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A randomized dose-response trial of aerobic exercise and health-related quality of life in colon cancer survivors

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Abstract

Objective: To examine the dose-response effects of aerobic exercise on health-related quality of life (HRQoL) among colon cancer survivors.

Methods: Thirty-nine stage I to III colon cancer survivors were randomized to 1 of 3 groups: usual-care control, 150 min·wk^{-1} of aerobic exercise (low-dose) and 300 min·wk^{-1} of aerobic exercise (high-dose) for 6 months. HRQoL outcomes included the Short Form (SF)-36 physical and mental component summary, Functional Assessment of Cancer Therapy-Colorectal, Pittsburgh Sleep Quality Index, Fear of Cancer Recurrence Inventory, Fatigue Symptom Inventory, and North Central Cancer Treatment Group bowel function questionnaire, assessed at baseline and post intervention. The primary hypothesis was that exercise would improve HRQoL outcomes in a dose-response fashion, such that high-dose aerobic exercise would yield the largest improvements in HRQoL outcomes.

Results: Over 6 months, the low-dose group completed 141 ± 10 min·wk^{-1} of aerobic exercise, and the high-dose group completed 247 ± 11 min·wk^{-1} of aerobic exercise. Over 6 months, exercise improved the physical component summary score of the SF-36 (P_{trend} = 0.002), the Functional Assessment of Cancer Therapy-Colorectal (P_{trend} = 0.025), the Pittsburgh Sleep Quality Index (P_{trend} = 0.049), and the Fatigue Symptom Inventory (P_{trend} = 0.045) in a dose-response fashion. Between-group standardized mean difference effects sizes for the above-described findings were small to moderate in magnitude (0.35–0.75). No dose-response effects were observed for the mental component summary score of the SF-36, the Fear of Cancer Recurrence Inventory, or bowel function.

Conclusion: Higher doses of aerobic exercise, up to 300 min·wk^{-1}, improve multiple HRQoL outcomes among stage I to III colon cancer survivors. These findings provide evidence that aerobic exercise may provide multiple health benefits for colon cancer survivors.

KEYWORDS

cancer, oncology, patient-reported outcome, physical activity, physical function, survivorship, wellness

1 | BACKGROUND

Approximately 1 million people are diagnosed with colon cancer each year worldwide.[1] As a result of earlier detection and more efficacious therapies, mortality from colon cancer has decreased over the past 50 years.[2] The long-term survival rate of colon cancer survivors who remain in remission is similar to the general population.[3] Despite improvements in survival, colon cancer survivors often report impairments in multiple dimensions of health-related quality of life (HRQoL) when compared with the general population. These impairments include inferior physical and mental wellness, higher rates of insomnia, persistent cancer-related fatigue, and impairments specific to colon cancer, such as anxiety about disease recurrence and bowel dysfunction.[4-9]

Among colon cancer survivors, physical activity volume declines during cancer therapy and often does not return to pre-diagnosis volumes after completing therapy.[10,11] This may explain, in part, why up to 90% of colon cancer survivors do not engage in the recommended minimum volume of 150 min·wk^{-1} of physical activity.[12] Cross-sectional studies demonstrate that larger volumes of physical activity are correlated with higher physical and mental wellness, better sleep quality, lower fatigue, less worry about disease recurrence, and better bowel function.[13-17] Prospective cohort studies demonstrate that increases in physical activity volume are correlated with improvements in HRQoL.[18-21] However, randomized trials have failed to demonstrate that exercise improves HRQoL among colon cancer survivors.[22] For example, 102 colon cancer survivors randomized to a 16-week moderate-intensity aerobic exercise program did not significantly improve HRQoL compared with a usual-care control group.[23] In another study, 46 colon cancer survivors randomized to a 12-week home-based aerobic walking program with behavioral counseling did not improve HRQoL compared with a control group who received weekly telephone contact.[24] These randomized trials have prescribed volumes of exercise that range from 60 to 150 min·wk^{-1}.[22] Larger volumes of exercise, such as 300 min·wk^{-1}, are associated with a lower risk of disease recurrence and premature mortality in colon cancer survivors.[25] It is plausible that a larger volume of exercise, such as 300 min·wk^{-1}, may also be necessary to promote improvements in HRQoL among colon cancer survivors.[26]

