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SYSTEMATIC REVIEW

Exercise Training in Oncology: Systematic Review and Clinical Practice Recommendations

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Abstract

Background: The emergence of exercise therapy as an important adjunct therapy following a cancer diagnosis dramatically increases the need for oncology professionals to inform and advise cancer patients on this modality. To guide clinical practice and ensure optimal safety and efficacy, oncology-specific evidence-based practice recommendations are required. *Methods:* We conducted a systematic review to identify all studies examining the effect of an exercise training intervention that included an objective measurement of cardiorespiratory fitness in adults diagnosed with cancer. Studies were assessed according to the Appraisal of Guidelines for Research and Evaluation (AGREE) II criteria. Despite considerable heterogeneity, structured exercise interventions significantly improved a variety of measures of cardiorespiratory fitness, body composition, global quality of life, fatigue, and depression. *Results:* Based on this evidence, we provide clinical practice exercise recommendations for curative-intent cancer patients both during and following adjuvant therapy. *Conclusion:* This summary provides important guidance to oncology and other health professionals giving exercise advice to individuals with cancer. **Health & Fitness Journal of Canada 2012;5(1):47-63.**

Keywords: Aerobic training, physical activity, malignancy, systematic review, recommendations

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Background

Among the first formal exercise guidelines were those by the American College of Sports Medicine (ACSM) and Centers for Disease Control (CDC) published in 1995. These landmark guidelines encouraged increased exercise participation in Americans of all ages for health promotion and disease prevention (Pate et al., 1995). Subsequently, exercise guidelines have been published promising /supporting reduced morbidity and secondary prevention of numerous chronic conditions (Warburton et al., 2006a, 2006b).

In stark contrast, investigation of the therapeutic role of exercise following a diagnosis of cancer has, until recently, received scant attention (Jones and Peppercorn) The use of conventional and novel cytotoxic therapies are associated with a diverse range of debilitating physiological (e.g., deconditioning, skeletal muscle atrophy, cardiac and pulmonary dysfunction) and patient-reported outcomes (PROs; e.g., fatigue, nausea, depression, anxiety) that impair recovery and increase susceptibility to concomitant age-related conditions (Jones et al., 2009). To address these concerns, several research groups have investigated the safety, feasibility, and efficacy of structured exercise interventions on a broad range of

physiological and psychosocial outcomes before, during, and/or following adjuvant therapy. Systematic reviews (Speck et al., 2010) and meta-analyses (Jones et al., 2011; McNeely et al., 2006) conclude that structured exercise is a safe and well-tolerated intervention associated with improvements in cancer-related symptoms and functional outcomes (Speck et al., 2010).

The emergence of exercise therapy as an important adjunct therapy following a cancer diagnosis dramatically increases the need for oncology professionals to inform and advise cancer patients on this modality. To guide clinical practice and ensure optimal safety and efficacy, oncology-specific evidence-based practice recommendations are needed. The ACSM recently published the first exercise guidelines for cancer patients (Schmitz et al., 2010b). Building on these opinion-based guidelines, we evaluated the safety and efficacy of exercise in adults with cancer and whether these effects differed by exercise prescription (e.g., type, intensity, duration) or medical (e.g., cancer type, treatment status) characteristics to inform (adopting the AGREE II criteria (Brouwers et al., 2010a, 2010b)) evidence-based practice recommendations to assist oncology professionals with exercise advice for cancer patients.

Methods

Study Search and Inclusion Criteria

A comprehensive literature review using OVID MEDLINE (1950 to 2011), Cochrane Central Register of Controlled Trials (1991 to 2011), AMED (1985 to 2011), EMBASE (1988 to 2011), PUBMED (1966 to 2011), SCOPUS (1950 to 2011) and WEB OF SCIENCE (1950 to 2011) using the following MeSH terms and text words: oncology, cancer, and neoplasms malignancies, exercise, physical activity, exercise therapy, exercise training, and aerobic. Relevant reference lists were also hand-searched.

All studies examining the effect of an exercise training intervention that included an objective measurement of cardiorespiratory fitness in adults diagnosed with cancer were deemed eligible. Studies with a participant mean age below 18 years (studies among children and adolescents with cancer), non-English, review article only, exercise behavior was the dependent variable (i.e., physical activity promotion studies), and assessed the effects of exercise in combination with other interventions (e.g., stress management, dietary counseling, yoga) were excluded. Given the considerable heterogeneity in measurement tools to assess the effects of exercise on the outcomes of interest, we only report data in which at least three independent studies used the specific measurement tool. Findings from epidemiological (observational) studies investigating the association between self-reported exercise and disease outcome (i.e., cancer-specific mortality and all-cause mortality) following a cancer diagnosis were also considered to inform practice recommendations, and are reviewed in a separate section [according to AGREE criteria, the level of evidence assigned to observational studies is 2 (overwhelming evidence) or 3].

