Diet And Nutrition In CAncer (The DANICA study):

The effect of a Mediterranean Diet intervention on cancer-related fatigue and mitochondrial function during chemotherapy

Study chair:	Amber S. Kleckner, PhD
Study co-investigators:	Erin Campbell, MD, MPH Thomas M. Campbell, II, MD Sue Czap, MS, RD, CSO Po-Ju Lin, PhD, RD, MPH Karen M. Mustian, PhD, MPH Luke J. Peppone, PhD, MPH Michelle Shayne, MD
Medical monitor and co-I:	Allison Magnuson, DO, MPH
Biostatistician:	Eva Culakova, PhD, MS
Laboratory chair:	Michelle C. Janelsins, PhD, MPH

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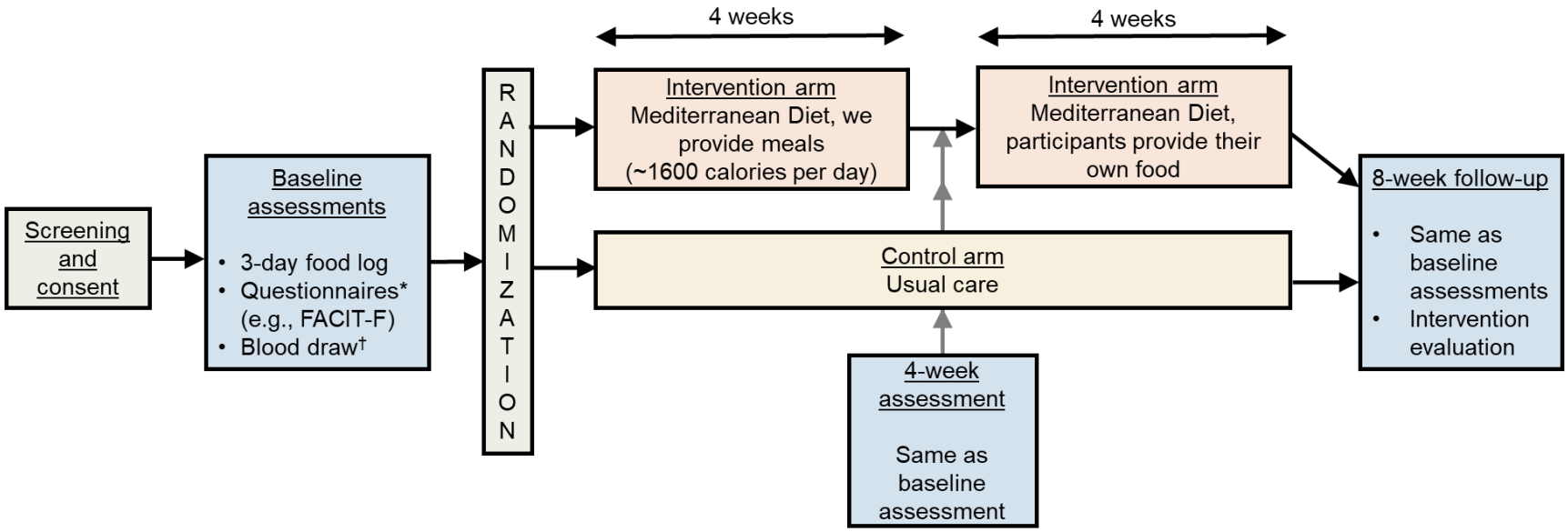
Table of Contents

Fig. 1. Study Schema



*Questionnaires include:

- On-study (baseline only)
- Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F): fatigue and quality of life questionnaire
- 14-item Mediterranean Diet assessment
- Aerobics Center Longitudinal Study (ACLS) physical activity questionnaire
- 3-day food record
- Symptom inventory questionnaire
- Brief Fatigue Inventory (BFI): fatigue questionnaire
- Functional Assessment of Cancer Therapy-Cognition (FACT-Cog) cognitive questionnaire
- Brief Pain Inventory (BPI): pain questionnaire
- Insomnia Sleep Index (ISI): sleep quality questionnaire

†Blood will be collected for metabolic assays, mitochondrial assays, and other mechanistic investigations

1. Purpose of the study

In this study, we will assess the feasibility of delivering an 8-week Mediterranean Diet intervention as well as the intervention's preliminary efficacy on cancer-related fatigue among patients undergoing chemotherapy, compared to usual care. In the first 4 weeks of the intervention, we will provide the participants with food and educate them on the principles and components of the Mediterranean Diet, while in the second 4 weeks participants will prepare their own food. In addition, we will evaluate changes in metabolism and mitochondrial function during 4 weeks of chemotherapy and determine how adherence to a Mediterranean Diet modulates these changes during these 4 weeks. These data will inform the design of a larger randomized clinical trial that evaluates the effects of the Mediterranean Diet vs. a behavioral control on cancer-related fatigue.

Aim 1: to evaluate the feasibility of delivering a Mediterranean Diet intervention, as measured by adherence at both 4 weeks and 8 weeks.

Aim 2: to evaluate the preliminary efficacy of a Mediterranean Diet vs. usual care to prevent cancer-related fatigue among patients with cancer undergoing chemotherapy, as assessed using the FACIT-F.

Mechanistic Aim: to evaluate the effects of the Mediterranean Diet on mitochondrial function (i.e., mitochondrial stress test) and blood-based metabolic biomarkers (e.g., fasting blood glucose, insulin).

2. Background and rationale

2.1 Background

2.1.1 Cancer-related fatigue in the cancer experience

Cancer-related fatigue affects up to 90+% of patients undergoing chemotherapy, depending on the type of cancer and treatment as well as the measure used to evaluate fatigue.[1,2] It is not relieved by sleep or rest, and its severity can greatly hinder the ability to perform activities of daily living and decrease quality of life. The mechanisms behind the etiology and pathophysiology of cancer-related fatigue seem to be related in part to inflammation,[3] but largely are not understood, thereby thwarting the development of effective preventative strategies and treatments. Cancer-related fatigue is one of the most debilitating symptoms in types of cancer that are typically treated outpatient with high cure rates, such as breast[4] and bladder[5] cancer. Fatigue trajectories tend to increase on average throughout the course of treatment with local maxima several days after each infusion cycle, and then recover after treatment, though fatigue often does not return to baseline.[6-9]

2.1.2 Link between nutrition, symptoms of cancer, and side effects of treatment

Cancer causes profound metabolic and physiological perturbations that can dysregulate metabolic processes and affect nutritional needs.[10,11] Symptoms vary with cancer type, but patients often experience weight loss (e.g., for cancers of the pancreas, stomach, esophagus, lung[12]) or weight gain (e.g., for cancers of the ovary[13] and breast[14-16]) and/or changes in gastrointestinal function (e.g., for colon cancer[12]). For these reasons, poor nutritional status has been documented in more than 50% of patients at the time of cancer diagnosis.[17] For these reasons, poor nutritional status has been documented in nearly 20% of patients with bladder cancer at the time of cancer diagnosis.[18]

Further, all of the major modalities of cancer treatment, including surgery, radiation, chemotherapy, and immunotherapy, can significantly impact nutritional needs, alter regular eating habits, and adversely affect how the body digests, absorbs, and metabolizes food.[17,19] These biochemical insults and side effects can all interact bidirectionally with metabolic function. For example, Dieli-Conwright et al.[20] recruited breast cancer patients to a longitudinal study during (neo)adjuvant chemotherapy. They showed that all metabolic measures associated with metabolic syndrome worsened during 12- to 18-week chemotherapy

treatment: waist circumference, blood pressure, fasting blood glucose concentrations, triglycerides, and high-density lipoprotein cholesterol. Indeed, metabolic toxicity is one of the top priority areas for research according to the National Cancer Institute (NCI) Symptom Management and Quality of Life Steering Committee.[21]

These systemic changes in metabolism and nutritional needs can be modulated by nutritional status. Patients who maintain adequate nutritional status exhibit better physical functioning, fewer clinical symptoms, better quality of life, and better overall survival than patients with poor nutritional status.[22,23] Also, those who have good nutritional status have better prognosis after curative surgery or radiation for cancer compared to those with poor nutritional status.[24-26] However, the role of nutrition therapy to circumvent serious side effects of cancer and its treatments during chemotherapy is in its infancy, and there are currently no evidence-based nutrition guidelines specifically for reducing or preventing cancer-related fatigue.[1]

2.1.3 Nutrition, cancer, and obesity

Historically, the chief goals of nutrition during cancer treatment were to prevent or reverse nutrient deficiencies, preserve lean body mass, and minimize nutrition-related side effects (loss of appetite, nausea, taste changes, or bowel changes) so as to maximize quality of life. Currently, however, approximately 70% of Americans are overweight with 40% obese,[27] and excess body mass complicates treatment and is also a risk factor for many symptoms (e.g., cancer-related fatigue,[28] chemotherapy-induced peripheral neuropathy,[29] pain[30]). While weight loss perhaps should not be a goal during cancer treatment, lifestyle habits that promote a healthy weight such as dietary changes have the potential to improve well-being and decrease side effects during cancer treatment and into survivorship.[31] Indeed, practicing oncologists in the United States recognize the importance of addressing a patient's excess body weight in standard cancer care.[32] Furthermore, obesity is associated with "chemoresistance," or lack of efficacy of standard chemotherapy regimens against the tumor.[11,33] Mechanisms by which obesity is associated with reduced efficacy include:

a. Chronic low-grade inflammation
b. Increased tumor-associated macrophages
c. Metabolic perturbations
d. Altered pharmacokinetics
e. Adipose tissue expansion
f. Impaired drug delivery

Improving overall diet quality can potentially improve the first three mechanisms—chronic low-grade inflammation, increase tumor-associated macrophages, and metabolic perturbations—*without weight loss*, and we hypothesize that improvements in metabolic function will improve symptom management and overall supportive care outcomes.

2.1.4 Nutrition as a behavioral intervention

The National Academy of Sciences emphasizes the importance of expanding cancer treatment to include promotion of a healthy lifestyle, including a healthy diet, weight management, and physical activity.[31] There have been many cross-sectional studies demonstrating that "higher quality" dietary patterns are associated with fewer symptoms during and after cancer treatment, as well as a reduced risk for recurrence and mortality.[34,35] The definition of "higher quality" varies, but usually refers to dietary patterns that are rich in fruits, vegetables, whole grains, unprocessed lean meat products (e.g., chicken breast, seafood) or lean protein sources, and low in added sugar and highly processed carbohydrates.[36-38] Moreover, patients with cancer intuitively understand the importance of nutrition: at least 70% of patients

take supplements to improve their nutritional status, a percentage that is much higher than individuals without cancer.[39,40] Some of these supplements are indeed beneficial, but many are inert and some are dangerous.[39] A 2018 systematic review and meta-analysis concluded with recommendations for high antioxidant intake from fruits and vegetables but *not* antioxidant supplements to prevent chronic diseases such as cancer,[41] which was corroborated in a 2020 study showing that antioxidant supplements increased the hazard of cancer recurrence.[42] Also, unfortunately, results of supplement studies are also often inconsistent,[40,43] so that guidelines for cancer survivors are not clear.[44] For example, in a recent review (Inglis et al.), we evaluated nutritional interventions for cancer-related fatigue and found that previous research on supplements for treating cancer-related fatigue such as ginseng and guaraná led to inconsistent findings.[43]