The COURAGE trial was a randomized controlled trial with the primary aim to examine the safety, feasibility, and biological efficacy of 150 and 300 min·wk^{-1} of aerobic exercise versus usual-care control over 6 months among men and women with a history of stage I to III colon cancer.[27] The primary and secondary biologic outcomes of the COURAGE trial have been published.[28-30] Patient-reported HRQoL outcomes were pre-specified as secondary study outcomes. Our hypothesis was that exercise would improve HRQoL outcomes in a dose-response fashion, such that high-dose aerobic exercise would yield the largest improvements in HRQoL outcomes.

2 | METHODS

2.1 | Study design and participants

The COURAGE trial was a single-center, phase II, randomized, 3-arm dose-response exercise trial.[27] Inclusion and exclusion criteria are presented in Table 1. Potentially eligible study participants were recruited through the Pennsylvania Cancer Registry. To minimize anticipated concerns regarding travel burden into the city of Philadelphia from surrounding suburbs, potentially eligible participants were recruited from Philadelphia County and 4 surrounding counties (Bucks, Montgomery, Chester, and Delaware). Using an envelope with the University of Pennsylvania School of Medicine logo, potentially eligible participants were sent 1 letter via postal mail that included an invitation to participate signed by the principal investigator, a 1-page flyer describing the study, the name, and contact information (email, telephone) of the study coordinator, and a brochure describing the Pennsylvania Cancer Registry. All participants provided written informed consent. This study was approved by the University of Pennsylvania Institutional Review Board (protocol #820449) and registered on clinicaltrials.gov as NCT02250053.

2.2 | Randomization and masking

Using a computer-generated randomization algorithm (ralloc procedure in Stata), participants were randomly allocated to 1 of 3 groups:

TABLE 1 Patient inclusion and exclusion criteria for study participation

Inclusion:
1. Histologically proven stage I-III colon cancer
2. Completed cancer treatment(s) within 36 months of entering the study
3. Self-reported participation of ≤150 min·wk^{-1} of moderate or vigorous intensity physical activity using the Paffenbarger Physical Activity Questionnaire[31]
4. Age ≥ 18 years
5. Provided written physician approval
6. No additional surgery planned within the 6-month intervention period
7. The ability to walk unaided for 6 minutes
Exclusion:
1. History of another primary cancer (other than non-melanoma skin cancer)
2. Evidence of distant metastatic disease
3. Pregnant or breast feeding
4. Unable to provide a baseline blood sample
5. Myocardial infarction or coronary revascularization procedure within the past 3 months
6. Uncontrolled hypertension (systolic blood pressure ≥ 180 mm Hg or diastolic blood pressure ≥ 100 mm Hg)
7. High-risk or uncontrolled cardiac arrhythmias
8. Clinically significant heart valve disease
9. Decompensated heart failure
10. A known aortic aneurysm
11. Any other condition which, in the opinion of the investigator, may impede testing of study hypotheses or make it unsafe to engage in the exercise program

usual-care control, low-dose aerobic exercise (150 min·wk^{-1}), or high-dose aerobic exercise (300 min·wk^{-1}). Randomization was stratified on cancer stage (American Joint Committee on Cancer 7th Edition: I vs II vs III). Participants and exercise intervention staff were not masked to treatment assignment.

