PROTOCOL:

Be-Active Study – Increasing Physical Activity for Cancer Survivors

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BACKGROUND

Rates of cancer survivorship are exponentially rising and there is a growing need to address the unique health challenges facing cancer survivors. Although cancer is the second leading cause of death in the United States, cancer death rates have decreased by 27% over the last decade[1]. Currently, there are >16.9 million cancer survivors in the US (~5% of the population) and it is estimated that rates of cancer survivorship will increase by an additional 31% by 2030 due to earlier detection and improved treatments[2]. Survivorship is also more complicated as the proportion of people with advanced cancers experiencing prolonged survival also increases due to the increased effectiveness of precision and immunotherapies. In advanced melanoma, for example, median overall survival among study volunteers receiving nivolumab plus ipilmumab extended beyond six years[3]. While these predictions are encouraging, cancer survivors, whether in remission or with extended disease stability, and of a variety of cancer types, face unique health challenges resulting from the disease which can persist well beyond the end of cancer treatment and reduce physical and mental health-related quality of life. For example, among cancer survivors, 32% report continued limitations in daily activities[4], 25% report persistent fatigue for years post-treatment[5], 18% report anxiety symptoms[6], 12-14% have clinical depression[7], and up to 80% report some level of fear of recurrence[8].

Physical activity (PA) is a modifiable lifestyle behavior which can help ameliorate these adverse health effects and is positively associated with numerous physiological and psychological health benefits. Findings from the American College of Sports Medicine's International Multidisciplinary Roundtable indicate that there is strong evidence that regular PA can improve common cancer-related side effects, namely anxiety, depression, fatigue, health-related quality of life, physical functioning, and cardiorespiratory fitness[9]. Physical activity is also associated with lower risk of all-cause mortality, cancer recurrence, and the likelihood of other comorbid chronic diseases (e.g., type 2 diabetes and cardiovascular disease)[10-12].

Although PA is important for cancer survivorship, the majority of cancer survivors do not meet recommended PA guidelines. Currently, it is recommended that cancer survivors engage in ≥150 min/week of moderate-intensity PA[9]. However, it is estimated that up to 47% of cancer survivors fail to meet this guideline as assessed via self-report PA measures[13-17]. This percentage is likely even higher, given that prior studies in cancer and non-cancer populations have shown three- to six-fold reductions in PA estimates when assessed via accelerometers (a wearable device to objectively-assess PA), versus self-report PA[18-20].

Despite strong evidence that regular PA has numerous health benefits for cancer survivors, *how to* promote sustained changes in PA among inactive cancer survivors is not well understood[21]. This is largely because the majority of high-quality randomized trials examining the effect of exercise training on health parameters for those living with cancer or beyond have utilized intense exercise training regimens, where supervised exercise is performed several times per week for multiple weeks at a laboratory or research center. While these studies are important and a necessary first step towards understanding the role of exercise in cancer prevention and survivorship, these strict exercise training protocols are unrealistic to implement on a large scale and have limited dissemination potential; thus it is necessary that effective and translatable interventions for increasing PA among cancer survivors are developed and implemented. In addition, there is a lack of evidence to inform whether these benefits extend to those survivors on extended treatments.

Automated, Internet-based PA programs allow for wide-scale dissemination at a relatively low cost. Pew Research data show that >90% of Americans use the Internet[22], making it an ideal medium for delivering behaviorally-based PA interventions, as it can reduce provider costs and reach larger numbers of individuals. Further, the cost of delivering an automated Internet program is low, and there is no added cost for enrolling additional participants, which is important from a translation perspective into healthcare settings.

Although eHealth interventions are widely used to promote PA and other lifestyle behaviors in 'non-clinical' settings or for patients with specific chronic diseases (e.g., CVD, diabetes), application of these technologies to promote PA in cancer survivors lags behind and is a relatively new concept[23]. A recent systematic review[23] identified only five Internet interventions targeting increases in PA among cancer survivors. Of those, only three were randomized trials with a control group, four used a self-report measure of PA, and four were <12 weeks in duration. While overall, these studies showed preliminary support that web-based interventions can increase PA among cancer survivors, additional research is clearly needed.

The proposed study addresses significant limitations in this area of research and examines the feasibility, acceptability, and preliminary efficacy of a 12-week, fully-automated Internet program for increasing PA among cancer survivors, by including those off all cancer treatment and those stable on continuous anticancer therapy - thereby adding to the scant body of literature examining the effect of Internet interventions in this population. It further extends the PA and cancer literature by using rigorous methodology (accelerometers) for assessing changes in PA, not limiting the inclusion criteria to one particular cancer type

(e.g., breast cancer only), utilizing a randomized design which allows for comparison to a usual care control condition, testing an Internet program that is driven by behavioral theory, incorporating the most effective behavioral intervention components (see Innovation), and addressing the need for longer-term interventions (>6 weeks) which also assess the maintenance of PA post-treatment (i.e., 24-wk assessment). Findings from this study have potential to lead to a larger trial with clinical implications for increasing PA in cancer survivors.

