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Preventing Breast Cancer Recurrence through a Tailored Lifestyle Intervention: The MyLIFE (My Lifestyle Intervention with Food and Exercise) Trial Rationale and Study Design

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Abstract

Breast cancer risk, and risk of associated co-morbidities such as cardiovascular disease, is highest among overweight or obese women with a previous history of breast cancer. The objective of this study is to test the effectiveness of a tailored nutrition, physical activity, and behavioral weight management intervention for breast cancer survivors against a widely available commercial weight management program. We hypothesize that an intervention tailored to the unique psychological, nutritional, and physical needs of breast cancer survivors will provide superior physiological and psychological benefits compared to an existing commercial program for the general population. To test our hypothesis, we initially conducted a focus group with both breast cancer survivors and oncology affiliated health care providers in order to illicit feedback to develop an intervention customized specifically to breast cancer survivors. Subsequently, in a randomized, multicenter trial, we are studying the effect of the tailored program on overweight/obese women (N=120) with a history of breast cancer (3 months to 5 years post-primary treatment) on body weight and composition, markers of systemic inflammation related to cancer and associated chronic diseases, physical activity habits, dietary intake, health-related quality of life, and program adherence and satisfaction. Assessments will be taken prior to study initiation immediately following the intervention and at 6 months post-intervention to assess long-term maintenance of weight, lifestyle behaviors, and impact on physiological markers of disease risk. This project is unique in that it addresses weight issues in a high risk, understudied population using a tailored approach.

Keywords: Breast cancer; Obesity; Behavioral intervention; Randomized controlled trial; Systemic inflammation Weight loss

Abbreviations: CWLP: Commercial Weight Loss Program; TLI: Tailored Lifestyle Intervention; IRB: Institutional Review Board; SAD: Sagittal Abdominal Diameter; DPBRN: Dietetics Practice Based Research Network; DASH: Dietary Approaches to Stop Hypertension; IPAQ: International Physical Activity Questionnaire; ASA-24: Automated Self-Administered 24 hour Recall System; WMQ: Weight Management Questionnaire; WEL: Weight Efficacy Lifestyle questionnaire

Introduction

Each year, over 220,000 [1,2] women in the United States are diagnosed with breast cancer; of these more than 12,000 are Florida residents [2,3]. While there are clear genetic risk factors for breast cancer, only 5-10% of all cases are thought to be hereditary [4]. A previous cancer diagnosis, physical inactivity, and obesity are associated with increased breast cancer risk and mortality; with obesity alone accounting for 30% of all breast cancer cases [5-7]. In fact, adipocytes in the breast tissue are essential for breast tumor development and progression [8]. Accordingly, survivorship is higher among women with a healthy weight [BMI 18-24.9 kg/m²] at diagnosis compared to overweight or obese women [9]. Weight gain post-diagnosis may be associated with increased risk of cancer-related death [10,11]. Breast cancer survivors are at increased mortality risk from non-cancer causes such as cardiovascular disease, type 2 diabetes, and other chronic

conditions compared with women never diagnosed and treated for cancer [12-14].

While some patients diagnosed with cancer make improvements in their dietary habits, most are no more likely to maintain these changes than the general population [15,16]. The American Cancer Society recommends adopting a healthy lifestyle including weight loss if overweight, consuming a healthy diet, and increasing physical activity as protective behaviors for cancer survival and recurrence prevention [17]. Although these are the recommendations, the effect of weight loss and the long-term maintenance of weight loss on breast cancer recurrence and/or survival after diagnosis are not known. Given the impact of weight status and physical inactivity on breast cancer risk,

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a recent review article calls for a clinical intervention to evaluate together the impact that fat loss and increasing physical activity will have on breast cancer progression [18]. Since women who are overweight/obese at diagnosis or who gain weight post-cancer diagnosis are at an increased risk for breast cancer recurrence, as well as increased morbidity and mortality, we predict that implementation of a successful weight management intervention for breast cancer survivors may have even greater benefits than for individuals in the general overweight/obese population.

