Dose–response effects of aerobic exercise on body composition among colon cancer survivors: a randomised controlled trial

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Background: Physical activity is associated with a lower risk of disease recurrence among colon cancer survivors. Excess visceral adipose tissue is associated with a higher risk of disease recurrence among colon cancer survivors. The pathways through which physical activity may alter disease outcomes are unknown, but may be mediated by changes in visceral adipose tissue.

Methods: Thirty-nine stage I–III colon cancer survivors were randomised to one of three 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. The prespecified key body composition outcome was visceral adipose tissue quantified using dual energy X-ray absorptiometry.

Results: Exercise reduced visceral adipose tissue in dose–response fashion (P trend = 0.008). Compared with the control group, the low- and high-dose exercise groups lost 9.5 cm² (95% CI: –22.4, 3.5) and 13.6 cm² (95% CI: –27.0, –0.1) in visceral adipose tissue, respectively. Each 60 min wk−1 increase in exercise predicted a 2.7 cm² (95% CI: –5.4, –0.1) reduction in visceral adipose tissue.

Conclusions: Aerobic exercise reduces visceral adipose tissue in dose–response fashion among patients with stage I–III colon cancer. Visceral adipose tissue may be a mechanism through which exercise reduces the risk of disease recurrence among colon cancer survivors.

Each year 83,000 people are diagnosed with stage I–III colon cancer in the United States (Siegel et al., 2014). Despite efficacious surgical and chemotherapeutic interventions, 25–40% of patients will experience recurrent and metastatic disease within 3 years of diagnosis (André et al., 2004), and 91% of those who recur within 3 years, die by 5 years (Sargent et al., 2005). Therefore, it is critical to identify additional therapies that may reduce the risk of recurrent disease and promote long-term survival in this population. Participation in physical activity after diagnosis of colon cancer is associated with a lower risk of recurrence and mortality (Meyerhardt et al., 2006). This observation is independent of various demographic, clinico-pathologic and treatment-related

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PATIENTS AND METHODS

Participants. Detailed study methods of the COURAGE trial are published (Brown et al, 2016). Potentially eligible participants were recruited throughout the metropolitan Philadelphia region. Participants were eligible if they were diagnosed with histologically proven stage I–III colon cancer; completed surgical resection and adjuvant chemotherapy within 36 months of entering the study; provided written informed consent and were self-reported. Daily caloric intake was quantified using 3-day food records that were analysed by a registered dietitian using the Nutrition Data System for Research software (v.2014). Clinical information including cancer stage and treatment were obtained from the state cancer registry, pathology reports or physician records.

Body composition outcomes. The prespecified key body composition outcome was visceral adipose tissue quantified using DXA. All other body composition outcomes were considered exploratory. Participants underwent whole-body DXA (Hologic Horizon, Bedford, MA, USA). Dual-energy X-ray absorptiometry scans were reviewed for quality assurance by a certified DXA technician who was blinded to the study group (Powers et al, 2014). The DXA scanner was calibrated daily using an anthropomorphic spine

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phantom and thrice weekly using a whole-body phantom. Dual-energy X-ray absorptiometry was used to quantify visceral adipose tissue (cm²), subcutaneous adipose tissue (cm²), fat mass (kg), lean mass (kg) and bone mineral density (g m⁻²) using Hologic APEX v.13.5 software (Bedford, MA, USA). Dual-energy X-ray absorptiometry-derived visceral adipose tissue has been validated against computed tomography-derived visceral adipose tissue ($r=0.93$; $P<0.001$; Micklefield et al, 2012), and has been used across a large body mass spectrum (Bredella et al, 2013). Other anthropometric outcomes that were measured in duplicate included height (m), body mass (kg), waist and hip circumferences (cm) and sagittal abdominal diameter (cm). Height and body mass were used to calculate body mass index (kg m⁻²).

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 among the three groups using Fisher’s exact test, and continuous baseline characteristics were compared among the three study groups using the Kruskal–Wallis test. This study was powered to detect changes in the co-primary study outcomes: soluble intercellular adhesion molecule-1 and soluble vascular cell adhesion molecule-1 (Brown et al, 2009), over 6 months we hypothesised a change in visceral adipose tissue of +14 cm² in the control group, +2.9 cm² in the low-dose group and –11.6 cm² in the high-dose group with a pooled standard deviation of ±11 cm². Against the hypothesis of a dose–response relationship, 39 participants provided ≥80% power with a type I error rate of 5%. All inferential analyses were conducted on an intention-to-treat basis. Normality of continuous variables was examined using graphical techniques. Results from the repeated-measures mixed-effects regression models are presented as least-estimated as fixed-effects in the regression model. Model fit was evaluated from baseline to 6 months in the three groups using the correlation between repeated measures. The baseline value of the dependent variable and cancer stage (randomisation stratification factor) were included as covariates in the regression models (Fitzmaurice et al, 2012). Group-by-time interaction terms were estimated as fixed-effects in the regression model. Model fit was examined using graphical techniques. Results from the repeated-measures mixed-effects regression models are presented as least-squares mean (LS Mean) ± standard error (s.e.). To evaluate the presence of a dose–response relationship across randomised groups, a test of trend was conducted by examining linear contrasts.