Diet interventions comprise nutrients that interact synergistically to reduce chronic inflammation, minimize oxidative stress, promote insulin sensitivity, and promote efficient metabolic processes.[45,46] In the realm of supportive care, Zick et al. developed a "fatigue reduction diet" that promoted a diet rich in fruits, vegetables, whole grains, and omega-3 fatty acids.[34] They confirmed compliance with the diet by quantifying serum carotenoids and omega-3 fatty acids and showed that the intervention significantly alleviated persistent cancer-related fatigue.[34] This study recruited cancer survivors; there are two randomized controlled studies to our knowledge that have tested a diet during chemotherapy.[47,48] Djuric et al. delivered a 12-month diet and exercise intervention via telephone among patients with breast cancer undergoing chemotherapy to prevent weight gain; those in the control arm received printed materials on diet and exercise.[47] The diet encouraged low-fat foods and a high quantity of vegetables, and those in the intervention group had significantly greater improvements in quality of life over the course of the intervention.[47] Villarini et al. also implemented a dietary intervention among patients with breast cancer undergoing chemotherapy; their primary goal was to prevent weight gain.[48] The dietary intervention lasted the duration of chemotherapy and was based on Mediterranean and macrobiotic recipes, i.e., it encouraged whole grains, fruits, vegetables, soy, yogurt, eggs, and occasional fish and discouraged sugar and saturated fat. Those in the intervention group lost significantly more fat mass without affecting basal metabolic rate or loss of fat-free mass; unfortunately symptom data were not reported.[48]

Despite the knowledge that nutrition is important for health outcomes, previous research shows that many struggle to change their dietary patterns. Even after a cancer diagnosis, a recent study by Du et al. showed that nutrient intake in cancer patients/survivors did not differ from individuals without a cancer diagnosis.[39] Moreover, von Gruenigen et al.[49] and Blanchard et al.[50] showed that only 15-20% cancer survivors consume 5 or more fruits and vegetables per day, which is similar to the general American population.[51] In general, adherence to dietary interventions tends to be poor.[50] For example, von Gruenigen et al. conducted a single-arm study in which patients with ovarian cancer were encouraged to consume 2 cups of fruit, 2.5 cups of vegetables, 3 servings of low-fat dairy foods, and 3 servings of whole grains per day; they were advised to limit consumption of red and processed meat.[52] On average, patients were not following those recommendations before the intervention and failed to achieve those goals after the intervention; there were no significant differences for any of the food groups comparing pre- vs. post-intervention ($p=0.09$).[52] Meal planning, shopping, and time for food preparation appear to be major barriers to dietary change. Successful interventions tend to involve nutrition education in addition to in-person group sessions, cooking classes, food-shopping field trips, and/or individualized counseling using social cognitive theory.[34,47,53] Importantly, it has been shown that patients who are of poor nutrition status are *less* compliant with recommended oral nutrition support (i.e., a milk-based beverage supplement),[54] potentially exacerbating their condition. Therefore, it will be crucial to design an intervention that patients will be motivated to embrace and will have a positive impact on outcomes.

2.1.5 The Mediterranean Diet

The Mediterranean Diet is one of the most widely studied dietary patterns. It is the traditional diet in Greece, Southern Italy, and Spain, and includes high consumption of fruit, vegetables, legumes, nuts and seeds, whole grains, and olive oil; moderate consumption of seafood, dairy products (e.g., cheese and yogurt but not whole milk or butter), eggs, poultry, and red wine with meals; and low consumption of sweet desserts, red meat, and highly processed foods. The PREvención con DIeta MEDiterránea (PREDIMED) study was the largest study to date implementing the Mediterranean Diet.[55,56] The participants were older men and women at risk for cardiovascular disease and the primary outcome was clinical events of cardiovascular disease. The study investigators provided participants with 1 L of extra virgin olive oil per week (50 mL/day for participants and the rest for family needs) or 30 g/day of mixed nuts (walnuts, almonds, hazelnuts; plus additional for family needs). Compliance was adequately high, and the diet successfully reduced the incidence of major cardiovascular events.[56]

The hypothesis herein is that adherence to the Mediterranean Diet during chemotherapy will prevent cancer-related fatigue. There have not been any studies in the literature assessing the effects of a Mediterranean Diet on cancer-related fatigue during chemotherapy, though the supporting inferences below have led us to our hypothesis: First, dysregulated metabolism is involved in the etiology of fatigue,[3,57] and the Mediterranean Diet is associated with reduced risk of metabolic syndrome.[58] The Mediterranean Diet is also high in nutrients that are particularly beneficial for metabolism including high amounts of protein and dietary fiber as well as nutrients such as polyphenols[59] and hydroxytyrosine.[60,61] Second, there is a well-known association between inflammation and cancer-related fatigue,[3] and the Mediterranean Diet modulates the balance between pro- and anti-inflammatory responses (specifically reduces leukocytes and platelets),[62] and protects against the inflammatory pathogenesis of cancer.[63,64] Next, diet quality is correlated with more severe fatigue in other conditions (e.g., multiple sclerosis,[65] type 2 diabetes,[66] chronic fatigue syndrome[67]). Although the pathophysiology of the fatigue might not be the same between these different conditions, it is reasonable to believe that there is at least some overlap.[68,69] In addition, a healthy microbiome could help reduce cancer-related fatigue,[43,70] and the Mediterranean Diet is high in dietary fiber and promotes health of the gut microbiome.[71] Furthermore, sleep quality is an important mediator between interventions such as yoga and cancer-related fatigue (co-investigators Lin, Mustian, et al.[72]), and adherence to the Mediterranean Diet has been associated with better sleep quality.[73] Lastly, depression is consistently associated with fatigue,[74] and the Mediterranean Diet has been associated with fewer depressive symptoms in older adults[75] as well as improved mood in young, healthy women.[76]

Importantly, a dietary intervention during chemotherapy should not thwart the antineoplastic mechanisms of the chemotherapy. The Mediterranean Diet has been shown to impede the development of various forms of cancer, though it is unclear if nutrition could modify the effects of the chemotherapy.[77-79] A 2019 preclinical study directly compared the effects of a high corn oil diet and a high extra virgin olive oil diet in a drug-induced breast cancer rat model and found that the corn oil diet promoted tumorigenesis significantly more than the olive oil diet via adaptations to metabolic and immune function.[80]

2.1.6 Mitochondrial dysfunction as a contributor to cancer-related fatigue

Mitochondrial dysfunction is increasingly recognized as a major contributor to fatigue due to mitochondria's essential role in energy production, generation and regulation of reactive oxygen species, and other physiological processes.[81] Mitochondria are inadvertent targets of chemotherapy (especially doxorubicin and oxaliplatin[82]); chemotherapy causes damage to the mitochondrial structure and function, as well as its DNA. Further, mtDNA is more susceptible to mutations and has poorer repair mechanisms than nuclear DNA, likely exposing it to worse damage from chemotherapy.[83] Indeed, reduction of mtDNA content in peripheral blood cells was significantly greater among those with worsening of cancer-related fatigue compared to those without fatigue in patients with early-stage breast cancer undergoing

chemotherapy.[84] There have been eight studies to our knowledge probing mitochondrial function in the context of cancer-related fatigue[84-90] including our own.[91] Six of these studies looked at associations between mitochondrial function and fatigue during treatment from radiotherapy,[85-90] one enrolled patients initiating anthracycline- or taxane-based chemotherapy,[84] and ours recruited survivors of breast cancer who underwent a variety of antineoplastic treatments.[91] Collectively, these studies show that fatigue is associated with less mtDNA,[84] downregulated mitochondrial gene expression,[86,88] and less complex III-linked respiration[87,88] but no changes in the activity of mitochondrial oxidative phosphorylation complex enzymes,[89] all in circulating blood cells. Our study in survivorship showed that lower mitochondrial gene expression was associated with greater subsequent improvements in fatigue over the course of study.[91] However, a major gap in the literature is that **mitochondrial function (i.e., efficiency of ATP production) and energy metabolism has not been thoroughly characterized in the context of cancer-related fatigue, especially as derived from chemotherapy treatment.**

2.2 Preliminary data

Dr. Amber Kleckner's primary mentor, Dr. Luke Peppone, performed a large, phase II multisite study evaluating the effects of fish oil vs. soybean oil supplementation on cancer-related fatigue in breast cancer survivors.[92] Compliance with the intervention was excellent, with 84.5% of all participants taking at least 90% of their supplements. Based on the literature, the hypothesis was that fish oil supplementation would alleviate fatigue more than soybean oil due to its high omega-3 fatty acid content and the observation that omega-3 fatty acids can alleviate fatigue.[93-96] However, soybean oil, despite containing no marine omega-3 fatty acids, has been shown to have antioxidant and anti-inflammatory properties.[97-99] In Dr. Peppone's study, all participants experienced reduction of fatigue over the course of the 6-week intervention, and those in the soybean oil group had a greater reduction.[92] These data demonstrate that dietary changes may have an impact on symptoms in cancer survivors including cancer-related fatigue.

As part of the study herein, we will collect blood samples to quantify mitochondrial function in circulating T cells and blood-based metabolic biomarkers. Dr. Amber Kleckner, the study chair, has developed a protocol to collect blood samples, isolate T cells, and measure real-time respiration in these cells.

2.3 Innovation

A major gap in the literature is whether implementing a healthy dietary pattern during chemotherapy can reduce symptom and side effect burden. This is one of the first randomized controlled trials to implement a dietary change during chemotherapy to address supportive care outcomes. It is the first to provide food based on the Mediterranean Diet during chemotherapy, and it is the first diet-based intervention during chemotherapy to look at cancer-related fatigue as the primary outcome.

One of the reasons that there are not effective preventative strategies or treatments for cancer-related fatigue is that its etiology is largely not understood. This study will use a powerful metabolic assay (respiration of freshly isolated human T cells) as well as a battery of standard metabolic assays (e.g., fasting blood glucose, insulin) to describe the effects of chemotherapy on metabolic function in unprecedented detail. These data will be valuable in drawing associations between metabolic health and patient-reported symptoms regardless of adherence to the Mediterranean Diet. These data will be able to inform the optimization of this dietary intervention for a follow-on randomized controlled trial.

3. Administrative organization

There is one participating *research site* in this study: University of Rochester Medical Center. There are several different groups and departments that will be involved:

1) The oncology clinics, where patients are seen for their cancer treatment. These include Wilmot Cancer Institute, Pluta Cancer Center, or another Wilmot satellite location. This is where patients can be approached, informed consent can be granted, questionnaires can be completed, and blood can be drawn.
2) Blood can also be drawn at a University of Rochester Laboratories (UR Labs) Patient Service Center.
3) The Cancer Control Psychoneuroimmunology Laboratory (CCPL), directed by Dr. Michelle Janelsins. This is where blood samples will be processed and stored; participants will not come here.
4) Flow Cytometry Facility, directed by Dr. Timothy Bushnell. This is where the Seahorse Extracellular Flux Analyzer is housed and where cellular respiration experiments will be conducted on the cells isolated from blood samples. Participants will not come here.

4. Study design

4.1 Brief description and specific aims

This will be a feasibility pilot randomized controlled trial performed at a single site. We will recruit 42 patients with cancer who are beginning a chemotherapy regimen and randomize them 2:1 to the intervention group or usual care (28 in the intervention arm and 14 in the usual care arm). The uneven allocation serves to improve recruitment, as some patients are disappointed to be assigned to the usual care arm, and allows us to get more information about the intervention. This will be an open label study (due to the nature of the intervention it is not possible to blind participants, and due to the active involvement of the PI in data acquisition, it is not feasible to blind the PI). At baseline, participants will complete an on-study form that includes demographics and clinical characteristics. They will complete a 3-day food record (ideally from two weekdays and one weekend day), a fasted blood draw, and several questionnaires [i.e., 14-Item Mediterranean Diet Assessment Tool,[100] Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F), Aerobics Center Longitudinal Study (ACLS) physical activity questionnaire, Brief Fatigue Inventory (BFI), 27-item Symptom Inventory, Functional Assessment of Cancer Therapy-Cognition (FACT-Cog), Brief Pain Inventory (BPI), Insomnia Severity Index (ISI)]. For the duration of the study, all participants will complete a daily diary that includes their average fatigue level that day. For 4 weeks, we will provide participants in the intervention group with food based on the Mediterranean Diet. We intend this food to be substituted or supplemented with other food of the patients' choosing, though we encourage participants to comply with the Mediterranean Diet for all meals and snacks. During this time we will also provide education regarding the principles and composition of the Mediterranean Diet and how to effectively implement it at home. This education will include materials that encourage behavior change to inspire motivation and adherence to the diet. At 4 weeks, participants will undergo a mid-point evaluation where they will complete the same assessments as at baseline except for the on-study form. For weeks 5-8, participants in the intervention group will be encouraged to follow the Mediterranean Diet though we will not provide food. During the 8-week intervention, we will be in contact with participants in both groups to monitor adverse events and discuss any barriers to consuming the diet (in the intervention group). At 8 weeks, participants will repeat the assessments and undergo an exit interview, which will last approximately 15-30 min. Participants will receive $20 total to complete baseline and post-intervention measures and those in the intervention group will receive free meals for 4 weeks. Those in the usual care group will be offered the intervention materials and one week of meals *gratis* at the conclusion of the study.

