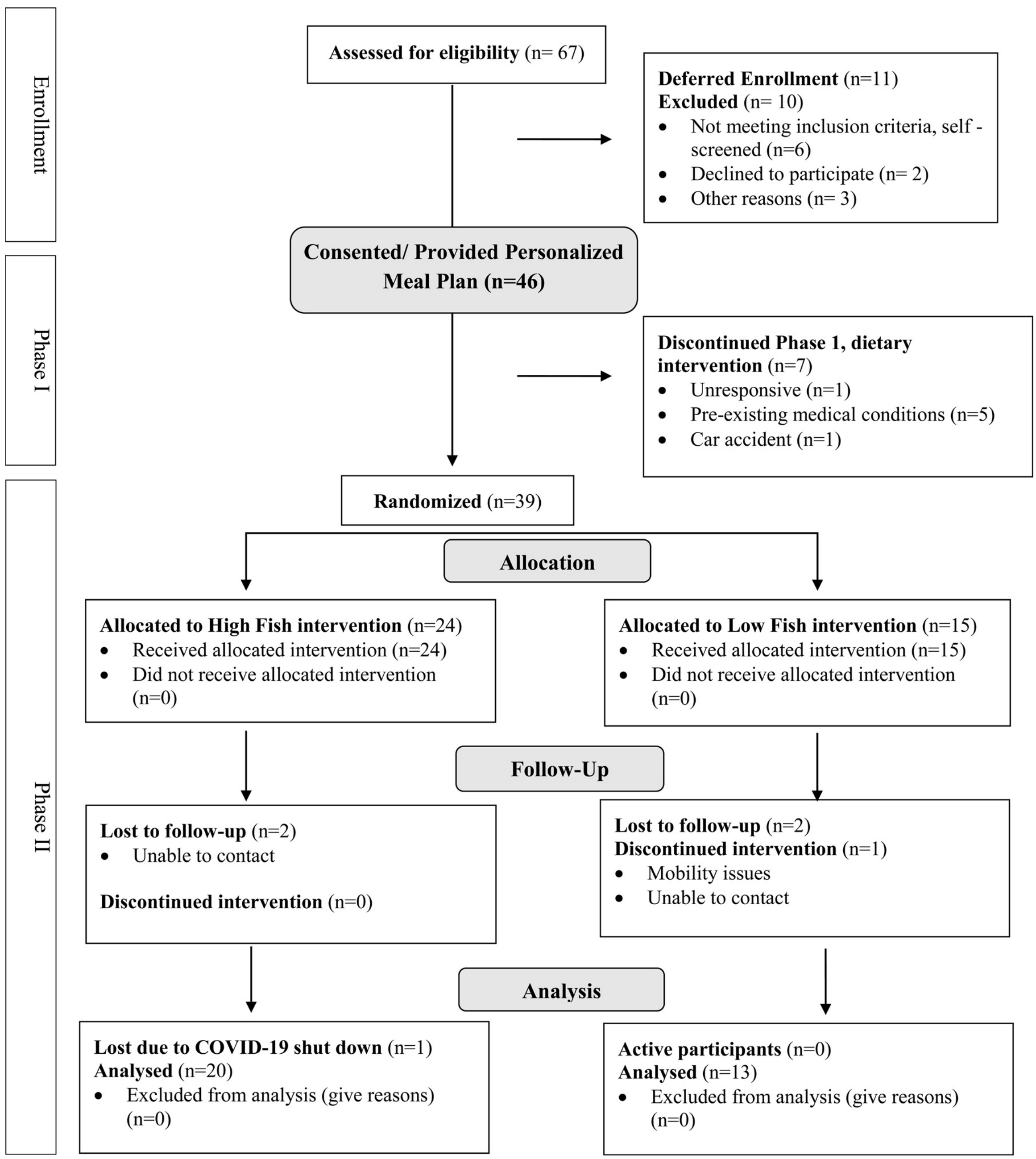


**Figure 2.** CONSORT flow chart.

ter initial collection of 24-hour DR and provided to each participant in written form to take home. The personalized meal plan included recommendations for total calorie consumption and associated number of servings of each dietary food group that should be consumed. Dietary factors including timing of meals, food preferences, and allergies/intolerances were also considered in the meal plan development. Participants were instructed to eat as usual and plan to follow the meal plan in 1 week, allowing time to collect baseline dietary information.

After visit one, during the first week of the study, participants were called to obtain two repeated 24-hour DR and compile a 3-day average for baseline dietary intake. Participants were instructed following the second call to begin following the personalized meal plan, which was provided to each participant during the initial visit and three additional phone calls were made during a 2-week period to assess adherence to the personalized meal plan and overall dietary quality.