RESULTS

Between January 2015 and August 2015, 39 colon cancer survivors were recruited and randomised with data collection ending in February 2016. Baseline characteristics of study participants are presented in Table 1. One participant did not provide endpoint data (97% follow-up rate).

Exercise prescription program variables have been described in detail (Brown et al, 2017). Briefly, over 6 months, adherence to the prescribed volumes of exercise in the low- and high-dose groups were 92.8 ± 2.4% and 89.0 ± 2.6%, respectively ($P=0.287$). Average exercise volume in the low- and high-dose groups were 141.5 ± 9.9 and 247.2 ± 10.7 min wk⁻¹, respectively ($\Delta$ between groups: 105.7 ± 14.6; $P<0.001$). Exercise intensity was 70.7 ± 0.8% of the age-predicted maximal heart rate and the proportion of exercise sessions validated with objective heart rate data was 96.8 ± 0.6%, both of which did not differ between the two exercise groups. There were no significant changes in self-reported caloric consumption ($P=0.743$).

Body composition outcomes using DXA are presented in Table 2. Exercise reduced visceral adipose tissue, the prespecified key body composition outcome, in dose–response fashion ($P_{\text{trend}}=0.008$; Figure 1A). Compared with the control group, the low- and high-dose exercise groups lost 9.5 cm² (95% CI: –22.4, 3.5) and 13.6 cm² (95% CI: –27.0, –0.1) in visceral adipose tissue, respectively. Each 60 min wk⁻¹ increase in exercise predicted a 2.7 cm² (95% CI: –5.4, –0.1) reduction in visceral adipose tissue. Exercise improved bone mineral density in dose–response fashion ($P_{\text{trend}}=0.015$). Compared with the control group, the low- and high-dose exercise groups gained 0.015 g m⁻² (95% CI: 0.001,

| Table 1. Baseline characteristics of the participants |
|------------------------------------------------------|
| Characteristic                                      | Total (n = 39) | Control (n = 13) | Low dose (n = 14) | High dose (n = 12) | P       |
| Age, %                                               |               |                 |                  |                   |         |
| <60 years                                            | 25 (64%)      | 9 (69%)         | 8 (57%)          | 8 (67%)           | 0.840   |
| >60 years                                            | 14 (36%)      | 4 (31%)         | 6 (43%)          | 4 (33%)           |         |
| Sex, %                                               |               |                 |                  |                   |         |
| Male                                                 | 15 (38%)      | 4 (31%)         | 7 (50%)          | 4 (33%)           | 0.601   |
| Female                                               | 24 (62%)      | 9 (69%)         | 7 (50%)          | 8 (67%)           |         |
| Body mass index, %                                   |               |                 |                  |                   |         |
| <25.0 kg m⁻²                                         | 7 (18%)       | 3 (23%)         | 2 (14%)          | 2 (17%)           | 0.884   |
| 25.0–29.9 kg m⁻²                                     | 12 (31%)      | 5 (38%)         | 4 (29%)          | 3 (25%)           |         |
| >30.0 kg m⁻²                                         | 20 (51%)      | 5 (38%)         | 8 (57%)          | 7 (58%)           |         |
| Energy intake, kcal day⁻¹                            | 1735 (1270–1962) | 1800 (1233–2110) | 1776 (1483–2111) | 1632 (1196–1739) | 0.725   |
| Cancer stage, %                                      |               |                 |                  |                   |         |
| I                                                    | 5 (13%)       | 1 (8%)          | 2 (14%)          | 2 (17%)           | 0.999   |
| 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%)           | 0.906   |
| Time since treatment, %                              |               |                 |                  |                   |         |
| <12 months                                           | 25 (64%)      | 8 (62%)         | 10 (71%)         | 7 (58%)           | 0.770   |
| >12 months                                           | 14 (36%)      | 5 (38%)         | 4 (26%)          | 5 (42%)           |         |