Intervention: For the first 4 weeks, those in the intervention arm will receive three meals per days compliant with the Mediterranean Diet. These meals will provide approximately 1,600 kcal/day (range 1,200-2,000 kcal/day) and will be evaluated by a registered dietitian with experience with patients with cancer (e.g., Po-Ju Lin, PhD, RD, MPH, or Sue Czap, RD) for appropriateness and nutrient adequacy. We will encourage participants to supplement the provided food with food of their choosing so as to satisfy hunger and thirst; the amount of food that is supplemented will vary greatly due to each individuals' nutrient needs, and we encourage that all food be compliant with the Mediterranean Diet. During this time participants will receive education on the principles and components of the Mediterranean Diet. This will include a phone- or computer conferencing-led education session, information packet, and cookbook, all of which were designed specifically for this study.

The questionnaires will be completed via Research Electronic Data Capture (REDCap) or via paper-and-pencil (participants' choice); the food record and daily diary will be completed on paper. They will be scored and entered into a secure database by the study team. Preliminary efficacy of the intervention on cancer-related fatigue will be assessed using the FACIT-F as a primary endpoint, and also via the BFI and symptom inventory. Adherence will be determined using the 14-Item Mediterranean Diet Assessment Tool.[100] Blood will collected and used immediately for real-time respiration assay on T cells, sent for analysis at UR Labs, and/or processed and stored at -80°C in the CCPL for later assays.

Specific aims:

Aim 1: to evaluate the feasibility of delivering a Mediterranean Diet intervention, as measured by adherence at both 4 weeks and 8 weeks.

> *The hypothesis is that those in the Mediterranean Diet group will score higher on the 14-Item Mediterranean Diet Assessment Tool at 4 weeks and 8 weeks.*
>
> *We will consider the feasibility of the intervention successful if >70% of participants who consent complete the study and if >70% of participants in the intervention group improve their Mediterranean Diet score at least one point[56,100] from baseline to 4 weeks and baseline to 8 weeks.*

Aim 2: to evaluate the preliminary efficacy of a Mediterranean Diet vs. usual care to prevent cancer-related fatigue among patients with cancer undergoing chemotherapy, as assessed using the FACIT-F.

> *We expect all measures of cancer-related fatigue to increase over the course of chemotherapy, though we hypothesize that the differences will be attenuated in the intervention group as assessed using the FACIT-F fatigue subscale score (primary aim: baseline to 4 weeks).*

Mechanistic Aim: to evaluate the effects of the Mediterranean Diet on mitochondrial function (i.e., mitochondrial stress test) and blood-based metabolic biomarkers (e.g., fasting blood glucose, insulin).

> *The hypothesis is that, at 4 weeks, those in the Mediterranean Diet group will have T cells that exhibit higher ATP turnover, a higher spare respiratory capacity, and a smaller proton leak compared to the controls. We also hypothesize that those in the Mediterranean Diet group will have lower fasting blood glucose and lower fasting insulin concentrations than those in the control group at 4 and 8 weeks.*

4.2 Subject population

We will recruit 42 patients with cancer undergoing chemotherapy from Wilmot Cancer Institute or a satellite clinic (e.g., Pluta Cancer Center). In particular, these patients will have a recent diagnosis of cancer (any type except brain cancer), and will represent a broad range of patients seen at Wilmot Cancer Institute including young and old; men and women; those of various ethnic and racial categories (**Table 1**); those who are underweight, normal weight, and overweight; those with and without underlying metabolic dysfunction (e.g., diabetes); and those undergoing various types of chemotherapy treatment.

From previous local studies completed by our group, we expect a 20% withdrawal rate, resulting in approximately 33 participants with evaluable data (approximately 22 in the intervention group and 11 in the usual care group).

No vulnerable classes of subjects such as fetuses, neonates, children, pregnant women, prisoners, institutionalized individuals, or decisionally impaired adults will be recruited.

Total planned enrollment: 42 participants

Table 1. Targeted/planned enrollment by ethnic and racial categories:

Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	2	1	3
Not Hispanic or Latino	26	13	39
Ethnic Category: Total of All Subjects	28	14	42
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	2	1	3
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	3	2	5
White	23	10	33
Racial Categories: Total of All Subjects	28	14	42

We will recruit males and females to this study and expect to recruit more females because a large number of participants will likely be recruited from the breast cancer clinic. Based on the characteristics of samples recruited for recently completed local studies by our group, we anticipate that the potential sample pool for the current study will be mostly White/non-Hispanic individuals, though we will encourage patients of other racial and ethnic groups to participate. The average age for studies conducted by our group tends to be approximately 65 years, though we would like to invite younger patients (e.g., in their 20's and 30's) and much older patients (e.g., in their 80's) to participate in our study as well. Children, individuals under the age of 18, as defined by the NIH Grants Policy Statement, will not be included because their nutritional intake is often determined by their parents/guardians/caregivers and their metabolic function is different than the adult population due to their growth and development during maturation.

4.3 Study interventions

Participants will be randomly assigned 2:1 to a Mediterranean Diet or usual care using a computer-generated random numbers table with blocks of 3 or 6. Patients will be stratified based on how frequently their chemotherapy is planned to be administered. One strata will include patients who plan to receive

weekly, biweekly (Q2w), or every 4-week (Q4w) regimens, and the other strata will include those on other regimens (e.g., Q3w). This stratification will allow us to account for who is at the "end" of a cycle and who is in the "middle" of a cycle at the 4- and 8-week assessment points.

4.3.1 Mediterranean Diet intervention

The first 4 weeks of the intervention we will provide food as well as a Mediterranean cookbook and tips to follow a Mediterranean Diet in the home. The menu will be based on the Mediterranean Diet Pyramid (**Fig. 2**) and the Mediterranean Exchange List developed by Djuric et al. (2008)[101] for implementation in research. These guidelines include categories of foods (e.g., dark green vegetables, high-monounsaturated fatty acids), goal amounts of each category, and foods that fall into each category. Consumption of all of the food provided to the participant will cause them to be adherent with the Mediterranean Diet intervention, and foods can be substituted with the participant still being adherent. Although red wine is recommended as part of the Mediterranean Diet, we will not recommend or provide any alcohol due to lack of research regarding the benefits/drawbacks of alcohol consumption on the efficacy of the chemotherapy or supportive care outcomes.[102-104] The menu will include meals every day for one week (7 breakfasts, 7 lunches, and 7 dinners) plus snacks, and then the menu will be repeated four times to span the four-week period. The provided food will be approximately 1,600 kcal/day (1,200-2,000 kcal), though participants will be encouraged to consume additional food to avoid hunger. These diets have been developed in conjunction with Dr. Tom Campbell, Dr. Erin Campbell, and their staff at the Highland Hospital's Weight Management & Lifestyle Center (NCT03045289). Their team has successfully developed and executed a plant-based diet intervention and is developing a Dietary Approaches to Stop Hypertension (DASH) diet intervention (NCT04048642). The Mediterranean Diet menu will be assessed for completeness and safety in conjunction with a registered dietitian (e.g., Po-Ju Lin, PhD, RD; Sue Czap, RD).

The food will be supplied by a combination of Project Lean Nation and a local grocery store/food supplier (e.g., Wegmans). Project Lean Nation meals are high in lean protein and vegetables; they are flash-frozen, which allows the structure and the nutritional contents to be preserved with minimal artificial preservatives. Twelve meals per week will be supplied by Project Lean Nation, and meals will either be provided to the patient at the hospital or delivered to the participants' homes once per week for 4 weeks. These meals include items such as the Falafel Plate, Spaghetti & Meatballs, and Pan-Roasted Salmon. We will then provide the rest of the food via a local grocery store/food supplier. We will give participants some key ingredients at the beginning of the study and have additional food delivered to their homes weekly via Instacart. This food will include breakfast items (e.g., oatmeal with nuts and dried fruit) as well as other Mediterranean Diet staples (e.g., olive oil, fresh greens, fresh fruit).

The composition of the meals will be based on following guidelines:[101,105]

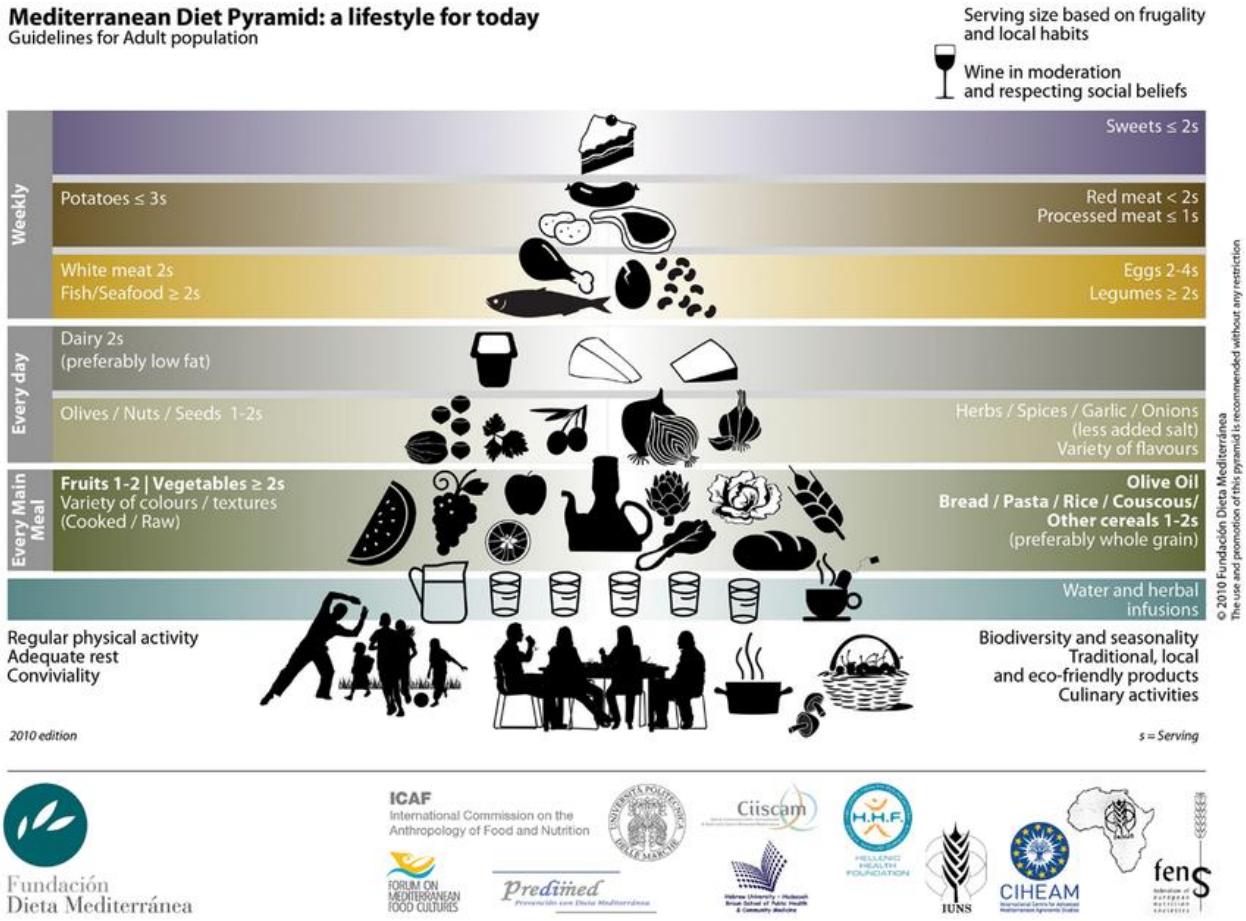


Fig. 2. The Mediterranean Diet guidelines.

