

Effects of a Structured Exercise Program on Physical Activity and Fitness in Colon Cancer Survivors: One Year Feasibility Results from the CHALLENGE Trial

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Abstract

Background: There is strong interest in testing lifestyle interventions to improve cancer outcomes; however, the optimal methods for achieving behavior change in large-scale pragmatic trials are unknown. Here, we report the 1-year feasibility results for exercise behavior change in the Canadian Cancer Trials Group CO.21 (CHALLENGE) Trial.

Methods: Between 2009 and 2014, 273 high-risk stage II and III colon cancer survivors from 42 centers in Canada and Australia were randomized to a structured exercise program (SEP; $n = 136$) or health education materials (HEM; $n = 137$). The primary feasibility outcome in a prespecified interim analysis was a difference between randomized groups of ≥ 5 metabolic equivalent task (MET)-hours/week in self-reported recreational physical activity (PA) after at least 250 participants reached the 1-year follow-up. Secondary outcomes included health-related fitness.

Results: The SEP group reported an increase in recreational PA of 15.6 MET-hours/week compared with 5.1 MET-hours/week in the HEM group [mean difference = +10.5; 95% confidence interval (CI) = +3.1–+17.9; $P = 0.002$]. The SEP group also improved relative to the HEM group in predicted VO_{2max} ($P = 0.068$), 6-minute walk ($P < 0.001$), 30-second chair stand ($P < 0.001$), 8-foot up-and-go ($P = 0.004$), and sit-and-reach ($P = 0.08$).

Conclusions: The behavior change intervention in the CHALLENGE Trial produced a substantial increase in self-reported recreational PA that met the feasibility criterion for trial continuation, resulted in objective fitness improvements, and is consistent with the amount of PA associated with improved colon cancer outcomes in observational studies.

Impact: The CHALLENGE Trial is poised to determine the causal effects of PA on colon cancer outcomes. *Cancer Epidemiol Biomarkers Prev*; 25(6); 969–77. ©2016 AACR.

Introduction

A growing number of epidemiologic studies have reported an association between postdiagnosis physical activity (PA) and

colorectal cancer outcomes (1–3). In a recent systematic review, Des Guetz and colleagues (1) analyzed six observational studies involving over 7,500 colorectal cancer survivors and reported that higher postdiagnosis PA was associated with a lower risk of colorectal cancer-specific mortality [HR = 0.61; 95% confidence interval (CI), 0.44–0.86] and a lower risk of all-cause mortality (HR = 0.62; 95% CI, 0.54–0.71). Although these findings are promising, the studies are limited by the observational designs with high risk of confounding, and the use of self-report measures of PA. Moreover, the critical question from a clinical perspective is whether any feasible exercise intervention can actually improve cancer outcomes. To address this issue, the American Society for Clinical Oncology has recently called for large-scale phase III trials to evaluate the effects of lifestyle interventions on cancer outcomes and to determine the best methods of behavior change (4).

Like all medical interventions, the effectiveness of an exercise intervention to improve cancer outcomes will depend on the willingness and ability of patients to complete it. Compared with biomedical interventions, however, exercise interventions are more challenging for patients because they require substantial personal motivation (i.e., the intervention must be performed by the patient). Moreover, exercise interventions to improve cancer

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outcomes will likely require substantial and sustained behavior change. Unfortunately, exercise interventions delivered through practical avenues such as telephone counseling, print materials, and web-based programs often induce only small behavioral changes that are unlikely to improve cancer outcomes (5, 6). Conversely, exercise interventions delivered through optimal avenues such as fully supervised programs by qualified professionals often induce larger behavioral changes as well as health-related fitness improvements (7, 8); however, their potential for large-scale dissemination is questionable. Consequently, there is legitimate concern in the oncology community about whether any pragmatic exercise intervention can actually motivate patients to increase their exercise behavior and fitness levels sufficiently to improve cancer outcomes.

To address this issue, the Canadian Cancer Trials Group launched the Colon.21 (CO.21) Trial, also known as the Colon Health and Life-Long Exercise Change (CHALLENGE) Trial (9, 10). The CHALLENGE Trial is an ongoing randomized trial examining the effects of a 3-year structured exercise program (SEP), compared with health education materials (HEM), on disease-free survival among 962 patients with high-risk stage II or stage III colon cancer who have completed adjuvant chemotherapy within the past 2–6 months. The exercise intervention in the CHALLENGE Trial was designed to balance the need for substantial behavior change with the desire for broad dissemination. The behavior change goal in the CHALLENGE Trial is to increase recreational PA from baseline by at least 10 metabolic equivalent task (MET) hours/week in the first 6 months and sustain this change for 3 years. Given the legitimate concerns about inducing substantial and sustained exercise behavior change in colon cancer survivors, the CHALLENGE Trial steering committee incorporated a feasibility analysis into the study protocol. For the study to continue, the SEP group was required to perform an average of at least 5 MET-hours/week more recreational PA than the HEM group after a minimum of 250 participants reached the 1-year follow-up. The purpose of the current article was to report the results of the feasibility analysis including the corollary changes in health-related fitness.

Materials and Methods

The design and methods of the CHALLENGE Trial (ClinicalTrials.gov identifier: NCT00819208) have been reported elsewhere (9, 10). The CHALLENGE Trial originally opened in Canada and Australia in 2009 and is currently accruing participants in 20 centers in Canada and 22 in Australia. The trial has since been expanded to a small number of centers in the United States, Israel, and Korea with further expansion planned to the United Kingdom and France. All centers are required to secure local ethics approval and all participants are required to provide informed consent.

Setting and participants

Colon cancer survivors are eligible for the trial if they have been diagnosed with high-risk stage II or stage III colon cancer, received adjuvant chemotherapy within the past 2–6 months, have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, are not currently meeting PA guidelines (i.e., the equivalent of 150 minutes/week of moderate intensity exercise), and are able to complete at least two stages of a submaximal treadmill test. Participants are stratified by center, disease stage, body mass index (≤ 27.5 kg/m² vs. >27.5 kg/m²), and ECOG

performance status before being randomly assigned to the SEP or HEM intervention.