2.3 | Exercise treatment plan

Aerobic exercise was performed over 6 months using study-provided in-home treadmills (LifeSpan Fitness, TR1200i, Salt Lake City, UT).[27] Participants were provided with a heart rate monitor to objectively record heart rate during each exercise session. Using a combination of in-person, telephone, and email communication, the exercise physiologist provided ongoing behavioral and clinical support and monitored exercise adherence to the study protocol throughout the duration of the study. Behavioral support was individualized to each participant to include the benefits of exercise for colon cancer survivors, strategies to integrate exercise into day-to-day activities, how to identify and overcome barriers to exercise, recruiting friends and family members to provide support in reaching their exercise goals, and how to set simple, measurable, attainable, realistic, and timely goals to promote exercise self-efficacy and compliance.[27] Exercise intensity was prescribed at 50% to 70% of the age-predicted maximum heart rate (equivalent to 3-6 METs[32]) using heart rate monitors. The low-dose and high-dose groups progressed towards of the goal of 150 or 300 min·wk^{-1} of exercise, respectively. Exercise adherence was calculated using the completed number of minutes divided by the prescribed number of minutes, with a maximum value of 100%.[28]

Participants randomized into the usual-care control group were asked to maintain their pre-study levels of physical activity and/or follow the recommendations provided by their physician. After completing 6-month measures, control group participants were provided with an in-home treadmill and individualized exercise program, like that of the 2 exercise groups. Upon study completion, all participants could keep their study-provided treadmills.

2.4 | Measurements

Demographic characteristics including age, sex, race, education, occupation, and marital status were self-reported. Smoking status and alcohol consumption were obtained from standardized questionnaires developed by the National Center for Health Statistics.[33] Clinical information including cancer stage and treatment with chemotherapy were obtained from cancer registry, pathology reports, or physician records.

2.5 | Study outcomes

HRQoL outcomes were assessed at baseline and 6 months. Physical and mental wellness was quantified using the Medical Outcomes Survey Short Form (SF-36[34]). The SF-36 includes 8 subscales (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health), which can be aggregated into the physical and mental component summary scores, where higher scores represent better physical and mental functioning. Colon cancer specific HRQoL was quantified using the Functional Assessment of Cancer Therapy-Colorectal (FACT-C[35]). The FACT-C includes 5 subscales (physical, social and family, emotional, functional, and colorectal cancer-specific well-being), which can be aggregated into a composite score, where a higher score represents better quality of life. Sleep quality was quantified using the Pittsburgh Sleep Quality Index (PSQI[36]). The PSQI includes 7 subscales (quality, latency, duration, efficiency, disturbance, medications, and dysfunction), which can be aggregated into a global sleep quality score, where a higher score represents poorer sleep quality. Fear of cancer recurrence was quantified using the Fear of Cancer Recurrence Inventory (FCRI[37,38]). The FCRI includes 8 subscales (triggers, severity, psychological distress, functioning impairments, insight, reassurance, and coping strategies) which can be aggregated into a composite score, where a higher score represents greater fears of cancer recurrence. Cancer-related fatigue was quantified using the Fatigue Symptom Inventory (FSI[39]). The FSI total disruption index was calculated by aggregating the questions relating to severity, frequency, daily patterns, and perceived fatigue interference, where a higher score represents greater burden of cancer-related fatigue. Bowel function was quantified using the North Central Cancer Treatment Group questionnaire.[40] The number of bowel movements per day and a bowel function score was calculated by aggregating the questions relating to symptoms of frequency, nocturnal bowel movements, cramping, incontinence, urgency, and clustering, such that a higher score represents poorer bowel function. The key outcomes of interest in this analysis were the composite or aggregated scores derived from each of the HRQoL questionnaires. However, each of the questionnaire subscales was explored in post hoc supplementary analysis for hypothesis generating purposes to guide the design of future studies.