This study is a randomized, behavioral lifestyle intervention for female breast cancer survivors. Specifically, the intervention is 3-months with a 6-month follow up to evaluate the effectiveness of a tailored lifestyle intervention designed to promote sustained weight loss and increased physical activity in an important and understudied population – overweight and obese breast cancer survivors, post-cancer treatment.

Objectives

This pilot study is funded through the University of Florida and will be conducted at both the University of Florida and at the University of North Florida. The study is approved by the Institutional Review Boards at each university. The primary aim of the study is to compare the impact of a Tailored Lifestyle Intervention (TLI) and a Commercial Weight Loss Program (CWLP) on weight change at post-intervention and long-term follow-up in a sample of overweight/obese female breast cancer survivors. The secondary aims are to compare the impact of the interventions at post intervention and long-term follow up on 1) changes in inflammation/chronic disease markers and 2) changes in health related quality of life and self-efficacy within this population. The study will be carried out in two phases: 1) focus groups to inform the TLI components, and 2) a randomized trial to compare the efficacy of TLI versus CWLP.

Methods

Phase 1: Focus groups to inform the Tailored Lifestyle Intervention (TLI): Focus groups will be conducted in both geographic locations to elicit input on topics and design of the TLI prior to beginning recruitment for the intervention. Two different populations will be recruited for the focus groups: breast cancer survivors and health care providers that are integral to the survivors' care including, but not limited to: social workers, physical therapists, registered dietitians, oncologists and breast surgeons. Each focus group will be led by either a trained research assistant or an investigator by asking probing questions meant to elicit feedback on different aspects of a behavioral intervention specifically tailored for breast cancer survivors. Topics for discussion for health care providers will include barriers to physical activity and proper nutrition as they relate to weight management for their breast cancer patients. Breast cancer survivors will be asked questions regarding beliefs on barriers and motivators of healthy lifestyle behaviors; the impact of family, friends, and health care providers on weight loss intentions and behaviors; and specific concerns about nutrition and physical activity as they relate to breast cancer survivorship. Each focus group will be asked about the pertinent components to designing a tailored weight loss program specifically for breast cancer survivors. Each focus group discussion will be recorded and transcribed for further content analysis by multiple members of the research team. Once a consensus is reached of the pertinent topics from each focus group, the collected data will be used in the design of the TLI group.

Phase 2: Randomized trial to compare the Tailored Lifestyle

Intervention to Weight Watchers: Individuals interested in participating in the randomized trial will call the Clinical Nutrition Lab at the University of Florida to complete a telephone screen interview. If they meet the initial study criteria, they will then be scheduled for an in-person screening assessment in order to determine their final eligibility for the study. If eligible, participants will attend a second visit where they will complete the initial study assessments (body composition, waist circumference, sagittal abdominal diameter, and several questionnaires), and receive their randomization assignment. Up to 120 eligible participants (up to 60 at the University of Florida in Gainesville and up to 60 at the University of North Florida in Jacksonville) will be randomized for inclusion in the study. These participants will be randomized to either the weekly group TLI (led by a registered dietitian) or to a CWLP (Weight Watchers). The intervention period for both groups is 3 months and will be offered to the participants at no cost. Randomization stratification will include BMI category and breast cancer stage. In order to create balanced groups, randomization will occur at the site level. Immediately following the 3 month intervention period, participants will undergo follow-up assessments to determine long-term physiological and behavioral changes. Similar assessments will occur for all participants 6 months after the intervention conclusion. Data analysis and reporting will begin immediately following this final assessment period.