STUDY AIMS

- **Primary aim 1:** Evaluate the feasibility, acceptability, and engagement with the EEP. Feasibility will be evaluated using a comprehensive approach which includes measures of screening (# screened/mo), recruitment (# enrolled/mo), randomization (% eligible who enroll), and retention (% completing study). Acceptability will be assessed by a program satisfaction questionnaire at each assessment time point. Intervention engagement will be measured by the number of website logins, video lessons viewed, homework assignments completed, frequency of exercise planning, number of exercise days, and total exercise minutes.
- **Primary aim 2:** Compare treatment groups on 12- and 24-week changes in PA (steps, MVPA, bouted MVPA). We will stratify patients whether or not they are on maintenance/continuous treatments or not.
- **Secondary aim:** Compare treatment groups on changes in sleep, weight, and other questionnaire measures (e.g., fatigue, distress, anxiety, depression, health-related quality of life, fear of recurrence) at 12 and 24 weeks.

RESEARCH PLAN

Study Overview and Randomization. 50 participants will be randomized in equal numbers (permutated block structure, matched by biological sex and cancer type) at baseline to receive the 12-week Energize! Exercise Program (EEP) or to a standard of care control condition (CON). Assessments of PA, fatigue, sleep, distress, anxiety, depression, weight, health-related quality of life, and fear of cancer recurrence will occur at baseline, 12 weeks (post-intervention), and 24 weeks (following 12-week no-contact follow-up period). Following the 24-week assessment, participants randomized to CON will have the opportunity to participate in the EEP, if they desire, and complete an additional assessment at 36 weeks (upon completion of the EEP). Participants randomized to EEP will be provided with CON newsletters following the 24-week assessment.

Recruitment & Enrollment. Participants will be primarily recruited via multiple avenues within the Lifespan Cancer Institute (LCI), the Miriam Primary Care Clinic, and the Oncology, Wellness, Lifestyle and Survivorship (OWLS) clinic. We will work with our LCI Patient Navigators and Advanced Care practitioners who work closely with oncology and radiation oncology and will help to identify patients who will be eligible. Clinical research assistants may also access healthcare records prior to patient visits to identify individuals who meet our inclusion criteria related to age, BMI, and duration of time following cancer treatment. If eligible based on that information, they may send them a message informing them about the study via the patient portal, the standard of care mechanism of contact, or ask patients about their physical activity levels at visits or via phone. Research assistants will either direct individuals to the online screener or help patients complete the online screener for the study. However, we may also work with other physician groups, post flyers, and advertise on various social media platforms (e.g., Facebook, Instagram, Twitter) to help spread the word about our research study. All interested individuals will complete an online screener to determine initial eligibility. If eligible, a research staff member will conduct a follow-up phone screen to confirm eligibility and schedule an orientation session where the study will be explained in detail and informed consent will be obtained. All participants will also be required to get physician clearance (see attached MD consent form) prior to randomization.

Participants. Individuals must have a confirmed cancer diagnosis and have either completed all cancer-directed treatment in the past 12 months or be on a maintenance/continuous treatment regimen. Individuals must also be 18-70 years of age, have a BMI between 18.5 and 45), have daily Internet access, free of any medical condition for which PA is contraindicated, and inactive, defined as engaging in <60 min/week of moderate-intensity PA over the past 3 months. Participants must also be English speaking, as the Internet program is currently in English. These broad inclusion criteria were selected to enhance generalizability of study findings and to provide us with preliminary data on the effectiveness of this program across cancer types.

Internet-based exercise program. Participants randomized to EEP will receive the 12-week Energize! Exercise Program. This theory-driven, behaviorally-based Internet program is designed to increase moderate-intensity exercise to a level consistent with national recommendations and can be accessed via the Internet on a computer, smartphone, or other mobile device. Prior to the start of the program, participants will attend a 30-minute webinar in which they will be taught how to navigate the study website and will be given the opportunity to ask questions. Upon starting the program, they will be given a weekly exercise goal that starts at 75 min/wk and progresses to 150 min/wk. Participants will be taught how to gauge exercise intensity and the type of PA that will count towards their PA goals (i.e., moderate-intensity aerobic PA such as brisk walking, cycling). Activities such as hatha yoga, strength training, and household (e.g., gardening or vacuuming) and occupational activities (e.g., waitressing or delivering packages), do not meet the specified criteria for 'purposeful aerobic exercise' and would not be counted. To promote a regular habit of exercise, participants will be encouraged to exercise 5 days/week.

Table 1: Video lesson titles

Week	Lesson title
1	Your exercise prescription
2	Exercise planning
3	Negative thoughts
4	Modifying your environment
5	Overcoming exercise barriers
6	Exercise enjoyment
7	Checking in with yourself
8	Managing exercise slips
9	Exercise motivation
10	Sitting less & moving more
11	Future-oriented mindsets
12	Thinking like a lifelong exerciser

Participants will also be instructed to watch a 10-15 minute video weekly (Table 1). To help participants apply the intervention content, they will complete weekly homework assignments corresponding to each video lesson (~10 min to complete). Example assignments include creating exercise routines to promote habit formation, journaling about the value of exercise and positive feelings associated with exercise, evaluating their progress, and problem solving around exercise barriers. Participants will also plan their exercise prior to the start of each week and submit that detailed exercise plan via the study website. In addition to their planned exercise, they will report their actual exercise performed (e.g., minutes/day, time of day, and type of activity). Computer-generated personalized feedback will be provided weekly based upon the data that was input from the previous week. Feedback messages are designed to be encouraging and motivational, praising individuals for meeting goals. When goals are not met, support and encouragement are provided along with specific recommendations for behavioral strategies to implement. If participants do not report their exercise on the study website in a given week, an automated email will be sent, reminding them to do so.