It is the goal that the meals are appetizing and enjoyable. The meals will include herbs and spices (e.g., oregano, garlic) and will not intentionally be low-salt or low-fat. To reiterate, all participants will be encouraged to supplement the meals with food that conforms to the Mediterranean Diet, especially olive oil, whole grains, fruit, and nuts; to eat as much as they want; and to consume their own meals and snacks in place of the provided meals if they prefer to do so, provided the supplemental food fits within the Mediterranean Diet plan. The provided food is offered primarily to enhance adherence to the diet. The day and the time of each meal will *not* be specified. Some sample menu items could include the following.

Breakfasts (approx. 400 kcal):

- Oatmeal with walnuts and raisins

Lunches or dinners (approx. 500 kcal):

- Pan-roasted salmon
- Spaghetti and meatballs
- Falafel
- Chicken taco

Snacks or side dishes (approx. 100 kcal):

- V8 beverage
- Nuts
- Fruit (fresh, dried, canned, or frozen)
- Whole wheat crackers with hummus

Most of the food will be either frozen or shelf-stable at room temperature and require minimal preparation. Storage and reheating instructions will be provided.

At the beginning of the study, participants in the Mediterranean Diet group will receive a cookbook that includes information about the Mediterranean Diet (e.g., history, purported benefits) as well as recipes and will be encouraged to follow its practices for snacks or any supplementary food. The meals provided in our cookbook are selected to be compliant with the Mediterranean Diet but also require little preparation and no rare ingredients (i.e., all ingredients should be readily available at the local grocery store). It will also include "snacks," or food that one can have on-hand that require little to no preparation. During week 3 or 4, participants will have an education session to discuss how to effectively implement a Mediterranean Diet into their routine. This session will be loosely based on a combination of behavioral theory and cognitive behavioral theory.[106] Participants will be taught a variety of strategies to promote behavior change, as listed in **Table 2.**

Strategies of behavior change	Action plan to promote adherence
Self-monitoring	Food log
Problem solving	Plan meals and grocery store trips
Goal setting	Definite time frame (4 weeks), weekly goals if applicable
Contingency management	Keep nutrient-dense snacks handy
Cognitive restructuring	Think of food as medicine
Social support	Involve spouse/roommates, especially those with whom participant shares meals
Stimulus control	Make sweets less accessible
Stress management	Positive attitude, acceptance, relaxation
Relapse prevention	Start each day anew; do not consider a day "ruined" if ate non-compliant food

Table 2. Strategies of behavior change (left column) with examples of how each could be implemented (right column)

In a standardized educational session, a member of the study staff will discuss each of the strategies, and then select a subset to focus on. In the second half of the intervention, participants will continue to receive a weekly check-in with the study team. As in the first half of the intervention, we will discuss barriers to adhering to the intervention and potential strategies to overcome those barriers.

Either Dr. Amber Kleckner (study chair) or a member of the study staff who was trained by Dr. Kleckner will deliver the intervention. The intervention will be standardized and include a checklist for the interventionalist to ensure fidelity of the intervention and to prevent drift. For interventions delivered by a staff member other than Dr. Kleckner, at least one out of five sessions will be either attended by Dr. Kleckner or audio-recorded; feedback will be provided to the interventionalist.

We will contact participants once a week so that we can check in, assess adverse events, and troubleshoot any issues with compliance.

4.3.2 Usual care group

Those in the usual care group will complete all the same study assessments as those in the intervention group. They will not receive any specific dietary advice, but they will be allowed to voluntary seek dietary advice from a registered dietitian, use resources at the Integrative Oncology Center, attend cooking classes, etc. There is currently no standard of care regarding nutritional prescriptions during chemotherapy. We will emphasize how their data are indispensable in understanding the nutritional habits and preferences of patients undergoing chemotherapy, and how these data will be used to optimize nutritional interventions in future studies. At the end of the 8-week intervention, the participants in the usual care group will be provided the intervention materials *gratis*, including one-week of Mediterranean Diet food and education materials.

4.4 Study outcomes/endpoints

4.4.1 Aim 1: Feasibility and adherence

The primary aim of our study is to assess feasibility of implementing a Mediterranean Diet intervention. Feasibility will be determined by our ability to recruit participants to the study and have them complete the intervention. Our goal is that at least 70% of participants in each group complete the 8-week intervention including 8-week assessments.

1. 14-item Mediterranean Diet assessment: As part of Aim 1, we will assess the adherence of the participants to the diet. Adherence will be assessed primarily from the 14-item Mediterranean Diet assessment tool that is used commonly in the literature, mostly for epidemiological studies but also for clinical trials.[100] We will ask participants to report their dietary habits over the last week. Questions include: 'How many servings of fruit do you consume per day?,' 'How many sweet or carbonated beverages do you consume per week?,' and 'How much olive oil do you consume on a given day?' We will deem a participant adherent if they show an improvement in score of at least 1 point from baseline to 4 weeks and baseline to 8 weeks. This cut-off has been established in the literature to be clinically relevant.[100]
2. 3-Day food record: We will further assess dietary habits using a 3-day food record at baseline (before randomization), week 4, and week 8. For this record, participants will write down what they ate, how much, and at what time for one weekend day and two week days (preferably consecutive, but not necessarily). The 3-day food record will give us a more nuanced snapshot of the foods the participants were consuming leading up to the study, as well as the foods that they consumed during the study period. It also includes timing of nutrient ingestion, which will provide insight into patients' nutrient habits during chemotherapy and circadian rhythm.[107] The food record will be completed at home, preferably in real-time. We will provide participants with a paper food record; there are also apps that participants can use on their phone to track food intake (e.g., Chonometer), though we will ask participants to transcribe the data to the questionnaire to submit to us. We will use NDSR software (Regents of the University of Minnesota, Minneapolis, MN) or a similar program to analyze dietary intake for macro- and micronutrients. The patient-reported 3-day food record was selected to assess diet instead of a 24-hour food recall, food frequency questionnaire, or weighed food record for this situation because 1) food intake can be entered in real time and does not rely on recall, and memories are not always accurate; 2) food frequency questionnaires inquire about more general meal patterns (e.g., How often do you eat fish?), and food intake during the cancer experience can be much different than "normal" and change rapidly over the course of

chemotherapy; the 3-day food record will be more accurate; 3) it is burdensome and sometimes not practical to weigh food before it is consumed; and 4) being participant-completed and not guided by an interviewer, participants might feel less self-conscious about eating "junk food" and be more honest. Additionally, food records tend to have higher correlations with blood carotenoid biomarkers than 24-hour recalls, diet history, and food frequency questionnaires.[108]

4.4.2 Aim 2: Patient-reported fatigue measures

Aim 2 of our study is assess the effects of the Mediterranean Diet on cancer-related fatigue, as assessed using the FACIT-F. Patients will complete this instrument at baseline, 4 weeks, and 8 weeks.

1. Functional Assessment of Chronic Illness-Fatigue (FACIT-F) questionnaire: The FACIT-F is a 40-item, validated, commonly used measure of fatigue that is comprised of 5 subscales: physical well-being, social well-being, emotional well-being, functional well-being, and fatigue-specific well-being.[109] It captures fatigue in these categories over the last 7 days. The 13-item FACIT-F fatigue subscale will be used as the primary aim.

4.4.3 Mechanistic aims: Metabolic measures

Blood will be collected at the Wilmot Cancer Institute, Pluta Cancer Center, a UR Lab Patient Service Center, or medical office and a trained study staff member will transport the samples to our facility. Participants will be requested to fast overnight (at least 8 hours) before the blood draw. The location will be selected to minimize subject burden and if possible we will perform blood draws at the same time as a regularly scheduled medical blood draws. If a participant is not fasted at the time of the blood draw, blood will still be drawn and a note will be made. The blood draw can occur the same day as their chemotherapy infusion, or at another time.

Approximately 40 mL of blood (around 3 tablespoons) will be drawn at baseline (week 0); approximately 40 mL will be drawn at 4 weeks, and approximately 20 mL of blood will be drawn at 8 weeks. This is a total of approximately 100 mL of blood over 9 weeks. We will collect the following:

1. At baseline and 4 weeks, we will collect blood in two light-green-top (sodium heparin) tubes (10 mL each, 20 mL total). These tubes will be inverted 8-10 times and stored at room temperature. They will be used the same day for T cell extraction and real-time metabolic assays for basal respiration, maximal oxygen consumption, etc.[110]
2. At baseline, 4 weeks, and 8 weeks, we will collect blood in two tubes (red top and/or serum separator); these will be sent to UR Labs for analysis and/or brought to the CCPL.

Live-cell metabolic assays will be conducted by Dr. Amber Kleckner or trained study staff. First, T cells will be isolated using established procedures,[111] and plated on a Seahorse 48-well plate. The Extracellular Flux XF instrument (also known as the Seahorse) in the Flow Cytometry Core will be used to perform a standard Mitochondrial Stress Test. This test involves injecting metabolic inhibitors onto the cells *ex vivo* to evaluate oxygen consumption rate and extracellular acidification rate (ECAR, i.e., change in pH), which provides detailed information regarding mitochondrial function.[57] Other metabolic measures will be assessed either by UR Labs or in the CCPL.

4.4.4 Exploratory aims and other symptoms and clinical factors

In order to assess the variation in fatigue over the course of a chemotherapy cycle, we will assess average fatigue at the end of each day using a single-item question on a daily diary.

To obtain more precise estimates on the effects of the Mediterranean Diet on cancer-related fatigue and metabolism we will account for several behavioral and clinical factors. For example, several patient-reported outcomes tend to be associated with fatigue (e.g., depression[74]) and we will adjust for these potential factors in our analyses.

1. Aerobics Center Longitudinal Study (ACLS) physical activity questionnaire: The ACLS captures current physical activity and exercise, including walking, climbing stairs, and weight training.[112] We will use this questionnaire to estimate the energy that each participant expends per week on physical activity.[113]
2. Symptom Inventory (SI): The symptom inventory (modified from the MD Anderson Symptom Inventory[114]) includes 19 items that are common in the cancer experience (e.g., pain, distress, lack of appetite, numbness and tingling, fatigue), as well as 8 items related to how much these symptoms interfere with activities of daily living and quality of life. As many symptoms often correlate with each other including fatigue (i.e., symptom clustering[115]), it is important to capture the change in many symptoms from baseline to post-intervention. Exploratory analyses will probe whether adherence to the diet or high consumption of any dietary component correlates with the change in any of these symptoms over time.
3. Brief Fatigue Inventory (BFI): The BFI is a 10-item fatigue questionnaire that is also validated and commonly used.[116] It captures fatigue *now* as well as the usual and worst in the last 24 h. It also includes 6 single-item questions regarding how fatigue has interfered with general activity, mood, work, etc.
4. FACT-Cog: The FACT-Cog is a 41-item questionnaire designed to assess cognitive challenges identified by patients with cancer.[117]
5. Brief Pain Inventory: The Brief Pain Inventory (BPI)-Short Form is a 15-item questionnaire designed to assess the severity of pain and its impact on functioning.[118]
6. Insomnia Severity Index (ISI). The Insomnia Severity Index (ISI) is a brief 7-item questionnaire that was designed to assess the severity of both nighttime and daytime components of insomnia.[119]

Some study data (e.g., questionnaires) will be collected electronically using REDCap software. REDCap is a secure, web-based application for building and managing online surveys and databases and is made available through the CTSI. REDCap will be used to send a secured web link to each study subject, and a built-in scheduling function will allow for re-contact at a pre-specified time to remind subjects to complete the questionnaires if needed. All data forms will be checked immediately by the REDCap system as they are being completed by the study subject to ensure completeness (i.e., that no question was skipped unintentionally), and a pop-up message feature will be used to encourage a response. For participants who prefer paper-based questionnaires, a paper version will be provided for them to complete and return to the study staff in person or in a postage-paid envelope. In this case, a study staff member will enter the responses into the REDCap database.