Results

A total of 2856 potential citations were identified; after initial review, 118 were deemed potentially eligible. On secondary review, 56 met inclusion criteria* involving a total of 3,289 adult cancer patients (n=2,289, physical activity; n=1,000, usual care control). The

overall study and exercise intervention characteristics are provided in Tables 1 and 2, respectively.

Study Adherence, Lost-to-Follow-Up, and Adverse Events

Thirty-four studies (61%) reported adherence to the exercise intervention, with a mean adherence of 85% ± 14% (range, 44% - 100%). The mean lost-to-follow-up rate was 12% ± 13% (range, 0% - 57%). There were no significant differences in exercise adherence or lost-to-follow-up rate based on exercise training modality or treatment status ($p>0.05$). Eight (14%) studies reported an adverse event (AE) during exercise testing or exercise training for a total of 23 AEs; a total patient adverse rate of 3.0% per 662 patients (Table 3).

Effects of Exercise on Cardiopulmonary Function, Body Composition, and PROs

Effects on cardiopulmonary and body composition are reported in Table 4. Peak oxygen consumption (VO_2peak) ($mL \cdot kg^{-1} \cdot min^{-1}$) was reported in 17 studies involving a total of 682 patients; 7 of these were randomized controlled trials that included a usual care (control group) involving a total of 334 patients. VO_2peak increased 2.3 $mL \cdot kg^{-1} \cdot min^{-1}$ [95% CI, 1.1 to 3.6; $p = 0.001$] with exercise training and decreased 1.0 $mL \cdot kg^{-1} \cdot min^{-1}$ [95% CI, –1.6 to –0.5; $p = 0.004$] in the (non-exercise) usual care from baseline to post-intervention (Table 4). Body mass and percent body fat decreased 1.1 kg [95% CI, –2.2 to –0.2; $p = 0.025$] and 0.8% [95% CI, –1.6 to –0.2; $p = 0.021$], respectively with exercise training from baseline to post-intervention. There were no significant changes in any body composition outcome in participants assigned to control group ($p > 0.05$).

Functional Assessment of Cancer Therapy – General (FACT-G) was reported in 9 studies; FACT-G increased 7.7 points [95% CI, –0.4 to 15.8; $p = 0.059$] with exercise training and increased 4.7 points [95% CI, –5.2 to 14.5; $p = 0.277$] in the control group from baseline to post-intervention. Significant changes were indicated for FACT-Anemia (FACT-AN) ($p = 0.001$) and FACT-Breast (FACT-B) ($p = 0.005$). There were no significant changes in any measure of QOL in the control group ($p > 0.05$) (Table 4). Concerning fatigue, Piper fatigue scores (used by 10 studies) decreased 1.1 points [95% CI, –0.2 to –2.1; $p = 0.019$] with exercise training and increased 0.2 points [95% CI, –1.4 to 1.7; $p = 0.803$] in the control group. Significant changes were indicated for FACT-Fatigue (FACT-F) ($p = 0.055$) and Linear Analogue Scale (LAS) ($p = 0.012$) (Table 5).

Effects on Select Cardiopulmonary Function and Patient-Reported Outcomes by Exercise Modality and Treatment Status

The VO_2peak increased 1.8 $mL \cdot kg^{-1} \cdot min^{-1}$ [95% CI, 0.5 to 3.1; $p=0.013$] and 3.9 $mL \cdot kg^{-1} \cdot min^{-1}$ [95% CI, 0.3 to 7.4; $p = 0.040$] with aerobic training alone and combined (aerobic plus resistance training), respectively. Resistance training alone did not cause significant changes in any cardiorespiratory fitness outcome ($p > 0.05$). QOL, as measured by the FACT-B, increased 9.9 points [95% CI, 0.3 to 20.1; $p = 0.050$] and 11.9 points [95% CI, 0.1 to 23.6; $p = 0.049$] with aerobic training only and combined training, respectively. Combined training caused significant changes in fatigue as measured by the Piper Fatigue scale ($p = 0.003$) and FACT-F ($p = 0.006$). Finally, resistance training only caused significant changes in QOL [FACT-B

Table 1: Study Characteristics (n = 56).