Interventions

Participants randomized to the HEM intervention receive general health education materials promoting PA and healthy nutrition as well as standard surveillance follow-up. Participants randomized to the SEP intervention receive an exercise guidebook developed specifically for colon cancer survivors (11) and work with a PA consultant (PAC) who delivers the intervention over a 3-year period. PACs are certified exercise specialists (e.g., exercise physiologists, personal trainers, physiotherapists) who receive either 1.5 days of training in Edmonton or from another PAC (i.e., "train the trainer" model). The training includes overviews of the trial, the role of the PACs, the theory of planned behavior, the behavioral support sessions, the tool box, handling drop outs, completion of forms, communication with the cancer center, and a practical demonstration of the health-related fitness testing. PACs are also required to submit a report to the Physical Activity Working Group and participate in a 1-hour conference call every 2 months to discuss any issues related to fitness testing, intervention delivery, and adherence.

The SEP intervention is based on the highly successful Diabetes Prevention Program (12) and Look AHEAD (13) studies with modifications and enhancements for colon cancer survivors (14–16). The key components of the SEP intervention include: (i) clear and challenging exercise goals, (ii) some supervised exercise sessions, (iii) free or low-cost access to a fitness facility, (iv) frequent and ongoing contacts including some face-to-face sessions with qualified staff, (v) individual tailoring of the intervention, (vi) written materials, and (vii) the application of behavior modification techniques based on a validated theoretical model. The goal of the SEP intervention is to increase recreational aerobic PA by at least 10 MET-hours/week from baseline in the first 6 months and sustain this change for 3 years. Participants are able to choose the type, frequency, intensity, and duration of aerobic exercise to meet the intervention goal.

The SEP intervention is comprised of three phases (Table 1). The first 6 months is an adoption phase that consists of bi-weekly face-to-face counseling sessions combined with supervised exercise, with the option of an additional supervised exercise session during alternate weeks. The second 6 months is a consolidation phase that consists of bi-weekly behavioral support sessions, which may be face-to-face with supervised exercise, or by telephone. The final 2 years are a maintenance phase that consists of monthly behavioral support sessions, which may be face-to-face with supervised exercise, or by telephone. The SEP intervention is guided by the theory of planned behavior (TPB; ref. 17) which has been validated for predicting and understanding exercise behavior in colorectal cancer survivors (15, 18–20). The counseling sessions cover 17 evidence-based behavior change techniques (Table 2; refs. 21, 22).

Primary and secondary feasibility measures

The primary outcome for the feasibility analysis was self-reported recreational PA as assessed by the validated and reliable Total Physical Activity Questionnaire (TPAQ; ref. 23). The TPAQ measures all types (occupational, household, recreational, and transportation) and parameters of PA (frequency, duration, and intensity) performed over the past month. The recorded activity is converted to MET-hours/week using the Compendium of

Table 1. Overview of the structured exercise program intervention in the CHALLENGE Trial

Program elements	Phase I (adoption)	Phase II (consolidation)	Phase III (maintenance)
	First 6 months	Second 6 months	Years 2 and 3
Behavior support sessions	12 mandatory face-to-face sessions; ideally biweekly but flexibility permitted. Deliver 12 of the 17 behavior change techniques in order relevant to patient.	12 mandatory sessions with option of face-to-face or telephone/email. Face-to-face strongly encouraged. Ideally biweekly but flexibility permitted. Deliver remaining 5 behavior change techniques and repeat others as appropriate for patient.	24 mandatory sessions with option of face-to-face or telephone/email. Face-to-face strongly encouraged. Ideally monthly but flexibility fine. Deliver any of the 17 behavior change techniques as appropriate for the patient.
Supervised exercise sessions	12 mandatory sessions combined with face-to-face counseling sessions. 12 strongly recommended sessions on alternate weeks if feasible for the center and agreed to by the patient.	12 strongly recommended sessions if face-to-face counseling continued.	24 strongly recommended sessions if face-to-face counseling selected.
Physical activity goal	Gradually increase recreational PA from baseline by 10 MET-hours/week. Focus is on aerobic exercise with flexibility in type, frequency, intensity, and duration.	If patient willing and able, further increase recreational PA from baseline by 20 MET-hours/week. If not, focus on maintaining/achieving 10 MET hours/week increase.	If patient willing and able, further increase recreational PA from baseline to a maximum of 27 MET hours/week. Patients may exceed 27 MET-hours/week on their own. If not, focus on maintaining/achieving 10 MET-hours/week increase.

Physical Activities (24). In the CHALLENGE Trial, the TPAQ is administered to all participants at baseline and every 6 months for 3 years. The feasibility analysis was restricted to recreational PA at baseline and 1 year.

Secondary feasibility outcomes included cardiorespiratory fitness, body weight, and circumferences, and objective physical functioning assessed at baseline, 6 months, 1 year, 2 years, and 3 years. Cardiorespiratory fitness is assessed using a submaximal, multistage, modified Balke treadmill protocol (25) with a validated prediction formula to estimate maximum volume of oxygen consumption (VO_{2max} ; ref. 26). Standing height and weight are measured by a balance beam scale and stadiometer. Waist and hip circumferences are determined using an anthropometric measuring tape (27, 28). Objective physical functioning is assessed by the Seniors' Fitness Test (29).

Statistical analyses

For each primary and secondary outcome, the mean and SD were calculated for all participants with available data at both baseline and 1 year. The mean and 95% CI for the change at 1 year from baseline were calculated for all participants with available data at both time points. As prespecified in the protocol, a Wilcoxon rank-sum test was used to compare the differences in mean change between the two randomized groups. Also as prespecified in the protocol, the trial would be stopped if the observed between group difference in the average MET-hours/week at 1 year was less than 5. Assuming that the SD of MET-hours/week was 20, with 250 participants included in the analysis, the probability to continue the study (i.e., the observed difference in the average MET-hours/week between two intervention arms is 5 or higher) was higher than 88% if the true difference was 8 MET-hours/week or higher. Because of missing data from some participants, it was decided that all participants randomized before March 1, 2014 would be included in the feasibility analysis. A database was locked for this analysis on April 2, 2015.