P-values are from the overall test of group differences. Data are median (interquartile range), or counts with percentages.
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Table 2. Body composition outcomes using DXA at baseline and change during 6 months

| Outcome                                      | Baseline (mean ± s.d.) | Δ baseline to month 6 (LS mean ± s.e.) | Δ from control (LS mean ± s.e.) |
|----------------------------------------------|------------------------|----------------------------------------|---------------------------------|
| Visceral adipose tissue, cm²                 |                        |                                        |                                 |
| Control                                      | 112.6 ± 55.2           | 5.31 ± 4.80                            | —                               |
| Low dose                                     | 131.3 ± 45.6           | -4.13 ± 4.53                           | -9.45 ± 6.60                    |
| High dose                                    | 154.2 ± 60.5           | -8.27 ± 4.89                           | -13.58 ± 6.86b                 |
| Test for trend                               |                         | P = 0.008                              |                                 |
| Subcutaneous adipose tissue, cm²             |                        |                                        |                                 |
| Control                                      | 388.4 ± 142.6          | -3.87 ± 8.64                           | —                               |
| Low dose                                     | 381.1 ± 138.6          | 1.70 ± 8.15                            | 5.57 ± 11.88                    |
| High dose                                    | 461.9 ± 110.9          | -17.86 ± 8.81*                         | -14.00 ± 12.34                 |
| Test for trend                               |                         | P = 0.222                              |                                 |
| Fat mass, kg                                 |                        |                                        |                                 |
| Control                                      | 32.8 ± 10.0            | -0.01 ± 0.49                           | —                               |
| Low dose                                     | 32.6 ± 7.6             | -0.13 ± 0.47                           | -0.12 ± 0.68                    |
| High dose                                    | 38.1 ± 11.9            | -0.71 ± 0.50                           | -0.70 ± 0.71                    |
| Test for trend                               |                         | P = 0.238                              |                                 |
| Lean mass, kg                                |                        |                                        |                                 |
| Control                                      | 49.9 ± 13.1            | 0.30 ± 0.35                            | —                               |
| Low dose                                     | 52.6 ± 11.1            | -0.06 ± 0.33                           | -0.36 ± 0.48                    |
| High dose                                    | 53.4 ± 13.8            | 0.01 ± 0.36                            | -0.29 ± 0.50                    |
| Test for trend                               |                         | P = 0.450                              |                                 |
| Bone mineral density, g cm⁻²                 |                        |                                        |                                 |
| Control                                      | 1.08 ± 0.10            | 0.006 ± 0.005                          | —                               |
| Low dose                                     | 1.03 ± 0.12            | 0.021 ± 0.005*                         | 0.015 ± 0.007b                 |
| High dose                                    | 1.02 ± 0.09            | 0.020 ± 0.005*                         | 0.013 ± 0.007                  |
| Test for trend                               |                         | P = 0.015                              |                                 |

Abbreviations: DXA = dual-energy X-ray absorptiometry; LS mean = least-squares mean; s.d. = standard deviation; s.e., 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 (randomisation stratification factor).

*aSignificantly different from baseline (within-group), p<0.05.

*bSignificantly different from control, p<0.05.

0.029) and 0.013 g m⁻² (95% CI: -0.001, 0.028) in bone mineral density, respectively. Post hoc sex-stratified body composition outcomes using DXA are presented for hypothesis generating purposes (Supplementary Table S1).

Anthropometric outcomes are presented in Table 3. The finding that exercise reduced visceral adipose tissue was reinforced by the observation that exercise reduced waist circumference (an anthropometric proxy for visceral adipose tissue) in dose–response fashion (P_trend < 0.001; Figure 1B). Compared with the control group, the low- and high-dose exercise groups lost 1.5 cm (95% CI: –4.0, 1.1) and 4.5 cm (95% CI: –7.1, –1.9) in waist circumference, respectively. Each 60 min wk⁻¹ increase in exercise predicted a 0.9 cm (95% CI: –1.4, –0.4) reduction in waist circumference. Changes in visceral adipose tissue were correlated with changes in waist circumference (r = –0.42; P = 0.009). Improvements in the waist-to-hip ratio did not reach statistical significance (P_trend = 0.054). No significant change in body mass was observed (P_trend = 0.280). Post hoc sex-stratified anthropometric outcomes are presented for hypothesis generating purposes (Supplementary Table S2).

No serious (grade ≥3) adverse events occurred. Non-serious (grade 1–2) adverse events have been reported in detail (Brown et al, 2017).