	No. (%)
Year of publication	
1980 - 1989	1 (2)
1990 - 1999	4 (7)
>2000	51 (91)
Country of publication	
US	24 (43)
Europe	17 (30)
Canada	8 (14)
Asia	2 (4)
Other	5 (9)
Study Design	
Randomized controlled trial	28 (50)
Pre-post, single-arm	28 (50)
Number of subjects	
Mean ± SD	55 ± 43
Range	8 – 242
0-20	15 (27)
21-50	16 (29)
>50	25 (44)
Sex	
Male	880 (27)
Female	2364 (73)
Age (yrs)	
Mean ± SD	52 ± 8
18-50	24 (47)
>50 – 60	20 (39)
>60	7 (14)
Cancer population / site	
Breast	23 (41)
Mixed	21 (38)
NSCLC / SCLC / Bronchogenic	4 (7)
Prostate	3 (5)
Leukemia	3 (5)
Colorectal	1 (2)
NHL / Hodgkin's	1 (2)
Study setting	
Before surgery	1 (2)
After surgery, during treatment	20 (36)
After surgery, after treatment	17 (30)
Mixed (during and after treatment)	4 (7)
Inoperable, during treatment	1 (2)
Pre-BMT*	5 (9)
Post-BMT*	9 (16)
Cancer treatment	
Multimodal therapies	25 (45)
Chemotherapy	19 (34)
Chemotherapy plus radiation	5 (9)
Endocrine therapy	2 (4)
Radiation	2 (4)
Other	2 (4)
Disease stage	
Curative	54 (96)
Palliative	2 (4)

*One study recruited patients in both the pre-BMT and post-BMT setting and therefore is included in both categories.

Table 2: Exercise Prescription Characteristics (n = 56).

	No. (%)
Intervention Length (weeks)	
Mean ± SD	13 ± 8
0-12	34 (61)
>12-23	14 (25)
>24	8 (14)
Not reported	0 (0)
Frequency (sessions/week)	
Mean ± SD	3.5 ± 1.3
0-2	7 (13)
3	31 (55)
>3	18 (32)
Not reported	0 (0)
Duration (minutes per session)	
Mean ± SD	34 ± 15
0-20	4 (7)
>20-30	30 (55)
>30	21 (38)
Not reported	1 (2)
Total exercise mins.wk^{-1}*	
Mean ± SD	112 ± 52
0-100	28 (51)
>100-149	14 (26)
≥150	13 (24)
Intensity (%)	
Mean ± SD	56 ± 26
30%-50%	20 (36)
>50%-70%	19 (34)
>70%	17 (30)
Not reported	0 (0)
Progression	
Yes	35 (63)
Not Reported	21 (38)
Exercise Training Safety Monitoring	
Reported	34 (61)
Not reported	22 (39)
Exercise Intervention Setting	
Supervised, clinic-based	15 (27)
Supervised, non clinic-based	21 (38)
Unsupervised, home-based	15 (27)
Mixed setting, supervised and unsupervised	5 (9)
Exercise Intervention Modality†	
Aerobic training + resistance training	18 (30)
Multiple aerobic training modalities	11 (18)
Cycle ergometry only	11 (18)
Treadmill / walking only	10 (16)
Resistance training only	6 (10)
Aerobic training + resistance training + stretching	3 (5)
Aerobic training + stretching	2 (3)

*calculated from reported mean frequency and duration of exercise sessions; †studies comparing more than one exercise training modality may be counted in one or more categories.

Table 3: Adherence, Lost-to-Follow-Up, and Adverse Events Overall and by Treatment Status and Exercise Modality.

Variable	Mean ± SD	no. (%)
Adherence		
Overall		
All studies, n=34, (%)	85 ± 14	
Range	44 – 100	
Not reported		22 (39)
Adherence by Exercise Modality		
Aerobic Training, n=22, (%)	86 ± 12	
Aerobic + Resistance Training, n=12, (%)	83 ± 18	
Resistance Training, n=4 (%)	83 ± 12	
Adherence by Treatment Status		
Off-Therapy, n=13	88 ± 13	
On-Therapy*, n=21	84 ± 15	
Lost-to-Follow-Up		
Overall		
All studies, n=56, (%)	12 ± 13	
Range	0 – 56	
Not reported	–	–
Lost-to-Follow-Up by Exercise Modality		
Aerobic Training, n=34, (%)	12 ± 11	
Aerobic + Resistance Training, n=21, (%)	13 ± 17	
Resistance Training, n=6, (%)	13 ± 8	
Lost-to-Follow-Up by Treatment Status		
Off-Therapy, n=23, (%)	11 ± 14	
On-Therapy*, n=33, (%)	13 ± 13	
Adverse Events		
Total Number of Adverse Events		23 (3.0) (23 patient events / 622 total number of patients)
Not reported, no. (%)		48 (86)