*Phase II*

Three weeks after the initiation of the personalized meal plan, participants attended the second investigational visit for data collection and to receive 6-week supply of pre-packaged frozen wild-caught Alaskan salmon or chunk light tuna in the event that participants had an aversion to salmon. Instructions for fish consumption, safe handling, storage, and recipes for preparation were provided. A fish consumption log was provided to each participant to record all study fish consumed and any other fish or seafood that was consumed during the phase II interventional period. Following visit two, three additional repeated, 24-hour DRs were collected reflecting adherence to the fish intervention and dietary quality.

*Outcome Measures*

*Feasibility and receptivity*

Recruitment rate was determined based on the percentage of participants who attended the initial visit and consented divided by the total number of individuals who received the study mailing. Receptivity was assessed using retention and attrition rates (percent of participants who completed and dropped out phase I and phase II). Adherence to the dietary intervention was evaluated using repeated 24-hour DR and the self-reported fish consumption log. Phone based 24-hour DR was used to evaluate: (1) compliance in completing repeated 24-hour DRs; and (2) adherence with the personalized meal plan (% consumption of recommended of total calories, grain, protein/meat, dairy, fruit, vegetables, and saturated fat). The fish consumption logs were used to assess adherence to Phase-II Omega-3LC intervention (% of participants who completed the 6-week fish intervention; and consumed $\geq$70% of the fish). Questions and/or issues related to the dietary intervention during both investigational phases were addressed during regular phone interviews. Feasibility of biospecimen collection was measured (% salivary samples collected of total attempts for collection). Safety of the intervention was determined by records of self-reported adverse events during routine phone calls and investigational visits.

*Self-reported psychoneurological symptoms (PNS)*

PNS were collected at each of the three investigational visits using scales described below. These scales were delivered in the same order to all participants using a research-designated laptop.

- Pain: The Brief Pain Inventory (BPI) short form is a pain assessment tool that has well-established reliability and validity for adult patients in trajectory studies of cancer and its symptoms (Caraceni, 2001; Daut et al., 1983). The arithmetic mean of the four severity items were used as a measure of pain severity, and the arithmetic mean of the seven interference items were used as a measure of pain interference. Total Pain scores were calculated by summing four severity items and seven interference items.
- Depressive symptoms: Depressive symptoms are measured in people with cancer using the Center for Epidemiological Studies Depression scale (CES-D) (Radloff, 1977), a 20-item self-report instrument comprised of factors for depressive affect, somatic symptoms, positive affect, and interpersonal relations. Participants reported the extent to which they experienced each symptom in the preceding week using a 4-point scale. The depressive index was calculated by summing the scores of all 20 items.
- Fatigue: The Brief Fatigue Inventory (BFI) is a 9-item, 11-point Likert scale (0-10) used to assess cancer-related fatigue and its impact on daily functioning. The three severity items and six interference items were tapped into single dimensions of fatigue severity and interference measures (Mendoza et al., 1999). A total fatigue score was calculated by summing all nine items. The BFI has demonstrated excellent reliability in clinical trials, with Cronbach's alpha ranging from 0.82 to 0.97 (Mendoza et al., 1999)
- Sleep disturbance: The 21-item General Sleep Disturbance Scale (GSDS) consists of items evaluating various aspects of sleep disturbance over the past week (Carney et al., 2011; Lee et al., 1999). Items were rated on a scale ranging from 0 (never) to 7 (every day). All items are summed to generate a total score ranging from 0 (no sleep disturbance) to 147 (extreme sleep disturbance). The reported Cronbach's alpha for the GSDS in the cancer population was 0.82 (Lee et al., 1999).
- Perceived stress: This was measured to account for the potential impact of stress on PNS, inflammation, and gut microbiome using the Perceived Stress Scale (PSS) (Kain et al., 2000). The PSS measures the degree to which situations in one's life are appraised as stressful. The 10 items are general in nature and focus on situations in the past month. A summary score was calculated to generate the PSS score.
- Salivary sample collection: To quantify inflammatory biomarkers, passive drool was collected in saliva collection kits at baseline and the third visit, kept on ice, and delivered to the University of Connecticut School of Nursing Biobehavioral Research Laboratory for storage and analysis. Saliva samples were analyzed using Simple Plex Cartridge (Multiplex) Kit (Proteinsimple, San Jose, CA) according to the manufactory protocol. Results of Inflammatory biomarkers were not the focus of this feasibility report therefore were not reported in this manuscript.