2.6 | Statistical analysis

Descriptive statistics presented for baseline variables include counts and proportions for categorical variables and means ± standard deviations for continuous variables. Categorical baseline characteristics were compared between the 3 groups using Fisher's exact test, and continuous baseline characteristics were compared between the 3 study groups using the Kruskal-Wallis test. This study was powered to detect changes in the co-primary biologic study outcomes: soluble intercellular adhesion molecule-1 and soluble vascular cell adhesion molecule-1.[28] However, the sample size provided adequate statistical power to identify effect sizes ≥0.30 for HRQoL outcomes. All inferential analyses were conducted on an intention-to-treat basis. Change in HRQoL outcomes was evaluated from baseline to 6 months between the 3 groups using repeated-measures mixed-effects regression models. This statistical approach includes all available data and accounts for the correlation between repeated measures. The baseline value of the dependent variable and cancer stage (because it was a randomization stratification factor) were included as covariates in the regression models. Group-by-time interaction terms were estimated as fixed-effects in the regression model. Results from the repeated-measures mixed-effects regression models are presented as least-square means ± standard error. Model fit was assessed using graphical techniques. Standardized mean difference effect sizes (*d*) were calculated to quantify the magnitude of treatment effect. Values of *d* at 0.2, 0.5, and 0.8 represent small, medium, and large treatment effects, respectively.[41] To evaluate the presence of a dose-response

relationship across randomized groups, a test of trend was conducted by examining linear contrasts. We did not adjust our type I error rate, and the results should be interpreted accordingly.

3 | RESULTS

Between January 2015 and August 2015, 39 colon cancer survivors were recruited and randomized with endpoint data collection ending in February 2016. Baseline characteristics of study participants are presented in Table 2. Over 6 months, adherence to the prescribed volumes of exercise in the low-dose and high-dose groups were 93 ± 2% and 89 ± 3%, respectively. Average exercise volume of the low-dose and high-dose groups were 141 ± 10 min·wk^{-1} and 247 ± 11 min·wk^{-1}, respectively (Δ between groups: 106 ± 15; $P < 0.001$).

HRQoL outcomes are presented in Table 3. At baseline, no statistically significant differences in HRQoL outcomes were observed among the 3 groups. Compared with the control group, over 6 months, the SF-36 physical health component summary score increased by 1.2 ± 6.3 ($d = 0.08$) in the low-dose group and 13.1 ± 6.5 ($d = 0.58$) in the high-dose group ($P_{trend} = 0.002$). No change was observed in the SF-36 mental health component summary score. SF-36 subscales that demonstrated significant improvements included physical functioning ($P_{trend} < 0.001$), role-physical ($P_{trend} = 0.035$), general health ($P_{trend} = 0.011$), and vitality ($P_{trend} = 0.025$; Supplementary Table 1). Compared with the control group, over 6 months, the FACT-C score increased by 7.6 ± 3.8 ($d = 0.49$) in the low-dose group and 6.8 ± 4.0 ($d = 0.58$) in the high-dose group ($P_{trend} = 0.025$). FACT-C subscales that demonstrated significant improvements included physical well-being ($P_{trend} = 0.037$), emotional well-being ($P_{trend} = 0.016$), and functional well-being ($P_{trend} = 0.015$; Supplementary Table 2). Compared with the control group, over 6 months, the PSQI decreased by 0.3 ± 1.0 ($d = -0.11$) in the low-dose group and 1.1 ± 1.1 ($d = -0.30$) in the high-dose group ($P_{trend} = 0.049$). PSQI subscales that demonstrated significant improvements included sleep quality ($P_{trend} = 0.043$) and sleep latency ($P_{trend} = 0.042$; Supplementary Table 3). No significant dose-response effects were observed for the FCRI composite score or subscales (Supplementary Table 4). Compared with the

TABLE 2 Baseline characteristics of the participants[a]