*"On-Therapy" defined as patient undergoing definitive primary therapy (i.e., chemotherapy, radiotherapy, small molecular inhibitor therapy) during study intervention

Table 4: Effects of Exercise Training on Cardiorespiratory Fitness and Body Composition Outcomes.

Measure	No. of Studies	*N*	Baseline		Post-intervention		Change		P
			Mean	SD	Mean	SD	Mean	95% CI	
Cardiorespiratory Fitness									
VO_2peak, mL·kg^{-1}·min^{-1}									
Exercise	17	682	23.8	6.4	26.1	7.6	+2.3	1.1 to 3.6	0.001
Control	7	333	23.1	5.4	22.1	5.1	−1.0	−1.6 to −0.5	0.004
VO_{2peak}, L·min^{-1}									
Exercise	10	421	1.69	0.43	1.92	0.60	+0.23	0.04 to 0.42	0.019
Control	5	195	1.72	0.19	1.66	0.19	−0.06	−0.17 to 0.04	0.194
Workload, Watts									
Exercise	10	315	109	47	126	52	+17	10 to 24	<0.001
Control	1	60	146	−	148	−	−2	−	−
Estimated VO_{2peak}, mL·kg^{-1}·min^{-1}									
Exercise	9	589	25.7	3.8	29.1	4.8	+3.4	2.0 to 4.7	<0.001
Control	2	149	30.9	1.2	33.1	2.4	+2.2	−8.6 to 13.1	0.230
6-min walk test, m									
Exercise	6	186	452	93	487	77	+35	16 to 54	0.005
Control	2	27	498	68	500	94	+2	−228 to 225	0.941
12-min walk test, m									
Exercise	8	401	916	239	1038	293	+122	38 to 207	0.011
Control	6	276	890	259	878	301	−12	−132 to 107	0.804
Body Composition									
Body mass, kg									
Exercise	17	696	78.1	8.7	77.0	7.8	−1.1	−0.2 to −2.2	0.025
Control	10	358	77.0	5.7	77.3	5.7	+0.3	−1.7 to 2.3	0.702
Body fat, %									
Exercise	11	648	30.6	5.4	29.8	6.0	−0.8	−1.6 to −0.2	0.021
Control	7	297	32.2	6.5	33.5	6.8	+1.3	−0.9 to 3.5	0.190
Lean body mass, kg									
Exercise	3	90	39.3	14.1	39.5	14.8	+0.2	−3.7 to 4.2	0.798
Control	2	87	46.5	4.9	45.9	5.5	−0.6	−6.2 to 5.2	0.437

Abbreviations: VO_2peak, peak oxygen consumption

Table 5. Effects of Exercise Training on Quality of Life, Fatigue, and Depression

Measure	No. of Studies	*N*	Baseline		Post-intervention		Change		
			Mean	SD	Mean	SD	Mean	95% CI	P
Quality of Life									
FACT-G, 0-104[†]									
Exercise	9	438	81.8	10.8	89.5	17.3	+7.7	–0.4 to 15.8	.059
Control	6	252	85.5	8.0	90.2	8.8	+4.7	–5.2 to 14.5	.277
FACT-AN, 0-188									
Exercise	2	222	117.0	23.9	126.1	23.7	+9.1	7.1 to 11.0	.011
Control	2	142	120.2	21.4	122.5	24.6	+2.3	–26.9 to 31.5	.500
FACT-B, 0-104									
Exercise	6	258	86.1	32.2	97.3	35.4	+11.2	5.1 to 17.3	.005
Control	5	207	84.4	36.7	83.8	36.4	–0.6	–4.4 to 3.0	.646
Fatigue									
Piper, 0 - 10									
Exercise	10	483	4.6	1.0	3.5	1.4	–1.1	–0.2 to –2.1	.019
Control	4	114	3.8	1.3	4.0	0.5	+0.2	–1.4 to 1.7	.803
FACT-F, 0-52[††]									
Exercise	8	472	35.1	6.8	38.5	4.2	+3.4	–0.9 to 7.8	.103
Control	5	305	37.4	4.5	37.4	2.9	0.0	–2.6 to 2.6	.984
FACT-F, 0-52[†††]									
Exercise	4	146	21.9	11.0	16.1	10.3	–5.8	–0.2 to 11.9	.055
Control	2	61	11.4	0.8	10.5	2.3	–0.9	–14.9 to 13.1	.563
Depression*									
CES-D, 0 - 24									
Exercise	5	313	13.5	4.8	9.9	3.0	–3.6	–6.3 to –0.7	.026
Control	3	175	10.0	4.0	8.8	2.4	–1.2	–5.4 to 3.1	.357
Beck Inventory, 0 - 63									
Exercise	3	222	10.1	3.7	6.1	2.4	–4.0	–10.5 to 2.5	.117
Control	2	140	11.9	1.6	10.9	0.8	–1.0	–7.4 to 5.3	.295
HADS, 0 - 21									
Exercise	3	126	4.8	2.6	4.7	2.6	–0.1	–2.1 to 1.7	.753
Control	1	70	3.1	–	1.3	–	–	–	–