Dietetic practice based research network (DPBRN)

A unique aspect of this study is that the Registered Dietitian Nutritionists (RDN) hired to lead the TLI groups will be chosen from the DPBRN. This group is an initiative of the Academy of Nutrition and Dietetics that consists of RDNs across the country in various clinical, community, and private practice settings that are interested in research. Practice Based Research Networks (PBRNs) serve two major roles; providing a framework for testing the effectiveness of previous well-controlled clinical trials in real world settings and furnishing a mechanism to speed the translation of research findings into clinical practice. Previous successful weight management trials, like the Diabetes Prevention Program and the Look AHEAD Study have been conducted in large metropolitan areas with substantial resources and highly trained interventionists [19,20]. Previous community based trials in clinical settings have demonstrated that research conducted in a highly controlled setting does not necessarily have the same effectiveness in a community setting [21]. Testing both the effectiveness and the process of delivering a behavioral weight management intervention in a community setting where the intervention is led by interventionists, here RDNs, outside of a large academic center, with patients with a history of chronic disease is imperative.

The RDNs for this study will be recruited through the DPBRN's listserv. Interested candidates will be provided with information about the study and then interviewed through a formal process to determine both practicality of delivering the intervention within their current work and life situation as well as their aptitude for the project. Interviews will be conducted over the telephone. Candidate RDNs will be asked to role play in a counseling situation as well as respond to various clinical situations to determine their aptitude for using motivational interviewing techniques. Once selected, RDNs will attend a one-day training that will review the study protocol, intervention materials, and allow time for reviewing and practicing motivational interviewing and group facilitation skills. The success of this design will also serve as a pilot model for conducting similar studies on a larger geographic scale.

Participants: Participants will include up to 120 overweight/obese women (BMI>27; aged 21-65) with a previous diagnosis of breast

cancer stages 1-3. All participants must be in breast cancer remission for 3 months to 5 years and must receive written medical clearance from their primary care or current oncology physician to enroll in the study. Participants who experience medical complications during the intervention will be withdrawn from the study.

Recruitment: Participants will be recruited primarily through the placement of posters, flyers, and brochures at oncology and radiology practices in Gainesville and Jacksonville. Flyers will also be posted at community health events, local cancer societies and through radio and newspaper advertising. Individuals' willingness to participate in the study will in no way affect their medical treatment.

Inclusion criteria

Participants included in the study will meet the following inclusion criteria: 1) female, 2) age 21-65, 3) BMI of 27-45 kg/m², 4) history of stage 1, 2, or 3 breast cancer, and 5) have completed primary treatments (chemotherapy, radiation, and/or surgical treatment) for breast cancer (with or without maintenance therapy) within the last 3 months to 5 years. Participants will be required to provide consent and have a letter of approval to participate from their physician. Participants must be willing/able to attend group meetings and assessments in Gainesville or Jacksonville and have been weight stable, (i.e. not lost/gained \geq 10 net lbs.) in the preceding 6 months, or since the end of primary treatment, whichever is more recent.

Exclusion criteria

Participants will be excluded from the study if they report a condition likely to influence treatment outcomes, their ability to participate in the treatment protocol, or for which the eating and physical activity behavior changes are contraindicated, including: history of bariatric surgery, pregnant, lactating, or planning on becoming pregnant in next 24 months, serious/chronic infectious disease, chronic malabsorption syndrome, chronic liver disease, chronic pancreatitis, current irritable bowel syndrome, congestive heart failure, uncontrolled angina within the past 6 months, history of musculoskeletal or chronic lung diseases that limit physical activity, uncontrolled or insulin-dependent diabetes, and/or uncontrolled hypertension. Participants also are excluded if they received cancer treatment within the past 5 years (other than for breast cancer) or have any other physical condition (other than history of breast cancer) deemed likely to limit 5-year life expectancy or significantly interfere with individuals' ability to participate in a lifestyle intervention involving eating and physical activity changes. Participants also are excluded if they are taking antipsychotic medications, monoamine oxidase inhibitors, systemic corticosteroids, chemotherapeutic medications, or weight-loss medications. Additional exclusion criteria include significant psychiatric disorder, illicit drug use or excessive use of alcohol, current participation in Weight Watchers or any other weight loss program or another research study; inability to read English at the 5th grade level, inability/unwillingness to provide informed consent or unwillingness to receive random assignment to TLI or CWLP.