Results

Flow of participants through the 1-year follow-up is presented in Fig. 1. Between June 2009 and February 2014, 273

participants (192 in Canada and 81 in Australia) were randomized to the SEP intervention ($n = 136$) or the HEM intervention ($n = 137$). The final analyses for the change in PA from baseline to 1 year included 211 participants (106 from the SEP arm and 105 from the HEM arm). The 62 participants not analyzed included 5 who were deemed ineligible after randomization, 33 who were not required to complete the 1 year questionnaire because of progressive disease ($n = 31$) or withdrawal of consent ($n = 2$), and 24 who did not complete the baseline or 1 year questionnaire for various reasons. Consequently, the primary analysis included over 90% of eligible participants who did not have progressive disease at 1 year.

Baseline characteristics

Table 3 provides the baseline clinical characteristics for the entire sample ($N = 273$) and the analyzed sample ($n = 211$) by randomized group assignment. In terms of the medical profile, 89% of participants were diagnosed with stage III colon cancer, 57% were treated with FOLFOX chemotherapy, and 74% have an ECOG performance status of 0. In terms of demographics, 54% are women and the median age is 60 years, with 31% over the age of 65 years. The groups were well-balanced on the baseline clinical characteristics in the overall and analyzed samples.

Intervention adherence

During the first 6 months, intervention participants completed an average of 82.8% of their 12 mandatory face-to-face counseling sessions, 82.6% of their mandatory supervised exercise sessions, and 22.1% of their optional but strongly recommended supervised exercise sessions. During the second 6 months, intervention participants completed 73.5% of their mandatory counseling sessions and 68.2% of their optional but strongly recommended supervised exercise sessions.

Feasibility outcomes

Table 4 provides the baseline and 1 year data for self-reported PA, cardiorespiratory fitness, and body weight and circumferences. In terms of the primary feasibility outcome, the SEP group reported an increase in PA of 15.6 MET-hours/week from baseline to 1 year compared with an increase of 5.1 MET-hours/week in the HEM

Table 2. Overview of the behavior change techniques utilized in the intervention arm of the CHALLENGE Trial

Topic	Description ^a
Introduction to the CHALLENGE Trial ^b (first session)	<ul style="list-style-type: none"> • Focus on developing rapport/relationship with the participant • Review the major goals and expectations of the CHALLENGE Trial • Provide a tour of the fitness facility and counseling center • Describe the aerobic equipment options available to the participant • Explain exercise intensity, how to monitor it, and why it is important • Explain how to record PA using PA log
Exercise orientation ^b (second session)	<ul style="list-style-type: none"> • Review and interpret baseline fitness test results • Discuss what to wear and how to hydrate properly while exercising • Complete activity inventory and discuss benefits of cross training • Review how to safely exercise and when to stop exercising
Goal setting	<ul style="list-style-type: none"> • Explain the difference between behavioral and health/performance goals • Explain the importance of setting SMART goals • Assist the participant in setting short/long behavior and health/performance goals • Create action steps to achieve behavioral and health/performance goals
Pedometers	<ul style="list-style-type: none"> • Provide the participant with a pedometer or encourage purchase • Describe the many health benefits of walking • Explain the motivational benefits of using a pedometer • Demonstrate how to use the pedometer • Encourage the participant to achieve at least 10,000 steps every day • Create a plan to help the participant increase steps per day
Fitness appraisal feedback	<ul style="list-style-type: none"> • (Completed after each fitness test at 6, 12, 24, and 36 months) • Complete the "Fitness Appraisal Form" for the participant • Explain the importance of fitness as a health indicator • Describe how fitness is expected to change with an appropriate PA program • Compare current fitness test results to previous test(s) as well as normative data • If improved, provide positive feedback; if not, provide reasons/solutions
Benefits of PA	<ul style="list-style-type: none"> • Ask about the most important PA benefits to the participant • Review the benefits of PA in general population • Review the unique benefits of PA for colon cancer survivors • Refer to this information in the future to motivate the participant
Barriers to PA	<ul style="list-style-type: none"> • Ask about the main barriers to PA for the participant • Discuss the most common barriers to PA in general population • Discuss unique barriers to PA in colon cancer survivors • Explain the importance of having a plan to address barriers • Address each specific barrier as it is raised by the participant
Environmental scan	<ul style="list-style-type: none"> • Explain the importance of having a supportive physical environment for PA • Explore what PA opportunities exist in the participant's local environment • Locate fitness facilities, walking trails, bike paths, and shops close to home • Explain the advantages of home exercise equipment • If interested, assist with the purchase of home exercise equipment
Social support	<ul style="list-style-type: none"> • (Participant is asked to bring their main PA support person to this session) • Describe the importance of social support for maintaining a PA program • Explain to the social support person the importance of their support • Brainstorm about tangible ways the support person can effectively provide support • Describe other strategies for support such as a buddy system or group exercise
Making PA fun	<ul style="list-style-type: none"> • Explain the importance of PA being fun and enjoyable for long term adherence • Ask what makes PA fun for the participant • Brainstorm how to make PA more enjoyable • Provide ideas (e.g., music, TV, new activities/locations, exercising with others)
Stimulus control	<ul style="list-style-type: none"> • Learn about stimulus control and how it affects behaviour • Provide examples of stimulus control for PA • Help participant establish appropriate stimuli in their environment • Discuss and design appropriate reward system
Decision balance sheet	<ul style="list-style-type: none"> • Explain the benefits of using a "Decision Balance Sheet" for complex decisions • Show the participant how to complete the "Decision Balance Sheet" • Provide example such as deciding between home equipment or gym membership • Refer to "Decision Balance Sheet" when making future important PA decisions
Detailed planning	<ul style="list-style-type: none"> • Explain importance of having a detailed plan for achieving PA goal • Create a detailed plan using the "Planning Worksheet" to achieve PA goal • Ensure detailed plan includes specifics on who, what, when, where, and how
Self-monitoring	<ul style="list-style-type: none"> • Discuss the importance of self-monitoring for successful behaviour change • Reinforce how to properly record PA and steps log sheets • Explain how self-monitoring informs goals, feedback, and reinforcements • Explain importance of continued self-monitoring after successful PA change