[†]In studies using the Functional Assessment of Cancer Therapy (FACT) system, the FACT-General score was the used as the default assessment. However, in circumstances where the FACT-G was not reported, we report the cancer-site specific score (e.g., FACT-Breast).

[*]Lower scores reflect lower fatigue and depression except where indicated; [††]Increased scores reflect lower fatigue; [†††]decreased scores reflect lower fatigue. Abbreviations: FACT-G, Functional Assessment of Cancer Therapy – General; FACT-AN, Functional Assessment of Cancer Therapy – Anemia; FACT-B, Functional Assessment of Cancer Therapy – Breast; FACT-F, Functional Assessment of Cancer Therapy – Fatigue; CES-D, Center for Epidemiologic Studies Depression Scale (short-form); HADS, Hospital Anxiety and Depression Scale.

Table 6. Association Between Post-Diagnosis Exercise Behavior and Cancer-Specific Mortality and All-Cause Mortality in Cancer Patients

Tumour Type	No. of Studies	Cancer-Specific Mortality			All-Cause Mortality		
		Risk Reduction (HR)	Exercise Dose	Dose Response	Risk Reduction (HR)	Exercise Dose	Dose Response
Breast	10	0.51-1.0 (multi-variate adjusted relative risk)	>1 time per week - ≥21 MET- hr.wk^{-1}	Yes: 5 studies No: 3 studies n/a: 2 studies	0.33-0.82 (multi-variate adjusted relative risk)	≥2 hr.wk^{-1} - ≥24.7 MET- hr.wk^{-1}	Yes: 5 studies No: 2 studies n/a: 3 studies
Colon/Colorectal	5	0.33-0.64 (multi-variate adjusted relative risk)	≥18 MET- hr.wk^{-1} - ≥27 MET- hr.wk^{-1}	Yes: 2 studies No: 2 studies n/a: 1 study	0.37-.60 (multi-variate adjusted relative risk)	≥18 MET- hr.wk^{-1} - ≥27 MET- hr.wk^{-1}	Yes: 2 studies No: 1 study n/a: 2 studies
Prostate	2	0.43 (for progression) – 0.65 (multi-variate adjusted relative risk)	≥9 MET- hr.wk^{-1}- walking ≥3 hr.wk^{-1} at ≥3 mph	Yes: 1 study No: 1 study	0.67 (multi-variate adjusted relative risk)	≥9 MET- hr.wk^{-1}	Yes: 1 study No: 1 study
Lung	1	n/a	n/a	n/a	0.67 (multi-variate adjusted relative risk)	≥9 MET- hr.wk^{-1}	n/a
Ovarian	1	n/a	n/a	n/a	0.69 (multi-variate adjusted relative risk)	≥2 hr.wk^{-1}	No
Primary glioma	1	n/a	n/a	n/a	0.64 (multi-variate adjusted relative risk)	≥9 MET- hr.wk^{-1}	Yes

Abbreviations: MET, metabolic equivalent.
Definitions: MET hr.wk-^{1}, METs per hour of each activity multiplied by hours per week of each activity. For example, ≥9 MET hr.wk^{-1} is equivalent to 30 minutes of moderate walking 5 d.wk^{-1} and ≥18 MET hr.wk^{-1} is equivalent to 60 minutes of moderate walking 5 d.wk^{-1}.
Data adapted from Ballard-Barbash et al. (in press).

(p = 0.049)] and [FACT-F (p = 0.044)].

