Title

Benefits of nature-based walking for breast cancer survivors.

Journal

BMJ open, 13(6)

ISSN

2044-6055

Authors

Shirazipour, Celina H
Raines, Carolina
Liu, Eileen
et al.

Publication Date

2023-06-01

DOI

10.1136/bmjopen-2022-071041

BMJ Open

Benefits of nature-based walking for breast cancer survivors

Celina H Shirazipour,[1,2] Carolina Raines ,[1] Eileen Liu,[1] Rachel M Ruggieri,[1] Jessica M Capaldi,[1] Bianca Luna-Lupercio,[1] Marcio A Diniz,[3] Gillian Gresham,[1] Neil Bhowmick,[3] Robert W Haile,[1] Arash Asher[4]

To cite: Shirazipour CH, Raines C, Liu E, *et al*. Benefits of nature-based walking for breast cancer survivors. *BMJ Open* 2023;**13**:e071041. doi:10.1136/bmjopen-2022-071041

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-071041).

Received 14 December 2022
Accepted 31 May 2023

[1]Department of Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, CA, USA
[2]David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA
[3]Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA
[4]Department of Physical Medicine and Rehabilitation, Cedars-Sinai Medical Center, Los Angeles, California, USA

Correspondence to
Dr Celina H Shirazipour; celina.shirazipour@cshs.org

ABSTRACT

Introduction Physical activity (PA) promotes significant physical and psychosocial benefits for breast cancer survivors. While evidence exists regarding recommendations for the frequency, duration and intensity of exercise that optimise PA benefits for cancer survivors, the role of the environment in achieving optimal outcomes has yet to be determined. This paper presents a protocol for a clinical trial to evaluate the feasibility of a 3-month nature-based walking programme for breast cancer survivors. Secondary outcomes assessed include the impact of the intervention on fitness, quality of life outcomes, and biomarkers of ageing and inflammation.

Methods and analysis The trial is a 12-week single-arm pilot study. Twenty female breast cancer survivors will engage in a supervised moderate intensity walking intervention in small groups in a nature reserve for 50 minutes three times per week. Data will be collected at baseline and end of study, and include assessment of inflammatory cytokines and anti-inflammatory myokines (TNF-α, IL-1ß, IL-6, CRP, TGF-ß, IL-10, IL-13), as well as ageing (DNA methylation, ageing genes) biomarkers; surveys (Patient-Reported Outcomes Measurement Information System-29, Functional Assessment of Cancer Therapy-General, Post-Traumatic Growth Inventory); and fitness assessments (6 min Walk Test, Grip-Strength, One Repetition-Maximum Leg Press). Participants will also complete weekly surveys assessing social support and participate in an exit interview. This is an important first step for future research on the influence of exercise environment on cancer survivor PA outcomes.

Ethics and dissemination This study was approved by the Cedars Sinai Medical Center Institutional Review Board (IIT2020-20). Findings will be disseminated through academic manuscripts, conferences, and community presentations.

Trial registration number NCT04896580.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will provide preliminary evidence to support future large-scale research on the influence of physical activity (PA) environments on the health and well-being of breast cancer survivors.
⇒ This study implements evidence-based behaviour change techniques crucial for promoting adherence.
⇒ Participating in a 3-month PA programme with walks three times a week may seem challenging and result in potential selection bias for individuals who are more motivated to be active and who have more leisure time.
⇒ As a time-limited pilot study, the protocol could not provide support for continued participation after 3 months, which may limit sustained behaviour change post-study.

INTRODUCTION

Female breast cancer has surpassed lung cancer as the most diagnosed cancer type, representing an estimated 11.7% of new cancer cases each year.[1] Furthermore, breast cancer is the second-leading cause of female deaths in the USA.[2] However, while female breast cancer incidence rates have been increasing, mortality has decreased. This improvement is partly due to earlier diagnosis of breast cancer, as well as advancements in breast cancer treatment.[2] The result is the ability to expand focus on post-treatment survivorship, particularly mitigating long-term side effects of cancer and its treatments, including accelerated ageing,[3] cognitive dysfunction, neuropathy, cardiac issues, fatigue, osteoporosis and obesity.[4]

Research on physical activity (PA) for cancer survivors often focuses on PA benefits, as well as ideal intensity and dosage.[5] Several studies have demonstrated strong evidence linking PA to improved physical and psychosocial health for breast cancer survivors (BCSs),[5 6] including improvements in bone health, sleep, anxiety, depression[5] and cancer-related treatment side effects, including physical functioning, cardiorespiratory fitness and fatigue.[7] Additionally, for BCS, PA is associated with reduced cancer recurrence, as well as improvements in all-cause mortality and breast cancer-related mortality.[8–10] PA guidelines for cancer survivors suggest 150–300 min per week of moderate-intensity aerobic exercise or 75–150 min of vigorous-intensity aerobic exercise (during treatment, this may need to be modified), as well as 2–3 days of resistance training incorporating

8–10 exercises of major muscle groups.[11] However, BCSs are unlikely to adhere to PA guidelines,[12 13] with adherence varying across the survivorship continuum[14] and based on cancer treatment.[12 15 16] One potential solution to improving PA participation is exploring opportunities for creating and delivering quality PA participation experiences. Research has demonstrated that PA location (ie, home vs hospital based), the presence of trainers and the type of PA may be influential in predicting PA participation.[17] While this provides a starting point, further research is necessary to be able to provide a wider array of evidence-based programming that can be tailored to each survivors' interests and thus be more likely to promote sustained participation.