DISCUSSION

A 6-month moderate-intensity aerobic exercise program among stage I–III colon cancer survivors resulted in significant linear dose–response reductions in visceral adipose tissue measured by DXA and waist circumference. The findings from this randomised trial provide mechanistic data to support observational evidence that suggests physical activity may lower the risk of recurrence and mortality among colon cancer survivors.

The linear dose–response reductions in visceral adipose tissue and waist circumference with increasing exercise volume are similar to prior dose–response exercise interventions in other populations (Kay and Fiatarone Singh, 2006). For example, among overweight and obese men and women with dyslipidaemia, increasing exercise volume produced larger reductions in visceral adipose tissue and waist circumference (Slentz et al, 2009). Excess visceral adipose tissue is associated with a higher risk of disease recurrence and mortality among colon cancer survivors (Xiao et al, 2016). Prior epidemiologic studies have often quantified visceral adipose tissue using quartiles or quintiles (Xiao et al, 2016), which challenges direct comparison of our results to these prior studies. In the general population, each 10 cm² increase in visceral adipose tissue is associated with an 8–10% increase in the risk of death (Kuk et al, 2006; Katzmarzyk et al, 2012). In our study, the low- and high-dose exercise groups lost 9.5 and 13.6 cm² in visceral adipose tissue, respectively, over 6 months compared with the control group. In a cohort of 536 colon cancer survivors, each 5 cm increase in waist circumference was associated with an 8–10% increase in the risk of colon cancer-specific and all-cause mortality (Haydon et al, 2006). In our study, the low- and high-dose exercise groups lost 1.5 and 4.5 cm in waist circumference, respectively, over 6 months compared with the control group. Collectively, these data suggest that the observed exercise-induced changes in body composition may hold clinical importance for colon cancer survivors.

In our study, we observed a modest, though not statistically significant, increase in visceral adipose tissue and waist circumference.
over 6 months among usual-care control group participants. This observation has been reported in the control groups of prior exercise trials (Slentz et al, 2009), and underscores the deleterious effect of continued sedentary behaviour. Excess energy intake is preferentially stored as visceral adipose tissue during extended periods of inactivity and continued sedentary behaviour. Excess energy intake is preferentially stored as visceral adipose tissue during extended periods of inactivity and continued sedentary behaviour. Excess energy intake is preferentially stored as visceral adipose tissue during extended periods of inactivity and continued sedentary behaviour.

Several polymorphisms within adiposity-related genes predict disease recurrence among colon cancer survivors (Sebio et al, 2014). Visceral adipose tissue is an active endocrine organ that secretes various bioactive compounds such as adipokines, cytokines, hormone-like factors and other metabolites (Ahima and Flier, 2000), that have been described (Brown et al, 2016), trial participants were younger than the population from which they were recruited. This has important implications for the generalisability of our findings to the broader population of colon cancer survivors. The duration of the exercise intervention was 6 months, and it is not known if the dose–response effects of exercise on visceral adipose tissue would be maximised or sustained over a longer time horizon. Trial participants were not recruited based on having excess visceral adipose tissue at baseline. It is not known if the exercise-induced reductions in visceral adipose tissue would be similar or larger in magnitude among a sample who all had excess visceral adipose tissue at baseline.

Information on the PI3K–Akt–mTOR pathway (McCurdy and Klemm, 2013). Activation of the PI3K–Akt–mTOR pathway is associated with the growth and progression of colon cancer metastases (Gulhati et al, 2011), and silencing of this pathway inhibits the growth of metastases by inducing cell-cycle arrest and apoptosis (Zhang et al, 2009).

Adiposity-related genes predict disease recurrence among colon cancer survivors (Sebio et al, 2015). For example, PPAR-γ rs1801282 regulates transcription factors for several genes that influence colon cancer growth (Sarraf et al, 1998). Furthermore, PPAR-γ rs1801282 predicts the progression from impaired glucose tolerance to type 2 diabetes (Kilpelainen et al, 2008; Brito et al, 2009). Physical activity reduces the risk of progression from impaired glucose tolerance to type 2 diabetes that is attributed to this polymorphism (Kilpelainen et al, 2008; Brito et al, 2009). Type 2 diabetes is associated with an inferior prognosis in colon cancer (Meyerhardt et al, 2003). Future research will be needed to discern if the disease-specific benefits of physical activity for colon cancer survivors are achieved through similar pathways as that of type 2 diabetes prevention.

