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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

Kerry S. Courneya · Janette Vardy · Sharlene Gill · Derek Jonker · Patti O'Brien · Christine M. Friedenreich · Haryana Dhillon · Rebecca K. S. Wong · Ralph M. Meyer · Jennifer J. Crawford · Kristin L. Campbell · Harry Prapavessis · Christopher O'Callaghan · Jane Turner · Lissa M. Spencer · Hidde P. van der Ploeg · Dongsheng Tu · Christopher M. Booth

Abstract The Colon Health and Life-Long Exercise Change (CHALLENGE) trial is evaluating the effects of a 3-year exercise program on disease-free survival in 962 patients with resected high-risk stage II or stage III colon cancer. The purpose of this commentary is to provide an update on the CHALLENGE trial. As of December 31, 2013, the trial had randomized 250 patients in 20 Canadian centers and 26 Australian centers, with further expansion planned. Early barriers to accrual are reported and strategies to improve accrual are discussed. Of the 250 patients randomized to date, 89 % have stage III colon cancer, 56 % were treated with leucovorin/5-fluorouracil/oxaliplatin-based chemotherapy, 58 % have a body mass index of at least 27.5 kg/m^2, 53 % are women, and the median age is 60 years. The CHALLENGE trial remains the only randomized controlled trial in colon cancer survivors that is examining the effects of an exercise program on disease-free survival.

Keywords Physical activity · Physical functioning · Quality of life · Randomized controlled trial · Symptoms · Survivorship

K. S. Courneya (✉) · J. J. Crawford
Faculty of Physical Education and Recreation, University of Alberta, E-488 Van Vliet Center, Edmonton, AB T6G 2H9, Canada
e-mail: kerry.courneya@ualberta.ca

J. Vardy · H. Dhillon · J. Turner · H. P. van der Ploeg
University of Sydney, Sydney, Australia

S. Gill
British Columbia Cancer Agency, Vancouver, Canada

D. Jonker
The Ottawa Hospital Cancer Center, Ottawa, Canada

P. O'Brien · C. O'Callaghan · D. Tu · C. M. Booth
Queen's University, Kingston, Canada

C. M. Friedenreich
Alberta Health Services, Calgary, Canada

R. K. S. Wong
Princess Margaret Hospital, Toronto, Canada

R. M. Meyer
Juravinski Hospital and Cancer Centre, McMaster University, Hamilton, Canada

K. L. Campbell
University of British Columbia, Vancouver, Canada

H. Prapavessis
Western University, London, Canada

L. M. Spencer
Royal Prince Alfred Hospital, Camperdown, Australia

H. P. van der Ploeg
VU University Medical Center, University of Sydney, Amsterdam, Netherlands

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Introduction

The Colon Health and Life-Long Exercise Change (CHALLENGE) trial [1] is a randomized controlled trial examining the effects of a 3-year exercise program on disease-free survival (DFS) in 962 patients with resected high-risk stage II or stage III colon cancer who have completed adjuvant chemotherapy within the past 2–6 months. The trial, led by the Canadian NCIC Clinical Trials Group in partnership with the Australian Survivorship Research Group, is also designated by the NCIC Clinical Trials Group as the Colon.21 (CO.21) trial. It was activated in December 2008, and the first patient was randomized in May 2009. The trial continues to accrue patients, deliver the exercise program, and conduct follow-up assessments. The purpose of this commentary is to provide an update on the CHALLENGE trial, including discussing the latest science supporting the trial hypothesis and design; early accrual barriers and strategies to improve accrual; baseline clinical characteristics of the patients randomized as of December 31, 2013; and preliminary data on the completion rate for the follow-up fitness testing and patient-reported questionnaires.

Overview of the CHALLENGE Trial

The rationale and methods of the CHALLENGE trial have been previously described [1]. The general objective of the CHALLENGE trial is to determine whether or not a structured exercise program improves DFS (primary end point) compared with standard written health education materials in colon cancer survivors who have completed adjuvant chemotherapy after surgical resection of high-risk stage II or stage III disease. Important secondary end points include overall survival; patient-reported outcomes, including quality of life, fatigue, anxiety, depression, and sleep quality; health-related fitness outcomes, including cardiovascular fitness, physical function, body mass index, and hip and waist circumference; safety and toxicity data; correlative biological markers associated with insulin-related growth factor; and an economic evaluation. The trial is also examining the impact of the behavioral support intervention on motivational outcomes from the theory of planned behavior [2], including intentions to exercise, attitudes toward exercise, support for exercise, and perceived control over exercise.