One potential PA environment that remains understudied among cancer survivors is nature. This study defines nature as an outdoor space 'that is partly or completely covered with grass, trees, shrubs or other vegetation.'[18] Most research on the physical and psychosocial benefits of nature-based PA has been conducted in the general population. In these studies, nature is suggested to be more effective than traditional PA environments (eg, home, gym, clinic) for improving cardiovascular and mental health.[19] For example, walking in nature has substantially greater benefits for well-being and physical health than walking in urban spaces,[20 21] including improvements in pain, sleep, immune function, postoperative recovery and general health, such as lower blood pressure.[22–37]

PA interventions in patients with breast cancer often focus on indoor settings,[38] including supervised gym or home-based exercise.[39–41] However, research has begun to highlight the potential benefits of outdoor activity with the introduction of the concept of therapeutic landscapes, revealing the value of these landscapes for survivorship health and psychosocial outcomes.[42 43] This concept suggests a potential link between health and location, with certain environments being more beneficial to health and healing.[42] Early research in this area focused on blue space and group activity, particularly dragon boating. The outcomes examined for blue space, focused largely on the psychosocial benefits, including improved social support and post-traumatic growth, and decreased fatigue.[44–47] To our knowledge, only a few studies have explored the impact of walking in nature on cancer survivors. For example, one study implemented a 1-week walking intervention for adolescent and young adult cancer survivors in a nature-rich environment, demonstrating positive results on well-being and post-cancer identity development.[48] Similarly, Ireland *et al*[49] found that walking and talking outdoors between 30 and 60 min a day, particularly in rural settings, enabled supportive conversations that promote recovery among BCS.[49] These studies highlight the potential importance of the location, and specifically outdoor nature-based environments, for promoting benefits for cancer survivors.[49] They provide an important foundation for intervention development. However, research gaps remain on the impact of long-term nature-based PA, as well as the effect of nature-based PA on clinically relevant cancer related biomarkers.

This study seeks to address these gaps through two research questions. First, what is the feasibility of a 3-month nature-based walking intervention for BCS? Feasibility will be measured through attendance (attending at least 25 out of the 36 sessions), retention (participation from baseline through final assessment), and percentage of patients approached who sign consent. The second research question asks: what are the short-term effects of a 3-month nature-based walking intervention on (A) well-being (as measured by Patient-Reported Outcomes Measurement Information System-29 (PROMIS-29), Functional Assessment of Cancer Therapy-General (FACT-G), Post-Traumatic Growth Inventory (PTGI), and PROMIS Social Support Surveys), (B) cancer-relevant biomarkers (biological ageing (DNA methylation, ageing genes) and inflammatory markers (inflammatory cytokines, anti-inflammatory myokines)) and (C) fitness outcomes (6 min Walk Test (6MWT), Grip-Strength test, 1-Repetition Maximum (RM) test)? Data collection will take place at baseline and 3 months.

METHODS AND ANALYSIS

Study design and participants

This is a 12-week single-arm pilot study to evaluate the impact of a nature-based walking programme on BCS. The Standard Protocol Items for Randomised trials recommendations for reporting of protocols were followed.[50 51] Twenty female BCS will engage in moderate intensity walking in a 600-acre nature reserve in the City of Los Angeles three times per week. Walks will take place in groups with other BCS, and participants will be always accompanied by a certified exercise physiologist (CEP), or members of the study team who have been trained by a CEP to deliver the intervention. Biomarkers, patient-reported outcomes, cardiorespiratory fitness, strength and vitals will be assessed at baseline and 12 weeks. Eligible participants are: (1) English-speaking, female ages 18–80 years diagnosed with primary stage 1–3 breast cancer; (2) between 3 and 21 months postactive treatment and (3) able to ambulate and complete baseline fitness assessments. Participants will not qualify if they have planned active treatment or major surgery within 3 months of the baseline visit, if they are more than 24 months post-active treatment at baseline or have grade 3 or higher peripheral neuropathy or known metastatic disease. See table 1 for a complete list of inclusion and exclusion criteria. Participants who withdraw before starting the intervention will be replaced. If participants experience an injury or if they become pregnant and remain in the study, the CEP will further tailor their walking programme and or intensity to accommodate the injury or pregnancy. The study began on 21 June 2021. We anticipate study completion Summer 2023. Flow chart of the study design is presented in figure 1.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
► Female previously diagnosed with breast cancer (clinical stages 1–3)	► Active treatment planned within the next 3 months
► Minimum of 3 months and a maximum of 21 months postactive treatment completion*	► Known metastatic disease ► More than 24 months postactive treatment at baseline
► Able to ambulate without assistance and complete baseline fitness assessments†	► Grade 3 or higher peripheral neuropathy
► Medical clearance to participate in the study including confirmation that the likelihood of coronary disease is low	► Major surgery within 3 months of baseline visit that would prohibit participation in the exercise intervention
► Ability to read, write and understand English	► Positive pregnancy test
► Age ≥18 years ► Written informed consent obtained from subject and ability to comply with the study requirements	► Answers 'yes' to any question on the PAR-Q questionnaire, unless cleared by physician
	► Currently meet physical activity guidelines (score of >23 on Godin-Shephard Leisure-Time Physical Activity Questionnaire).

Long-term hormonal/biological treatments are acceptable.
*Active treatment includes chemotherapy, biological therapy, radiation therapy, surgery and any combination.
†Baseline fitness assessments include 6 min walk test, hand grip test, 1-RM leg press.
PAR-Q, Physical Activity Readiness Questionnaire; 1RM, 1-Repetition Maximum.

Recruitment

Participants will be recruited through physician referrals. If a potential participant indicates interest during a medical visit, study staff will follow-up to discuss the study and answer questions. Participants can also be recruited through flyers distributed to community partners.

Study setting

The exercise programme will be delivered at a 605-acre nature and park conservation area in the City of Los Angeles, located near the research team's medical institution. Since heat and air quality are challenges to outdoor PA in Los Angeles, air quality indicators and weather predictions will be monitored prior to each walking session. Two hours prior to each walking session, the CEP will assess air quality and weather conditions for the region and contact participants to reschedule if conditions are not favourable. The CEP will check and record the temperature on https://www.weather.gov/, and the air quality measurements from two sources: the AirNow website and the AtmoTube Pro. AirNow (http://gispub.epa.gov/airnow/) is a website developed by the US Environmental Protection Agency, the Centers for Disease Control and Prevention and other federal agencies to provide interactive maps of air quality and fire conditions. The website allows users to enter a zip code for data and drill down to see data for a single air quality monitor. The monitor provides data on Ozone, PM 2.5, PM10, NO2 and CO. AtmoTube Pro is a portable outdoor air quality monitor that the CEP will carry during the green space walking sessions to record air quality in real time. The device detects PM 1, PM 2.5 and PM10 pollutants, dust, pollen, soot, mould and volatile organic compounds. It also measures atmospheric pressure, temperature and humidity. It is currently considered the most accurate portable air quality monitor. Any session likely to occur in high heat (greater than 85°F/29.44°C) or poor air quality (PM 2.5 150 or greater) as well as other weather not feasible for safe walks (the park shuts down in rain due to risk of mudslides), will be rescheduled for a different time of day or another day of the week.