*Statistical Analysis*

Statistical analyses were conducted using the SPSS (version 27) and R (version 4.0.2) software packages. Feasibility and receptivity were calculated using descriptive statistics. Summary statistics pertaining both to baseline characteristics and self-reported PNS at the three visits were generated for each of the study groups. Independent *t* tests were used to compare the baseline PNS in our cohort and reference PNS from the literature. Linear mixed-effect models (LME) using the lme4 package in R were performed to examine the effect of high and low omega-3LC dietary (via fish) group on PNS (Bates et al., 2015). Time and groups were included as independent variables and PNS were included as dependent variables. Random intercept and random slope of BCS were considered in the LME. Cohen's d for the pre-post changes of PNS outcome variables were calculated for the effect size for the paired *t* test.

## Results

*Feasibility and Receptivity*

*Recruitment and receptivity (Fig. 2)*

Mailings were sent out to 936 BCS inviting them to participate between October 2018 and January 2020. Sixty-seven (7.2%) of the BCS were approached via phone calls and 61 (6.5%) were self-identified as eligible for the study. Of these, 46 (75.4% of self-identified/4.9% of original mailing) were consented to phase I of the study. The overall retention rate was 71.7% (33/46) based upon all participants recruited. All participants (100%, 46/46) completed phase I, but 7 patients (15.2%, 7/46) did not advance to phase II. Five participants (13.2%, 5/38) dropped in phase II and one participant was lost to follow up due to COVID-19 restrictions on research activity.

*Adherence to personalized meal plan*

The response rates to the three repeated 24-hour DRs at baseline, the end of phase I, and phase II were 97.1%, 84.1%, and 71.9%, respectively. Among 33 participants who completed the study, 30 (90.9%) participants completed all 24-hour DRs. As illustrated in Figure 3, the mean percentages of participants who met dietary recommendations for each of the food groupings ranged from 0% to 71%. Total calorie intake was the category with the highest adherence, whereas lowest adherence was observed for the protein/meat food grouping. The mean adherence (across all meal plan groupings) to the dietary meal plans in phase I and II were 54.1% and 57.4%, respectively. The overall adherence to dietary meal plan (mean adherence to the targeted food groups and completion of

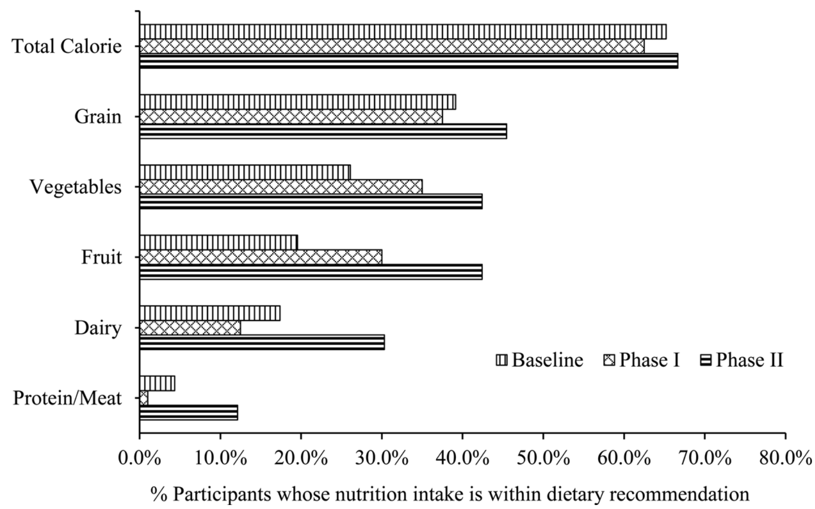


**Figure 3.** Percentage of participants whose nutrition intake is within the dietary recommendation of each major food group at baseline, during phase I, and during phase II of the intervention.

**Table 1**
Fish Log Completion and Adherence to Fish Intervention (n = 33)

| | All (N = 33) | High omega-3LC (n = 20) | Low omega-3LC (n = 13) | p [a] |
|---|---|---|---|---|
| Fish log returned | | | | 1.00 |
| Yes | 31 (93.9%) | 19 (95.0%) | 12 (92.3%) | |
| No | 2 (6.1) | 1 (5.0%) | 1 (7.7%) | |
| Interventional fish consumed | | | | 1.00 |
| 100% | 23 (69.7%) | 14 (73.6%) | 9 (69.2%) | |
| 70%-99.9% | 8 (24.2%) | 5 (25.0%) | 3 (23.1%) | |

[a] Fisher exact test was performed to test statistical significance in the analysis of contingency tables.

phone recalls) was 67.1%. Supplemental Figure 1 outlines the percentage of participants with dietary intakes below, within, or above the recommendation for food groups and dietary components.