Characteristic	Total ($n = 39$)	Control ($n = 13$)	Low-Dose ($n = 14$)	High-Dose ($n = 12$)
Age, %				
<60 y	25 (64%)	9 (69%)	8 (57%)	8 (67%)
≥60 y	14 (36%)	4 (31%)	6 (43%)	4 (33%)
Sex, %				
Male	15 (38%)	4 (31%)	7 (50%)	4 (33%)
Female	24 (62%)	9 (69%)	7 (50%)	8 (67%)
Race, %				
White	31 (80%)	8 (62%)	12 (86%)	11 (92%)
Black	6 (15%)	3 (23%)	2 (14%)	1 (8%)
Other	2 (5%)	2 (15%)	0 (0%)	0 (0%)
Education, %				
High school or less	7 (18%)	1 (8%)	4 (29%)	2 (17%)
Some college	8 (20%)	3 (23%)	2 (14%)	3 (25%)
College degree or more	24 (62%)	9 (69%)	8 (57%)	7 (58%)
Retired, %	11 (28%)	3 (23%)	5 (36%)	3 (25%)
Marital status, %				
Married or living with partner	27 (69%)	9 (69%)	5 (64%)	9 (75%)
Divorced, widowed, never married	12 (31%)	4 (31%)	5 (36%)	3 (25%)
Smoking history, %				
Never	23 (59%)	10 (77%)	6 (43%)	7 (58%)
Former	14 (36%)	3 (23%)	7 (50%)	4 (33%)
Current	2 (5%)	0 (0%)	1 (7%)	1 (8%)
Consume ≥1 alcoholic drink/week, %	23 (59%)	7 (54%)	9 (64%)	7 (58%)
Stage, %				
I	5 (13%)	1 (8%)	2 (14%)	2 (17%)
II	14 (36%)	5 (38%)	5 (36%)	4 (33%)
III	20 (51%)	7 (54%)	7 (50%)	6 (50%)
Chemotherapy, %	28 (72%)	10 (77%)	10 (71%)	8 (67%)
Time since treatment, %				
≤12 months	25 (64%)	8 (62%)	10 (71%)	7 (58%)
>12 months	14 (36%)	5 (38%)	4 (26%)	5 (42%)

[a]Data are counts and percentages (%).

TABLE 3 Health-related quality of life outcomes at baseline and change during 6 months

Outcome	Baseline (Mean ± SD)	Δ Baseline to Month 6 (LS Mean ± SE)	*P* Time Effect	Δ from Control (LS Mean ± SE)	*P* Group Effect
Short-form 36					
Physical health component score					
Control	73.9 ± 25.0	−7.4 ± 4.6	0.108	—	—
Low-dose	80.0 ± 18.3	−6.2 ± 4.3	0.147	1.2 ± 6.3	0.506
High-dose	79.2 ± 16.1	5.7 ± 4.6	0.221	13.1 ± 6.5	0.002
Test for trend		*P* = 0.002			
Mental health component score					
Control	73.5 ± 18.8	2.7 ± 3.0	0.359	—	—
Low-dose	80.7 ± 15.5	−0.7 ± 2.8	0.812	−3.4 ± 4.1	0.405
High-dose	73.5 ± 17.6	4.1 ± 3.0	0.175	1.4 ± 4.2	0.749
Test for trend		*P* = 0.566			
Functional assessment of cancer therapy—Colorectal					
Control	115.2 ± 18.9	−4.8 ± 2.8	0.089	—	—
Low-dose	113.1 ± 13.7	2.8 ± 2.6	0.282	7.6 ± 3.8	0.048
High-dose	109.6 ± 14.0	2.0 ± 2.8	0.487	6.8 ± 4.0	0.090
Test for trend		*P* = 0.025			
Pittsburgh sleep quality index					
Control	6.75 ± 4.4	0.4 ± 0.7	0.617	—	—
Low-dose	4.46 ± 3.0	0.1 ± 0.7	0.910	−0.3 ± 1.0	0.799
High-dose	4.91 ± 2.9	−0.7 ± 0.8	0.376	−1.1 ± 1.0	0.336
Test for trend		*P* = 0.049			
Fear of cancer recurrence inventory					
Control	52.2 ± 26.0	−6.3 ± 7.7	0.416	—	—
Low-dose	57.1 ± 23.3	−5.5 ± 7.3	0.450	0.8 ± 10.6	0.942
High-dose	68.7 ± 29.7	−20.9 ± 7.9	0.008	−14.6 ± 11.0	0.184
Test for trend		*P* = 0.265			
Fatigue symptom inventory					
Control	6.9 ± 11.9	0.1 ± 2.5	0.982	—	—
Low-dose	3.8 ± 7.2	0.9 ± 2.4	0.718	0.8 ± 3.5	0.817
High-dose	12.7 ± 17.2	−5.9 ± 2.6	0.021	−6.0 ± 3.6	0.096
Test for trend		*P* = 0.045			
Bowel function					
Control	2.5 ± 2.3	−1.1 ± 0.4	0.012	—	—
Low-dose	1.4 ± 1.7	0.2 ± 0.4	0.600	1.3 ± 0.6	0.028
High-dose	2.2 ± 2.3	−0.7 ± 0.4	0.131	0.4 ± 0.6	0.490
Test for trend		*P* = 0.369			