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 national guidelines for physical activity (less than 150 min of moderate-intensity exercise per week), and are able to complete at least two stages of a submaximal treadmill test. Participants are stratified by center, disease stage (high-risk stage II disease versus high-risk stage III disease), body mass index (27.5 kg/m^2 or below versus more than 27.5 kg/m^2), and ECOG performance status (0 versus 1) before being randomly assigned to a standard comparison arm or an experimental arm.

The comparison arm receives general health education materials about physical activity and nutrition as well as standard surveillance follow-up. The experimental arm receives an exercise guidebook developed specifically for colon cancer survivors [3] and a physical activity consultant (PAC) for a period of 3 years, who delivers a behavioral support program designed to help participants increase and maintain their exercise. The behavior support intervention is delivered in three phases. Phase 1 is an intensive intervention for the first 6 months with biweekly face-to-face sessions and supervised exercise with the option of additional weekly supervised exercise sessions during the alternate weeks. Phase 2 is a reduced intervention for the second 6 months involving biweekly behavioral support sessions which may be face-to-face or by telephone. If face-to-face behavioral support sessions are chosen, the addition of a supervised exercise session is strongly encouraged. Phase 3 is a minimal intervention for years 2 and 3 that involves monthly behavioral support sessions which may be face-to-face or by telephone. Again, if face-to-face behavioral support sessions are selected, a supplemental supervised exercise session is strongly encouraged.

The behavioral support sessions consist of standard behavior change techniques, including learning about exercise science principles, exercise benefits for colon cancer survivors, how to self-monitor, how to set goals, developing a detailed exercise plan, time management techniques, making exercise fun, overcoming barriers, an environmental scan, stimulus control, how to secure social support, application of a decision balance sheet, step counting with pedometers, and fitness appraisal feedback. In phase 1 (months 1–6) the goal is to increase gradually recreational physical activity by at least ten metabolic equivalent task (MET) hours per week, which is about 150 min of moderate-intensity (four MET hours) exercise per week or 75 min of vigorous-intensity (eight MET hours) exercise per week. The focus is on aerobic exercise, and the participant is able to choose the type, frequency, intensity, and duration of aerobic exercise to meet the intervention goal. In phase 2 (months 7–12), the PAC and study participants reflect on whether the physical activity targets are being met and what barriers/facilitators might further increase physical activity. The focus during phase 3 (months 13–36) is to provide ongoing motivational support to participants as they seek to maintain their lifestyle change.

The primary end point is 3-year DFS, which is highly correlated with overall survival in patients with resected colon cancer [4] and is accepted as a suitable end point for registration trials by the Food and Drug Administration. Most

adjuvant trials in colorectal cancer (CRC) are now designed with 3-year DFS as the primary end point. In the CHALLENGE trial, DFS is defined as the time from randomization to the first event of recurrent disease (local or distant), a new primary tumor, or death from any cause. This end point includes development of second colon primary tumors and any other new primary tumors [5]. The study sample size of 962 is designed to detect an improvement in DFS at 3 years from 75 to 81 %, consistent with a 25 % reduction in the risk of a DFS event (hazard ratio of 0.75). In pivotal trials of adjuvant chemotherapy, this magnitude of benefit has previously led to a major change in practice and policy [6, 7]. The trial will also evaluate overall survival as an important secondary end point.

Patients in both study arms will undergo routine surveillance imaging and carcinoembryonic antigen testing to monitor them for disease recurrence. In the initial protocol, the imaging was done every 6 months for the first 3 years and annually for years 4 and 5. International guidelines have recently moved toward less frequent imaging given the concerns of unnecessary radiation exposure and the limited evidence in support of more frequent testing [8, 9]. Accordingly, the CO.21 protocol has been amended to reduce the frequency of imaging to annually for 3 years.

Secondary patient-reported outcomes include quality of life, fatigue, anxiety, depression, and sleep quality, which are assessed by standardized questionnaires every 6 months. Health-related fitness outcomes are assessed at 6 months, 1 year, 2 years, and 3 years, and assessment includes a submaximal treadmill test, the 6-min walk, height and weight to estimate body mass index, waist and hip circumference, and several brief tests of physical functioning. The assessments also include a blood collection, a brief measure of exercise motivation, a safety profile, and an economic evaluation every 6 months.