Screening, baseline and end of the study visits will happen at Cedars Sinai Medical Center in a fully equipped rehabilitation gym with adjoining rooms for phlebotomy and survey completion.

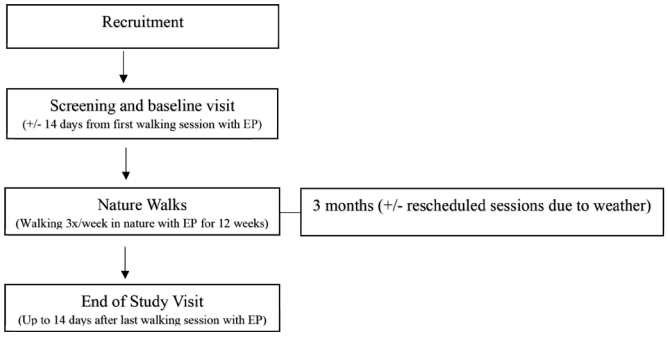

Figure 1 Flow chart of the study design. EP: Exercise Physiologist

Nature walks

Walks will happen on routes predetermined by the research team in a 600-acre nature reserve in Los Angeles, California. All participants will walk the same path three times per week for 12 weeks. Sessions will consist of 5 minute warm-up, a 40 minute walk at a constant moderate intensity (40%–59% of their heart rate (HR) reserve, and 5 minute cooldown and stretch). The CEP will monitor session intensity by tracking participants' HR with a Fitbit. The intervention will be tailored to each participant's physical fitness and ability levels—determined from baseline assessments. As participant fitness improves during the intervention, the trainer will adjust

the pace of the walks to maintain moderate level intensity. Sessions will take place in small groups of 3–5 participants either earlier in the morning or later in the afternoon when weather conditions are more favourable for in Los Angeles for outdoor PA. Participants are encouraged to keep the same day and walk session times throughout the intervention. After each walk, study staff will complete activity logs on REDCap to record whether the session took place, how many people attended and reasons for any participant missing a session.

While participants will be discouraged from engaging in structured PA outside of the intervention, participants may still be exposed to nature environments (gardens, parks) or participate in other types of PA during the intervention. To determine any contamination of the intervention through outside exposure to nature or other PA, participants will complete weekly surveys asking if they have engaged in any non-study PA in outdoor spaces and, or gyms, how time was spent (fully engaged–watching family/friend engage in the space), frequency, and duration.[52] PA participation outside of study can also be determined based on Fitbit data. Participants are encouraged to wear their study provided Fitbit 24/7 and to log any activities on the device.

During each walking session, the CEP will monitor for adverse events (AEs). CEP and study staff will report any AE to the principal investigators (PIs) within 24 hours of the event. The physician investigator will determine the severity of the event and decide the course of action to be taken, including no changes in the exercise intervention, reducing, modifying, or discontinuing the exercise intervention, or the requirement of other medical or surgical intervention. All serious AE will be reported to the Institution Review Board within 10 days.

Fitbit

To track activity data, participants will wear a study-provided Fitbit wrist-worn activity monitor (Fitbit charge 4) for the duration of the intervention. Each participant will use a participant-specific, study-created Fitbit account. Study staff will download activity data at the participant's mid-study time point (6 weeks) and at the end of study visit. Synced Fitbit data will be downloaded from Fitbit and Fitabase. During the exercise session, the CEP will remind participants to wear and sync their Fitbit at the beginning and end of each walking session. The study coordinator will check the participant's Fitbit account to ensure it has been synced recently (within the last 7 days). If it has not been synced, the coordinator will contact the patient.

Measurements

Primary outcome

Adherence

Adherence will be measured through (1) attendance (frequency of walking sessions attended and number of sessions modified due to weather); (2) retention (participation from baseline through the final assessment) and (3) percentage of patients approached who sign consent.

Secondary outcomes

Well-being

Participants will complete the PROMIS 29, FACT-G, PTGI and PROMIS social support surveys at baseline and 3 months. They will also complete the PROMIS positive affect survey at the end of each week.

Patient-Reported Outcomes Measurement Information System-29

PROMIS-29[53] is a short-form health-related quality-of-life measure that assesses seven different quality of life domains (depression, anxiety, physical function, pain interference, fatigue, sleep disturbance and ability to participate in social roles and activities).[53] All domains are measured on a 5-point scale, with anchors changing for each domain.[54] PROMIS-29 is a common measure used among cancer survivors and has demonstrating strong reliability and validity.[54]

Functional Assessment of Cancer Therapy-General

The FACT-G[55] is a 27-item survey that assesses four domains of health-related quality of life specific to adult patients with cancer: physical, social/family, emotional and functional well-being.[55] Items are measured on a 5-point Likert-type scale anchored at 0 (not at all) to 4 (very much). Responses are meant to identify the prevalence of symptoms over the previous 7 days.

Post-Traumatic Growth Inventory

PTGI[56] is a 21-item scale that assesses five factors of post-trauma growth: relating to others, new possibilities, personal strength, spiritual enhancement and appreciation.[56] Items are scored on a 6-point scale, anchored at 0 (did not experience this change) to 5 (experienced this change to a very great degree).[56] PTGI had demonstrated reliability and validity in patients with cancer.[56–58]

Social support

Participants will be asked to complete the short-form of three PROMIS surveys: emotional support survey (eight items) assesses perceived feelings of being cared for and valued as a person and having confidant relationships[59 60]; informational support (eight items), evaluates the perceived availability of helpful information or advice[60]; and instrumental support (eight items), estimates the perceived availability of assistance with material, cognitive or task performance.[60] These surveys have demonstrated clinical validity in the cancer population.[61]

PROMIS positive affect

The PROMIS positive affect[60] survey presents participants with 15 different positive feelings (cheerful, happy, interested) and asks them to rate the extent to which they experienced each feeling over the previous 7 days (1 not at all—5 very much). This survey is a reliable and valid measure for use among cancer survivors.[61 62]

Biomarkers

Ageing (DNA methylation, ageing genes) and inflammatory biomarkers (inflammatory cytokines and anti-inflammatory myokines: TNF-α, IL-1ß, IL-6, CRP, TGF-ß, IL-10, IL-13) will be collected at baseline and 12 weeks. The epigenetic clock DNA methylation pattern will be assessed from the buffy coat of blood draws before and after the exercise study. The biological ageing will be measured by Illumina EPIC array analysis of 353 clock CpGs, where 193 get hypermethylated and 160 get hypomethylated with age.[63] Inflammatory and anti-inflammatory cytokines will be quantified using the ELISA.[64] The assay will be performed according to the manufacturer's protocol. For the blood collection, participants will be asked to fast for 10 hours. Blood draws will happen at the same time of the day on both visits to assure inflammatory markers' consistency. All samples will be banked until they can be run at the same time.