There are a total of 11 questionnaires and survey assessments that will be completed. The on-study form will be completed at baseline only; the daily diary will be completed every day; the others will be completed at baseline, 4 weeks, and 8 weeks.

- On study (demographics and clinical characteristics; baseline only)
- FACIT-F (fatigue)

- Daily diary (single-item fatigue question)
- 14-item Mediterranean Diet assessment
- 3-day food record
- ACLS (activity)
- Symptom inventory
- BFI (fatigue)
- FACT-Cog (cognition)
- BPI (pain)
- ISI (sleep)

The daily diary will take about 10 seconds each day and the other questionnaires should take approximately 30-45 minutes total to complete.

4.5 Timeline

Upon opening of the study, we expect to recruit approximately 2-3 participants per month for 16 months. Data will be entered as they come in; some metabolic biomarker assays will be performed from fresh samples and some will be performed in batch upon collection of the last sample. Data analysis will take place in the subsequent months. These data will be used to inform follow-on randomized controlled trials. It is our goal that at least two manuscripts—one describing the patient-reported outcomes and one describing the metabolic outcomes—will be submitted for publication within one year of the study closing. It is also likely that a third mixed methods manuscript describing dietary habits and preferences of patients undergoing chemotherapy will arise from the exit interviews at the end of the study.

4.6 Design considerations

Why the Mediterranean Diet? The Mediterranean Diet is one of the most common dietary plans that is studied by nutrition researchers and has shown large health benefits, especially for cardiovascular disease.[56] The diet is appealing for researchers and for the public because it is relatively easy to implement—many of the meals are common in American culture and it is not too restrictive. In general, the meals are very appetizing. The Mediterranean Diet has components that are particular beneficial to metabolism such as high fiber, low glycemic index, and rich in micronutrients such as polyphenols, α-lipoic acid, and B vitamins.[120]

Why during chemotherapy? An intervention during chemotherapy, rather than after, could substantially prevent both reversible and permanent chemotherapy-related metabolic dysfunction that contributes to cancer-related fatigue. Indeed, while some metabolic toxicity is reversible, some can persist long into survivorship (longest follow-up thus far: 6 years[8]). Also, a cancer diagnosis is often seen as a "window of opportunity" for behavior change including exercise[121] and smoking cessation,[122] though less research has been done for nutrition.[123] From a psychological standpoint, during cancer treatment, food sometimes shifts roles from pleasure to medicine,[124] motivating some patients to make healthy choices and empowering them to take charge of that aspect of their life. Dietary interventions have been implemented successfully during[47,48] and after[34,125,126] chemotherapy treatment, though it is unclear which treatment stage is "best" for attenuation of fatigue or other supportive care outcomes.[127]

Behavioral interventions such as exercise tend to confer the largest benefits for symptoms in survivorship vs. during treatment,[128] but this is because patients' symptoms are naturally improving after cessation of treatment. Longer follow-up time points are needed to evaluate whether an intervention during vs. after chemotherapy will lead to overall less symptom burden. Also, it is our hope that patients will learn new healthy recipes and eating patterns that are sustained into survivorship.

Why a randomized clinical trial and not a single arm feasibility study? In order to evaluate the effects of the Mediterranean Diet on cancer-related fatigue, a control group is required to assess the change in fatigue over time without the intervention. If we determine that this study is not feasible and participants in the intervention group do not follow a Mediterranean Diet, we will still have important longitudinal data to correlate fatigue measures with diet metrics and metabolic measures over the course of chemotherapy.

Why randomize 2:1? Participants who sign up for a nutrition intervention study are often motivated to make dietary changes. By randomizing 2:1, each participant has a larger chance of getting the intervention and fewer participants will be disappointed not to receive the intervention right away. This ratio will still give us enough power (with n=42 participants total) to detect changes in fatigue. In addition, uneven allocation will provide us with more data about the intervention without increasing our sample size.

Why provide food? Meal planning, grocery shopping, and preparing food are large barriers dietary change, especially during chemotherapy.[38] We believe that if we overcome these barriers to consuming the Mediterranean Diet at the onset of the intervention while we provide education, we will have greater adherence. In addition, meal provision is an established technique to facilitate behavior change, as people learn types of food that fit within the diet and serving size.[129]

Why include patients with underlying metabolic disorder? Will it reduce the ability to detect changes? Diabetes is the most common metabolic disorder, and at least 15-20% of patients have diabetes as a co-morbidity with their cancer.[130,131] The literature on the interaction between metabolic disease and supportive care outcomes is in its infancy, and while these conditions are complex, heterogeneous, and ever-changing, there are possible overarching interactions that could be curtailed with dietary interventions. We would like to recruit people with and without metabolic disease to ensure that this intervention is feasible among both, and in the future we would like to further investigate the specific interactions between cancer, preexisting metabolic disease, and cancer-related fatigue.

5. Inclusion and exclusion criteria

Participants will be selected to represent a broad range of patients with varying demographics (e.g., age, race), and incoming metabolic functioning (e.g., diabetes). This study will not be powered for any subgroup analyses. Participants will be excluded who have dietary allergies or intolerances (e.g., celiac disease), because the diets will be standardized and we do not want to inadvertently introduce any allergens or triggers.

Inclusion criteria (Participants must…):

1. Have a diagnosis of stage I-III cancer,
2. Be scheduled to receive chemotherapy and have at least 6 weeks remaining,
3. Be able to speak English,
4. Be at least 18 years old,
5. Be willing to adhere to study procedures, and
6. Be able to provide written informed consent.

Exclusion criteria (Participants must not…):

1. Be on enteral or parenteral nutrition,
2. Be pregnant (confirmed by pregnancy test at the start of chemotherapy treatment), as pregnant women have different nutrition needs than non-pregnant women,[132]
3. Have a brain tumor,
4. Have any plan to get radiation to the head,

5. Have specific dietary needs that a Mediterranean Diet cannot meet (e.g., allergies to nuts, gluten intolerance), or already be following the Mediterranean Diet (i.e., have a score ≥10 on a modified 14-item Mediterranean Diet questionnaire).

Patients who are following a vegetarian or vegan diet will be eligible because it is possible to adhere to the Mediterranean Diet without eating meat or animal products. None of our study participants have to eat the food we provide (meat, animal products, or other food), and our study dietitian is available to all of our participants to help find appropriate substitutions and protein sources. (Participants will "lose" a point on the adherence questionnaire for not eating fish, but they do not need to obtain a perfect score to be considered adherent.)

Patients who have 6 weeks remaining will be eligible to participate in this 8-week trial because fatigue often persist for 2 weeks or more after a chemotherapy infusion.[133] Indeed, these two- to three-week recovery periods are built into some chemotherapy regimens. We are incorporating this "recovery" period into the eligibility and study timeline. For example, a person that has their last infusion scheduled 6 weeks away will be eligible.

6. Recruitment methods

6.1 Identification and recruitment

Participants will be recruited using the Cancer Control group's established procedures. Before recruitment, approval will be obtained by the Cancer Control Disease Working Group, the James P. Wilmot Cancer Institute Clinical Trials Peer Review and Monitoring Committee (PRMC), as well as the University of Rochester Medical Center (URMC) Research Subject Review Board (RSRB). Potential participants will be identified using three methods: (1) screening medical records, (2) direct referral from providers (e.g., nurses and physicians), and (3) flyers.

6.1.1 Identification and recruitment via medical records

Potentially eligible participants will be identified in a HIPAA-compliant manner by study personnel via review of scheduled outpatient appointments. The study team will then review any potential candidates. Medical records typically show a recent pregnancy test, presence of metastases, dietary allergies, and any current or recent use of enteral or parenteral nutrition. If a patient appears to be eligible, the study team will contact the treating physician to notify them of a potential candidate and obtain approval to speak with the patient. The physician or another clinical staff member will initially assess whether the participant has any interest in participating in a clinical trial to investigate a dietary intervention and cancer-related fatigue. If the patient is interested, the provider will refer the individual to the study team. Our team will meet with the patient to discuss the study or send information about the study via mail or myChart with our contact information. The study team will then meet with the candidate (immediately after their oncology appointment or at a later date; in person or via phone or computer) to discuss the study activities in detail and review eligibility. If the patient is eligible, study personnel will explain the details of the study and obtain informed consent from those who agree to participate (paper-based or eConsent). If the person is eligible and gives informed consent, a baseline/randomization appointment will be scheduled. At this point they will be given a 3-day food record to bring completed to the baseline assessment and the baseline questionnaires (or access to the questionnaires via REDCap).

6.1.2 Identification and recruitment via direct referral from nurses and physicians.

We are working with several oncologists (including, but not limited to, our co-investigators Drs. Magnuson and Shayne) and their medical team (e.g., nurses, physician assistants) to identify potential patients at the University of Rochester who are likely eligible for our study. If the patient is eligible based on information in the medical records and from the physician and medical team, we will request that the physician refer the patient to us (or obtain the physician's permission to contact the patient) to discuss our study.

6.1.3 Flyers

We designed a flyer that will be placed in locations designated for such use that advertises our study. Patients with a recent diagnosis of cancer can contact us directly for more information. We will contact their treating oncologist to ensure the patient meets eligibility criteria before consenting them.

6.2 Screening

For convenience to the patient, we will make every effort to combine the patient's clinic appointment with study assessments. To protect the privacy of potential subjects, we will conduct recruitment discussions in a private location.

Dr. Kleckner or a member of the study team will meet the patient (in person or remotely) to explain the project and invite them to participate. We expect that some patients will decline to participate, and we want to ensure that we not approach the same patient twice. Therefore, we will keep a screening log containing the following information:

- Screening ID (1, 2, 3…)
- Name
- Date of contact
- Medical record number
- Where/how we talked to the patient (e.g., clinic location, phone)
- Whether the patient was eligible or not
- If ineligible, the reason they are ineligible
- Whether the patient ultimately consented or declined
- If declined consent, the reason for declining consent
- If consented, the subject ID in the study (e.g., 101, 102, 103, …)

We will obtain permission to approach and confirm with the treating medical oncologist that they are appropriate for the study prior to discussing the study with patients.

7. Consent process

7.1 Written consent

For participants who are interested in participating, a member of the study team will meet with the potential participant in a private room. She or he will go through the consent form with the patient face-to-face to ensure comprehension. They will then be given the option to sign the consent form. Dr. Kleckner (study chair) will be available to answer any questions the potential participant may have about any aspect of the study prior to consenting and throughout the entire study period. The participants will also have access to the registered dietitians at the Integrative Oncology and Wellness Center at Pluta Cancer Center

(e.g., Sue Czap, RD) if they have other diet-related questions. Potential participants will be allowed to take the consent form home to think about and discuss with family or friends; each potential participant will have sufficient time to consider participation. To minimize coercion, the study team will emphasize that participation is completely voluntary and their cancer care will not be affected by their participation in the study.