(Continued on the following page)

Table 2. Overview of the behavior change techniques utilized in the intervention arm of the CHALLENGE Trial (Cont'd)

Topic	Description ^a
Time management	<ul style="list-style-type: none"> • Describe the 5 components of effective time management • Discuss effective strategies and tips for time management • Complete "Time Management Worksheet" with the participant • Explain how to overcome lack of time as a barrier to PA
"When all is well" booster session	<ul style="list-style-type: none"> • (Used when participant is doing well and feels support is no longer needed) • Discuss the importance of continued support/supervised PA despite success • Describe the importance of exercise maintenance and relapse prevention • Discuss the desire for further increases or changes in the PA program • Anticipate new challenges between now and the next behavioural support session
Exercising beyond the CHALLENGE Trial ^b (final session)	<ul style="list-style-type: none"> • Discuss how to keep exercising now that the CHALLENGE Trial is over • Ask about the anticipated challenges of exercising without the support of the trial • Address concerns raised by the participant using previous change techniques • Complete the "Fitness Appraisal Form" for the final fitness testing comparison • Create a plan using the "Planning Worksheet" for life-long PA change • Thank the participant and provide them with a signed "Certificate of Graduation"

Abbreviations: FITT, frequency, intensity, time, and type; SMART, specific, measurable, attainable, realistic, timeframe.

^aAll behavioral support sessions begin by reviewing the PA/step logs since the previous session (typically 2 weeks or 1 month) to determine if the PA goal was achieved and if further increases in PA are desired. All behavioral support sessions end with a detailed PA prescription for next 2 weeks or 1 month that follows the FITT principle and incorporates the specific topic of the session where feasible.

^bThese 3 sessions are completed in the specified order but the remaining sessions are completed in any order that is deemed most relevant to the participant.

group (mean between group difference = +10.5; 95% CI, +3.1–+17.9; $P = 0.002$). For predicted VO_{2max} the SEP group increased by 1.6 mL/kg/minute from baseline to 1 year compared with a decrease of 0.6 mL/kg/minute in the HEM group (mean between group difference = +2.2; 95% CI = –4.6–+9.1; $P = 0.068$). There were no differences in body weight or circumferences.

Table 5 reports the baseline and 1 year data for objective physical functioning. For the 6-minute walk, the SEP group improved from baseline to 1 year by 59 meters compared with 31 meters in the HEM group (mean between group difference = +29; 95% CI = +0.4–+57; $P < 0.001$). The SEP group also improved relative to the HEM group for the 30-second chair stand (mean between group difference = +1.6 repetitions; 95% CI = +0.6–+2.7; $P < 0.001$), the 8-foot up and go (mean between group difference = –0.4 seconds; 95% CI = –0.7––0.2; $P = 0.004$), and the sit and reach (mean between group difference = +2.1 centimeters; 95% CI = –0.6–+4.7; $P = 0.08$). There were no differences in upper body functioning measures.

Discussion

The SEP intervention in the CHALLENGE Trial increased self-reported recreational PA by 15.6 MET-hours/week from baseline to 1 year compared with 5.1 MET-hours/week in the HEM group. The increase in the SEP arm exceeded the initial 6-month goal of 10 MET-hours/week and achieved the second 6-month goal of an increase of 10–20 MET-hours/week. The increase in the HEM arm of 5.1 MET-hours/week is not unexpected and likely resulted from the motivated sample, the health education materials, and the fitness testing. The 10.5 MET-hours/week between group difference equates to approximately 3.5 hours/week of moderate intensity exercise (at 3 METs) or 1.75 hours/week of vigorous intensity exercise (at 6 METs). The magnitude of this between-group behavior change difference compares favorably to other exercise interventions in colorectal cancer survivors that have reported increases compared with usual care of between 30 and 60 minutes/week of moderate intensity exercise (14, 30–33).

Moreover, the amount of exercise behavior change achieved in the CHALLENGE Trial is consistent with the amount of

exercise associated with improved colorectal cancer outcomes in observational studies. In their systematic review and meta-analysis, Schmid and Leitzmann (3) reported that an increase of 10 MET-hours/week of postdiagnosis PA was associated with a 28% lower risk of all-cause mortality and a 25% lower risk of colorectal cancer-specific mortality. Furthermore, the increase in PA from 16 to 32 MET-hours/week in the SEP arm is within the range of benefit for colorectal cancer outcomes. Specifically, two studies (34, 35) have applied spline curves to test for a threshold of association independent of predetermined MET categories and reported risk reductions starting between 6–12 MET-hours/week and continuing up to 30–35 MET-hours/week.

Consistent with the increase in self-reported recreational PA, the SEP intervention also improved several health-related fitness outcomes. Predicted VO_{2max} trended towards an improvement of 2.2 mL/kg/minute in the SEP group compared with HEM. VO_{2max} is an established predictor of mortality in many populations (36, 37). In a systematic review of 33 studies with over 100,000 participants (36), an increase in VO_{2max} of 3.5 mL/kg/minute was associated with a 13% lower risk of all-cause mortality. We also observed a significant improvement in the 6-minute walk in the SEP group of 59 meters which was superior to the HEM group. A change in the 6-minute walk of between 43 and 54 meters is considered clinically meaningful in several patient populations (38–40). Furthermore, the 6-minute walk is prognostic for survival in patients with several chronic diseases (41–43) including lung cancer (44).

Importantly, the SEP intervention improved the health-related fitness parameters that were expected to improve with an aerobic exercise intervention. Specifically, the SEP intervention improved VO_{2max} , the 6-minute walk, the 30-second chair stand, the 8-foot up and go, and the sit and reach. It did not improve the fitness parameters that were not expected to improve with an aerobic exercise intervention such as upper body functioning or body weight and circumference. Overall, the changes in health-related fitness are consistent with the focus of the SEP intervention on promoting aerobic exercise rather than strength exercise or weight loss.