Fitness physical assessments

To evaluate subjects' cardiorespiratory fitness and strength, the following physical assessments will be performed during the baseline and end of study visit:

6-minute Walk Test

This fitness test assesses distance walked over 6 min. It is considered a valid measure of functional status.[65] The CEP will administer the test according to the original procedures described in the American Thoracic Society guidelines.[65] 6MWT is valid and reliable in patients with cancer, with high test–retest reliability.[65 66]

Hand Grip Strength

This assessment measures the maximum isometric strength of the hand and forearm muscles.[67] The Hand Grip Strength test is a reliable and valid predictor of muscular strength and endurance and is a less burdensome alternative to more strenuous physical testing.[68] The participant will complete the test using a JAMAR hand-grip strength dynamometer sitting with an elbow bent at a 90° angle. The test will be performed two times on each hand regardless of dominance. It is a valid and reliable measure in patients with cancer.[67 69]

1-RM leg press

This assessment measures lower body strength.[70] The test involves using a leg press machine (LINK LD-3 Dual Function leg press, BATCA Fitness Systems, Raleigh, North Carolina, USA) at different weights to find the highest load needed to perform one leg press.[70] The heaviest lifted load should be reached within three to six attempts.[70] It is a valid and reliable measure for cancer survivors.[70]

Qualitative measures

Exit interview

After completing their end-of-study visit, participants have the option to engage in a virtual exit interview with one of the study PIs with expertise in qualitative research (CHS). The one-on-one interview is unstructured and focuses on understanding participants' experiences with the nature walks, any outcomes experienced from the intervention, and how the intervention could be improved in the future. Interviews will be audio recorded and will take approximately 45 min to 1 hour. Substantial discussion occurred as to the timing and location of the interview. To allow the interview to account for all study experiences, the interview takes place after the end of study visit (±30 days). Due to the timing, as well as participant preference and feasibility of scheduling, the interviews will take place via phone or Zoom. Previous research has highlighted that there is no difference in interview quality between in-person and phone or virtual interviews, and this has been confirmed by our own previous qualitative research. However, we do understand that in a study focusing on location, there is a salience—particularly for those with cognitive impairments post-treatment, for remembering information when in the actual location. To still capture this 'in the moment' information on group discussions and experiences, without burdening the participant with an in-person additional study procedure, the walk leaders were asked to take field notes about their experiences, conversations with and among participants, and participant feedback, including perspectives about the location.

Field notes

Following each walking session, all members of the study team present at the walk will log field notes detailing observations of the participants and the environment. Field notes will facilitate an improved understanding of participants' experiences.[71] These notes will also be used to refine intervention delivery for future iterations of this study. Alternate considerations included using digital voice recorders or paper and pen to take notes during the walks; however, it was determined that this approach may interrupt the natural flow of conversation between the research team and participants. Indications of monitoring of conversation and the walks on behalf of staff may also make participants self-conscious, limiting their willingness to talk and be open about their experiences with their peers and the research team during the sessions.[71]

Study visits

Informed consent and screening

Interested individuals will be presented with an informed consent form. Before signing the consent form, the potential participant will have the opportunity to discuss the study with a member of the study team. Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. All screening procedures must be performed within 30 days prior to enrolment unless otherwise stated.

During screening, study staff will review oncological medical history via chart abstraction, collect demographics (age, race, ethnicity, marital status and employment status), review subject eligibility criteria, and administer the Godin-Shephard Leisure-Time Questionnaire

(GLTEQ)[72] and the Physical Activity Readiness Questionnaire (PAR-Q)[73] via REDCap. The GLTEQ asks potential participants to self-report leisure-time PA.[72] This allows responders to be classified into categories based on their PA levels. Only those classified as insufficiently active (based on cut-off points specific to cancer survivors)[72] will be included in the study.[74] After completing the GLTEQ, potential participants will also be asked to complete the PAR-Q. The PAR-Q is a self-screening tool used to identify those at risk of developing a cardiovascular event when initiating an exercise programme.[11 73 75] It includes several questions followed by several additional follow-up questions to better tailor pre-exercise recommendations based on relevant medical history and symtomatology.[11] It is a valid tool that can identify cardiorespiratory symptoms in cancer survivors.[11] Further medical clearance will be obtained during a usual care visit with the physician investigator.

Baseline visit

Baseline visit procedures may be done the same day as the consent/screening visit or up to ±14 days of the first walking session. The baseline visit must be completed within 14 days of enrolment. Any assessments performed for clinical indications (not only for study eligibility) could be used for baseline values even if they were done before obtaining informed consent.

During the baseline visit, study staff will administer the pregnancy test (for women of childbearing potentials), collect blood samples to measure the biological ageing and inflammation biomarkers previously mentioned, set up the Fitbit, and distribute the baseline questionnaires. The CEP will collect anthropometric data (weight and height), vital signs (resting blood pressure and HR) and will perform the fitness physical assessments previously described. The CEP will acquire participants' body weight and height by accessing their medical history. If body weight information is not current, the CEP will measure participants' body weight at the time of the visit (SCALETRONIX 5002 mobile stand-on scale, Welch Allyn, Skaneateles, New York, USA). The CEP will measure resting HR right after the participants have answered the surveys and had time to rest using a fingertip pulse oximeter (Oxywatch, MD300C15 pulse oximeter, ChoiceMMed, Hamburg, Germany), and blood pressure using participants' preferred arm (Classic Series, aneroid sphygmomanometer, BV Medical, Barrington, Illinois, USA).