*Adherence to fish intervention*

In considering adherence to the fish log completion and the fish intervention (Table 1), 33 participants completed the investigation and 31 (94%) of the logs were returned. A total of 74.2% of participants who returned the log consumed 100% of the quantity assigned (Table 1). Reasons provided regarding consumption below assigned quantity included: (1) loss of interest in eating salmon; (2) difficult to prepare/daughter allergic; (3) unable to finish the 6-ounce portion; (4) fell over a holiday; (5) forgot one at work. Participants who did not return the log indicated that they lost/forgot. Of participants who returned fish logs, all consumed ≥70% of the fish intervention and were classified as adherent. There were no differences in completion/return of logs or adherence between the high or low fish groupings.

*Feasibility of salivary sample collection*

Of 46 participants recruited, 45 (97.8%) participants provided passive drool (salivary) samples at baseline and 33 (100%) participants provided samples at the final follow-up visit. The salivary sample collection process took an average of 10 minutes to complete. No issues were reported with saliva collection and participants considered the procedure easy to follow. Although most participants reported dry mouth and a degree of difficulty producing the quantity of saliva we requested, three participants experienced extreme dry mouth and took longer than 20 minutes to provide adequate volume (two vials of 1 mL each) of saliva for two vials collected at baseline, and two upon study completion.

*Safety related to interventional procedures*

Careful procedural planning focused on safe storage of fish, safe delivery (research team to participants and participants to their homes), safe storage and handling of fish upon preparation, and consumption at home. No intervention-related adverse events were reported.

*Demographic and Clinical Characteristics*

The demographic characteristics are described in Table 2. The majority of participants were aged 59.3 (± 11.8) years, primarily White (80.4%), Non-Hispanic (95.7%), married (63.0%), and college degree or higher (67.4%). All participants underwent some form of breast surgery; of those, 21.7% had chemotherapy, 34.8% had radiation therapy, and 30.5% had combined chemotherapy and radiation therapy. A total of 45.7% of the cohort were taking breast cancer maintenance medication (e.g., aromatase inhibitors, tamoxifen) during study participation. Most of the participants (67.4%) reported that they consumed fish ≤1 serving weekly, and 56.5% described their physical activity (PA) as sedentary.

*Psychoneurological symptoms at baseline*

Preliminary data analysis from the initial 46 participants revealed that BCS had an elevated level of perceived stress (14.7 ± 7.2) compared with adult group aged 55-64 (11.9 ± 6.9, n = 282, t = 2.54, $p < .05$) (Cohen, 1988). The average score of the CES-D in BCS was 13.0 (±9.5) and 30.4% of the BCS had a score ≥16 and were at risk for clinical depression (Lewinsohn et al., 1997). The summation score of fatigue severity (13.8 ± 6.5) and interference (18.5 ± 15.0) is markedly elevated in BCS survivors compared with the reported scores (8.2 ± 6.6, t = –5.37, $p < .001$, and 5.3