7.2 eConsent

In lieu of the paper-based consent document, consent may occur remotely using the RSRB-approved eConsent document provided via REDCap. The study staff will screen for potential participants using the above screening procedures and initiate contact via the following methods: 1) the treating oncologist or a member of the medical team (e.g., nurse practitioner) will introduce the study to the participant via a clinic appointment (in person or telehealth) and inquire if it would be okay for our study team to contact them, 2) with approval of the treating oncologist or a designee, a recruitment letter will be mailed to the potential participant briefly describing the study and asking them to contact us if they would like more information, and 3) with approval of the treating oncologist or a designee, a message will be sent to the potential participant via eRecord (myChart) briefly describing the study and asking them to contact us if they would like more information. If a potential participant is interested, the study team will talk to the person on the phone and obtain verbal permission from the patient to send a copy of the eConsent via email or text message stating, "Because URMC can't control the security of email or text messages once we send them, we need your permission to text or email you. Do you want to receive a copy of the consent document and a link to the eConsent via text or email?" Verbal permission from the patient will be documented. We will email or text the eConsent in the form of a pdf document and set up a phone call or Zoom meeting (participant's choice) to formally go over the consent document. In a separate email or text, we will provide a link to the eConsent document as well as instructions on how to access the eConsent—we will use verification with a passcode based on known information (e.g., the patient's home zip code). No personal health information will be sent via any emails/texts. The eConsent documents may be viewed on computers, electronic tablets, or smartphones. The pdf copy of the eConsent and the REDCap eConsent will have identical information; it will be optional for the person to review the consent before the study team discusses it with them. After a member of the study team reviews the consent document with the participant over the phone or computer, they will have the opportunity to electronically sign the eConsent via REDCap. The person obtaining consent will initiate the eConsent process from within REDCap for their name and a timestamp to appear on the study participant's signed consent form. Once the eConsent form is signed and submitted, the patient and/or legally authorized representative will be able to receive a print out of the paper copy, download a pdf, and/or receive an email with a PDF attachment of the signed consent form.

7.3 The consent document

The informed consent document will provide consent for the entire study, though consent may be withdrawn at any time. Because this study includes only one "phase," we will not ask participants to re-consent during the study. The consent form will also contain information regarding HIPAA authorization, if participants consent to be contacted for future research studies, preferred method of contact (i.e., phone, text, email).

For individuals who are eligible and who provide informed consent, the following information will be entered into a secure electronic database (e.g., Excel on a password-protected computer). This information is needed in case contact is required after the study and/or the participant requires payment through the mail.

- Participant ID number (used to identify the subject on all study forms and notes)
- Name
- Subject phone number
- Subject email address
- Medical Record number
- Date of informed consent
- Date of registration

If a participant requests to waive or alter elements of the informed consent document, they will not be allowed to participate in the study; the one exception is that they do not need to provide consent to using email communication to participate in the study. Similarly, if a patient requests to waive documentation of consent, they will not be allowed to participate. We will reiterate that the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. If a patient waives or alters HIPAA Authorization, the patient will also not be allowed to participate. We will explain why the study cannot be conducted without the use or disclosure of protected health information (PHI), and describe the plan to protect identifiers from improper use and disclosure. We will explain that all forms will be held in a locked location for at least 6 years, and disposal of forms will occur in a confidential manner. PHI will not be reused or disclosed to any other person or entity except (i) as required by law, (ii) for authorized oversight of the research study, or (iii) for other research for which the use or disclosure of PHI would be permitted by the HIPAA Privacy Rule.

8. Study procedures

8.1 Overview of study

We will be conducting a pilot randomized clinical trial testing the preliminary efficacy of an 8-week Mediterranean Diet intervention during chemotherapy to prevent cancer-related fatigue among patients with cancer. We will also gain mechanistic insight into cancer-related fatigue and the ability of the Mediterranean Diet to modulate it via a thorough assessment of metabolic parameters. Participants in the intervention arm will receive education regarding the Mediterranean Diet with respect to its components, purported health benefits, and specific guidelines for implementation. In order to improve adherence, in weeks 1-4, participants will receive food (approximately 1,600 kcal/day) compliant with the Mediterranean Diet. All participants will complete questionnaires and provide blood at baseline, 4 weeks, and 8 weeks.

8.2 Study procedures, assessments, and participant activities

8.2.1 Screening procedures

A pregnancy test at the start of chemotherapy is the only test that is needed for screening (and only for females who are pre-menopausal), and this is part of standard care for cancer treatment and should be in the medical record. A history of a hysterectomy or tubal ligation is also acceptable to determine if a woman is not pregnant. All other exclusion criteria—needs for enteral or parenteral nutrition, metastases to the head, plans to have radiation to the head, dietary allergies, dietary intolerances, specific dietary needs—are included in the medical record or will be known to the patient. Thus, eligibility will usually be apparent before the consent form is provided to the patient. If there are any screen failures, we will retain the information in a screening log as described in §6.2 to avoid approaching them again.

8.2.2 Source of record or measures

The Clinical Record contains weight, height, current menopausal status, Karnofsky Performance Status (KPS) or Eastern Cooperative Oncology Group (ECOG) Performance Status, comorbidities, cancer stage, surgical procedures, types and doses of treatments, and other clinical characteristics. The study team will use the medical record to complete as much of this as possible. All other questionnaires will be completed by the participant, and all other measures will be obtained by the study team with the participant or the participants' blood samples.

8.2.3 Research registration

Documentation of study participation will be included in OnCore for those subjects enrolled in the research study.

8.2.4 Assessment locations

The assessments will take place in one of two locations: 1) at the clinic, and 2) at home (or wherever is convenient for the participant). The blood draws will take place at the clinic, which comprises the Wilmot Cancer Institute, Pluta Cancer Center, or a UR Labs Patient Service Center. The questionnaires will be completed via REDCap (or, alternatively, paper-based, if the participant prefers) and can be completed at the clinic or at home (or wherever is convenient). The consent will be completed at the clinic or remotely.

8.2.5 Randomization procedures

Randomization will be revealed to the participant at the end of the baseline assessments, before delivering the instructional portion of the intervention.

We will employ two treatment arms in a 2:1 allocation ratio:

1. Mediterranean Diet: an 8-week intervention entailing education of the Mediterranean Diet and delivery of Mediterranean Diet-inspired meals for 4 weeks.
2. Usual care: completion of assessments, with no intervention and usual care for their cancer.

Consented subjects will be randomized with a computer-generated random numbers table with block sizes of 3 and 6 and stratified based on how frequently they will be receiving chemotherapy (weekly, biweekly, or every 4 weeks vs. other). The random numbers tables will be generated centrally by Dr. Culakova, the project biostatistician, or a designee. A total enrollment of 42 subjects is planned.

Participants cannot be blinded due to the nature of the intervention. PI blinding is also not feasible given that the PI will play an active role in recruitment, intervention delivery, data acquisition, and analysis.

8.2.6 Duration of the study

Participants will participate in the study for approximately 9 weeks: participants will have approximately 1 week to complete at-home baseline assessments (3-day food log and questionnaires), and then the study lasts 8 weeks.

8.2.7 Schedule of assessments

Baseline assessments will optimally be collected before the first infusion of chemotherapy, though assessments will not delay chemotherapy. Baseline assessments after chemotherapy is initiated is permissible as long as the patient has at least 6 more weeks of chemotherapy. 4-Week assessments will occur approximately during week 4 (during week 3-5); 8-week assessments will occur approximately during week 8, the last week of the intervention (week 7-9). However, this may be adjusted to accommodate factors such as the participant or researcher's schedule. Because of the immediate and transient effects that chemotherapy has on fatigue,[134] we will aim to have assessments at least 3 days after an infusion. Optimally, the post-intervention assessments will occur during the last week of the intervention, while the participant is still on the diet, so that we can probe metabolic markers that may change quickly after cessation of the diet. **Table 3** describes two common chemotherapy regimens, but others exist and we will work around clinic activities to collect assessments.

Study Week	0	1	2	3	4	5	6	7	8
Study activities	Consent, Baseline assessments				4-week assessments				8-week assessments
Infusion number (for patients on biweekly regimens)		1		2		3		4	
Infusion number (for patients on weekly regimens)		1	2	3	4	5	6	7	8
Infusion number (for patients on an every 4-week regimen)		1				2			
Infusion number (for patients on an every 3-week regimen)		1			2			3	

Table 3. Schedule of chemotherapy infusions and study activities for two example chemotherapy regimens.

8.2.8 Data collection tables

A Clinical Record form will be completed by the study team using the medical record. **Table 4** lists study-related activities that the participants will experience (weeks 0-8).

Assessment	Study Goal	Assessment Location	Baseline (approx. during week 0)	Week 4	Week 8
On-study data/participant form	Demographics and clinical characteristics	Clinic or home	✓		
3-Day Food Record	Normal dietary habits	Home	✓	✓	✓
ACLS	Physical activity habits	Clinic or home	✓	✓	✓
Functional Assessment of Chronic Illness-Fatigue (FACIT-F)	Aim 1 (patient-reported fatigue)	Clinic or home	✓	✓	✓
14-item Mediterranean Diet assessment tool	Aim 2 (adherence)	Clinic or home	✓	✓	✓
Symptom inventory	Exploratory	Clinic or home	✓	✓	✓
Brief Fatigue Inventory (BFI)	Exploratory	Clinic or home	✓	✓	✓
Brief Pain Inventory (BPI)	Exploratory	Clinic or home	✓	✓	✓
FACT-Cog	Exploratory	Clinic or home	✓	✓	✓
Insomnia Severity Index (ISI)	Exploratory	Clinic or home	✓	✓	✓
Daily diary	Exploratory	Home	Daily for weeks 1-8		
Blood draw	Aim 3 (biomarkers of metabolism and fatigue)	Clinic	✓	✓	✓

Table 4. Study-related assessments.

8.3 Plans for return of research results

All data collected as part of this study will be for research purposes only and subjects will be explicitly told that the experiment will not provide information as to their health status. At the end of the study, after all data have been collected and analyzed, we will post a link to our study findings on our lab website for participants to see.

9. Risks to subjects

9.1 Risks to subjects and adequacy of protection against risk

9.1.1 Weight loss due to the intervention

Some studies have documented weight loss upon adoption of the Mediterranean Diet despite consuming calories *ad libitum*.[135] Our intervention diet will be *ad libitum* and participants will be encouraged to satisfy thirst and hunger. However, due to the satiating nature of the Mediterranean Diet compared to the typical Western diet, and the fact that they are initiating chemotherapy, there is a chance that patients could enter a calorie deficit and lose weight during the course of the intervention. If the patient is overweight or obese, slow weight loss will not be considered an adverse event (less than approximately 3% of their body weight per week). Weight measured from clinical visits will be recorded by study staff and used to assess rapid weight loss. If a patient experiences rapid, unintentional weight loss, as monitored and determined by the treating oncologist, the physician will determine how to intervene. It is important to determine what is causing the weight loss. If it is suspected that the study meals are contributing, the physician could recommend:

- Reviewing food records to see if there are any new foods that the patient is consuming from the intervention diet that they could have an unexpected reaction to; for example, there could be an ingredient to which the participant has an intolerance, leading to nausea and/or diarrhea and contributing to the weight loss,
- Discontinuing consumption of all study-related foods, and/or
- Other relevant actions on the patient-level.

Rapid, unintentional weight loss could be a symptom of another underlying condition, such as the onset of diabetes, cachexia, etc. If it is determined that the study foods are not contributing to the weight loss, the physician will decide if it is safe for the patient to continue with the study. We will follow the Common Terminology Criteria for Adverse Events (CTCAE), version 5,[136] to record weight loss as an adverse event:

- Weight loss 5 – <10% from baseline with no intervention indicated will be considered a Grade 1 adverse event.
- Weight loss of 10 – <20% from baseline and indicated nutritional support will be considered a Grade 2 adverse event.
- Weight loss ≥ 20% from baseline with indicated tube feeding or total parenteral nutrition will be considered a Grade 3 adverse event.

We will follow the treatment team and registered dietitians' recommendations for nutritional interventions due to any weight loss.

Weight loss can cause anxiety in patients with cancer. However, knowing that this dietary intervention usually results in weight loss, particularly in people who are overweight, can be reassuring in that weight loss is due to dietary change and not a manifestation of progressive cancer, particularly if there are no other concerning symptoms.