End of study visit

At the end of the 12-week exercise intervention and up to 14 days from the last walking session with CEP, participants will schedule the end of study visit. This visit will be scheduled at a similar time to the baseline visit to keep the inflammatory markers consistent. During this visit, study staff will administer the same surveys from the baseline visit, collect blood samples to measure the same biological and inflammatory biomarkers, and sync and export Fitbit data. The CEP will also collect anthropometric data, vital signs and perform the same physical assessments as in the baseline visit.

Patients will be followed for expected AE through the medical record until the End of Study visit. However, if this visit is not completed, patients will be followed for AE until study withdrawal or 12 weeks after the first exercise session with CEP, whichever comes first. Overall study time and events are presented in table 2.

Removal rules

Patients can be removed from the study at any time at their request, or they may be withdrawn at the discretion of an investigator for safety, behavioural or administrative reasons. The reason(s) for discontinuation will be documented and include: participant voluntarily withdraws (follow-up permitted), participant withdraws consent (termination of treatment and follow-up), participant is unable to comply with protocol requirements, participant sustains an extensive injury, is diagnosed with a new major disease that makes continuation in the protocol unsafe, the treating or study physician determines continuation on the study would not be in the participant's best interest, participant sustains an injury or develops an issue that makes them unable to be independently ambulatory (requires a walker, cane or other assistance to ambulate), participant skips at least 30% of the expected exercise sessions (10 sessions), or misses more than 2 weeks' sessions in a row (6 sessions in a row). Additionally, participants are required to let study team know 30 min before their scheduled session if they are going to be late. CEP will wait 15 min for individuals to arrive. Participants will be considered late if they arrive more than 15 min after the start of the session. If a participant is late more than 30% of sessions, the study team will consider moving the individual to a different session or removing her from the study. When the participant is removed from the protocol, she will be asked to return for an end of study visit.

Patient and public involvement statement

This study assesses the feasibility of a nature-based PA intervention that has the potential to facilitate recovery for BCS. Although the participants are not involved in the study design, once it is open to enrolment, they will participate in the recruitment, screening and consenting processes before commencing the intervention. Eligible participants will engage in a 12-week walking programme, prephysical and postphysical assessments, and surveys. They will share their feedback at the end of the study interview. However, they will not actively aid in the sharing of information.

STATISTICAL ANALYSIS

All quantitative data collection will be performed using R package V.4.2.2. For the analysis of the primary endpoint, the null hypothesis will be tested that the proportion of adherent patients is no more than 70% using an exact binomial test at a 10% nominal significance level with

Table 2 Study time and events table

Assessments	Screening	Baseline	Walks	End of study visit
Informed consent	x			
Medical history	x			
Demographics	x			
Medical clearance	x			
PAR-Q	x			
Pregnancy test*		x		
Godin-Shephard Leisure-Time Questionnaire	x	x		x
Height		x		
Weight		x		x
Vitals (BP and HR)		x		x
Strength (grip strength, leg press)		x		x
6 min walk test		x		x
Blood sample collection		x		x
Banked blood sample		x		x
Biological ageing markers		x		x
Inflammatory markers		x		x
Patient-Reported Outcomes Measurement Information System (PROMIS 29)		x		x
Functional Assessment of Cancer Therapy-General		x		x
Post-traumatic Growth Inventory		x		x
PROMIS emotional support		x		x
PROMIS informational support		x		x
PROMIS instrumental support		x		x
PROMIS Adult Positive Affect-Short Form			x	
Activity surveys/logs			x	
Wearable activity monitor (Fitbit)		x†	x†	x†
Reminders to wear and sync Fitbit			x	x
Walking programme			x	
Concomitant medications		x		x
Adverse events			x	x
Exit interview				x

*Pregnancy test for women of childbearing potential only.
†Participant instructed to wear activity monitor for duration of their participation in this study.
BP, blood pressure; HR, heart rate; PAR-Q, Physical Activity Readiness Questionnaire.

3.5% as the actual significance level. As a pilot study with limited sample size, the statistical analysis aims to estimate the magnitude of intervention effect from baseline to end of the study visit. This will inform the investigators when planning a future larger study. If the proportion of adherent patients is greater or equal to 18 patients, then we will reject the null hypothesis and declare the study as feasible. Otherwise, the intervention will be revised and adapted to improve feasibility in subsequent trials.

Power analysis was based on the primary endpoint and, therefore, analysis of secondary endpoints is underpowered and will be exploratory. For analysis of the secondary endpoints, means and SDs will be computed for continuous measures and proportions for count data. Changes will be analysed between baseline and end of study using a paired t-test. All data will have 95% CIs computed.

Qualitative data will be analysed using reflexive thematic analysis.[76] Quality of qualitative data collection

and analysis will be guided by an assessment of thematic analysis research quality consisting of 20 questions, which cover domains including adequate choice and explanation of methods and methodology, and development and justification of analysis.[77]

DISCUSSION AND CONCLUSION

In 2006, the Institute of Medicine published a report that detailed the many medical, functional and psychosocial challenges of cancer survivorship.[78] This report catalysed a focus on post-treatment care as critical to the long-term health of cancer survivors. BCSs are at higher risk of a number of comorbidities as a result of their cancer and cancer treatment, including higher mortality rates, disability, obesity, cardiovascular disease (CVD), depression and anxiety.[20 79–81] PA has proven to be beneficial in improving for physical, emotional, cancer-related effects,[5–7] all-cause and breast cancer-related mortality,[8–10] as well as important comorbidities, such as fatigue and CVD.[4 39] PA also impacts important biochemical mechanisms implicated in cancer biology including inflammation and biological ageing.[82]

PA is influenced by many nuanced mechanisms. Literature has explored the type, frequency, duration and intensity of PA that may promote optimal benefits for BCS.[11 83] However, the unique role of the PA environment in influencing outcomes for cancer survivors is still largely unexamined. This pilot study is an important first step to a more comprehensive and robust understanding of the role of PA environment on the health of cancer survivors.

Data management

REDCap, a HIPAA-compliant database, will be used to collect survey data and manage CEP notes. The CEP and clinical research coordinator will be responsible for data processing and will follow all procedural documentation. Database lock will occur once quality assurance procedures have been completed. All procedures will meet Food and Drug Administration (FDA) guidelines for the handling and analysis of data for clinical trials.