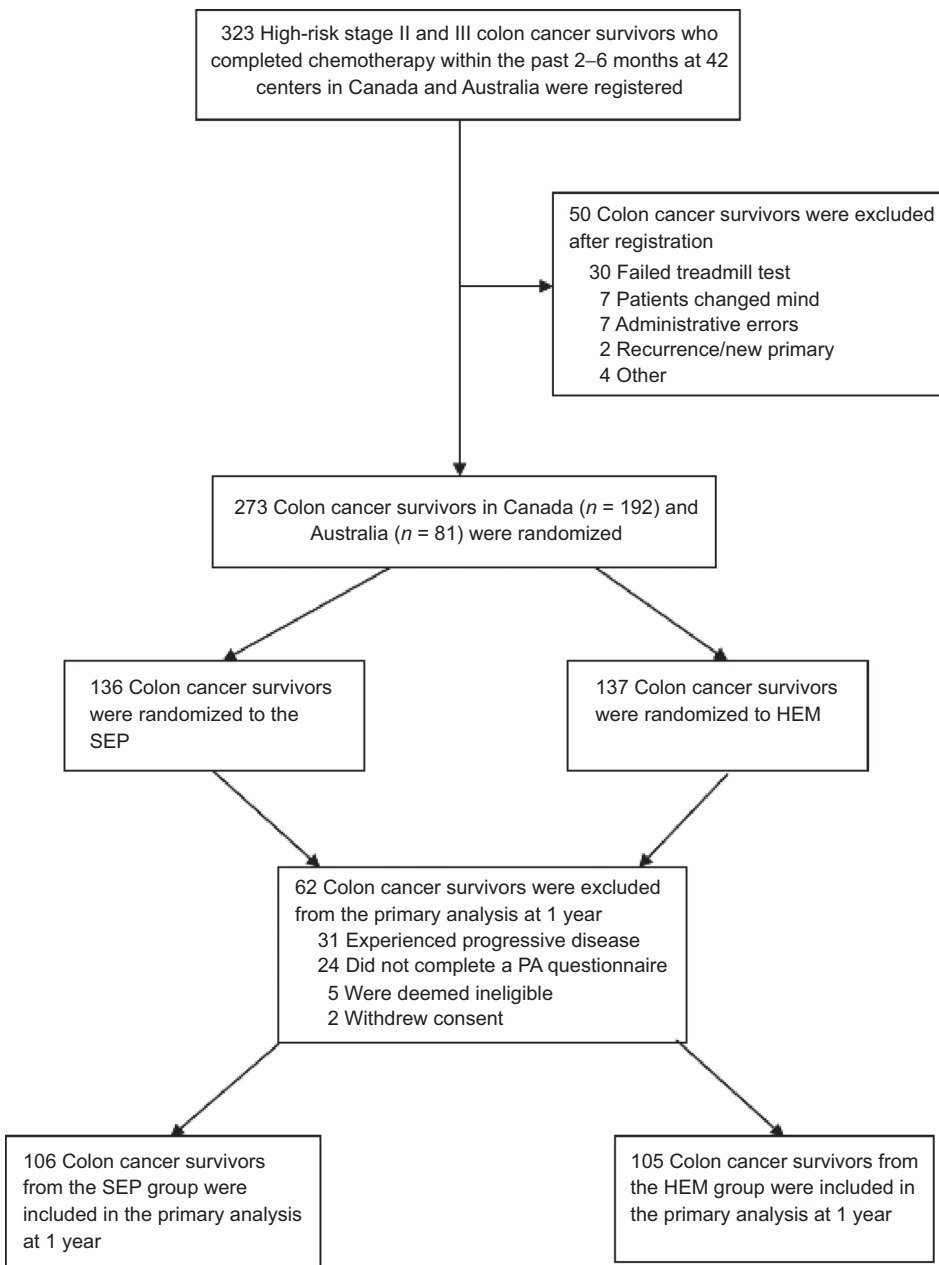


Figure 1. Flow of the first 273 participants through the 1-year follow-up in the CHALLENGE Trial. Note: reasons for exclusion are not reported separately by study arm to maintain blinding to the primary outcome of disease-free survival.

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The behavioral and health-related fitness improvements in the CHALLENGE Trial are especially noteworthy given that the intervention was delivered over a 1-year period by over 100 different PACs from 42 centers in two countries. The vast majority of exercise interventions in cancer survivors have assessed short-term behavioral changes (<6 months) in a limited number of centers (5, 6). Moreover, the small number of trials that have included longer term follow-up and broader implementation have often produced the smallest behavioral and fitness changes (5, 6), highlighting the well-known trade-off between reach/feasibility and effectiveness.

The effectiveness of the SEP intervention in the CHALLENGE Trial is likely based on the challenging exercise behavior change goal, the inclusion of some supervised exercise ses-

sions, the frequent and continuing contacts, the theoretically-based behavior change techniques, and the ongoing training and monitoring of the PACs (12). A recent systematic review and meta-analysis (45) of exercise behavior change interventions in patients with diabetes noted that interventions were more effective if they included specific behavior change techniques such as planning, prompting, social support, goal setting, time management, personalizing benefits, and overcoming barriers; all of which are included in the CHALLENGE Trial. Moreover, the interventions were also more effective if they utilized ≥ 10 behaviour change techniques (17 are utilized in the CHALLENGE Trial) and were underpinned by a theory or model of behavior change, such as the theory of planned behavior.