Update on the Science Supporting the CHALLENGE Trial

The scientific rationale for the CHALLENGE trial was based on epidemiological studies showing strong inverse associations between exercise levels after a colon cancer or CRC diagnosis and risk of death from cancer and all causes [10, 11]. Since the initiation of the CHALLENGE trial, additional research has been published that further strengthens the rationale for and the scientific basis of the CHALLENGE trial. This research has recently been summarized in two systematic reviews and meta-analyses [12••, 13••]. In one review, Des Guetz et al. [12••] identified seven observational studies involving over 8,000 CRC survivors published between 2006 and 2013. Overall, higher postdiagnosis physical activity was associated with a lower risk of cancer-specific mortality (hazard ratio 0.61; 95 % confidence interval 0.44–0.86) and a lower risk of all-cause mortality (hazard ratio 0.62; 95 % confidence interval 0.54–0.71). Nevertheless, despite the reliable and meaningful associations documented in these reviews, the studies remain limited by the observational designs, self-report measures of physical activity, and high risk of confounding. Moreover, the critical question is whether any feasible exercise intervention can actually improve DFS. Consequently, the need for a definitive phase III trial on the effects of a pragmatic exercise program on DFS in colon cancer survivors remains.

The CHALLENGE trial also includes a correlative component that will focus on potential mechanisms of how exercise may influence DFS in colon cancer survivors. One proposed mechanism is the insulin-like growth factor pathway, although other mechanisms will also be explored. Moreover, two recent studies suggest that the link between exercise and colon cancer survival may depend on the expression of particular molecular markers. For example, Morikawa et al. [14] reported that physical activity was strongly associated with CRC survival in patients with negative status for nuclear cadherin-associated protein 1 activation but not in patients with positive status for nuclear cadherin-associated protein 1 activation. As a second example, Meyerhardt et al. [15] reported a statistically significant interaction between physical activity and p27 expression that showed that physical activity was associated with a nonsignificant increased risk of colon cancer mortality for tumors with loss of p27 but a significant decreased risk for tumors with expression of p27. These emerging data suggest that the benefit of physical activity on outcomes in colon cancer survivors may depend on molecular tumor markers. Consequently, the correlative component of the CHALLENGE trial will be able to examine potential predictive markers of exercise program benefit in colon cancer.

Finally, since the inception of the CHALLENGE trial, the first systematic review and meta-analysis of exercise interventions in CRC survivors has been published, focusing on health-related fitness and patient-reported outcomes. Cramer et al. [16••] identified only five randomized controlled trials, involving 238 CRC survivors. The studies were of modest quality, and only one study had more than 50 patients. Moreover, only a limited number of fitness and quality-of-life end points were assessed. The results showed no effects of exercise on quality of life or fatigue; however, significant effects were reported for physical fitness. On the basis of the insufficient evidence and lack of safety data, Cramer et al. concluded that no recommendation can be made concerning whether exercise should be part of routine care for CRC survivors. In the CHALLENGE trial, health-related fitness and patient-reported outcomes are important secondary outcomes, and the trial will provide valuable data on the role of exercise in affecting these outcomes.

Early Accrual, Barriers, and Strategies To Improve Accrual

The CHALLENGE trial was centrally activated in December 2008, and the first patient was randomized in May 2009. The CHALLENGE trial was intentionally launched in a phased and graduated fashion because of the novel partnerships that needed to be developed between cancer centers and physical activity experts. We began with a pilot phase in which the trial was opened in seven key cancer centers in Canada and Australia that had existing partnerships with exercise specialists. Once these centers had demonstrated the initial feasibility of this unique collaboration, the trial was opened in additional centers in Canada and Australia.

The major obstacle in broadly opening the CHALLENGE trial was to find exercise partners for the cancer centers without existing relationships. Each center was allowed to develop its own collaboration, but several options were suggested. One option was to partner with a physical therapist who already worked at the cancer center or local hospital. The advantages of this option included a highly qualified professional, often with experience working with cancer patients, at a relatively low cost if the salary is already covered by the hospital. A second option was to partner with a cardiology clinic at the local hospital. The advantages of this option included a highly qualified exercise specialist experienced in working with high-risk patients, and access to state-of-the-art exercise testing and training facilities. A third option was to link with an academic department at a local university such as a physical therapy, kinesiology, or exercise science department. This option has the advantages of securing a highly qualified exercise specialist familiar with research methods, and access to state-of-the-art exercise testing and training facilities. A final option was to partner with an exercise specialist in the community. The benefits of this option are a qualified exercise specialist with access to community-based facilities. As of December 31, 2013, the CHALLENGE trial was open in 20 centers in Canada and 26 centers in Australia.