**Table 2**
Demographic and Clinical Characteristics of High and Low Omega-3LC Group

| Demographic | All(N = 46) | High omega-3LC (n = 27) | Low omega-3LC (n = 19) | *p* |
|---|---|---|---|---|
| Age | 59.3 ± 11.8 | 59.2 ± 12.0 | 59.5 ± 11.9 | .77 |
| Race | | | | .27 |
| White | 37 (80.4%) | 23 (96.3%) | 14 (73.7%) | |
| Black | 3 (6.5%) | 1 (3.7%) | 2 (10.5%) | |
| Latino | 2 (4.3%) | 2 (7.4%) | 0 (0%) | |
| Other | 4 (87.0%) | 1 (3.7%) | 3 (15.8%) | |
| BMI | 29.1 ± 6.6 | 21.1 ± 6.5 | 30.5± 6.7 | .31 |
| Education | | | | .16 |
| Some college or less | 15 (32.6%) | 7 (25.9%) | 8 (42.1%) | |
| College degree | 17 (37.0%) | 13 (48.2%) | 4 (21.1%) | |
| Master or Ph.D. | 14 (30.4%) | 7 (25.9%) | 7 (36.8%) | |
| Marital status | | | | 1.00 |
| Married | 29 (63%) | 17 (62.9%) | 12 (63.2%) | |
| Other | 17 (37%) | 10 (37.0%) | 7 (36.8%) | |
| Physical activity | | | | .53 |
| Sedentary | 26 (56.5%) | 15 (55.6%) | 11 (57.9%) | |
| Moderate | 19 (41.3%) | 12 (44.4%) | 7 (36.8%) | |
| Strenuous | 1 (2.2%) | 0 (0%) | 1 (5.3%) | |
| Surgery | | | | .84 |
| Lumpectomy | 3 (13.0%) | 3 (11.1%) | 3 (15.8%) | |
| Lumpectomy + lymph nodes removal | 14 (30.4%) | 9 (33.3%) | 5 (26.3%) | |
| Mastectomy | 26 (56.5%) | 15 (55.6%) | 11 (57.9%) | |
| Chemotherapy | | | | .72 |
| Yes | 24 (52.2%) | 13 (48.1%) | 11 (57.9%) | |
| No | 22 (47.8) | 14 (51.9%) | 8 (42.1%) | |
| Radiation | | | | .95 |
| Yes | 30 (65.2%) | 17 (63.0%) | 13 (68.4%) | |
| No | 16 (34.8%) | 10 (37.0%) | 6 (31.6%) | |
| BC maintenance medication | | | | 1.00 |
| Yes | 21 (45.7%) | 12 (44.4%) | 9 (47.4%) | |
| No | 25 (54.3%) | 15 (55.5%) | 10 (52.7%) | |
| Baseline fish consumption | | | | .69 |
| ≤Once/week | 32 (69.6%) | 20 (74.1%) | 12 (63.2%) | |
| Twice/week | 11 (23.9%) | 5 (18.5%) | 6 (31.6%) | |
| ≥ 3 times/week | 3 (6.5%) | 2 (7.4%) | 1 (5.3%) | |

**Table 3**
Psychoneurological Symptoms in BCS at Baseline (n = 46)

| | All (N = 46) | High omega-3LC (n = 27) | Low omega-3LC (n = 19) | *p* |
|---|---|---|---|---|
| Stress (PSS) | 14.7 ± 7.2 | 13.9 ± 6.3 | 15.7 ± 8.4 | .45 |
| Sleep disturbance (GSDS) | 42.7 ± 12.9 | 45.4 ± 13.1 | 38.9 ± 11.8 | .27 |
| Depression (CES-D) | 13.0 ± 9.5 | 12.8 ± 8.5 | 13.4 ± 11.0 | .08 |
| Pain (BPI) | | | | |
| BPI severity | 2.5 ± 1.9 | 2.5 ± 2.0 | 2.4 ± 1.9 | .85 |
| BPI interference | 2.0 ± 2.6 | 2.1 ± 2.2 | 1.9 ± 1.9 | .69 |
| BPI total | 2.9 ± 1.8 | 2.9 ± 1.9 | 2.8 ± 1.6 | .72 |
| Fatigue (BFI) | | | | |
| BFI severity (sum) | 4.6 ± 2.2 | 4.9 ± 2.2 | 4.2 ± 2.1 | .72 |
| BFI interference (sum) | 3.1 ± 2.5 | 3.0 ± 2.5 | 3.2 ± 2.5 | .77 |
| BFI total | 3.7 ± 2.2 | 3.8 ± 2.2 | 3.7 ± 2.2 | .91 |

PSS = Perceived Stress Scale; GSDS = General Sleep Disturbance Scale; CES-D = Center for Epidemiologic Studies Depression scale; BPI = Brief Pain Inventory; BFI = Brief Fatigue Inventory.

± 9.0, t = –8.35, $p < .001$) in community-dwelling older adults (Shuman-Paretsky et al., 2014). Baseline PNS descriptions are reported in Table 3. There were no significant differences between the two interventional groups (Table 3).

*Effect of dietary intervention on PNS*

Linear mixed-effect model was conducted on 33 BCS with complete dataset to evaluate the initial efficacy of the dietary intervention. BCS from the high omega-3LC dietary group (n = 20) had a significant decrease in perceived stress ($p < .05$), sleep ($p < .001$), depression ($p < .001$), pain (BPI total pain, $p < .01$), and fatigue ($p < .01$) over the course of intervention (Fig. 4). There were trends of symptom improvement in the low omega-3LC group (n = 13); however, the difference did not reach statistical significance, possibly owing to small sample size. As illustrated in Table 4, estimates of Cohen's d revealed small to median effect sizes of a personalized omega-3LC intervention in reducing the PNS.