Table 3. Baseline characteristics for the first 273 randomized participants to reach the 1-year follow-up and the 211 randomized participants included in the primary analysis in the CO.21 (CHALLENGE) Trial

Variable	Complete sample		Analyzed sample	
	SEP (n = 136)	HEM (n = 137)	SEP (n = 106)	HEM (n = 105)
	No. (%)	No. (%)	No. (%)	No. (%)
Age, years				
<65	96 (71%)	92 (67%)	71 (67%)	71 (68%)
≥65	40 (29%)	45 (33%)	35 (33%)	34 (32%)
Median (range)	59 (28-84)	61 (19-80)	60 (32-84)	61 (19-80)
Sex				
Male	63 (46%)	63 (46%)	46 (43%)	46 (44%)
Female	73 (54%)	74 (54%)	60 (57%)	59 (56%)
Body mass index, kg/m ²				
≤27.5	58 (43%)	59 (43%)	41 (39%)	49 (47%)
>27.5	78 (57%)	78 (57%)	65 (61%)	56 (53%)
Performance status (ECOG)				
0	100 (74%)	101 (74%)	77 (73%)	75 (71%)
1	36 (26%)	36 (26%)	29 (27%)	30 (29%)
Disease stage				
High risk II	15 (11%)	14 (10%)	14 (13%)	12 (11%)
III	121 (89%)	121 (88%)	92 (87%)	93 (89%)
Number of positive lymph nodes				
0	16 (12%)	21 (15%)	15 (14%)	12 (11%)
1+	120 (88%)	116 (85%)	91 (86%)	93 (89%)
Type of chemotherapy				
FOLFOX	52 (38%)	54 (39%)	35 (33%)	41 (39%)
FOLFOX (±agent)	25 (18%)	24 (18%)	20 (19%)	21 (20%)
Capecitabine	21 (15%)	24 (18%)	18 (17%)	20 (19%)
5-fluorouracil	17 (13%)	5 (4%)	15 (14%)	3 (3%)
Other	21 (15%)	30 (22%)	18 (17%)	20 (19%)
R-PARQ results				
Answered no to all questions	69 (51%)	70 (51%)	50 (47%)	54 (51%)
Answered yes to ≥1 question	67 (49%)	67 (49%)	56 (53%)	51 (49%)
Months from diagnosis to randomization, median (range)	12 (0-16)	12 (8-17)	12 (0-16)	12 (8-17)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FOLFOX, folinic acid (leucovorin), fluorouracil, oxaliplatin (Eloxatin); HEM, health education materials; R-PARQ, revised physical activity readiness questionnaire; SEP, structured exercise program.

Our interim feasibility analysis has some limitations. First, we have only reported exercise behavior change after 1 year of a 3-year intervention. Substantial declines in lifestyle behaviors after 6 months or 1 year are well-known (46); however, these declines often occur after an intervention is ceased (47), whereas the SEP intervention in CO.21 will continue for the full 3 years (9). Second, we have relied on a self-report measure of PA which, although validated, has well-known limitations (48). Nevertheless, there is an acceptable correlation between self-reported and

accelerometer-assessed PA in colon cancer survivors (49) and the health-related fitness changes are consistent with the self-reported PA results. Finally, our results may only apply to promoting aerobic exercise; not strength exercise, nutrition, multiple health behaviors, or weight loss (50, 51).

In conclusion, the CHALLENGE Trial remains the only randomized controlled trial designed to examine the effects of a SEP intervention on disease-free survival in colon cancer survivors. The results of this feasibility analysis suggest that the SEP

Table 4. Effects of the structured exercise program on physical activity and health-related fitness at 1 year in the CO.21 (CHALLENGE) Trial

Variable	Baseline M (SD)	1 Year M (SD)	Mean change M (95% CI)	Group difference in mean change	
				M (95% CI)	P value
Self-reported recreational physical activity, MET hours/week					
Exercise program (n = 106)	16.5 (22.4)	32.1 (30.7)	+15.6 (+9.9-+21.4)	+10.5 (+3.1-+17.9)	0.002
Health education (n = 105)	16.6 (19.2)	21.7 (20.2)	+5.1 (+0.4-+ 9.9)		
Predicted VO _{2max} , mL/kg/min					
Exercise program (n = 86)	33.2 (24.5)	34.8 (10.9)	+1.6 (-3.6-+6.8)	+2.2 (-4.6-+9.1)	0.068
Health education (n = 76)	32.9 (19.1)	32.3 (8.9)	-0.6 (-5.0-+3.8)		
Weight, kg					
Exercise program (n = 115)	82.8 (19.6)	84.0 (20.1)	+1.2 (0.0-+2.3)	+1.3 (-0.5-+3.1)	0.38
Health education (n = 112)	79.7 (18.1)	79.5 (16.4)	-0.2 (-1.5-+1.2)		
Hip circumference, cm					
Exercise program (n = 99)	107.7 (11.8)	107.8 (10.8)	+0.2 (-0.9-+1.2)	-0.1 (-1.5-+1.4)	0.90
Health education (n = 99)	105.2 (9.2)	105.4 (9.1)	+0.2 (-0.8-+1.2)		
Waist circumference, cm					
Exercise program (n = 99)	100.0 (15.1)	99.2 (14.4)	-0.7 (-2.1-+0.6)	-1.2 (-3.2-+0.8)	0.31
Health education (n = 99)	97.5 (14.2)	97.9 (13.7)	+0.4 (-1.1-+1.9)		

Abbreviations: CI, confidence interval; M, mean; MET, metabolic equivalent task; n, sample size; SD, standard deviation.

Table 5. Effects of the structured exercise program on physical functioning at 1 year in the CO.21 (CHALLENGE) Trial