Early in the recruitment process, we identified several key barriers to accrual and developed strategies to address these barriers (Table 1). One major barrier was patients living out of town and having too far to travel. This barrier arose because the first 12 behavioral support sessions required face-to-face visits. We considered delivering an exclusively telephone-based behavioral support program but decided against this option because the evidence for a substantial increase in exercise from telephone counseling alone is modest [17, 18]. Consequently, to address this barrier, we emphasized that the face-to-face sessions required only 12 visits over the first 6 months. After that period, participants could choose telephone counseling for the next 2.5 years. We also noted the significant flexibility for when the 12 sessions must occur. Although the goal is roughly biweekly sessions, participants can complete up to four sessions in any one month and as little as one session in a month. This allows participants to capitalize on any other planned visits to the city during that time (e.g., medical appointments, visiting family/friends, shopping, entertainment).

A second early barrier was patients being deemed too active. As noted earlier, patients were excluded if they were already meeting the exercise guidelines for cancer survivors [19, 20] of at least 150 min of moderate-intensity exercise during leisure time (not household or work activities) in a typical week over the past month. The exercise screening questionnaire allows patients to report light-intensity, moderate-intensity, and vigorous-intensity exercise separately as a way of reducing the overreporting of light-intensity-exercise minutes as moderate-intensity-exercise minutes [21]. Nevertheless, it is well known that people tend to overreport the amount of exercise they do, especially the intensity. If patients report too much exercise, we follow up and ask patients (1) if they reported their "typical" week or if it was it their "best" week or the amount they "tried" to exercise, (2) if they included any household chores or occupational activities, and (3) if they could describe activities in the moderate-intensity category and remind them that moderate-intensity activities need to result in an increased heart rate, increased breathing rate, and light sweating.

A third early barrier was staff reporting that the patient does not "look like an exerciser." We emphasized that all patients should be approached about the trial even if they do not look like the prototypical exerciser. If patients respond that they are "too old" or "unable to exercise," we explain (1) that they are never too old to exercise as research has shown that exercise is safe and beneficial for people even into their 80s, (2) the exercise program is individualized to take into account their level of fitness and any health issues, and (3) they will never be asked to do more than they are able and willing to do safely. Other barriers and strategies are reported in Table 1.

We also revisited two key eligibility criteria to determine if the trial could be opened to a broader clinical group. We considered including rectal cancer survivors but decided against this change. Although there is some evidence that exercise may be associated with outcomes in rectal cancer survivors, the data are limited and modest [22]. Moreover, the limited data in the adjuvant setting were not enough in our view to overcome the large amount of evidence in the primary prevention setting suggesting that exercise is unrelated to the risk of developing rectal cancer [23, 24]. We also considered including all stage II colon cancer survivors rather than just high-risk stage II colon cancer survivors. Again, we decided against this change because of the very low event rate in lower-risk stage II colon cancers [25].

As of December 31, 2013, we had randomized 250 patients in Canada and Australia, with accrual increasing each year (Fig. 1). We are currently recruiting additional centers in

Table 1 Summary of early barriers and strategies to improve accrual in the Colon Health and Life-Long Exercise Change (CHALLENGE) trial

Early barrier to accrual	Strategy to improve accrual
Patient lives out of town/too far to travel	Emphasize only 12 face-to-face sessions over the first 6 months. The patient can then choose telephone counseling for the next 2.5 years. Note the significant flexibility for when the 12 visits can occur. Patients can complete between 1 and 4 visits in a month. Capitalize on other visits the patient makes to the city/cancer center
Patient reports too much exercise	Review the self-report closely and make sure that the patient has reported (1) a "typical" exercise week, not the "best" week, (2) only leisure-time exercise, not household or occupational activities, and (3) moderate-intensity exercise, not light intensity exercise (e.g., increased heart rate, breathing)
Patient is not/does not look like "an exerciser"	Remind staff that all patients should be approached regardless of their appearance. If patients say I am "too old" or "unable to exercise," explain that (1) no one is too old to exercise, and exercise is safe and beneficial for people in their 80s, (2) the exercise program takes into account any health problems, (3) they will never be asked to do more than they are able and willing, and (4) if they can get through surgery and chemotherapy, exercise will be easy
Patient does not want to return to cancer center	Offer to conduct exercise and counseling sessions at another location
Patient starts exercise when trial mentioned during chemotherapy	Mention that the trial is only for patients who are not already exercising. Mention that exercising after chemotherapy will be easier
Patient fails to complete 2 stages of the baseline fitness test	Allow the patient to complete the test a 2nd time if the patient is anxious/tired/weak. Allow the patient to practice if the patient is inexperienced/awkward on the treadmill