Data monitoring

Adherence to the protocol, Good Clinical Practices, and institutional policy will be monitored by the PIs through biweekly study meetings, and additional one-on-one meetings with the clinical research coordinator and CEP. In addition, the institution's Cancer Clinical Trials Office Quality Management Core (QMC) will conduct focused internal monitoring visits and audits for data quality and protocol adherence annually. QMC reports will be forwarded to the Data and Safety Monitoring Committee (DSMC). QMC has the authority to request more frequent reviews or focused safety monitoring if it is deemed appropriate for any reason. The audit will be independent from the investigators.

Safety monitoring

PIs will oversee the progress and safety of the study. They will maintain continuous safety monitoring for the duration of the study by reviewing subject and study data. AEs and unanticipated problems are not expected, but if they occur, they will be documented and reported according to Cedars-Sinai's IRB policies and procedures. If the PIs become aware of any new safety information that may place subjects at increased risk than what was previously known, they will promptly notify the IRB and, if warranted, enrolment may be held until the PIs determine whether a modification to the study is necessary and the informed consent documents are updated accordingly. It is the responsibility of the PIs to adhere to the data safety monitoring plan throughout the life of the study.

In addition, the DSMC will provide another layer of data and safety oversight. The annual DSMC findings and recommendations will be reported in writing to the PI as a summary letter. These letters will also be forwarded to Cedars-Sinai Medical Center's IRB. The DSMC may increase or decrease the frequency of study review, at their discretion.

ETHICS AND DISSEMINATION

Ethics approval for this study has been obtained from the Cedars-Sinai Medical Center Institutional Review Board (IIT2020-20). Should amendments to the protocol be required, they will be documented by the PIs. The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to the implementation.

Findings will be shared with participants who received the intervention. We plan to publish the study results in peer-reviewed journals and share our findings at academic conferences. Findings will also be shared with clinics and community organisations to support programme decision-making.

Twitter Celina H Shirazipour @CHShirazi

Contributors All the authors have contributed substantially to the conception and design of this manuscript. All contributed to drafting the original and revised version. All have approved the final version of this manuscript and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. CS: conceptualisation, methodology, validation, formal analysis, investigation, resources, writing—original draft, writing—reviewing and editing, supervision. CR: investigation, writing—original draft, writing—review and editing. EL: investigation, data curation, writing—review and editing, project administration. RMR: investigation, writing—review and editing. JMC: investigation, data curation, writing—review and editing, project administration. BL-L: investigation, writing—review and editing. MAD: validation, formal analysis. GG: validation, resources, writing—review and editing. RWH: conceptualisation, methodology, writing—review and editing. NB: conceptualisation, methodology, validation, resources, writing—review and editing. AA: conceptualisation, methodology, validation, investigation, resources, writing—original draft, writing—review and editing, supervision.

Funding This project is supported by Cedars-Sinai Cancer.

Competing interests All the authors declare that they have not received any payments, gifts, or services or have any competing financial or non-financial interests or personal relationships and activities that could have appeared to influence the work reported in this paper.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Carolina Raines http://orcid.org/0000-0001-9031-8546