Usual care control condition. Participants randomized to the usual care control condition will receive a newsletter, twice per month for the first 3 months, to help optimize retention rates. Consistent with information available to individuals via the National Cancer Institute and traditional survivorship care plans, these newsletters will focus on the health benefits of regular PA for cancer survivors, national PA guidelines, general information for initiating a PA program, exercise safety, gauging exercise intensity, and different types of exercise. Strategies for facilitating behavior change will not be included in these newsletters.

Feasibility, acceptability, and intervention engagement. Feasibility will be evaluated using a comprehensive approach which includes measures of screening (# completing online and phone screens/mo), recruitment (# enrolled/mo), randomization (% eligible who enroll), retention (% completing study), and treatment adherence (adherence to intervention)[24]. These data will be used to develop and refine recruitment and assessment procedures, modify and improve intervention components, and inform sample size estimates for a larger efficacy trial. Acceptability will be assessed by a program satisfaction questionnaire. Participants will provide feedback on their overall satisfaction with the program, the program structure (e.g., planning, homework and feedback messages), and intervention content (e.g., video lessons). Further each week, as part of their homework, participants will be asked 3 brief questions about whether the information provided within the video lesson was helpful, informative, and whether it motivated them to exercise. There will also be an open-ended question to provide additional feedback. Intervention engagement will be generated automatically from the study website and measured by the number of website logins, video lessons viewed, homework assignments completed, frequency of exercise planning, number of exercise days, and total exercise minutes.

Assessment measures. Assessment will be completed at baseline, 12 weeks and 24 weeks (36-week assessment will also be conducted for CON participants who opt to enroll in the EEP following completion of their 24-week assessment visit). Participants will be compensated $25 for completing weight, physical activity, and questionnaire measures (described below) at 12 weeks and also at 24 weeks (36 weeks if applicable), but not baseline. Participants will primarily be compensated with cash, but should the option of gift card or check will also be available for special circumstances (i.e., the participant is unable to come to an in-person visit).

Physical Activity. Physical activity will be objectively-assessed using the previously validated Actigraph accelerometer[25-27]. Participants will wear the accelerometer on their waist for 1 week, at each assessment, during all waking hours. Weekly MVPA (PA above validated count cut-point for moderate-intensity)[26], bouted MVPA (moderate-intensity PA occurring in bouts ≥10 min; measure of purposeful/ structured exercise), and daily steps will be computed. Intervention groups will be compared on these PA measures at 12 and 24 weeks. Self-reported physical activity will also be assessed using the Paffenbarger physical activity questionnaire.

Weight. Weight will be assessed at each assessment to the nearest 0.1 kg using standard procedures.

Questionnaire measures. Demographics, exercise history and exercise goals, and health literacy (*Single Item Literacy Screener[28])* will be assessed at baseline. A secondary aim of this trial is to examine intervention arms on measures of physical and mental well-being and PA constructs at 12 and 24 weeks. Health-related quality of life will be assessed using the *SF-36*. This previously validated and widely used questionnaire measure eight domains of health status: physical functioning, physical role limitations, bodily pain, general health perceptions, energy/vitality, social functioning, emotional role limitations, and mental health. Fatigue will be assessed using the *Brief Fatigue Inventory* which has been previously validated in a cancer population and is used to assess the severity of fatigue and the impact of fatigue on daily functioning. Individuals are queried about fatigue over the past week, current fatigue, and usual and worst fatigue in the past 24 hours. Sleep quality will be assessed using the *Pittsburgh Sleep Quality Index* which has been shown to have good reliability and validity. This 19-item self-rated questionnaire assesses sleep quality and disturbances over a 1-month time interval. Psychological distress will be assessed using the single-item *Distress Thermometer* developed by the National Comprehensive Cancer Network and asks patients to rate their distress on a scale of 0-10. Anxiety and depression will be assessed via the *Brief Symptom Inventory-18* which is a widely used to assess psychological symptoms of cancer survivors and has subscales related to somatization, depression, and anxiety. Fear of recurrence will be measured using the severity and trigger subscales of the *Fear of Recurrence Scale[29].* Physical activity constructs will include previously validated measures of exercise enjoyment (*Physical Activity Enjoyment Scale*), exercise self-efficacy (*Self-Efficacy for Exercise Scale*), exercise motivation (*Behavioral Regulation Exercise Questionnaire-2*), and exercise barriers (*Physical Activity Barriers After Cancer*). Program satisfaction will be assessed via a series of questions at 3 months.

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