Canada, Australia, and elsewhere. In the 2014, the CHALLENGE trial will open in centers in Israel and the USA. We anticipate a further increase in accrual as these new centers become activated. There are also ongoing discussions with partners in other countries that may join the CHALLENGE trial.

Baseline Characteristics of Randomized Patients in the CHALLENGE Trial

Table 2 provides a summary of some of the clinical characteristics of the 250 patients randomized as of December 31, 2013. In terms of the medical profile, 89 % of participants have stage III colon cancer, 56 % were treated with leucovorin/5-fluorouracil/oxaliplatin-based chemotherapy, 74 % have an ECOG performance status of 0, and 58 % have a body mass index of at least 27.5 kg/m^2 (half way between

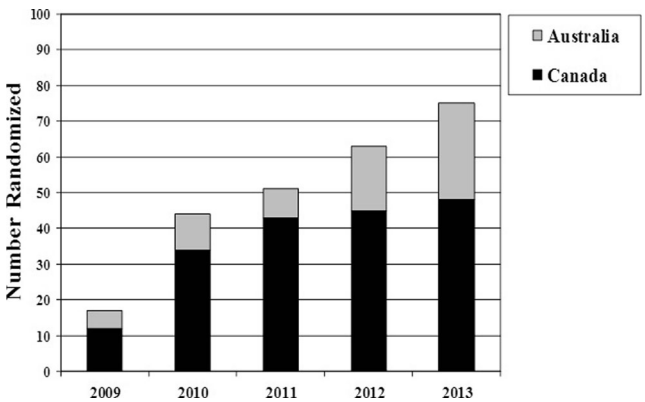

Fig. 1 Accrual to the Colon Health and Life-Long Exercise Change trial by year and country

Table 2 Baseline characteristics of randomized patients (N=250) in the CHALLENGE trial as of December 31, 2013

Variable	No.
Age[a] (years)	
<50	41 (16 %)
50–59	80 (32 %)
60–69	98 (39 %)
≥70	31 (12 %)
Sex	
Male	118 (47 %)
Female	132 (53 %)
Body mass index (kg/m^2)	
≤27.5	104 (42 %)
>27.5	146 (58 %)
Performance status (ECOG)	
0	184 (74 %)
1	66 (26 %)
Disease stage	
II	28 (11 %)
III	222 (89 %)
Number of positive lymph nodes	
0	32 (13 %)
1+	218 (87 %)
Type of chemotherapy	
FOLFOX only	91 (36 %)
FOLFOX (with or without experimental agent)	49 (20 %)
Capecitabine	42 (17 %)
5-Fluorouracil	22 (9 %)
Other	46 (18 %)
R-PARQ results	
Answered no to all questions	128 (51 %)
Answered yes to at least one question	122 (49 %)

ECOG Eastern Cooperative Oncology Group, *FOLFOX* leucovorin, 5-fluorouracil, and oxaliplatin, *R-PARQ* revised Physical Activity Readiness Questionnaire

[a] Median age 60 years

Table 3 Adherence to completion of the questionnaires and physical fitness testing in the CHALLENGE trial as of December 31, 2013