Abbreviations: LS Mean, least-squares mean; SD, standard deviation; SE, standard error.

Changes in outcomes are estimated using a linear mixed-effects regression model that adjusted for the baseline value of the dependent variable and cancer stage (randomization stratification factor).

control group, over 6 months, FSI increased 0.8 ± 3.5 (d = 0.08) in the low-dose group and decreased 6.0 ± 3.6 (d = −0.75) in the high-dose group (P_{trend} = 0.045). No significant dose-response effects were observed for bowel function. A dose-response effect was observed for the number of bowel movements, such that exercise reduced daily bowel movement frequency (P_{trend} = 0.001; Supplementary Table 5).

4 | CONCLUSIONS

A 6-month moderate-intensity aerobic exercise program among stage I to III colon cancer survivors improved several patient-reported HRQoL outcomes including physical function, cancer-specific quality of life, sleep quality, and fatigue in a dose-response fashion, such that 300 min·wk^{-1} was associated with the largest improvements these outcomes. The findings from this randomized controlled trial support the hypothesis that larger volumes of aerobic exercise may be necessary to improve HRQoL outcomes among colon cancer survivors.

4.1 | Clinical implications

An improvement of approximately one-half of a standard deviation (d = 0.5) is considered a minimally clinically important difference for patient-reported HRQoL measures.[42] Therefore, the magnitude of

improvement for several outcomes in this study, including the SF-36 physical subscale, FACT-C, and FSI, are consistent with a clinically meaningful benefit. The findings from this trial contrast with prior randomized trials that have been unable to demonstrate significant improvements in HRQoL among colon cancer survivors. The reasons our findings differ from prior trials are not entirely clear but may relate to several factors. First, our study demonstrated that exercise affects HRQoL outcomes in a dose-response manner. Prior trials have examined volumes of exercise that ranged from 60 to 150 min·wk^{-1}, which may have been an insufficient volume to promote improvements in HRQoL. Second, prior studies have been unable to significantly improve self-reported physical activity compared with usual care[24] or have reported control group crossover (eg, control group participants engaging in exercise) due to the inability to blind participants to their assigned intervention,[23] resulting in an attenuation of the exercise-induced HRQoL effects. In our study, mean objectively measured exercise adherence was below prescribed levels in both arms of the trial (93 ± 2% in low-dose and 89 ± 3% in high-dose), but the completed exercise volumes were likely higher than prior trials. Third, it has been noted that younger colon cancer survivors (<60 years) may be particularly prone to impairments in HRQoL and are often motivated to engage in healthy risk-reducing behaviors.[4,7,43] Our study sample was significantly younger than the population-based registry from which they were recruited,[27] and 64% of our sample was <60 years. Our study sample was younger than some,[23,44] but not all prior studies.[24] Fourth, over 6 months, the control group in our trial reported deteriorations in several HRQoL outcomes including the SF-36 physical health component summary score and the FACT-C. Such deteriorations have not been observed in prior studies of colon cancer survivors.[23,24,44] The reasons for the observed deteriorations among participants in the control group are not clear. In this situation, exercise may help to prevent the deterioration of HRQoL.[45] The ability to rapidly implement these findings into clinical practice may be challenging. The majority of colon cancer survivors do not engage in adequate physical activity.[12] Our study population was motivated to enroll into a clinical trial, was provided with an in-home treadmill, and received individualized behavioral support to promote adherence to the study protocol. Given the benefits of exercise and lifestyle modification, further research is necessary to understand how to disseminate efficacious behavioral interventions into the oncology clinic.