*Effect of dietary intervention on nutrition consumption*

The omega 6:omega 3 ratios were significantly decreased in both high and low omega-3LC groups ($p < .001$) at week 10 compared with baseline (Fig. 5A). Participants in both omega-3LC groups also had significant increase in Vitamin D ($p < .001$) and Vitamin E ($p < .01$) consumption at week 10 compared with baseline (Fig. 5B, 5C). There were no significant changes in other food groupings over the course of intervention.

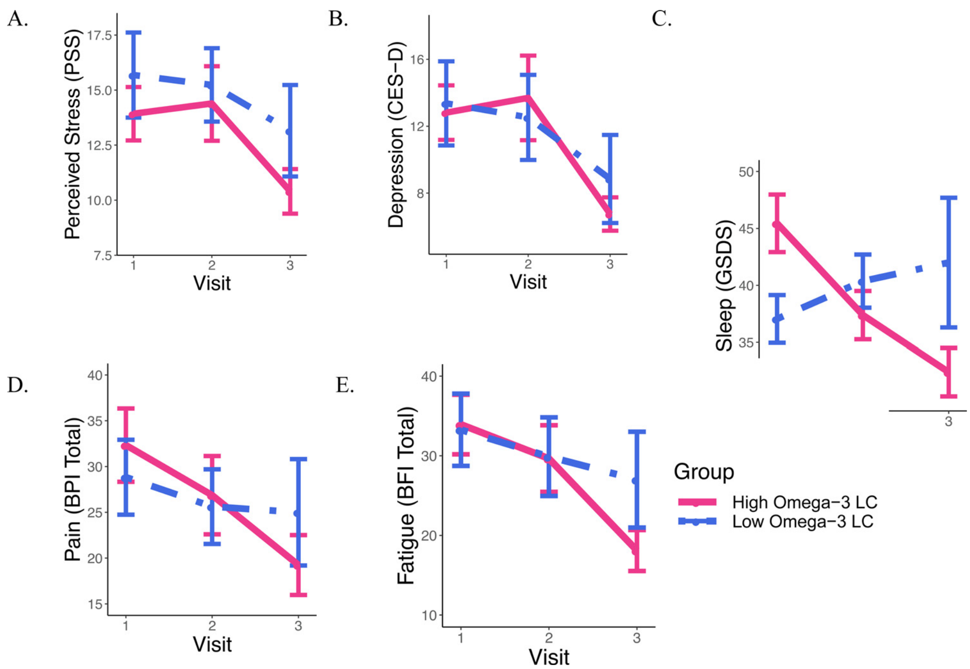


**Figure 4.** Effect of omega-3LC intervention on psychological symptoms. Mean = mean change from baseline; P = significance; Cohen's d = effect size of the mean; 95% confidence Interval = interval range

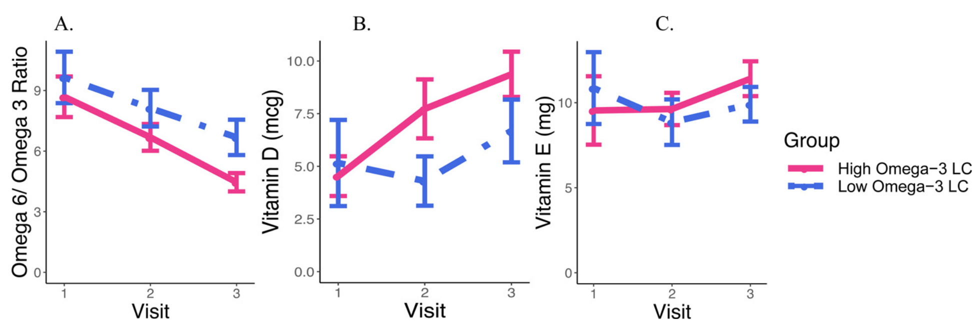


**Figure 5.** Effect of omega-3LC intervention on nutritional intakes. Y axis = Dietary Omega 6: Omega 3 ratio; X axis (1 = Initial visit at baseline, 2 = 3-week follow-up visit and start of intervention; 3 = post intervention).

**Table 4**
Cohen's d for the Pre-Post Changes of PNS Using a Paired-Sample *t* Test (n = 33)

| | Mean (± SD) pre-post changes | *p* | Cohen's *d* | 95% Confidence interval |
|---|---|---|---|---|
| Stress (PSS) | −2.58 (± 6.34) | <.05 | 0.41 | 0.14-0.67 |
| Sleep disturbance (GSDS) | −7.61 (± 17.59) | <.05 | 0.43 | -0.10=0.86 |
| Depression (CES-D) | −3.82 (± 6.90) | <.01 | 0.55 | 0.32-0.86 |
| Pain (BPI total) | −4.58 (± 19.24) | .09 | 0.24 | -0.08-0.66 |
| Fatigue (BFI total) | −9.15 (± 21.80) | <.05 | 0.42 | 0.08-0.88 |

PNS = psychoneurological symptoms; SD = standard deviation; PSS = Perceived Stress Scale; GSDS = General Sleep Disturbance Scale; CES-D = Center for Epidemiologic Studies Depression scale; BPI = Brief Pain Inventory; BFI = Brief Fatigue Inventory.