Variable	Baseline	6 months	1 year	2 years	3 years
Questionnaires					
Quality of life					
FACIT-F	230/250 (92.0 %)	189/198 (95.5 %)	141/149 (94.6 %)	76/82 (92.7 %)	40/43 (93.0 %)
SF-36	232/250 (92.8 %)	192/206 (93.2 %)	153/167 (91.6 %)	89/101 (88.1 %)	44/50 (88.0 %)
HADS	231/250 (92.4 %)	188/198 (94.9 %)	140/149 (94.0 %)	76/82 (92.7 %)	40/43 (93.0 %)
PSQI	229/250 (91.6 %)	185/198 (93.4 %)	141/149 (94.6 %)	74/82 (90.2 %)	40/43 (93.0 %)
Physical activity					
SCDE	231/250 (92.4 %)	187/198 (94.4 %)	138/149 (92.6 %)	76/82 (92.7 %)	37/43 (86.0 %)
TPAQ	230/250 (92.0 %)	183/198 (92.4 %)	141/149 (94.6 %)	75/82 (91.5 %)	38/43 (88.4 %)
Health economics					
WPAI	232/256 (90.6 %)	182/206 (88.3 %)	151/167 (90.4 %)	88/101 (87.1 %)	43/50 (86.0 %)
30-day resource use diary	–	175/203 (86.2 %)	135/163 (82.8 %)	87/100 (87.0 %)	40/49 (81.6 %)
Fitness testing					
Submaximal treadmill test	248/250 (99.2 %)	181/195 (92.8 %)	132/148 (89.2 %)	72/80 (90.0 %)	38/42 (90.5 %)
Senior's fitness test	248/250 (99.2 %)	181/195 (92.8 %)	132/148 (89.2 %)	72/80 (90.0 %)	38/42 (90.5 %)

FACIT-F Functional Assessment of Chronic Illness Therapy-Fatigue, *HADS* Hospital Anxiety and Depression Scale, *PSQI* Pittsburgh Sleep Quality Index, *SCDE* Social Cognitive Determinants of Exercise, *SF-36* Short-Form Health Survey, *TPAQ* Total Physical Activity Questionnaire, *WPAI* Work Productivity and Activity Impairment

overweight and obese). In terms of demographics, 53 % of the sample are women, and the median age is 60 years, with 84 % older than 50 years. Just over half indicated at least one health issue on the revised Physical Activity Readiness Questionnaire [26] that required physician approval for them to participate in the study. These data indicate a sample of colon cancer survivors who have modest health and functioning and a high risk of recurrence. Nevertheless, the representativeness and generalizability of our sample with regard to the broader colon cancer population is unclear.

Adherence to Follow-up Testing and the Intervention Program

Table 3 provides a summary of the follow-up completion rate for the physical fitness testing and patient-reported questionnaires as of December 31, 2013. We have achieved completion rates of over 90 % for most of the patient-reported questionnaires and the physical fitness tests at most of the assessment time points. These data suggest that patients are willing and able to complete the physical fitness testing and patient-reported questionnaires in both arms of the trial, resulting in limited missing data for these important secondary outcomes.

Although quantitative data are not yet available, qualitative feedback from the PACs suggests good adherence to the intervention protocol by most patients. Patients have demonstrated high adherence to the face-to-face behavioral support/supervised exercise sessions during the first 6 months. Moreover, many patients are choosing to continue with the face-to-face sessions after the first 6 months rather than opting for telephone counseling. Finally, the PACs are reporting that most patients are achieving the physical activity behavior change goal of ten MET hours or more per week as well as improving their physical fitness on follow-up testing. These data suggest that the behavioral support program is achieving its goal of increasing and maintaining exercise behavior. Exercise adherence will be formally evaluated in a preplanned interim analysis after the first 250 patients have completed 1 year of study intervention.

Conclusions

To our knowledge, the CHALLENGE trial remains the only randomized controlled trial of an exercise program in colon cancer survivors with DFS as the primary end point. To date, the CHALLENGE trial has demonstrated that cancer centers can partner with exercise specialists to accrue to a multinational phase III exercise trial. The trial has also demonstrated that colon cancer survivors are able and willing to complete regular physical fitness testing and to adhere to a practical program of behavior change that is likely to increase their physical activity and fitness. With 250 patients randomized as of December 31, 2013, the CHALLENGE trial is already one of the largest exercise trials in any cancer survivor group and the largest in colon cancer. The trial is already adequately

powered to examine many of the important secondary 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 in improving cancer outcomes remains a compelling issue for cancer patients and cancer care professionals [27]. Ultimately, the CHALLENGE trial will provide important data to inform clinical practice and public policy recommendations concerning exercise for colon cancer survivors.

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Compliance with Ethics Guidelines

Conflict of Interest Kerry S. Courneya, Janette Vardy, Sharlene Gill, Derek Jonker, Patti O'Brien, Christine M. Friedenreich, Haryana Dhillon, Rebecca K.S. Wong, Ralph M. Meyer, Jennifer J. Crawford, Kristin L. Campbell, Harry Prapavessis, Christopher O'Callaghan, Jane Turner, Lissa M. Spencer, Hidde P. van der Ploeg, Dongsheng Tu, and Christopher M. Booth declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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