There are several limitations to this trial. The primary limitation to this trial is the small sample size, which limited our statistical power to examine other body composition outcomes. The small sample size allowed for numeric differences in baseline body composition and anthropometric measures. Our analyses plan prespecified that the baseline value of the dependent variable would be included in the model to account for baseline differences; however, we cannot rule out that the observed differences may be partly due to regression to the mean. The small sample size also reduces the generalisability of our findings. As we have previously described (Brown et al, 2016), participants were not recruited based on having excess visceral adipose tissue at baseline. It is not known if the exercise-induced reductions in visceral adipose tissue would be similar or larger in magnitude among a sample who all had excess visceral adipose tissue at baseline.

In conclusion, the findings from this randomised trial demonstrated the dose–response effects of moderate intensity aerobic exercise to favourably reduce visceral adipose tissue among selected patients recently treated for stage I–III colon cancer. The findings from this randomised trial may be useful to healthcare practitioners.

### Table 3. Anthropometric outcomes at baseline and change during 6 months

| Outcome                      | Baseline (mean ± s.d.) | Δ baseline to month 6 (LS mean ± s.e.) | Δ from control (LS mean ± s.e.) |
|------------------------------|------------------------|---------------------------------------|---------------------------------|
| **Body mass, kg**            |                        |                                       |                                 |
| Control                      | 83.7 ± 22.1            | 0.43 ± 0.61                           |                                 |
| Low dose                     | 86.2 ± 13.1            | -0.51 ± 0.57                          | -0.95 ± 0.84                    |
| High dose                    | 92.2 ± 24.3            | -0.32 ± 0.62                          | -0.76 ± 0.87                    |
| Test for trend               |                        |                                       | P = 0.280                       |
| **BMI, kg m²**               |                        |                                       |                                 |
| Control                      | 29.2 ± 6.0             | 0.14 ± 0.22                           |                                 |
| Low dose                     | 29.5 ± 4.3             | -0.17 ± 0.21                          | -0.31 ± 0.30                    |
| High dose                    | 32.5 ± 6.9             | -0.11 ± 0.23                          | -0.25 ± 0.32                    |
| Test for trend               |                        |                                       | P = 0.354                       |
| **Waist circumference, cm**  |                        |                                       |                                 |
| Control                      | 98.0 ± 17.1            | 1.62 ± 0.94                           |                                 |
| Low dose                     | 98.7 ± 11.9            | 0.16 ± 0.89                           | -1.46 ± 1.29                    |
| High dose                    | 106.9 ± 14.6           | -2.90 ± 0.94*                         | -4.52 ± 1.34*                   |
| Test for trend               |                        |                                       | P < 0.001                       |
| **Hip circumference, cm**    |                        |                                       |                                 |
| Control                      | 103.4 ± 13.5           | 1.85 ± 1.42                           |                                 |
| Low dose                     | 104.5 ± 10.3           | 0.18 ± 1.34                           | -1.67 ± 1.95                    |
| High dose                    | 110.6 ± 15.0           | 0.02 ± 1.45                           | -1.84 ± 2.03                    |
| Test for trend               |                        |                                       | P = 0.518                       |
| **Waist to hip ratio**       |                        |                                       |                                 |
| Control                      | 0.94 ± 0.09            | -0.005 ± 0.01                         |                                 |
| Low dose                     | 0.94 ± 0.07            | 0.001 ± 0.01                          | 0.005 ± 0.016                   |
| High dose                    | 0.97 ± 0.09            | -0.029 ± 0.012*                       | -0.023 ± 0.016                  |
| Test for trend               |                        |                                       | P = 0.054                       |
| **Sagittal abdominal diameter, cm** |                  |                                       |                                 |
| Control                      | 22.6 ± 4.0             | 0.45 ± 0.32                           |                                 |
| Low dose                     | 22.4 ± 3.6             | 0.01 ± 0.30                           | -0.43 ± 0.44                    |
| High dose                    | 23.9 ± 4.0             | 0.01 ± 0.32                           | -0.45 ± 0.46                    |
| Test for trend               |                        |                                       | P = 0.200                       |

Abbreviations: BMI = body mass index; LS mean = least-squares mean; s.d = standard deviation; s.e = 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 (randomisation stratification factor).

*Significantly different from baseline (within-group), P ≤ 0.05.

**Significantly different from control, P < 0.05.**
providers to improve the specificity of exercise prescriptions for colon cancer survivors. The findings from this randomised trial are also useful for investigators to begin to understand the mechanistic pathways that are hypothesised to mediate the relationship between exercise and disease outcomes in this population. Visceral adipose tissue may be a mechanism through which exercise reduces the risk of disease recurrence among colon cancer survivors.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DISCLAIMER

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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