Intervention Groups

Tailored lifestyle intervention (TLI)

The TLI will be a 3-month weight management program tailored to the specific needs of women in remission from breast cancer based on the data collected from focus groups. This duration was selected to match a 3-month Weight Watchers membership and as an effective period to observe a reduction in weight loss. While sessions will include

standard topics such as self-monitoring, increasing physical activity, healthy eating, problem solving, and building social support, these sessions will be specifically tailored to women who have had breast cancer and various treatments. Groups will consist of 10-15 participants and will be led by a RDN recruited and selected from the DPBRN. All group leaders will participate in a motivational interviewing training session so that the intervention is effective in the manner in which it was designed. Participants will be remunerated for taking part of the 3 month and 6 month follow up assessments. Initially, individual sessions will occur followed by 12 weeks of group sessions. During the weekly sessions, the RDN will use group motivational interviewing techniques when appropriate to strengthen participants' motivation for improving their nutrition and activity behaviors to promote sustained weight loss. Participants will self-select foods, as opposed to utilizing meal replacements or a "prescribed" meal plan, with the goal of reducing energy intake to promote a 1-2 pound weight loss per week. Emphasis will be placed on following a Dietary Approaches to Stop Hypertension (DASH) eating style with an emphasis on fruits, vegetables, nuts, legumes and seafood. Participants will set weekly goals that will be built upon throughout the program.

Community weight loss program (CWLP)

The CWLP group will receive a 3-month commercial weight loss program (i.e., Weight Watchers) at no cost. During the active phase of the study, these individuals will be encouraged to attend the weekly meetings at their local weight watchers center and also have online access to the program. The 3-month membership during the active study period will be paid by the study, whereas longer-term participation will be at the cost of the participant. CWLP participants will not be prohibited from continuing to attend Weight Watchers during the 6-month follow-up period.

Assessment and Outcome Measures: Measurements are taken at the screening visit, randomization/baseline, post-intervention, and follow-up assessment visits. The following is a description of the measures that will be collected at each visit, and Table 1 displays the time points at which these measures will be collected (Tables 1 and 2).

Statistical Analysis

The number of participants required for this study was determined from data in the literature and our own experiences with weight management interventions; we expect a decrease in body weight of approximately 5-10% from baseline to week 13. A sample size of 102 will be sufficient to detect a 5% difference in weight between the two groups with over 99% power using a two-sided 0.05 significance level to detect a standardized effect of 2 standard deviations. We anticipate a 15% attrition rate over the 9 month study period, so we expect 102 participants, or 51 per randomization assignment, to complete the intervention and attend the final assessment.

Participants will be randomized to treatments in blocks of size 2. Blocks will be formed based on body mass index (27-34.9 and 35-45 kg/m²) and cancer stage (i.e. stage 1, 2, or 3). To account for pre-randomization drops (i.e., screening failures and PI withdrawals) and an anticipated 15-20% attrition rate during the intervention and follow up periods, up to 220 participants will be consented and screened. This should provide for 102 participants at study completion. Participants will be randomized at their second screening visit if they continue to meet the study criteria. Reasons for exclusion will be recorded and reported as these exclusion criteria may provide additional insight into the barriers breast cancer survivors experience when seeking assistance with weight loss and making lifestyle changes. Participants

	Screening	Randomization/Baseline (Month 0)	Post-intervention (Month 3)	Follow-up (Month 9)
Body weight	X	X	X	X
Height	X			
Blood pressure	X		X	X
Lipids/inflammatory markers (venous sample)	X		X	X
HgA1c	X		X	X
Fasting glucose	X		X	X
Dietary intake (ASA-24)	X		X	X
Body composition		X	X	X
Waist circumference		X	X	X
Sagittal abdominal diameter		X	X	X
Accelerometry		X	X	X
IPAQ		X	X	X
QLQ-30 and BR-23		X	X	X
WEL		X	X	X
WMQ			X	X
Program Evaluation			X	X