Variable	Baseline M (SD)	1 year M (SD)	Mean change M (95% CI)	Group difference in mean change	
				M (95% CI)	P value
6-minute walk, m					
Exercise program (n = 93)	535 (126)	594 (114)	59 (+38–+81)	+29 (+0.4–+57)	<0.001
Health education (n = 93)	522 (100)	553 (92)	31 (+12–+49)		
30-second chair stand, no.					
Exercise program (n = 98)	13.4 (4.2)	17.5 (5.1)	+4.1 (+3.3–+4.9)	+1.6 (+0.6–+2.7)	<0.001
Health education (n = 97)	14.1 (3.9)	16.5 (5.3)	+2.5 (+1.7–+3.2)		
8-foot up and go, sec					
Exercise program (n = 99)	5.2 (1.1)	4.7 (0.9)	–0.5 (–0.7––0.4)	–0.4 (–0.7––0.2)	0.004
Health education (n = 98)	5.2 (1.2)	5.1 (1.3)	–0.1 (–0.3–+0.1)		
Sit and reach, cm					
Exercise program (n = 99)	–3.2 (11.3)	0.8 (11.0)	+3.9 (+2.0–+5.8)	+2.1 (–0.6–+4.7)	0.08
Health education (n = 98)	–1.3 (10.0)	0.6 (10.9)	+1.9 (–0.1–+3.8)		
30 second arm curl, no.					
Exercise program (n = 99)	16.2 (4.8)	20.1 (5.1)	+3.9 (+3.0–+4.8)	+0.5 (–0.9–+1.9)	0.18
Health education (n = 98)	15.7 (4.4)	19.1 (5.9)	+3.4 (+2.3–+4.5)		
Back scratch, cm					
Exercise program (n = 97)	–7.2 (11.6)	–7.1 (10.5)	+0.1 (–1.7–+1.9)	+1.0 (–1.6–+3.6)	0.16
Health education (n = 95)	–6.9 (11.3)	–7.8 (12.0)	–0.9 (–2.7–+1.0)		

Abbreviation: n, sample size.

intervention is being successfully implemented in a multicenter international trial and is producing substantial behavior change and improvements in health-related fitness that appear sufficient for determining their causal effects on colon cancer outcomes. Moreover, the trial will provide valuable data on exercise motivation and behavior change that will inform the implementation of this program into widespread practice should it be warranted. The role of lifestyle interventions in improving cancer outcomes remains a compelling issue for cancer survivors and cancer care professionals (4).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

- Des Guetz G, Uzzan B, Bouillet T, Nicolas P, Chouahnia K, Zelek L, et al. Impact of physical activity on cancer-specific and overall survival of patients with colorectal cancer. *Gastroenterol Res Pract* 2013;2013:1–6.
- Je Y, Jeon JY, Giovannucci EL, Meyerhardt JA. Association between physical activity and mortality in colorectal cancer: a metaanalysis of prospective cohort studies. *Int J Cancer* 2014;133:1905–13.
- 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.
- Ligibel JA, Alfano CM, Hershman D, Ballard RM, Bruinooge SS, Courneya KS, et al. Recommendations for obesity clinical trials in cancer survivors: American Society of Clinical Oncology Statement. *J Clin Oncol* 2015;33:3961–7.
- Bluethmann SM, Vernon SW, Gabriel KP, Murphy CC, Bartholomew LK. Taking the next step: a systematic review and meta-analysis of physical activity and behavior change interventions in recent post-treatment breast cancer survivors. *Breast Cancer Res Treat* 2015;149:331–42.
- Goode AD, Lawler SP, Brakenridge CL, Reeves MM, Eakin EG. Telephone, print, and web-based interventions for physical activity, diet, and weight control among cancer survivors: a systematic review. *J Cancer Surviv* 2015;9:1–23.
- Mishra SI, Scherer RW, Snyder C, Geigle PM, Berlanstein DR, Topaloglu O. Exercise interventions on health-related quality of life for people with cancer during active treatment. *Cochrane Database Syst Rev* 2012;8:CD008465.