## Discussion

This investigation generated an abundance of data related to feasibility of investigational procedures, dietary composition, psychoneurological symptomatology, and salivary cytokine collection in a cohort of BCS. The outcomes of this investigation provide evidence to support further research using a personalized meal-planning and omega-3LC approach for symptom self-management. Our feasibility outcomes support the utility of our investigational design and procedures in achieving the targeted investigational outcomes.

Recruitment, although slower than anticipated, was steady and stable with minimal attrition during the investigational period. Our enrollment rate was lower than the reported rates of other breast cancer survivorship research that also used direct mailing as a primary recruitment method (Irwin et al., 2008). Phone calls with non-enrollers revealed that excessive years post treatment, self-identification as not meeting investigational criteria, or personal aversion to fish or salmon were the primary reasons that participants declined to participate. Previous clinical trials targeting cancer survivors have identified recruitment barriers including language challenges, low health literacy, disbelief of the benefits of diet and exercise interventions, interference with work/family responsibilities, symptom burden, and burdens related to research procedures (Aycinena et al., 2017; Brown et al., 2000; Ford et al., 2017; Ott et al., 2006). Although not directly observed in this study, these barriers may explain why 869 BCS did not make the initial phone calls to participate. Additionally, the mailing method we used included some BCS who did not meet eligibility criteria, which may confound the true recruitment rate in our study. Notably, one of the benefits of recruiting BCS from a large cancer center is that trust was formerly established through direct cancer care, serving as a key facilitator of recruitment. More tailored mailings via the cancer registry combined with other recruitment strategies, i.e., social media advertisement, should be considered in future studies to enhance recruitment.

The overall retention rate of this two-phase interventional study was 72% which is consistent with the reported rates from previous dietary interventional studies in cancer survivors (Adams et al., 2015; Irwin et al., 2008; Koutoukidis et al., 2019). Of note, physical limitation due to medical/health conditions, time limitations, and/or issues with availability to return phone calls were the primary reasons for dropout. Our procedures of regularly calling patients and building rapport with research participants increased participant engagement and reduced no-show appointments. Specifically, persistent attempts to contact the participants via phone was effective in retaining participants who had busy life/work schedules. In this study, only five (11%) participants dropped out due to loss of contact. Flexibility in scheduling research phone calls and in-person visits was also found to be highly beneficial in maintaining study retention. Additionally, using a recruitment/enrollment tracking database, and building rapport were effective in supporting retention. Effects of our retention strategies were consistent with the findings of others (Meneses et al., 2013).

Higher quality of dietary consumption has been associated with lower inflammatory load in BCS, with implications for better health outcomes (Orchard et al., 2018). Overall, adherence to the personalized meal plan across groupings was moderate in this investigation. A recent investigation by Park et al. (2019) evaluated and scored dietary adherence, in a larger cohort of 154 BCS participating in an exercise intervention study, also reported only moderate adherence to the dietary recommendations (Park & Kerstetter, 2019). Notably, adherence to the plan improved for all categories (total calories, grain, saturated fat, vegetables added sugars, fruit, dairy, and meat/protein) during phase II, supporting the importance of follow-up and continued support for dietary behavior change. The procedure of conducting eight repeated phone calls in this investigation to collect 24-hour DR data are likely to explain improvement noted in phase II for individual food groupings. A recent systematic review conducted by Goode et al. (2015) evaluated efficacy of telephone, print, and web-based interventions in initiating dietary behavior change and concluded that telephone interventions are preferable (Goode et al., 2015). Future investigations should be designed to include telephone support that is specific to the personalized meal plan. Additionally, including texting or emailing regularly with reinforcing messages and use of telephone mobile app technologies could be incorporated to reinforce personalized dietary recommendations (Goode et al., 2015; McCarroll et al., 2015; Quintiliani et al., 2016). Collectively, broadreach (i.e., non-face to face) and long-term follow up is necessary for sustained dietary change in BCS (Goode et al., 2015; Greenlee et al., 2016).