- **Body weight:** Assessed using the Seca digital scale.
- **Height:** Assessed using a digital wall mounted stadiometer (Heightronic 235).
- **Blood pressure:** Systolic and diastolic blood pressure will be assessed at each time point using an appropriately sized cuff and after the participant has been sitting quietly for at least 10 minutes. Blood pressure is consistently measured on the left arm of each participant, unless they have experienced lymphedema or other side effects of breast cancer/breast cancer treatment, making the right arm a better choice for blood pressure assessment.
- **Waist circumference:** Waist circumference will be measured in triplicate at the top of the iliac crest using a tension controlled tape measure upon exhalation.
- **Sagittal abdominal diameter:** Sagittal abdominal diameter will be measured in triplicate using a Holtain Kahn caliper at the top of the iliac crest upon exhalation.
- **Body composition:** Change in fat and fat free mass will be determined by air displacement plethysmography (Bodpod, COSMED, Inc).
- **Lipids, HgA1c, glucose and inflammatory/metabolic disease biomarkers:** A phlebotomist will take a 45 ml (3 tbsp) sample of arterial blood to assess total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, HgA1c, glucose, and circulating soluble and cellular factors associated with inflammation and cancer biology (i.e., CRP, estrogen, etc) (Table 2).

Table 1: Participant assessment plan.

who experience cancer recurrence or a new cancer diagnosis will be removed prior to data analysis.

The statistical analysis for the primary end-point will be done by Student's t-test to determine the difference between groups for the weight loss between TLI and CWLP groups (adjusted for age and gender) assuming a normal distribution of the results. The secondary endpoints 1) changes in inflammation/chronic disease markers and 2) changes in health related quality of life and self-efficacy within this population will be assessed using analysis of covariance (ANCOVA) using the baseline values as covariates (i.e. baseline LDL-cholesterol). Additionally, we will compare the effect of weight loss on changes in inflammation/chronic disease markers assessed by ANCOVA.

Discussion

Excess adiposity is a modifiable risk factor for breast cancer development. In addition, obesity is associated with multiple comorbidities and increased recurrence in breast cancer survivors. While this association is well accepted, the impact of losing weight and weight loss maintenance in breast cancer survivors is unknown [44]. Therefore, this randomized, multicenter clinical trial will examine the effectiveness of a tailored lifestyle intervention compared to a standard commercial weight loss program on the specific high-risk population of overweight/obese breast cancer patients. This study serves to add to the dearth of literature regarding the impact of weight loss on markers of systemic inflammation that are associated with recurrence of breast cancer.

Epidemiologic and observational studies have found inconsistent findings on the best dietary pattern to reduce the risk for breast cancer risk and development. In addition, a few randomized clinical trials have tested low fat diets on both the incidence and the recurrence of breast

cancer again with conflicting results. For instance, Prentice et al., [45] found a prescribed dietary plan limiting total fat intake to 20% of total calories and increasing fruit, vegetable and grains in post-menopausal women did not reduce the risk for development of invasive breast cancer over an approximate 8 year follow-up period. Similarly, Pierce et al. showed that [46] a diet high in fruit, vegetables, and fiber and low in fat did not prevent breast cancer recurrence or death in women with early stage breast cancer after an approximate seven-year follow-up. On the other hand, Chlebowski et al., [47] found that a low fat diet with a moderate weight loss prevented relapse of breast cancer in women receiving treatment for breast cancer, particularly those with estrogen negative tumors. While promising, the primary aim of this study was to test the effect of a low fat diet on breast cancer recurrence, not weight loss. While the primary aim of MyLIFE is to compare the effectiveness of two different interventions (TLI versus CWLP) on weight loss and weight maintenance our outcomes will also contribute to our understanding of how varying eating patterns and weight loss impact. Thus, the primary aim of MyLIFE is to evaluate the effect of weight loss on markers of inflammation associated with breast cancer recurrence with secondary analyses including eating patterns.