Probability: High probability that some weight loss will be experienced, especially in patients with excess body fat; low probability that a dangerous amount of weight will be lost

Magnitude: Weight loss can range from low to high, or weight gain can occur

Duration: Short- to long-term

9.1.2 Gastrointestinal upset due to the intervention

With a change in diet, and especially in large changes in diet, participants could experience constipation, diarrhea, nausea, heartburn, etc. These effects usually subside after several days, but the participant always has access to the study chair, Dr. Kleckner, as well as the study registered dietitian to discuss how to relieve these effects. The physician will determine if gastrointestinal symptoms are consistent with initiation of chemotherapy or if they could be due to the diet.

Probability: Moderate

Magnitude: Low to high

Duration: Short-term

9.1.3 Emotional distress due to the intervention or the outcome measures

There is a chance that participants could become emotionally distressed by the expectation to consume all of the food provided to them. We will reassure each patient regularly that the food is there to enhance adherence to the Mediterranean Diet for our study, but they are not limited to these foods and they do not need to consume them.

Our questionnaires contain information that might be distressing or private (e.g., "I am satisfied with family communication about my illness" from the FACIT-F). We will remind the patients that they do not have to answer any questions they are not comfortable answering, and they can take a break or stop answering the questionnaires at any time.

Probability: Low

Magnitude: Low

Duration: Short-term

9.1.4 Risks from a blood draw

Bruising, bleeding, and pain could occur where the blood samples are taken. Sometimes, drawing blood causes people to feel lightheaded or even faint. To avoid these risks, all blood will be drawn at the Wilmot Cancer Institute or UR Labs by trained staff. Specifically, to minimize the chance of bruising and the slight chance of infection associated with blood collection, the labs employ standardized hospital procedures for blood collection, and use a trained phlebotomist and sterile materials. Participants will be encouraged to be well hydrated before and after the blood draw, and to consume food soon after the blood draw.

Probability: Low

Magnitude: Low

Duration: Short-term (days at the most)

9.1.5 Breach of confidentiality

There is always a risk of a breach of confidentiality in which sensitive medical information could become known to persons outside the research team. To avoid leakage of sensitive information, only Dr. Kleckner (the study chair) and any individual designees will have access to the screening log and the file that links subject name with subject number (both will be encrypted); these files will be stored on a

password-protected computer in her private office in the Cancer Control Unit in Saunders Research Building. All data files will reference participants by a non-identifiable Participant ID and will be stored on Dr. Kleckner's computer and secure servers at URMC. Paper consent forms will be stored in a locked cabinet also in her office. E-Consent forms will be stored in a URMC Box drive accessible to only Dr. Kleckner and the study coordinator. If Dr. Kleckner shares data with any other researcher for analyses, all data will be deidentified (i.e., void of name, birthdate, and contact information). Presentation of data in the form of posters, presentations, and manuscripts, either in private or public settings, will not have any identifiable information. Dr. Kleckner and all other co-investigators participate in ethical training in accordance with URMC policies (e.g., online coursework via the CITI collaborative).

Probability: Very low

Magnitude: Low to high

Duration: Unknown

9.1.6 Risk to groups or society

There are no known risks to groups or societies.

9.2 Alternatives to participation

The patient can seek other nutritional services in addition to or instead of participating in this study. Patients may choose to not participate in the study without penalty or effects on subsequent medical care.

10. Potential benefits to participants

Participants may or may not directly benefit from this study. Participants will be provided with information on the Mediterranean Diet as well as healthy Mediterranean Diet meals for 4 weeks, which they have the option of eating instead of or in addition to food they purchase and prepare on their own. We predict that the diet will have a positive effect on their symptoms, though it may not.

11. Costs for participation

There will be no costs to the participants or the participants' insurance for assessments, screening tests, instruments/equipment, or parking. The participants will be responsible for travel to and from the research site. The participants will be responsible for storing the meals (in the freezer or refrigerator) and heating the prepared meals, if desired.

There might be concern that eating a Mediterranean Diet is more expensive than a participants' previous eating habits. However, the recipes that we are providing cost approximately $4.50/meal for lunch and dinner. If the participants are avoiding restaurants, red meat, and prepared foods, it is likely that they will spend less.[137,138] Indeed, when directly assessing food cost based on amount of nutrients purchased, a Mediterranean Diet specifically[139] and a more healthful diet in general[140] is not more expensive than a less healthy diet.

12. Payment for participation

Participants will receive $20 after they finish the study.

13. Participant withdrawals

Participants may discontinue participation in the study at any time if they do not wish to take part any longer. Participants may be withdrawn from the study by research personnel if it is deemed in their best interest to no longer participate or in the case of lack of cooperation, non-compliance, or other administrative reasons. In the event that a participant does withdraw from the study, the information they have already provided will be kept in a confidential manner. A 10-20% withdraw rate is built into the study design and recruitment goal, so there should not be a need to replace participants who withdraw before completing the study. Participants may opt to not engage any of the assessments (e.g., any given questionnaire, blood draw, etc.), and still complete the rest of the study. For participants who do not complete study, available data will be utilized during the analysis.

14. Privacy and confidentiality of participants and research data

14.1 Steps taken to protect privacy

14.1.1 Assignment of Participant Identification (ID) number

The study team will assign a numerical Participant ID to each subject once they have signed the consent form (e.g., 101, 102, etc.). Notes and databases will use this number and the subject's first and last initials as identifiers to ensure data integrity. Other identifying information will not exist on these forms. A complete list of study participants with Participant ID, name, and contact information will be maintained separately for the purpose of contacting subjects if necessary; this database will be maintained for at least six years after the study is complete. This linkage information will be maintained and only accessible to Dr. Kleckner, the study chair, who will provide individuals with private access only if necessary. All data files will reference participants by the Participant ID and will be stored on Dr. Kleckner's computer and secure servers at URMC.

14.1.2 Assessments performed in discrete locations

All study activities will be performed in discrete locations at URMC. In-person consent will be performed in a private room, usually where their oncology appointments typically take place (e.g., Wilmot Cancer Institute, Pluta Cancer Center). Blood draws will be performed in clinic locations where blood is typically drawn.

14.2 Study teams' access to participant information

eRecord will be used to help screen patients and extract data. Only those with proper training will have access to this database and medical records.

Some study data will be collected electronically using REDCap software, and any eConsents will be conducted using REDCap. REDCap is a secure, web-based application for building and managing online surveys and databases and is made available through the CTSI. Study data in REDCap will only by accessed by members of the study team.

All other study data—paper-and-pencil forms, biological samples—will be labeled with Participant ID and participant initials and not identifiable information. Only members of the study team or those analyzing the data/samples will have access to these.

All data will be compiled into several databases that will identify participants by Participant ID and *not* name or contact information. If data are shared in the future with other researchers (e.g., a trainee), only

databases without identifiable information will be shared and access will only be given to that specific individual.

14.3 Contacting participants

This is an 8-week study, and participants will be contacted throughout the study period. We will check in with participants approximately weekly to assess adverse events and ask how they are doing. We will also schedule appointments and remind participants of appointments. For these contacts, we will ask if phone, text, or email is preferred. REDCap software also contacts participants with reminders to complete questionnaires.

14.4 Data confidentiality, storage, and sharing

Paper-based data will be stored in a locked cabinet in Dr. Kleckner's office in the Cancer Control division of URMC in Saunders Research Building. Electronic data will be stored on Dr. Kleckner's desktop computer in her office in Saunders research building. The Cancer Control Unit is an office suite secured by electronic key cards; Dr. Kleckner's personal office is secured by a traditional key; Dr. Kleckner's file cabinet is secured by a unique traditional key; and Dr. Kleckner's computer is password-protected. Electronic research records are stored on URMC's password-secured and firewall-protected networks. These are the same methods of security used for patient medical records. Biological samples will be stored in the CCPL (Director: Janelsins, co-investigator). In the rare case that any data are transferred outside of the University, only deidentified databases will be shared with approved individuals for private access. Databases will be transferred through URMC's HIPAA-compliant box.com under the direction of Dr. Kleckner or a designee, with oversight by the Cancer Control Information Technology staff. We anticipate that data will only be shared for research purposes only, but it is possible that data could be used for teaching or other purposes. To reiterate, all shared data will be deidentified.

Only members of the study team will have access to the stored data, and only members of the study team and CCPL will have access to the stored biological samples. All individuals who have access to the data will need to complete human subject training as required by URMC. Participants' individual research records will not be shared with their treating physician, unless they provide consent or the subject's treating physician is a study physician, in which case they will have access to study data as a study co-investigator. Overall study results may be presented to participants, faculty, and staff at URMC after completion of the study. Study results will be presented at local meetings and seminars and professional meetings, published, and reported on clinicaltrials.gov.

All study data will be kept for at least six years after the study and all reports and publications are complete.

15. Data/sample storage for future use

All data (information and human blood samples) collected for the current study will be used in post-hoc analyses as appropriate. These analyses could provide preliminary data for future studies. Blood samples will be stored and data will be used for future studies only with prior consent of subjects. The consent form contains appropriate language related to banking and subjects are given the option to have their samples stored or to have them destroyed following analysis of the study hypotheses. Long-term data and sample storage will be in the same locations as described in §14.4.

Any individual who would like access to deidentified raw data or samples must submit a request to the study chair (i.e., Dr. Kleckner) via a written request (e.g., email). If Dr. Kleckner considers the project

appropriate, she will approve a release of the data or samples and transfer the data/samples in a safe, HIPAA-compliant manner as described in §14.4.

16. Data analysis and monitoring

16.1 Adverse event reporting

An **adverse event** is any symptom, sign, illness, or experience that develops or worsens during the study, whether or not the event is considered related to the intervention. To assess the severity of adverse events, we will use the CTCAE, version 5,[136] recommended by the NCI. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each adverse event based on this general guideline:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to adverse event.

A **serious adverse event** is any adverse medical experience that results in death, or is life-threatening, or requires inpatient hospitalization of at least 24 hours, or prolongs existing hospitalization, or results in persistent or significant disability/incapacity, or causes a congenital anomaly/birth defect, or requires medical or surgical intervention to prevent permanent impairment or damage.

Each adverse event will be evaluated in regard to whether the adverse event was potentially a consequence of the intervention. Attribution will be categorized into one of five categories (**Table 5**). The subject's referring oncologist, designee, or study medical monitor will determine the grade and attribution.

Attribution	Description
Unrelated	The adverse event is clearly NOT related to the intervention
Unlikely	The adverse event is doubtfully related to study intervention
Possible	The adverse event may be related to study intervention
Probable	The adverse event is likely related to study intervention
Definite	The adverse event is clearly related to study intervention

Table 5. An assessment of the relationship between the adverse event and the study intervention will be categorical.

With that information, **we will only report the following events**:

- Serious, related, and unexpected events will be reported to the Data Safety Monitoring Committee and the RSRB in an expedited manner.
- Grade 4 or 5 events regardless of attribution will be reported to the RSRB at each continuing review.

We are paying close attention to weight loss and gastrointestinal distress, so we will closely monitor these symptoms but only report them to the RSRB if they fit the description above.

16.2 The Data Safety Monitoring Committee

The James P. Wilmot Cancer Institute Data Safety Monitoring Committee (DSMC) will serve as the DSMC of record for this study. The DSMC provides oversight of study progress and safety by review of accrual and events at regularly scheduled meetings. The frequency of review is determined by the size, risk, and complexity of the trial.

Dr. Kleckner, the study chair, will conduct continuous review of data and subject safety. The Investigator will submit annual progress reports according to the timing set by the DSMC for review. The review will include the number of subjects enrolled, withdrawals, and serious adverse events (both expected and unexpected). A copy of the Adverse Event spreadsheet along with the Progress Report will be submitted to the DSMC for review. Actual review dates will be assigned when the first participant is accrued.

Any serious adverse event that is serious, related, and unexpected will be reported within 10 calendar days to both the Safety Coordinator (e.g., Sarah Strause) and the RSRB. The DSMC Chair will determine whether further action is required, and when subject safety is of concern. When subject safety is of concern, an interim meeting may be called.