Concerning treatment status, during therapy exercise was associated with a non-significant increase in VO_2peak [+2.2 $mL \cdot kg^{-1} \cdot min^{-1}$, 95% CI, –0.9 to 5.4; p = 0.134] with significant decrease in the control group [–1.0 $mL \cdot kg^{-1} \cdot min^{-1}$, 95% CI, –1.7 to –0.2; p=0.025]. Following therapy, VO_2peak increased 2.4 $mL \cdot kg^{-1} \cdot min^{-1}$ [95% CI, 1.1 to 3.7; p = 0.002] in the exercise group and was unchanged in the control group (p = 0.284). There were no significant differences in any PRO either during or following therapy.

Association Between Exercise Behaviour and Survival

A total of 20 observational studies examined the association between self-reported exercise and prognosis following a cancer diagnosis (Table 7). Overall, 15 (75%) studies reported a significant inverse relationship between exercise and prognosis (cancer-specific or all-cause mortality) with a range of risk reduction between 15% to 61% and 18% to 67% for cancer-specific mortality and all-cause mortality, respectively. Finally, the dose of exercise required for mortality reduction was not uniform either within or between cancer populations ranging from one exercise session$\cdot wk^{-1}$ to ≥27 MET-hr$\cdot wk^{-1}$ (equivalent to ≥450 min$\cdot wk^{-1}$ of moderate intensity exercise).

Discussion

Overall short-term, moderate-intensity structured exercise training is a feasible, safe, and well-tolerated adjunct therapy for cancer patients treated with curative-intent both during and following adjuvant therapy. Overall, the demonstrated benefits of exercise training, the promising epidemiological data of the inverse association between regular exercise and prognosis, combined with the low incidence of events, suggest that the risk-to-benefit ratio favours the recommendation of exercise for all cancer patients

Only 8 of the 56 (14%) eligible studies stated that AEs were monitored during study conduct. As such, it is not clear whether the low incidence of AEs reflects the true safety of exercise training in persons with cancer or less than optimal monitoring and reporting of AEs in these trials. A cancer diagnosis and the use of conventional and novel anticancer therapies are expected to increase the risk of exercise-related AEs (Jones et al., 2009; Jones et al., 2008). Cancer is a heterogeneous disease varying considerably in anatomic location, physiologic consequences, and cancer therapy; thus, the risk of an exercise-related event is likely highly dependent on these factors. Unfortunately, given the paucity of studies reporting AE monitoring, it was not possible to conduct sensitivity analyses to examine whether the prevalence of AEs differed as a function of cancer type, stage of disease, therapeutic modality, or exercise intervention. Comprehensive monitoring as well as reporting of AEs is mandatory for all studies investigating the efficacy of exercise training in the oncology setting.

The ability of cancer patients to exercise is also demonstrated by the excellent adherence (85%) and minimal lost-to-follow-up (12%) rates. Both rates are considered superior to conventional 'accepted' values for clinical trials as defined by Consolidated Standards of Reporting Trials (CONSORT) (Altman et al., 2001). Significant selection bias may exist because of the transparent nature of exercise training studies resulting in recruitment of patients with better health

status and highly motivated to participate in 'health-oriented' studies. Only 27% of patients screened for study participation were deemed eligible, and, of these, ~40% of these were allocated to study group(s), equating to ~10% of screened patients. Corresponding data for cytotoxic drug trials varies dramatically and is highly dependent on the nature of drug class, study design, and the anticipated risk-to-benefit ratio of the intervention. Nevertheless in the UK, participation in cancer clinical trials is ~12% of incident cases (Stead et al., 2011). It is not clear whether the current findings are generalizable to the cancer population at large; however, as the field as exercise oncology continues to broaden it will of great interest to learn whether the current safety and tolerability of exercise applies to this wider population of patients.