The study design presented here is unique in that focus groups will be conducted prior to beginning the intervention in order to tailor the program specifically to survivors of breast cancer. Not only will the focus groups be conducted with survivors, but also with health care providers that are integral to their care including breast surgeons, RDNs, nurses, case workers, psychologists, and physical therapists. The feedback from these focus groups will be used to guide the development of the motivational group sessions. Topics will include barriers to losing weight, social support, self-image, and items necessary to create the most enabling intervention specifically geared to this group. Given the challenges of long-term weight loss maintenance in the general

Biomarkers	Relevance to Breast Cancer and Obesity
TNF α	Pro-inflammatory cytokine that is increased in with obesity and plays a role in all steps of tumorigenesis [22]
Insulin	High levels of insulin are positively associated with obesity, increased expression of leptin and leptin receptors in some breast cancers [23-25]
Leptin	Promotes cell growth and proliferation in breast cancer [26,27]
IL6	Pro-inflammatory cytokine secreted by adipose tissue which induces cell proliferation/survival and angiogenesis; used as a prognostic tool associated with poor survival [28-30]
C-Reactive Protein	Elevated levels are associated with obesity and decreased survival of breast cancer patients [31,32]
SHBG	Decreases the amount of bioavailable estradiol and is negatively associated with obesity [33,34]
Adiponectin	Low levels in obesity result in insulin resistance [35].
Estradiol	The most active plasma estrogen which is elevated in obesity and strongly correlates with breast cancer risk [36,37]
VEGF	Can be induced by leptin, causes angiogenesis and elevated levels are associated with increased adiposity [38,39]

Table 2: Biomarkers to be assessed prior to, after intervention the 3 month intervention period and at follow-up

- **Dietary intake:** Changes in food intake will be assessed using the National Cancer Institute's Automated Self-Administered 24-hour recall system (ASA-24) [36]. The ASA-24 is free to researchers and requires Internet access. It uses a validated 3-pass method to evaluate food intake in the previous 24 hour period. Data are analyzed using the USDA Nutrient Database for food group, nutrient, and energy intake. At the screening visit, participants will be given instructions on how to complete the recalls and be asked to have these completed prior to their randomization visit.
- **Change in medical status:** Completed by study staff using Medical Update form.
- **Physical activity:** Energy expenditure will be assessed using both objective measurement (via triaxial accelerometer) and subjective assessment (via the International Physical Activity Questionnaire, or IPAQ) [40]. To objectively determine energy expenditure and change in purposeful physical activity, participants will wear a triaxial accelerometer (Sensewear Armband, Bodymedia, Inc.) on their upper left arm (unless contraindicated by complications due to breast cancer/breast cancer treatment) for 7 days prior to beginning the intervention, upon completing the 12-week intervention, and prior to completing their final assessment visit. Participants will also complete the IPAQ. The IPAQ is a 27-item self-report questionnaire that assesses physical activity in five activity domains (job-related, transportation, housework/house maintenance/caring for family, recreation/sport/leisure time, and time spent sitting). Comparisons of the IPAQ to activity monitor suggests that the results are roughly comparable for total physical activity ($r=.55$) and vigorous physical activity ($r=.71$), but less comparable for moderate physical activity ($r=.21$) [40].
- **Health-related quality of life:** Health-related quality of life will be assessed using the European Organization of Research and Treatment of Cancer – Quality of Life (QLQ-30) and the breast-cancer specific addendum (BR-23). The QLQ-30 is a 30-item self-report measure that assesses five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea/vomiting) and one global health and quality of life scale. A study of the measure's psychometric properties supported the hypothesized scale structure of the measure (all Cronbach's alpha coefficients $\geq .70$ except for "role functioning" which is X) [41]. The BR-23 is a 23-item self-report addendum that contains five subscales which assess aspects of quality of life specific to breast cancer. The measure has sufficient internal consistency (Cronbach's alphas ranging from .70 to .90 in the United States [42]).
- **Self-efficacy:** Participants' self-efficacy to abstain from eating in a variety of situations will be assessed using the Weight Efficacy Lifestyle (WEL) questionnaire. The WEL is a 20-item self-report measure containing five subscales assessing self-efficacy to abstain from eating when 1) experiencing negative emotions, 2) food is readily available, 3) experiencing social pressure to eat, 4) experiencing physical pain/discomfort, and 5) engaging in positive/enjoyable activities. The five subscales have adequate internal consistency (Cronbach's alpha values ranging from 0.70 to 0.90) as well as significant correlation with each other (r -values ranging from .39 to .66), which suggests that there is a global construct of weight self-efficacy [43].
- **Weight Management Strategies:** The frequency of participants' utilization of specific weight management strategies will be assessed using the Weight Management Questionnaire (WMQ). The WMQ was developed internally and there are currently no published data on the measure's validity or reliability. Examples of strategies that are assessed include frequency of self-weighing, self-monitoring of food intake and physical activity, meal planning, and decreasing portion sizes.