REFERENCES

1 Sung H, Ferlay J, Siegel RL, *et al*. Global cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71:209–49.
2 Siegel RL, Miller KD, Fuchs HE, *et al*. Cancer statistics, 2022. *CA Cancer J Clin* 2022;72:7–33.
3 Mandelblatt JS, Zhai W, Ahn J, *et al*. Symptom burden among older breast cancer survivors: the thinking and living with cancer (TLC) study. *Cancer* 2020;126:1183–92.
4 Bodai BI, Tuso P. Breast cancer survivorship: a comprehensive review of long-term medical issues and Lifestyle recommendations. *Perm J* 2015;19:48–79.
5 Campbell KL, Winters-Stone KM, Wiskemann J, *et al*. Exercise guidelines for cancer survivors: consensus statement from international Multidisciplinary Roundtable. *Med Sci Sports Exerc* 2019;51:2375–90.
6 Speck RM, Courneya KS, Mâsse LC, *et al*. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *J Cancer Surviv* 2010;4:87–100.
7 McNeely ML, Campbell KL, Rowe BH, *et al*. Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. *Cmaj* 2006;175:34–41.
8 Cannioto RA, Hutson A, Dighe S, *et al*. Physical activity before, during, and after chemotherapy for high-risk breast cancer: relationships with survival. *J Natl Cancer Inst* 2021;113:54–63.
9 Lahart IM, Metsios GS, Nevill AM, *et al*. Physical activity, risk of death and recurrence in breast cancer survivors: A systematic review and meta-analysis of Epidemiological studies. *Acta Oncol* 2015;54:635–54.
10 Schmid D, Leitzmann MF. Association between physical activity and mortality among breast cancer and colorectal cancer survivors: a systematic review and meta-analysis. *Ann Oncol* 2014;25:1293–311.
11 Liguori G, Feito Y, Fountaine C, *et al*. *ACSM's guidelines for exercise testing and prescription*11th edn. Philadelphia, PA: Wolters Kluwer, 2022.
12 Smith SG, Chagpar AB. Adherence to physical activity guidelines in breast cancer survivors. *Am Surg* 2010;76:962–5.
13 Pinto BM, Trunzo JJ, Reiss P, *et al*. Exercise participation after diagnosis of breast cancer: trends and effects on mood and quality of life. *Psycho-Oncology* 2002;11:389–400.
14 Kirkham AA, Bonsignore A, Bland KA, *et al*. Exercise prescription and adherence for breast cancer: one size does not FITT all. *Med Sci Sports Exerc* 2018;50:177–86.
15 Underwood JM, Townsend JS, Stewart SL, *et al*. Surveillance of demographic characteristics and health behaviors among adult cancer survivors-behavioral risk factor surveillance system, United States, 2009. *MMWR Surveill Summ* 2012;61:1–23.
16 Irwin ML, Crumley D, McTiernan A, *et al*. Physical activity levels before and after a diagnosis of breast carcinoma: the health, eating, activity, and Lifestyle (HEAL) study. *Cancer* 2003;97:1746–57.
17 Wong JN, McAuley E, Trinh L. Physical activity programming and counseling preferences among cancer survivors: a systematic review. *Int J Behav Nutr Phys Act* 2018;15:48.
18 What is open space/green space. United States environmental protection agency; 2022.
19 Pretty J, Peacock J, Sellens M, *et al*. The mental and physical health outcomes of green exercise. *Int J Environ Health Res* 2005;15:319–37.
20 Frumkin H, Bratman GN, Breslow SJ, *et al*. Nature contact and human health: A research agenda. *Environ Health Perspect* 2017;125:075001.
21 Sinharay R, Gong J, Barratt B, *et al*. Respiratory and cardiovascular responses to walking down a traffic-polluted road compared with walking in a traffic-free area in participants aged 60 years and older with chronic lung or heart disease and age-matched healthy controls: a randomised, crossover study. *Lancet* 2018;391:339–49.
22 Han JW, Choi H, Jeon YH, *et al*. The effects of forest therapy on coping with chronic widespread pain: physiological and psychological differences between participants in a forest therapy program and a control group. *Int J Environ Res Public Health* 2016;13:255.
23 Astell-Burt T, Feng X, Kolt GS. Does access to neighbourhood green space promote a healthy duration of sleep? novel findings from a cross-sectional study of 259 319 Australians. *BMJ Open* 2013;3:e003094.
24 Morita E, Imai M, Okawa M, *et al*. A before and after comparison of the effects of forest walking on the sleep of a community-based sample of people with sleep complaints. *Biopsychosoc Med* 2011;5:13.
25 Li Q, Kobayashi M, Inagaki H, *et al*. A day trip to a forest park increases human natural killer activity and the expression of anti-cancer proteins in male subjects. *J Biol Regul Homeost Agents* 2010;24:157–65.
26 Li Q, Morimoto K, Kobayashi M, *et al*. A forest bathing trip increases human natural killer activity and expression of anti-cancer proteins in female subjects. *J Biol Regul Homeost Agents* 2008;22:45–55.
27 Park SH, Mattson RH. Effects of flowering and foliage plants in hospital rooms on patients recovering from abdominal surgery. *Hortte* 2008;18:563–8.
28 Ulrich RS. View through a window may influence recovery from surgery. *Science* 1984;224:420–1.
29 Brown SC, Lombard J, Wang K, *et al*. Neighborhood greenness and chronic health conditions in Medicare beneficiaries. *Am J Prev Med* 2016;51:78–89.
30 de Vries S, Verheij RA, Groenewegen PP, *et al*. Natural environments—healthy environments? an exploratory analysis of the relationship between Greenspace and health. *Environ Plan A* 2003;35:1717–31.
31 Kardan O, Gozdyra P, Misic B, *et al*. Neighborhood Greenspace and health in a large urban center. *Sci Rep* 2015;5:11610.
32 Maas J, Verheij RA, de Vries S, *et al*. Morbidity is related to a green living environment. *J Epidemiol Community Health* 2009;63:967–73.
33 Maas J, Verheij RA, Groenewegen PP, *et al*. Green space, Urbanity, and health: how strong is the relation? *J Epidemiol Community Health* 2006;60:587–92.
34 Stigsdotter UK, Ekholm O, Schipperijn J, *et al*. Health promoting outdoor environments--associations between green space, and health, health-related quality of life and stress based on a Danish national representative survey. *Scand J Public Health* 2010;38:411–7.
35 Ray H, Jakubec SL. Nature-based experiences and health of cancer survivors. *Complement Ther Clin Pract* 2014;20:188–92.
36 Duncan MJ, Clarke ND, Birch SL, *et al*. The effect of green exercise on blood pressure, heart rate and mood state in primary school children. *Int J Environ Res Public Health* 2014;11:3678–88.
37 Markevych I, Thiering E, Fuertes E, *et al*. A cross-sectional analysis of the effects of residential greenness on blood pressure in 10-year old children: results from the Giniplus and Lisaplus studies. *BMC Public Health* 2014;14:477.
38 Stalsberg R, Bertheussen GF, Børset H, *et al*. Do breast cancer patients manage to participate in an outdoor, tailored, physical activity program during adjuvant breast cancer treatment, independent of health and socio-demographic characteristics? *J Clin Med* 2022;11:843.
39 Meneses-Echávez JF, González-Jiménez E, Ramírez-Vélez R. Effects of supervised exercise on cancer-related fatigue in breast cancer survivors: a systematic review and meta-analysis. *BMC Cancer* 2015;15:77.
40 Montaño-Rojas LS, Romero-Pérez EM, Medina-Pérez C, *et al*. Resistance training in breast cancer survivors: A systematic review of exercise programs. *Int J Environ Res Public Health* 2020;17:6511.
41 Cheng KKF, Lim YTE, Koh ZM, *et al*. Home-based multidimensional survivorship programmes for breast cancer survivors. *Cochrane Database Syst Rev* 2017;8:CD011152.
42 Liamputtong P, Suwankhong D. Therapeutic landscapes and living with breast cancer: the lived experiences of Thai women. *Soc Sci Med* 2015;128:263–71.
43 English J, Wilson K, Keller-Olaman S. Health, healing and recovery: therapeutic landscapes and the everyday lives of breast cancer survivors. *Soc Sci Med* 2008;67:68–78.
44 McDonough MH, Sabiston CM, Crocker PRE. An interpretative phenomenological examination of Psychosocial changes among breast cancer survivors in their first season of Dragon boating. J Appl Sport Psychol 2008;20:425–40.
45 McDonough MH, Sabiston CM, Ullrich-French S. The development of social relationships, social support, and Posttraumatic growth in