Adherence to the fish intervention was high in both the high and low omega-3LC groups. Compliance with the fish log reflecting consumption of fish intervention was highly successful with adequate instructions for recording. To our knowledge, this is the first intervention using high-omega-3LC-containing fish while also providing personalized meal plans based upon the Nutrition and Physical Activity Guidelines for Cancer Survivors. Zuniga et al. (2019) reported a significant improvement in general fish consumption related to a Mediterranean-style dietary intervention in BCS (Zuniga et al., 2019). These results support that BCS are generally receptive to recommendations to consume more fish. In contrast, baseline fish consumption in this cohort was well below current guidelines and further research should focus on barriers to fish consumption in this population.

Our procedure for collection of salivary biospecimens yielded excellent compliance with minimal missing data. Although all participants who completed the investigation provided saliva samples in adequate quantities, some experienced low saliva production (xerostomia) requiring more time than anticipated. Future investigations targeting participants at risk for xerostomia, should consider incorporating use of sensory food cues to promote increased saliva production, expediting the collection process, and improving participant experience (Morquecho-Campos et al., 2019).

As anticipated, BCS in this study cohort presented with elevated PNS compared with standardized data (Cohen, 1988; Lewinsohn et al., 1997; Shuman-Paretsky et al., 2014). Further, a significant decrease in PNS was observed in the high omega-3LC group, supporting the efficacy of a dietary fish intervention towards PNS reduction. Baseline and follow-up dietary data provided us with data-based insights into nutrients that are lacking in this population and highlighted the potential for food aversions. Salmon as consumed in this investigation is a rich source of omega-3LC and Vitamin D. We report that the omega-6 to omega-3 ratio was significantly decreased in both high and low omega-3LC groups and Vitamin D was significantly increased compared with baseline. With this finding, we conclude that the fish intervention displaced other omega-6-laden foods, thereby improving the ratio of these fatty acids, with the most robust effect in the high omega-3LC group. Hence, consumption of wild caught Alaskan salmon at an amount 12 ounces/week impacted this ratio more significantly, closer to what is recommended for optimal outcomes, compared with the low omega-3LC group 6 ounces/week (Simopoulos, 2002). Salmon offers a safe, low-mercury source of omega-3LC and is an optimal fish choice for BCS. Based upon our findings, the patients were highly receptive to salmon as the dietary intervention and this receptivity continued throughout the intervention making salmon a highly feasible choice.

### *Limitations*

Although our findings provide a roadmap for dietary interventions in cancer survivors, our findings are limited by sample size and the relative homogeneity of our cohort. Absence of a control group posed a significant limitation to the design and associated outcomes. Further larger-scale investigations are necessary with a cohort that encompasses greater racial and ethnic diversity, particularly related to investigational outcomes (i.e., PNS and salivary cytokines) to assess the potential for generalizability.

## Conclusion

The outcomes of this investigation provide evidence to support further research using a personalized meal-planning and omega-3LC approach for symptom self-management. This study's preliminary findings support evidence that delivery of personalized dietary intervention is feasible and safe. The higher consumption level of dietary omega-3LC via fish was well-tolerated and effective in reducing PNS in BCS. Adherence to dietary recommendations were moderate and continually improving over the study course, suggesting that continuing support and enforcement is needed to enhance dietary behavioral change. The utility of our investigational design and procedures in achieving the targeted investigational outcomes were efficiently integrated and feasible.

*Implications for Practice*

Given that there is significant evidence that PNS symptoms are elevated in BCS compared with national averages among American adults, expanded focus is necessary regarding potential interventions for lifestyle change as a means to reduce the symptom experience and potentially enhance productivity and quality of life in survivorship (Ganz et al., 2011; Gwede et al., 2008; Hamood et al., 2018; Lee et al., 2020; Reinertsen et al., 2010; Roiland & Heidrich et al., 2011; Schreier et al., 2019). Increased consumption of omega-3LC, and specifically more fish, is encouraged as a component of the Nutrition and Physical Activity Guidelines for Cancer Survivors (Rock et al., 2012). The guidelines emphasize that nutrients should be obtained through dietary sources, not supplements, unless consumed under medical supervision, making education around dietary behaviors a priority in meeting these guidelines (Rock et al., 2012). Given our report of low baseline fish consumption, BCS should be encouraged to consume a minimum of two-three, 3-ounce servings of low mercury fish per week as a "preformed" source of omega-3LC. Salmon and chunk light tuna are excellent sources of omega-3LC, while also relatively low in contaminants compared with other larger fish species (USDA, 2016). The feasibility data we report support that BCS were receptive to this level of fish consumption.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pmn.2022.03.007.

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