Program Evaluation: This brief measure assesses participants' views about the degree to which they found various aspects of the program to be useful/helpful. Examples of program aspects to be evaluated include study materials, effectiveness of the group leader, and meeting facilities.

population and the additional challenges of having been treated for breast cancer, we believe this tailored approach will lead to more robust and more sustained changes than a conventional weight loss program.

While being overweight contributes to a 30% increase in a women's risk in developing breast cancer, additional studies have shown that physical activity contributes to an approximately 30% decrease in breast cancer risk mortality. With that said, few interventions have examined the impact of the combination of these two factors: reducing obesity and increasing physical activity in the development and prognosis of breast cancer [18]. Mohammadi et al., [48] completed a cross sectional analysis of Iranian breast cancer survivors and found an association between better eating habits and more physical activity, and greater perceived quality of life. The findings of this study indicate that breast cancer survivors can have an improved quality of life through attention to nutrition and physical activity. The behavioral intervention presented here will include a tailored approach to not only improving dietary choices, but also increasing physical activity, thus addressing the need for more randomized clinical trials to test the impact of both weight loss and increasing physical activity on the risk of breast cancer recurrence.

After the 13-week intervention proposed, the authors expect to see a 9% body weight loss in the TLI. Although CWLP participants are likely to also experience a degree of weight loss, the authors anticipate that mean weight losses will be greater among the TLI participants,

as this intervention will address specific barriers to healthy eating, exercise and weight control that arise in this population. In addition to the primary outcome of weight reduction, cancer and systemic inflammatory markers will be measured prior to beginning the study, at the end of the intervention, and at the 6-month follow-up assessment. As previously mentioned, obesity is associated with the development of multiple systemic and metabolic disease whereby physical inactivity is a major contributor to the development [49]. Furthermore, it is known that regular exercise prevents or at least delays the onset of many of these complications independent of weight loss [50]. Multiple studies have identified inflammation as a key association between obesity and the development of these chronic diseases, including cancer [49]. Importantly, exercise and loss of adipose tissue promotes numerous molecular and cellular changes which negatively affect inflammation and positively affect immunoregulation [49]. Thus, we propose that if participants are successful in making weight-related lifestyle changes, they should experience a decrease in chronic systemic inflammation which in turn may result in a reduced risk of breast cancer recurrence.

There are, however, challenges this trial is likely to face. Specifically, our basis for comparing the TLI to CWLP is that breast cancer survivors have unique and potentially additional barriers to making sustained lifestyle changes compared with women who have never experienced breast cancer. Thus, we predict that helping the women overcome these barriers will be more difficult than when working with overweight, yet healthy, adults. The first phase of this project is meant to allow us to

identify many of these potentially unique barriers while the second phase of the project will allow us address these obstacles through the intervention structure itself rather than as they arise. We feel this approach will lead to greater sustained weight and behavior outcomes in this unique population.

Thus, due to the number of confounding factors our platform addressed, we feel the tailored lifestyle intervention and its application presented here can serve as a platform to develop tailored lifestyle interventions for other high-risk populations.

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