a dragon boating team for breast cancer survivors. *J Sport Exerc Psychol* 2011;33:627–48.
46 Mitchell TL, Yakiwchuk CV, Griffin KL, *et al*. Survivor Dragon boating: a vehicle to reclaim and enhance life after treatment for breast cancer. *Health Care Women Int* 2007;28:122–40.
47 Denieffe S, Castineira C, Denny M. The impact of Dragon boating for fatigue in cancer survivors. J Nurse Pract 2021;17:1019–22.
48 Albers T, Weiss LA, Sleeman SHE, *et al*. Evaluation of a positive psychology group intervention in nature for young cancer survivors to promote well-being and post-cancer identity development. *J Adolesc Young Adult Oncol* 2021;10:726–34.
49 Ireland AV, Finnegan-John J, Hubbard G, *et al*. Walking groups for women with breast cancer: Mobilising therapeutic assemblages of walk, talk and place. *Soc Sci Med* 2019;231:38–46.
50 Chan A-W, Tetzlaff JM, Altman DG, *et al*. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200.
51 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al*. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
52 Gilchrist K, Brown C, Montarzino A. Workplace settings and wellbeing: Greenspace use and views contribute to employee wellbeing at peri-urban business sites. Landsc Urban Plan 2015;138:32–40.
53 Hays RD, Spritzer KL, Schalet BD, *et al*. PROMIS(®)-29 V2.0 profile physical and mental health summary scores. *Qual Life Res* 2018;27:1885–91.
54 Seneviratne MG, Bozkurt S, Patel MI, *et al*. Distribution of global health measures from routinely collected PROMIS surveys in patients with breast cancer or prostate cancer. *Cancer* 2019;125:943–51.
55 Webster K, Cella D, Yost K. The functional assessment of chronic illness therapy (FACIT) measurement system: properties, applications, and interpretation. *Health Qual Life Outcomes* 2003;1:79.
56 Tedeschi RG, Calhoun LG. The Posttraumatic growth inventory: measuring the positive legacy of trauma. *J Trauma Stress* 1996;9:455–71.
57 Wang L, Chen S, Liu P, *et al*. Posttraumatic growth in patients with malignant bone tumor: relationships with psychological Djustment. *Asian Pac J Cancer Prev* 2018;19:2831–8.
58 Brunet J, McDonough MH, Hadd V, *et al*. The Posttraumatic growth inventory: an examination of the factor structure and Invariance among breast cancer survivors. *Psycho-Oncology* 2010;19:830–8.
59 Hahn EA, Devellis RF, Bode RK, *et al*. Measuring social health in the patient-reported outcomes measurement information system (PROMIS): item Bank development and testing. *Qual Life Res* 2010;19:1035–44.
60 PROMIS list of adult measures. Healthmeasures; 2021. Available: https://www.healthmeasures.net/explore-measurement-systems/promis/intro-to-promis/list-of-adult-measures
61 Cook KF, Jensen SE, Schalet BD, *et al*. PROMIS measures of pain, fatigue, negative affect, physical function, and social function demonstrated clinical validity across a range of chronic conditions. *J Clin Epidemiol* 2016;73:89–102.
62 Quach CW, Langer MM, Chen RC, *et al*. Reliability and validity of PROMIS measures administered by telephone interview in a longitudinal localized prostate cancer study. *Qual Life Res* 2016;25:2811.
63 Horvath S. DNA methylation age of human tissues and cell types. *Genome Biol* 2013;14:R115.
64 Tabatabaei MS, Ahmed M. Enzyme-linked immunosorbent assay (ELISA). *Methods Mol Biol* 2022;2508:115–34.
65 Enright PL. The six-minute walk test. *Respir Care* 2003;48:783–5.
66 Holmes MD, Chen WY, Feskanich D, *et al*. Physical activity and survival after breast cancer diagnosis. *JAMA* 2005;293:2479–86.
67 Nordenskiöld UM, Grimby G. Grip force in patients with rheumatoid arthritis and Fibromyalgia and in healthy subjects. A study with the Grippit instrument. *Scand J Rheumatol* 1993;22:14–9.
68 Trosclair D, Bellar D, Judge LW, *et al*. Hand-grip strength as a Predictor of muscular strength and endurance. J Strength Cond Res 2011;25:S99.
69 Oldervoll LM, Loge JH, Lydersen S, *et al*. Physical exercise for cancer patients with advanced disease: a randomized controlled trial. *Oncologist* 2011;16:1649–57.
70 Češeiko R, Thomsen SN, Tomsone S, *et al*. Heavy resistance training in breast cancer patients undergoing adjuvant therapy. *Med Sci Sports Exerc* 2020;52:1239–47.
71 Allen M. *The SAGE encyclopedia of communication research methods*. California: SAGE Publications, 2017.
72 Amireault S, Godin G, Lacombe J, *et al*. The use of the Godin-Shephard leisure-time physical activity questionnaire in oncology research: a systematic review. *BMC Med Res Methodol* 2015;15:60.
73 Warburton DER, Jamnik VK, Bredin SSD, *et al*. The physical activity readiness questionnaire for everyone (PAR-Q+) and electronic physical activity readiness medical examination (ePARmed-X+). *Health Fit J Can* 2011;4:3–17.
74 Amireault S, Godin G. The Godin-Shephard leisure-time physical activity questionnaire: validity evidence supporting its use for classifying healthy adults into active and insufficiently active categories. *Percept Mot Skills* 2015;120:604–22.
75 Goodman JM, Thomas SG, Burr J. Evidence-based risk assessment and recommendations for exercise testing and physical activity clearance in apparently healthy individuals. *Appl Physiol Nutr Metab* 2011;36:S14–32.
76 Braun V, Clarke V. *Thematic Analysis: a practical guide*. London: SAGE Publications, 2020.
77 Braun V, Clarke V. One size fits all? What counts as quality practice in (Reflexive) thematic analysis. Qual Res Psychol2021;18:328–52.
78 Medicine Io, Council NR. *From cancer patient to cancer survivor: lost in transition*. Washington, DC: The National Academies Press, 2006.
79 Alfano CM, Peng J, Andridge RR, *et al*. Inflammatory Cytokines and Comorbidity development in breast cancer survivors versus Noncancer controls: evidence for accelerated aging. *J Clin Oncol* 2017;35:149–56.
80 Rowland JH, Bellizzi KM. Cancer survivors and survivorship research: a reflection on today's successes and tomorrow's challenges. *Hematol Oncol Clin North Am* 2008;22:181–200.
81 Maccormick RE. Possible acceleration of aging by adjuvant chemotherapy: a cause of early onset Frailty? *Med Hypotheses* 2006;67:212–5.
82 Thomas RJ, Kenfield SA, Jimenez A. Exercise-induced biochemical changes and their potential influence on cancer: a scientific review. *Br J Sports Med* 2017;51:640–4.
83 Denlinger CS, Sanft T, Armenian S, *et al*. NCCN guidelines for patients survivorship for healthy living. 2021. Available: https://www.nccn.org/patients/guidelines/content/PDF/survivorship-hl-patient.pdf