Contrary to our hypothesis, we did not observe significant dose-response reductions in the FCRI. Colon cancer survivors rank fear of disease recurrence as their primary health concern.[46] Low-level risk perceptions, worry, and anxiety about disease recurrence are common in this population.[7] In a cross-sectional study of 10 969 colorectal cancer survivors, higher volumes of physical activity were associated with a significantly lower fear of disease recurrence in a linear dose-response fashion.[13] Although we did not observe a statistically significant dose-response effect on the FCRI summary score, the high-dose group reported significant improvements on the FCRI subscales including psychological distress ($P = 0.009$), functional impairment ($P = 0.005$), insight ($P = 0.006$), reassurance ($P < 0.001$), and coping ($P = 0.047$), whereas no significant changes were observed in the control or low-dose groups. These findings provide preliminary data to justify additional research to examine the potential role of exercise to manage or mitigate concerns regarding disease recurrence in this population.

There are several strengths to this study. The randomized design that included the use of 2 distinct exercise doses allowed us to understand how HRQoL outcomes change along the exercise dose curve. Both exercise groups had excellent adherence (~90%). Follow-up was robust, with only 1 participant being lost to follow-up (97% completion rate). Despite the small sample size, 21% of study participants reported being non-white race. Our HRQoL outcomes included a variety of validated, well-characterized HRQoL questionnaires.

4.2 | Study limitations

There are several limitations to this study. The small sample size likely limited our statistical power to detect significant changes in the mental health component score of the SF-36 and bowel function questionnaires. The small sample size allowed for numeric, but non-statistically significant, differences in baseline HRQoL values. We expected this may occur, and our analysis plan pre-specified that the baseline value of the dependent variable would be included in the model to account for baseline differences; however, we cannot rule out the possibility that the observed differences may be partly due to regression to the mean. The small sample size also reduces the generalizability of our findings and precluded our ability to conduct subgroup analysis to identify factors that may moderate the relationship between exercise dose and HRQoL outcomes (such as age). We did not recruit study participants based on having poor HRQoL at baseline. Although we identified statistically significant dose-response patterns across randomized group for several HRQoL outcomes, the benefit was often small or modest in effect size. It is unknown if exercise would yield the same magnitude of benefit among individuals with poor HRQoL at baseline. It is plausible that such participants may derive larger benefits from exercise. However, the converse is also possible, such that high volumes of exercise may not be feasible for participants with poor HRQoL, such as poor physical functioning or severe cancer-related fatigue. Study participants were not blinded to treatment group assignment. Therefore, social desirability bias cannot be excluded, which may overestimate the efficacy of exercise on these outcomes. We did not adjust our type I error rate; thus, the possibility of false-positive findings cannot be ruled out.

5 | CONCLUSION

In conclusion, the findings from this randomized trial demonstrate the dose-response effects of moderate-intensity aerobic exercise to improve multiple HRQoL outcomes and suggest that a high-dose of aerobic exercise (300 min·wk^{-1}) may be needed to improve physical function, cancer-specific quality of life, sleep quality, and fatigue among early-stage colon cancer survivors. These findings suggest that higher volumes of aerobic exercise are necessary to improve HRQoL outcomes in colon cancer survivors.

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CONFLICTS OF INTEREST STATEMENT

The authors declare no conflicts of interest. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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