Our findings corroborate the conclusions of prior systematic reviews and meta-analyses that exercise is associated with significant improvements in cardiopulmonary function, body composition, and select PROs (Jones et al., 2011; McNeely et al., 2006). For example, VO_2peak increased, on average, 2.3 $mL \cdot kg^{-1} \cdot min^{-1}$ or 8.8% from baseline to post-intervention and declined 1.0 $mL \cdot kg^{-1} \cdot min^{-1}$ or 4.3% in the control group. Structured exercise interventions in non-cancer clinical populations typically report a ~15% in VO_2peak with aerobic-based training following traditional prescription guidelines (3 – 5 $d.wk^{-1}$ at 50% to 75% of baseline VO_2peak for 12 – 15 weeks)(Warburton et al., 2006a). The reasons for the smaller magnitude of VO_2peak improvement in cancer patients compared with non-cancer clinical patients remains to be elucidated but may reflect fundamental differences in exercise prescription 'dose' being evaluated between clinical populations (e.g., lower dose of exercise being delivered to cancer patients) or the cardiovascular response to exercise in cancer patients that are, or have received, combination adjuvant therapy. Nevertheless, an improvement in VO_2peak of 2.3 $mL \cdot kg^{-1} \cdot min^{-1}$ may be clinically meaningful, particularly in view of the significant decline observed in patients randomized to usual care control. The prognostic importance of VO_2peak as well as measures of exercise capacity have been firmly established in healthy and diseased populations (Lauer, 2011); VO_2peak is also a significant independent predictor of survival in persons with cancer (Jones et al., 2012; Jones et al. 2010b). Such findings may have important implications for mortality risk prediction, physiological evaluation, and design of therapeutic intervention in cancer patients.

Our results support prior findings indicating that structured physical activity is associated with significant improvements in *body habitus*. Such improvements may be clinically important since excess body weight is associated with increased risk of death following the diagnosis of several forms of cancer, relative to normal weight women (Rock and Demark-Wahnefried, 2002). There is considerable interest in examining the effects of exercise in combination with nutritional advice to prevent weight gain or induce weight loss in breast cancer patients and whether such effects impact prognosis. It is important to note, however, that weight loss is not a desirable outcome in all oncology settings. Specifically, an 'obesity paradox' may exist wherein elevated BMI is associated with improved prognosis in certain cancer populations experiencing cancer- or cancer therapy-associated

wasting syndrome or cachexia (Franceschi et al., 2001; Halabi et al., 2007; Halabi et al., 2005; Kanashiki et al., 2005). The vast majority of studies reviewed here included curative-intent patients where weight loss is likely a more salient therapeutic goal. Additional studies are required that investigate the effects of exercise on *body habitus* among patients with advanced disease. In such scenarios, it appears reasonable to speculate that exercise training, particularly resistance training, may counteract cancer-induced wasting / cachexia through several potential mechanisms including skeletal muscle hypertrophy and augmentation of antioxidant machinery as observed in patients with heart failure and chronic obstructive pulmonary disease (COPD) (Casaburi, 2000).

Consideration of PROs is now considered an integral aspect of care in all realms of oncology practice and management (Dow et al., 1999; Loerzel et al., 2008; Meneses and Benz, 2010; Morgan, 2009; Pagani et al., 2010). Our results are concordant with prior reports indicating that exercise training is associated with statistically significant in different measures of QOL and fatigue. Exercise oncology research to date has tested the efficacy of exercise on PROs in cancer patients in mostly a ubiquitous fashion. However, as the field continues to progress, it will become increasingly important to adopt a more targeted approach to test the efficacy of exercise therapy as a means to improve PROs in cancer patients. One potential strategy is for trials in which QOL or fatigue is a primary endpoint to recruit only 'at-risk' individuals (i.e., those with high fatigue or low QOL). An equally important consideration is the type / nature of the control group. For instance, to control for the potential 'social' aspects of exercise interventions (i.e., Hawthorne effects), attention-control groups wherein participants randomized to non-exercise groups receive the same timing / type of social interaction as the exercise group are required. Few exercise oncology trials with QOL or fatigue as the primary aim has adopted such criteria, which may partially explain the somewhat inconsistent responses in PROs following an exercise intervention (Schmitz et al, 2010a).

Unfortunately, given the considerable heterogeneity, it was feasible only to conduct sensitivity analyses as a function of exercise modality (e.g., aerobic vs. resistance training) or treatment status (e.g., during vs. after therapy). Concerning exercise modality, aerobic training was the only intervention associated with consistent improvements across different measures of cardiorespiratory fitness and body composition. Intriguingly however, for changes in VO_2peak – the gold standard assessment of cardiorespiratory fitness, the combination of aerobic and resistance training was the most efficacious. A similar intriguing finding was that the effect of exercise training was associated with significant improvements in VO_2peak following but not during cytotoxic therapy. Differences in exercise adherence do not appear responsible for these findings, suggesting that either the direct effects of anticancer therapy or therapy-induced toxicity causes attenuation of the normal cardiovascular adaptations to exercise training (Jones et al., 2009). Clearly, these findings are exploratory and no study to date has formally compared whether combined training is superior to either aerobic or resistance training alone in cancer patients or efficacy of exercise during versus following cytotoxic therapy.