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8. Mishra SI, Scherer RW, Geigle PM, Berlanstein DR, Topaloglu O, Gotay CC, et al. Exercise interventions on health-related quality of life for cancer survivors. *Cochrane Database Syst Rev* 2012;8:CD007566.
9. Courneya KS, Booth CM, Gill S, O'Brien P, Vardy J, Friedenreich CM, et al. The Colon Health and Life-Long Exercise Change trial: a randomized trial of the National Cancer Institute of Canada Clinical Trials Group. *Curr Oncol* 2008;15:279–85.
10. Courneya KS, Vardy J, Gill S, Jonker D, O'Brien P, Friedenreich CM, et al. Update on the Colon Health and Life-Long Exercise Change trial: a phase III study of the impact of an exercise program on disease-free survival in colon cancer survivors. *Curr Colorectal Cancer Rep* 2014;10:321–8.
11. Vallance J, Lesniak SL, Belanger LJ, Courneya KS. Development and assessment of a physical activity guidebook for the Colon Health and Life-Long Exercise Change (CHALLENGE) trial (NCIC CO.21). *J Phys Act Health* 2010;7:794–801.
12. Group DPPR. The Diabetes Prevention Program (DPP) description of lifestyle intervention. *Diabetes Care* 2002;25:2165–71.
13. Group IAR. The Look AHEAD study: a description of the lifestyle intervention and the evidence supporting it. *Obesity* 2006;14:737–52.
14. Courneya KS, Friedenreich CM, Quinney HA, Fields AL, Jones LW, Fairley AS. A randomized trial of exercise and quality of life in colorectal cancer survivors. *Eur J Cancer Care* 2003;12:347–57.
15. Forbes CC, Blanchard CM, Mummery WK, Courneya KS. A comparison of physical activity correlates across breast, prostate and colorectal cancer survivors in Nova Scotia, Canada. *Support Care Cancer* 2014;22:891–903.
16. McGowan EL, Speed-Andrews AE, Blanchard CM, Rhodes RE, Friedenreich CM, Culos-Reed SN, et al. Physical activity preferences among a population-based sample of colorectal cancer survivors. *Oncol Nurs Forum* 2013;40:44–52.
17. Ajzen I. The theory of planned behavior. *Organ Behav Hum Decis Process* 1991;50:179–211.
18. Courneya KS, Friedenreich CM. Determinants of exercise during colorectal cancer treatment: an application of the theory of planned behavior. *Oncol Nurs Forum* 1996;24:1515–723.
19. Courneya KS, Friedenreich CM, Arthur K, Bobick TM. Understanding exercise motivation in colorectal cancer patients: a prospective study using the theory of planned behavior. *Rehabil Psychol* 1999;44:68–84.
20. Speed-Andrews AE, Rhodes RE, Blanchard CM, Culos-Reed SN, Friedenreich CM, Belanger LJ, et al. Medical, demographic and social cognitive correlates of physical activity in a population-based sample of colorectal cancer survivors. *Eur J Cancer Care* 2012;21:187–96.
21. Michie S, Abraham C, Whittington C, McAteer J, Gupta S. Effective techniques in healthy eating and physical activity interventions: a meta-regression. *Health Psychol* 2009;28:690–701.
22. Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. *Ann Behav Med* 2013;46:81–95.
23. Friedenreich CM, Courneya KS, Neilson HK, Matthews CE, Willis G, Irwin M, et al. Reliability and validity of the Past Year Total Physical Activity Questionnaire. *Am J Epidemiol* 2006;163:959–70.
24. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc* 2000;32:S498–S504.
25. Pollock ML, Foster C, Schmidt D, Hellman C, Linnerud AC, Ward A. Comparative analysis of physiologic responses to three different maximal graded exercise test protocols in healthy women. *Am Heart J* 1982;103:363–73.
26. American College of Sports Medicine. ACSM's guidelines for exercise testing and prescription. Philadelphia, PA: Lippincott Williams & Wilkins; 2013.
27. Gledhill N, Jamnik V. The Canadian Physical Activity, Fitness and Lifestyle Approach (CPAFLA). Ottawa, CA: Canadian Society for Exercise Physiology; 2003.
28. NHIBI Obesity Education Panel. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. *National Institutes of Health Obes Res* 1998;6:51S–209S.
29. Rikli R, Jones C. Development and validation of a functional fitness test for community-residing older adults. *J Aging Phys Act* 1999;7:129–61.
30. Hawkes AL, Chambers SK, Pakenham KI, Patrao TA, Baade PD, Lynch BM, et al. Effects of a telephone-delivered multiple health behavior change intervention (CanChange) on health and behavioral outcomes in survivors of colorectal cancer: a randomized controlled trial. *J Clin Oncol* 2013;31:2313–21.
31. Morey MC, Snyder DC, Sloane R, Cohen HJ, Peterson B, Hartman TJ, et al. Effects of home-based diet and exercise on functional outcomes among older, overweight long-term cancer survivors RENEW: a randomized controlled trial. *JAMA* 2009;301:1883–91.
32. Ligibel JA, Meyerhardt J, Pierce JP, Najita J, Shockro L, Campbell N, et al. Impact of a telephone-based physical activity intervention upon exercise behaviors and fitness in cancer survivors enrolled in a cooperative group setting. *Breast Cancer Res Treat* 2012;132:205–13.
33. Pinto BM, Papandonatos GD, Goldstein MG, Marcus BH, Farrell N. Home-based physical activity intervention for colorectal cancer survivors. *Psychooncology* 2013;22:54–64.
34. Meyerhardt JA, Giovannucci EL, Ogino S, Kirkner GJ, Chan AT, Willett W, et al. Physical activity and male colorectal cancer survival. *Arch Intern Med* 2009;169:2102–8.
35. Meyerhardt JA, Heseltine D, Niedzwiecki D, Hollis D, Saltz LB, Mayer RJ, et al. Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. *J Clin Oncol* 2006;24:3535–41.
36. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, et al. Cardio-respiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA* 2009;301:2024–35.
37. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *New Engl J Med* 2002;346:793–801.
38. Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH. Interpreting small differences in functional status: the six minute walk test in chronic lung disease patients. *Am J Respir Crit Care Med* 1997;155:1278–82.
39. O'Keefe ST, Lye M, Donnellan C, Carmichael DN. Reproducibility and responsiveness of quality of life assessment and six minute walk test in elderly heart failure patients. *Heart* 1998;80:377–82.
40. Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. *J Am Geriatr Soc* 2006;54:743–9.
41. Boxer R, Kleppinger A, Ahmad A, Annis K, Hager D, Kenny A. The 6minute walk is associated with frailty and predicts mortality in older adults with heart failure. *Congest Heart Fail* 2010;16:208–13.
42. Lucas C, Stevenson LW, Johnson W, Hartley H, Hamilton MA, Walden J, et al. The 6-min walk and peak oxygen consumption in advanced heart failure: aerobic capacity and survival. *Am Heart J* 1999;138:618–24.
43. Pinto-Plata V, Cote C, Cabral H, Taylor J, Celli B. The 6 min walk distance: change over time and value as a predictor of survival in severe COPD. *Eur Respir J* 2004;23:28–33.
44. Kasyrnjanova G, Correa JA, Kreisman H, Dajczman E, Pepe C, Dobson S, et al. Prognostic value of the six-minute walk in advanced non-small cell lung cancer. *J Thorac Oncol* 2009;4:602–7.
45. Avery L, Flynn D, van Wersch A, Sniehotta FF, Trenell MI. Changing physical activity behavior in type 2 diabetes: a systematic review and meta-analysis of behavioral interventions. *Diabetes Care* 2012;35:2681–9.
46. Dombrowski SU, Knittle K, Avenell A, Araujo-Soares V, Sniehotta FF. Long term maintenance of weight loss with non-surgical interventions in obese adults: systematic review and meta-analyses of randomised controlled trials. *BMJ* 2014;348:g2646.
47. Middleton K, Patidar S, Perri M. The impact of extended care on the longterm maintenance of weight loss: a systematic review and metaanalysis. *Obes Rev* 2012;13:509–17.
48. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. *Med Sci Sports Exerc* 2008;40:181–8.
49. Boyle T, Lynch BM, Courneya KS, Vallance JK. Agreement between accelerometer-assessed and self-reported physical activity and sedentary time in colon cancer survivors. *Support Care Cancer* 2015;23:1121–6.
50. Goodwin PJ, Segal RJ, Vallis M, Ligibel JA, Pond GR, Robidoux A, et al. Randomized trial of a telephone-based weight loss intervention in postmenopausal women with breast cancer receiving letrozole: the LISA trial. *J Clin Oncol* 2014;32:2231–9.
51. Rock CL, Flatt SW, Byers TE, Colditz GA, Demark-Wahnefried W, Ganz PA. Results of the Exercise and Nutrition to Enhance Recovery and Good Health for You (ENERGY) trial: a behavioral weight loss intervention in overweight or obese breast cancer survivors. *J Clin Oncol* 2015;33:3169–76.