Serious adverse events that are related and expected or unrelated and unexpected will be reported to the Committee for review at the quarterly meeting. Serious adverse event reports will include sufficient detail so that the DSMC can determine the severity, toxicity grade, expectedness, treatment required, and a follow-up report documenting resolution of if there are sequelae. Serious adverse events that require detailed reports (but not necessarily expedited) are expected, related, non-hematologic toxicities of grade 3, 4 or 5.

17. Data analysis plan

17.1 Sample size determination

This is a two-arm randomized controlled trial that will assess feasibility of delivering a Mediterranean Diet intervention to patients undergoing chemotherapy, as well as the preliminary efficacy of a Mediterranean Diet intervention vs. usual care on the prevention of cancer-related fatigue. Our sample size is based on our fatigue outcome as measured using the FACIT-F fatigue subscale, which is a 13-item scale with responses that range from 0-4; the FACIT-F subscale score ranges from 0-52 and a higher score indicates greater wellbeing and less fatigue.[109] The minimal clinically important difference for the FACIT-F is 3 points.[141]

We plan to recruit a total of 42 participants and randomize them in a 2:1 ratio, intervention: control (28:14) using computer-generated block randomization with blocks of 3 or 6. Patients will be stratified based on how frequently their chemotherapy is planned to be administered. One strata will include patients who plan to receive weekly, biweekly (Q2w), or every 4-week (Q4w) regimens, and the other strata will include those on other regimens (e.g., Q3w). Thus, those in the first strata will complete 4-week and 8-week assessments for our study at the end of a chemotherapy cycle, while those in the second strata will be completing assessments in the middle of their cycle. (If there are

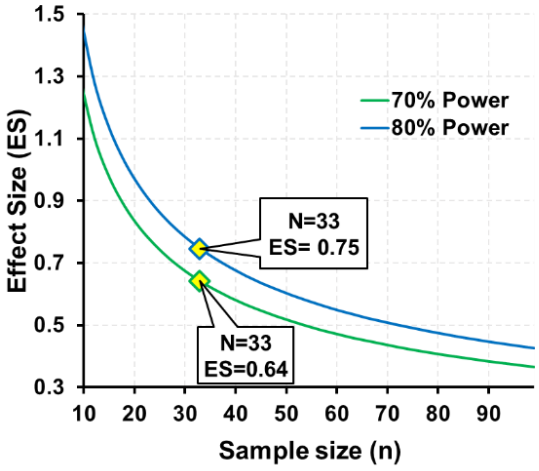


Fig. 3. Effect size vs. sample size at 70% and 80% power with 33 participants on the study.

dose delays or changes to the chemotherapy schedule, we will still collect assessments at the originally planned time.) We estimate attrition between approximately 20 and 25%, thus we estimate to retain 33 (22:11) evaluable patients. This sample size is appropriate for small randomized pilot studies and it will allow us to obtain preliminary estimates of descriptive statistics [mean, standard deviation (SD), and confidence intervals (CI)].[142] The primary endpoint is the change in fatigue as measured by FACIT-F from baseline (T1) to 4 weeks (T2). Assuming a correlation[143] of 0.50 between T1 and T2 FACIT-F measurements, a total sample size of n=33 will provide 80% power at the 0.15 two-sided significance level to detect an effect size (ES, standardized mean between-group difference) of 0.75 of the intervention effect on change in T2-T1 FACIT-F using analysis of covariance (ANCOVA) with T1 FACIT-F as a covariate (**Fig. 3**). The estimates of T1-T2 correlation and attrition rate are based on our prior studies.

Feasibility is often determined for nutrition interventions among 10-15 participants (e.g., [144,145]); pilot preliminary efficacy studies usually recruit 20-30 (e.g., [34,76]). **Table 6** below shows prior studies that are similar to this one, including their sample size.

Study	n	Population	Intervention	Outcome	Results
Zick et al. (2017)[34]	30	breast cancer survivors	Fatigue reduction diet vs. General Health Curriculum (time and attention control) for 3 months	Brief Fatigue Inventory	From baseline to 3-months, fatigue improved by 44±39% in diet group compared to 8±34% in the control group (p=0.01)
Skouroliakou et al. (2018)[125]	70	breast cancer survivors	Mediterranean Diet for 6 months vs. handout	serum antioxidant capacity and body composition	The dietary intervention based on Mediterranean Diet improved serum antioxidant capacity, body composition, and glycemic profile.
McMillan et al. (2011)[76]	27	healthy women in their 20's	Mediterranean Diet vs. control for 10 days	Profile of Mood States	A group × time interaction demonstrated that the Mediterranean Diet reduced fatigue (p=0.16) and improved vigor (p<0.01).
Okumatsu et al. (2017 and 2019)[126,146]	32	female breast cancer patients on endocrine therapy (after adjuvant treatment)	1200 kcal/day diet + exercise vs. control	cancer-related fatigue (exact measure not stated)	Fatigue decreased 39% in the intervention group and was stable in the control group.
Lee et al. (2015)[147]	24	young, healthy women	Mediterranean Diet vs. habitual diet for 10 days (cross-over)	mood, cognition, and cardiovascular measures	Improvements in mood (contentment, alertness, confusion), cognition (memory recall), and cardiovascular function (augmentation pressure) were observed with the Mediterranean Diet.
Djuric et al. (2011)[47]	40	breast cancer patients beginning chemotherapy	Nutrition and diet intervention for 12 months	body weight and body composition	Body fat percentage increased in the control arm and decreased in the intervention arm

Table 6. Prior studies that are similar to this one, including sample size.

17.2 Data Handling, Rigor, Quality, and Reproducibility:

Data will be entered in REDCap electronic forms and electronically collated in a HIPAA-compliant REDCap database managed by our Division. After collation, data will be audited electronically and visually, as needed, for errors. Appropriate graphical or statistical diagnostics methods will be employed in each of the analyses to evaluate distribution of variables (e.g., to identify shape of the distribution and outliers) and also to evaluate the model assumptions (e.g., if deviation from the statistical assumptions is found, we will use alternative methods such as transformations[148] or nonparametric analyses[149,150]). Outliers that are detected will be investigated to determine if they are due to error. If not, analyses will be conducted with and without them to assess sensitivity. Because this is a preliminary efficacy study, unless stated otherwise, all hypothesis testing will be at the two-sided 0.15 level as appropriate for screening trials.[151] SAS, JMP, and/or R software will be used for the analyses. Following the intent-to-treat principle, all randomized survivors will be analyzed in the arm as allocated, regardless of their compliance with the intervention or Mediterranean Diet contamination in the control group.

Although participants will be randomly assigned, differences may be present between study arms on demographic or clinical variables. Study arms will be compared on baseline demographic (e.g., age), clinical (e.g., cancer diagnosis, type of chemotherapy), and behavioral (e.g., physical activity, smoking) variables. If significant imbalance is found for a variable, it will be included as a covariate in subsequent analyses following standard practice.

17.3 Missing Data

Every effort will be made to facilitate participants' completion of questionnaires and provision of blood samples. However, some missing data are inevitable. The magnitude and the reasons for missing data will be recorded and tabulated according to treatment group. If a large proportion of data is missing we will conduct sensitivity analyses using appropriate statistical methods (e.g., maximum likelihood, multiple imputations).[152,153] If the estimates are similar to the ones obtained from the simpler analysis of only complete cases, we will report the complete-case analysis results.[154]

17.4 Statistical analysis

17.4.1 Aim 1: Feasibility and adherence

Our primary aim is to evaluate the feasibility of delivering a Mediterranean Diet patients undergoing chemotherapy. Despite us providing food to participants, we expect that there will be variability in dietary intake in the Mediterranean Diet arm due to participants not liking the taste of the meal(s), inconvenience, social barriers (e.g., eating out with friends, family, colleagues), cravings, symptoms such as nausea and diarrhea, etc. Adherence will based on consumption of key dietary components (e.g., fruits, vegetables, olive oil, fish) and avoidance of red meat, sweet or carbonated beverages, and commercial sweets and pastries.[100] Success will be deemed if >70% of participants who consent complete the study and if >70% of participants in the intervention arm improve their Mediterranean Diet score[100] from pre- to post-intervention. Adherence to the provided diet will yield 13 out of 14 points on the 14-item scale[100] (1 point for consumption of wine). The Mediterranean Diet score is commonly used in epidemiological studies to assess the relation between adherence to the Mediterranean Diet and prediabetes, metabolic syndrome, inflammation, etc.[155,156] Between arm difference in Mediterranean Diet score will be evaluated by two-sample t-test.

17.4.2 Aim 2: Patient-reported fatigue

To provide estimates of efficacy comparing the Mediterranean Diet to usual care for alleviating fatigue, we will evaluate between-arm difference in mean change in FACIT-F fatigue subscale score from baseline to 4 weeks in an ANCOVA model. The outcome will be FACIT-F fatigue score at 4 weeks with arm included as a fixed effect and FACIT-F fatigue score at baseline as a covariate. To assess the moderating effect of the baseline level of fatigue we will test arm×baseline interaction. To further evaluate the longitudinal trajectory of fatigue and the maintaining effect of the intervention, we will incorporate FACIT-F fatigue score measured at all time points (T1, T2, T3) in a repeated measures linear mixed model. The impact of patient's variables (e.g., age, gender, body mass index) on the results will be assessed by adding the covariates to the models. The results of the analyses together with the estimates of distribution parameters (e.g., mean, SD) of T1-T3 FACIT-F fatigue score values as well as the change scores will be used in planning a future randomized trial.

We expect all measures of cancer-related fatigue to increase over the course of chemotherapy, though we hypothesize that the differences will be attenuated in the intervention group. We will also compare our baseline-to-post-intervention change scores to those obtained via historical controls (e.g., Janelsins et al., 2018[157]).

17.4.3 Mechanistic aims

We will assess the preliminary efficacy of the Mediterranean Diet intervention on metabolic measures including mitochondrial function from freshly isolated T cells.[57,110,111] We will also obtain preliminary data on effects of the Mediterranean Diet vs. usual care on established metabolic biomarkers from blood samples. In an exploratory analysis, we will use similar models as in Aim 2 to assess Mediterranean Diet score with biomarkers of metabolic function. We will use both ANCOVA models looking at data at 4 or 8 weeks adjusting for baseline values, and longitudinal models incorporating data from time points T1-T3. This battery of biomarkers will be assessed to determine which are the most useful, and which others we should include in follow-up studies. Special statistical considerations may arise and will need be addressed during the analysis of biomarkers, including the need for transformation and missing data due to the detection limits.[158-160]

17.4.4 Exploratory analyses

In an exploratory analysis, we will correlate Mediterranean Diet score with patient-reported fatigue using the FACIT-F fatigue score at 4 weeks and 8 weeks. We expect that the majority of participants will improve their Mediterranean Diet score, and that 4 and 8 week scores will range from 5-14 in the intervention group[100] (higher is better). We expect that the fatigue subscale of the FACIT-F will range from 0-43 out of 52 based on a historical dataset (Kleckner et al.;[161] a higher score indicates less) and that FACIT-F total scores will range from 44-160 out of 160[161] (higher is better well-being). We will also assess correlations between baseline Mediterranean Diet score (proxy for improvement in diet quality) and change in fatigue to evaluate the influence on baseline diet on the development of fatigue. Further, we will assess the change in the Mediterranean Diet score and the change in fatigue to see if a greater shift in diet led to a greater prevention of fatigue.

Other measures collected via patient-reported outcome questionnaires (e.g., BFI, Fact-Cog) will be analyzed using similar methodology as outlined in the Aim 2 (FACIT-F score analysis).

Because of the small sample size in this study and the resulting low statistical power, these secondary and exploratory analyses will be interpreted very cautiously and only used to aid in the designing of a study for our larger trial and generation of new hypotheses.

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