Table 7: Evidence-Based Clinical Practice Exercise Recommendations for Cancer Patients.

Recommendation	Description	Grade of Evidence
Recommendation 1	Following completion of adjuvant therapy, exercise participation for 3-5 $d \cdot wk^{-1}$ at 60-75% heart $rate_{reserve}$ (moderate intensity), ≥20 - 45 $min \cdot d^{-1}$ or ≥9 MET-$hrs \cdot wk^{-1}$ is supported by evidence level of This recommendation is concordant with the guidelines set forth by the ASCM that cancer patients follow the 2008 Physical Activity Guidelines (http://www.health.gov/PAGuidelines/).[10]	**Level 2; Grade B**
Recommendation 2	During adjuvant therapy, we recommend exercise participation for 3 $d \cdot wk^{-1}$ at 60-75% heart $rate_{reserve}$, ≥20 - 45 $min \cdot d^{-1}$	**Level 2; Grade B**
Recommendation 3	There is no evidence to support that the prescription of exercise either during or following the completion of adjuvant therapy should be modified to account for any medical characteristics in adults diagnosed with cancer. Nevertheless, cancer is a heterogeneous disease varying considerably in location, pathogenesis, and therapeutic management. As such, although supporting is currently lacking, it is logical that medical characteristics need to be considered when developing exercise recommendations for cancer patients. Modification of the exercise guidelines provided in recommendations 1 and 2 is advised based on individual patient medical characteristics and clinical experience.	**Level 2; Grade C**
Recommendation 4	There is insufficient evidence to support modification of any exercise prescription components (frequency, intensity, duration, modality, and progression) either during or following the completion of adjuvant therapy. There is also no evidence to support that exercise recommendations either during or following the completion of adjuvant therapy should be modified to account for setting (supervised vs. unsupervised) or timing (before, during, or following adjuvant therapy).	**Level 2; Grade C**

Abbreviations: N/A, not applicable.

Recommendations

Based on the available literature, the following evidence-based clinical practice exercise recommendations are proposed* (Table 8). A practical approach to screening and prescribing exercise for cancer patients is available (Jones et al., 2010a). *These recommendations assume that all patients have been evaluated for pre-exercise screening risk assessment (using available tools such as the Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) and have been cleared for exercise participation (Warburton et al., 2011).

Areas of Research Requiring Further Investigation

This review provided persuasive information for investigation of several questions in exercise oncology research. These include but are not limited to the following:

- Based on the current evidence, the reporting of AE in exercise oncology trials is less than optimal. The adoption of consistent and rigorous AE reporting standards is required to ensure high-quality research in exercise oncology research.
- There is considerable variation in the outcome assessments used to evaluate the efficacy of structured exercise on changes in physiologic and PROs in cancer patients. In terms of the latter, there is currently no accepted gold standard assessment of QOL or fatigue in oncology however investigators should strive to adopt global QOL scales (e.g., FACT system) utilized in the high quality exercise – cancer randomized trials wherever appropriate. In contrast, cardiopulmonary exercise testing with direct gas exchange measurement is considered the gold standard assessment of cardiorespiratory fitness in humans and is the preferred method of testing in the majority of oncology settings (Jones et al., 2008).
- Cancer patients have markedly impaired cardiorespiratory fitness across the cancer survivorship continuum (i.e., diagnosis to palliation) (Jones et al., submitted) Mechanistic studies are required to elucidate the underlying limitations to exercise in different cancer populations. Such knowledge will inform the design of optimal exercise training and rehabilitation programs in the oncology setting.
- Elucidation of the most appropriate exercise prescription for cancer patients before, during, and following therapy. Adequately powered clinical trials are required to compare the effects of different exercise prescriptions on physiologic and psycho-social outcomes across different cancer diagnoses and stages (curative vs. palliative); exercise dose-response studies are also required.
- Large-scale randomized trials of exercise on disease outcomes or validated surrogate endpoints of recurrence / prognosis as well as cardiovascular indices are paramount. Prior to the initiation of such trials it will be important to elucidate the molecular underpinnings of the exercise to ensure the optimal safety and efficacy of exercise in the oncology setting. Thus, we stress the importance of adopting a translational (bench-to-bedside) scientific approach to exercise oncology research exploiting hypothesis-driven preclinical and phase I-II clinical studies to inform

adequately powered, mechanistically-driven phase III trials.

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